Supplementary Information

Supplementary Information SI1:

Image Exclusion Criteria:

Each image segmentation was individually examined by a neuroimaging expert at each site by overlaying the segmentation label of each structure on the T1-weighted brain scan. Further, we collected study-wide statistics (means and standard deviations) as well as histogram plots in order to identify non-normally distributed data and major outliers. A subject was considered a statistical outlier if its volume was >2.698 standard deviations away from the global mean. For each subject that was marked as a statistical outlier, individual sites were asked to re-inspect the subject's segmentation in order to verify that it was properly segmented. If a subject was a statistical outlier, but was properly segmented it was kept in the analysis. Otherwise the subject was removed.

Age at Illness Onset:

Four samples were not included in the early age of onset analysis because of missing information on age of onset (CODE, Rotterdam study) or too small sample sizes (Clinical Depression Dublin N=7, Edinburgh N=6), see **Table S8**. Four samples were not included in the late age of onset analysis because of missing information (CODE, Rotterdam study) or too small sample sizes (Edinburgh N=9, QTIM N=6), see **Table S9**. Patients with early and late age of onset were separately compared to controls and then with each other. Illness stage analyses split patients into first-episode patients and recurrent-episode patients, which were separately compared with controls and then with each other. Three samples were excluded from the first episode patients analysis because of missing information on recurrence (Edinburgh) or too small sample sizes (CODE N=0, Imaging Genetics Dublin N=8), see **Table S5**. One sample was not included in the recurrent episode analysis because of missing information (Edinburgh), see **Table S6**.

Severity Analyses:

Unfortunately, not all sites used the same symptom severity measurements, with nine sites reporting HDRS-17 measurements and four sites reporting BDI-II (see **Table S11 and S12**). One additional site (SHIP-trend) used the Patient Health Questionnaire (PHQ-9), but the total score was converted to a BDI-II total score on basis of a common metric developed for 11 depression questionnaires including the PHQ-9 and BDI-II by Wahl et al. (1). Symptom severity scores were analyzed separately as combining them could provide biased estimates of effects (2) and only three sites had severity scores using both tests.

Additional Meta-analysis Details:

Using this meta-analytical framework we were able to combine data from multiple sites and weigh individual effect size estimates by level of precision. All meta-analysis models were fit using the restricted maximum likelihood method (REML; (3)). Percent differences were calculated for each effect size difference in order to restate the difference in terms of percent change in brain volume. Percent difference is the meta-analyzed mean difference between cases and controls divided by the meta-analyzed mean volume in controls (x 100) for each trait. In addition to meta-analyzed Cohen's *d* effect size estimates and percent differences, we calculated heterogeneity scores (I^2) for each structure, which provide the percent of the total variance in effect size that can be explained by heterogeneity alone (4). Lower values of I^2 indicate lower variance in the effect size estimation across studies.

References
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3. Harville DA (1977) Maximum Likelihood Approaches to Variance Component Estimation and to Related Problems. *Journal of the American Statistical Association* 72(358):320-338.
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Supplementary Information SI2:

We performed *post hoc* power analysis to estimate the sample sizes required to replicate the effects observed in this study. Sample size estimates are the number of subjects required in each group (in a case-control comparison) to detect an effect with 80% power at a nominal significance level (P = 0.05) for a two-sided t-test assuming unequal variance. All power estimates were obtained using the *pwr* package (version 1.1.1) in R.

Supplementary Information SI3:

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MPIP: The MPIP Munich Morphometry Sample comprises images acquired as part of the Munich Antidepressant Response Signature Study and the Recurrent Unipolar Depression (RUD) Case-Control study performed at the MPIP, and control subjects acquired at the Ludwig-Maximilians-University, Munich, Department of Psychiatry. We wish to acknowledge Anna Olynyik and

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Conflicts of interest:
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Author contributions:
Protocol design, quality testing, and meta-analysis: L.S., D.P.H., T.G.M.V., N.J.
Data collection, processing, analysis and funding: L.S., D.J.V., T.G.M.V., P.G.S., T.F., N.J.. E.L., H.T., A.H., W.J.N., M.W.V., M.A.I., K.W., H.J.G., A.B., K.H., H.V., D.H., M.C., J.L., S.N.H., I.B.H., R.G-M., B.K., O.G., B.C-D., M.E.R., L.T.S., N.T.M., G.I.D., K.L.M., S.E.M., N.G.M., N.A.G., M.J.W., G.B.H., G.M.M., E.M.F., A.C., L.S.V., M.J.V., N.J.V., I.M.V., H.W., K.S., E.S., C.N., D.S., C.K., B.Z., T.N., A.M.M., M.P., H.C.W., J.E.S., B.R.G., P.J.C., F.H.F., M.R., B.W.J.H.P., P.M.T., D.P.H.
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All authors contributed edits and approved the content of the manuscript.

Supplementary Tables

Supplementary Table S1: ENIGMA - Major Depressive Disorder Working Group Demographics. Age (in years), sex, and MDD patients-control breakdown for participating sites

Supplementary Table S2: ENIGMA - Major Depressive Disorder Working Group Clinical characteristics of MDD patients. Percentage of MDD patients using antidepressant medication, percentage of first episode and recurrent episode MDD patients, percentage of acutely depressed and remitted MDD patients, severity of symptoms, and age of onset of MDD breakdown for participating sites

Supplementary Table S3: Instrument for diagnosing Major Depressive Disorder and exclusion criteria by site.

Supplementary Table S4: Image acquisition and processing by site.

Supplementary Table S5: Full meta-analytic results for each mean structure for the first episode MDD patients versus Controls comparison controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

Supplementary Table S6: Full meta-analytic results for each mean structure for the recurrent MDD patients versus Controls comparison controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

Supplementary Table S7: Full meta-analytic results for each mean structure for the first episode MDD patients versus recurrent MDD patients comparison controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

Supplementary Table S8: Full meta-analytic results for each mean structure for the early age of onset (≤ 21) MDD patients versus Controls comparison controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

Supplementary Table S9: Full meta-analytic results for each mean structure for the late age of onset (> 21) MDD patients versus Controls comparison controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

Supplementary Table S10: Full meta-analytic results for each mean structure for the late age of onset (> 21) MDD patients versus early age of onset (≤ 21) MDD patients comparison controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

Supplementary Table S11: Full meta-analytic results for each mean structure for the association between symptom severity and brain volumes within MDD patients based on the HDRS-17 questionnaire controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

Supplementary Table S12: Full meta-analytic results for each mean structure for the association between symptom severity and brain volumes within MDD patients based on the BDI-2 questionnaire controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

Supplementary Table S13: Full meta-analytic results for each mean structure for the MDD patients versus Controls comparison (excluding remitted patients) controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

Supplementary Table 14: Adjusted means and standard errors for each site including the total number of subjects (N) for each structure and split into MDD patients and controls (CTL). Means are adjusted for age, sex, scan center, and ICV using the *lsmeans* package in R.

Supplementary Table 15: Full results from the moderator analyses of mean age, field strength of scanner, percent of acute patients, FreeSurfer version used for processing, percent of patients taking antidepressants, and percent of patients taking antipsychotics. Effect sizes for the meta-regression models were available from all 15 sites (percent of patients taking antipsychotics was not available in MMDP 1.5T and MMDP 3T).

Supplementary Table S16: Meta-analytic results for each mean structure for the diagnosis * sex interactive effect in the full sample of MDD patients and Controls while controlling for age, sex, diagnosis, scan center and ICV. Adjusted Cohen's d is reported.

Table S1. ENIGMA - Major Depressive Disorder Working Group Demographics. Age (in years), sex, and MDD patients-control breakdown for participating sites

Study #	Study name	Age Controls (Mean ± SD)	Age MDD (Mean ± SD)	% Female Controls	% Female MDD	Total N Controls	Total N MDD	Total N
1	**NESDA**	40.5 ± 9.8	37.2 ± 10.4	65	65	66	156	222
2	**Imaging Genetics Dublin**	36.7 ± 13.0	41.6 ± 10.8	56	63	52	52	104
3	**Clinical Depression Dublin**	30.2 ± 8.2	32.9 ± 9.1	45	42	94	36	130
4	**CODE**	40.0 ± 13.3	41.0 ± 12.0	58	65	74	102	176
5	**CLING**	25.1 ± 5.2	36.3 ± 11.6	60	53	321	49	370
6	**SHIP**	55.4 ± 12.8	53.5 ± 11.8	45	71	441	139	580
7	**SHIP-trend**	50.6 ± 14.3	49.4 ± 12.2	44	66	952	323	1275
8	**Sydney**	47.0 ± 23.2	35.8 ± 22.0	57	65	106	214	320
9	**QTIM**	22.9 ± 3.2	23.1 ± 2.7	69	82	262	38	300
10	**Rotterdam study**	64.6 ± 11.1	60.7 ± 9.8	53	72	4408	69	4477
11	**Bipolar Family Study**	23.2 ± 2.4	23.0 ± 3.1	68	61	62	18	80
12	**DepOx**	30.3 ± 10.0	30.1 ± 10.6	58	63	31	38	69
13	**MPIP**	49.1 ± 13.1	48.0 ± 13.8	58	56	222	368	590
14	**MMDP 1.5T**	27.4 ± 10.7	31.3 ± 12.2	64	51	44	53	97
15	**MMDP 3T**	30.2 ± 11.2	36.2 ± 14.5	63	55	64	73	137
	Combined					**7199**	**1728**	**8927**

Table S2. ENIGMA - Major Depressive Disorder Working Group Clinical characteristics of MDD patients. Percentage of MDD patients using antidepressant medication, percentage of first episode and recurrent episode MDD patients, percentage of acutely depressed and remitted MDD patients, percentage of patients with a co-occurring anxiety disorder, age of onset of MDD and severity of symptoms breakdown for participating sites

Study #	Sample	% Antidepressants users	% Antipsychotics users	% First episode MDD/Recurrent episode MDD	% Acute MDD/ Remitted MDD	Age of onset MDD (mean ± SD)	% co-occurring anxiety disorder	HDRS-17[a] Severity MDD (mean ± SD)	BDI-II[b] Severity MDD (mean ± SD)	IDS-SR[c] Severity MDD (mean ± SD)
1	**NESDA**	37	0	44/56	100/0	24.3 ± 11.0	60			25.4 ± 12.0
2	**Imaging Genetics Dublin**	71	0	15/85	100/0	25.3 ± 12.8	0	23.6 ± 5.0	33.1 ± 11.7	
3	**Clinical Depression Dublin**	92	0	50/50	100/0	29.6 ± 9.2	0	20.8 ± 5.1		
4	**CODE**	0	0	0/100	100/0	NA	0			38.2 ± 11.6
5	**CLING**	94	12	45/55	94/6	30.4 ± 10.6	18	20.0 ± 4.3	21.9 ± 9.8	
6	**SHIP**	17	1	55/45	NA	38.1 ± 13.2	37		11.7 ± 10.3	
7	**SHIP-trend**	17	5	37/63	NA	36.2 ± 14.3	NA		12.4 ± 8.1	
8	**Sydney**	61	24	12/88	17/83	24.6 ± 17.2	19	12.2 ± 6.9		
9	**QTIM**	24	0	61/39	24/76	17.8 ± 3.5	29	NA	NA	
10	**Rotterdam study**	29	4	45/55	100/0	NA	11	NA	NA	
11	**Bipolar Family Study**	17	0	NA	NA	21.4 ± 3.3	0	5.4 ± 5.7		
12	**DepOx**	0	0	50/50	100/0	25.6 ± 9.1	3	22.9 ± 4.3		
13	**MPIP**	84	7	27/73	87/13	35.2 ± 14.0	14	24.9 ± 6.6	14.2 ± 10.9	
14	**MMDP 1.5T**	25	NA	75/25	100/0	23.6 ± 11.5	19	12.6 ± 7.2		
15	**MMDP 3T**	55	NA	45/55	100/0	23.4 ± 11.9	30	12.0 ± 7.0		

[a] Measured with the Hamilton Depression Rating Scale (HDRS-17; range: 0-52)
[b] Measured with the Beck Depression Inventory (BDI-II; range: 0-63)

[c] Measured with the Inventory of Depressive Symptomatology-Se;f report (IDS-SR; range: 0-84)

Table S3: Instrument for diagnosing Major Depressive Disorder and exclusion criteria by site

Sample	Instrument for diagnosing MDD	Exclusion criteria
NESDA	CIDI interview	MDD subjects: presence of axis-I disorders other than MDD, panic disorder, social anxiety disorder, or generalized anxiety disorder and any use of psychotropic medication other than stable use of SSRIs or infrequent benzodiazepine use (i.e., equivalent to 2 doses of 10 mg of oxazepam 3 times per week or use within 48 hours prior to scanning). Control subjects: no Axis-I diagnosis, no medication use. All subjects: presence or history of major internal or neurological disorder, dependence on or recent abuse (past year) of alcohol and/or drugs, hypertension, and general MRI contraindications.
Imaging Genetics Dublin	SCID-1 interview	MDD subjects: comorbid psychiatric disorders (Axis I or Axis II, other than MDD), Treatment with antipsychotics or mood stabilizers, age <18 or >65, Control subjects: no Axis-I diagnosis, no medication use. All subjects: history of neurological or other severe medical illness, head injury or severe substance abuse in their lifetime history and general MRI contraindications.
Clinical Depression Dublin	SCID-1 interview	MDD subjects: comorbid psychiatric disorders (Axis I or Axis II, other than MDD), Treatment with antipsychotics or mood stabilizers, age <18 or >65, Control subjects: no Axis-I diagnosis, no medication use. All subjects: history of neurological or other severe medical illness, head injury or severe substance abuse in their lifetime history and general MRI contraindications.
CODE	SCID interview	MDD: Presence of any other Axis-1 diagnosis; Acute risk for suicide (in contrast to suicidal ideation); History of psychotic symptoms, bipolar disorder, or dementia; Schizotypal, antisocial or borderline personality disorder; Use of psychotropic medication within two weeks prior to the start of the study; No current psychotherapeutic treatment. Control subjects: No history of or current Axis-1 or 2 disorders. All subjects: History of or current neurological disorder or brain injury; Serious medical condition; Severe cognitive impairment; Substance-related abuse or dependence disorder; Use of psychotropic medication; Use of central-acting medication; Pregnancy; General MRI contraindications.
CLING	ICD-10 interview	MDD subjects: past or actual presence of other axis I diagnoses other than anxiety disorders, alcohol/cannabis abuse and tobacco dependence; neurological or other medical conditions that could be related to affective symptoms Control subjects: no medical history, including neurological and psychiatric history, as well as no previous or actual use of psychotropic medication

SHIP	M-CIDI interview	MDD subjects: presence of axis-I disorders other than MDD, anxiety disorders, conversion, somatization and eating disorder. Control subjects: no lifetime diagnosis of depression, no antidepressiva, and severity index=0 All subjects: We removed subjects with medical conditions (e.g. a history of cerebral tumor, stroke, Parkinson's diseases, multiple sclerosis, epilepsy, hydrocephalus, enlarged ventricles, pathological lesions) or due to technical reasons (e.g. severe movement artifacts or inhomogeneity of the magnetic field).
SHIP-trend	M-CIDI interview	MDD subjects: no special exclusion criteria Control subjects: no lifetime diagnosis of depression, no antidepressiva, and severity index=0 All subjects: We removed subjects with due to medical conditions (e.g. a history of cerebral tumor, stroke, Parkinson's diseases, multiple sclerosis, epilepsy, hydrocephalus, enlarged ventricles, pathological lesions) or due to technical reasons (e.g. severe movement artifacts or inhomogeneity of the magnetic field).
Sydney	SCID interview	MDD subjects: presence of axis-I disorders other than MDD, panic disorder, social anxiety disorder, or generalized anxiety disorder. Control subjects: no Axis-I diagnosis, no medication use. Exclusion criteria for all subjects included medical instability (as determined by a psychiatrist), history of neurological disease (e.g. tumour, head trauma, epilepsy), medical illness known to impact cognitive and brain function (e.g. cancer), intellectual and/or developmental disability and insufficient English for neuropsychological assessment. All subjects were asked to abstain from drug or alcohol use for 48 hours prior to testing and informed about a drug screen protocol.
QTIM	CIDI interview	MDD subjects: presence of axis-I disorders other than MDD, anxiety disorders Control subjects: antidepressant use, psychiatric disorders All subjects: relatedness between subjects, left handedness, history of neurological or other severe medical illness, head injury or current or past diagnosis of substance abuse, use of cognition affecting medication and general MRI contraindications
Rotterdam study	SCAN interview	MDD subjects: Persons who screened positive for depressive symptoms on CESD but did not meet criteria for MDD from SCAN interview. Persons who screened positive for depressive symptoms on CESD and then did not undergo SCAN interview. Presence of axis-I disorders other than MDD and anxiety disorders (DSM-IV). Persons with MRI contraindications. Control subjects: use of psychoanaleptics, MRI contraindications.
Bipolar Family Study	SCID interview	MDD subjects: presence of other axis I diagnoses. Control subjects: no medical history, including neurological and psychiatric history, as well as no previous or actual use of psychotropic medication

		All subjects: any major neurological disorder, learning disability, or any history of head injury that included loss of consciousness and any contraindications to MRI.
DepOx	SCID interview	MDD subjects: presence of axis-I disorders other than MDD and anxiety disorders (DSM-IV), clinically significant risk of suicidal behaviour, having contraindications to escitalopram treatment or being treated with psychotropic medication less than three weeks before the study (five weeks in the case of fluoxetine) Control subjects: current or past history of Axis I disorder as defined by DSM-IV Both groups: major somatic or neurological disorders, pregnancy or breast-feeding, contra-indications to MR imaging or concurrent medication which could alter emotional processing
MPIP	M-CIDI/SCAN interview	1. Munich Antidepressant Response Signature (MARS) study MDD subjects (clinical consensus diagnosis or M-CIDI (since 2008)): depressive syndromes secondary to any medical or neurological condition (e. g., intoxication, drug abuse, stroke), the presence of manic, hypomanic or mixed affective symptoms, lifetime diagnosis of alcohol dependence, illicit drug abuse or the presence of severe medical conditions (e.g., ischemic heart disease). Patients with bipolar depression were excluded for the current MR study. Control subjects: age > 65, MMSE<27, presence of severe somatic diseases or lifetime history of the following axis I disorders as assessed by the M-CIDI interview: alcohol dependence, drug abuse or dependence, possible psychotic disorder, mood disorder, anxiety disorder including OCD and PTSD, somatoform disorder, dissociative disorder NOS, and eating disorder 2. Recurrent unipolar depression (RUD) study MDD subjects (SCAN interview): presence of manic episodes, mood incongruent psychotic symptoms, the presence of a lifetime diagnosis of intravenous drug abuse and depressive symptoms only secondary to alcohol or substance abuse or to medical illness or medication. Control subjects: presence of severe somatic diseases or life-time history of anxiety and affective disorders according to the Composite International Diagnostic-Screener (CIDI-S) All subjects: gross incidental MR findings such as territorial infarction, tumor, hydrocephalus, malformations and anatomical deviations (e.g. enlarged ventricles) that prevent appropriate image processing were additional exclusion criteria. 3. MR images of 9 additional controls acquired at the LMU, Munich, meeting equivalent criteria as the RUD control sample were included.
MMDP 3T	SCID interview	MDD subjects: presence of axis-I disorders other than MDD and anxiety disorders (DSM-IV). Control subjects had to have no psychiatric history, as assessed with the SCID-I/P

		Symptom severity was assessed using the 17-item Hamilton Depression Rating Scale (HDRS-17) and the Global Assessment of Functioning Scale (GAF). Control subjects also received these measures to rule out the presence of sub-threshold psychiatric illness. Exclusion criteria for all groups were: (1) substance-use related disorder within the past 6 months as determined by the SCID; (2) lifetime history of substance dependence as measured by the SCID; (3) PTSD as determined by the SCID; (4) treatment with anti-cholinergic or typical (first generation) anti-psychotic medication; (5) use of alcohol or illicit psychoactive substance within 48 h of testing; (6) untreated medical illness such as uncontrolled diabetes or other endocrine disorders eg. Cushing's; (7) history of head injury with loss of consciousness; (8) history of neurological disease; and (9) past treatment with electroconvulsive therapy (ECT), transcranial magnetic stimulation, or psychotherapy within the past year. (10) English comprehension lower than a grade 6 reading level.
MMDP 1.5T	SCID interview	MDD subjects: presence of axis-I disorders other than MDD and anxiety disorders (DSM-IV), Control subjects had to have no psychiatric history, as assessed with the SCID-I/P Symptom severity was assessed using the 17-item Hamilton Depression Rating Scale (HDRS-17) and the Global Assessment of Functioning Scale (GAF). Control also received these measures to rule out the presence of sub-threshold psychiatric illness. Exclusion criteria for all groups were: (1) substance-use related disorder within the past 6 months as determined by the SCID; (2) lifetime history of substance dependence as measured by the SCID; (3) PTSD as determined by the SCID; (4) treatment with anti-cholinergic or typical (first generation) anti-psychotic medication; (5) use of alcohol or illicit psychoactive substance within 48 h of testing; (6) untreated medical illness such as uncontrolled diabetes or other endocrine disorders eg. Cushing's; (7) history of head injury with loss of consciousness; (8) history of neurological disease; and (9) past treatment with electroconvulsive therapy (ECT), transcranial magnetic stimulation, or psychotherapy within the past year. (10) English comprehension lower than a grade 6 reading level.

MDD: Major Depressive Disorder; CIDI: the Composite International Diagnostic Interview; SCID: Structured Clinical Interview for DSM disorders; SCAN: Schedules for Clinical Assessment in Neuropsychiatry; CESD: Center for Epidemiologic Studies Depression scale; DSM: Diagnostic and Statistical Manual of Mental Disorders; MRI: Magnetic Resonance Imaging; OCD: Obsessive Compulsive Disorder; PTSD: Posttraumatic Stress Disorder.

Table S4: Image acquisition and processing by site

Sample	Scanner vendor and type	Acquisition parameters	Freesurfer version	Slice orientation	Operating system
NESDA	3T Phillips Achieva/Intera	3D gradient-echo T1-weighted sequence. TR=9 msec; TE=3.5 msec; flip angle 8º, FOV = 256 mm; matrix: 25x62x56; in plane voxel size = 1 mm × 1 mm x 1 mm; 170 slices.	5.0	Sagittal	Linux-centos4_x86_64
Imaging Genetics Dublin	3T Phillips Achieva	A sagittal T1 3D TFE was used to scan all participants. TR=8.5 msec; TE=3.9 msec; FOV = 256 mm, AP: 256 mm, RL: 160 mm; matrix: 256×256.	5.3	Sagittal	Mac OS
Clinical Depression Dublin	1.5T Siemens Vision	3D-MPRAGE T1-weighted sequence. TR=11.6 msec; TE=4.9 msec; FOV=230 mm; matrix 512 x 512, slice thickness: 1.5 mm.	5.3	Coronal	Mac OS
CODE	3T Siemens Trio (4 Sites), 3 T Philips Achieva (1 site)	Siemens: T1 mprage, voxel size 1 mm x 1 mm x 1 mm; TR=1900 msec; TE=2.52 msec; Sample 1: 192 slices, Sample 2: 176 slices (except 1 site: 192) Philips: T1 3D-TFE, voxel size 1 mm x 1 mm x 1 mm; TR=8.3 msec; TE=3.8 msec; 170 slices.	5.3	Sagittal	Ubuntu 12.04 LTS (Linux 64bit)
CLING	3T Siemens Tim Trio	Standard 3D T1-weighted turbo fast low angle shot (turbo FLASH); voxel size 1 mm x 1 mm x 1mm (based on the ADNI protocol (Jack et al. 2008); TR=225 msec; TE=3.26 msec, FOV=256 x 256 x 192	5.1	Sagittal	Linux
SHIP	1.5T Siemens Avanto	3D T1-weighted (MP-RAGE/ axial plane); TR=1900 msec; TE=3.4 msec; Flip angle=15°; voxel size 1 mm x 1 mm x 1 mm	5.1	Axial	Centos6_x86_64

SHIP-trend	1.5T Siemens Avanto	3D T1-weighted (MP-RAGE/ axial plane); TR=1900 msec; TE=3.4 msec; Flip angle=15°; voxel size 1 mm x 1 mm x 1 mm	5.1	Axial	Centos6_x86_64
Sydney	3T GE MR750	3D T1-weighted sequence. TR=7.2 msec; TE=2.78 msec; matrix =256; FOV=240; No. slices=196; thick=0.9mm; inplane resolution=0.9375	5.1	Coronal	Linux_Ubuntu12.04_64
QTIM	Bruker 4T Whole-body MRI	3D T1 weighted sequence. TR=1500 msec; TE=3.35 msec; flip angle=8°, 256 or 240 (coronal or sagittal) slices, FOV=240 mm, matrix 256x256x256 (or 256x256x240)	5.1	Coronal, then sagittal following software upgrade.	Linux-centos4_x86_64-stable-pub-v5.1.0
Rotterdam study	1.5T Signa Excite - General Electric Healthcare, Milwaukee, USA, software version 11x	3D GRE T1 weighted sequence. TR= 13.8 msec; TE=2.8 msec; TI=400 ms; Flip angle=20°; FOV=25cm2; maxtrix 416 x 256; voxel size 1 mm x 1 mm x 1 mm.	4.5	Axial	
Bipolar Family Study	1.5T GE Signa	T1-weighted sequence. TR=500 msec; TE=4 msec; flip angle 8°; matrix 192 x 192; 180 slices; voxel size 1.25 mm x 1.25 mm x 1.20 mm; FOV=24, phase FOV 1	5.3	Coronal	linux 6, x86_64, kernel 2.6.32
DepOx	3T Siemens Tim Trio	T1 weighted sequence. TR=1100 msec; TE=4.8 msec; TI=2040 msec; voxel size 0.78 mm x 0.8 mm x 0.78 mm on a 208 x 256 x 200 grid,	5.3	Transversal	Suse Linux x86_64
MPIP	1.5T GE and Siemens (the latter: only few cases)	#1: T1-weighted SPGR sagittal 3D volume. TR=1030 msec; TE=3.4 msec; 124 slices; matrix=256x256; FOV=23.0x23.0 cm2; voxel size=0.8975 mm x0.8975 mm x 1.2-1.4 mm; flip angle=90°; birdcage resonator. #2: same scanner as #1, platform update Signa Excite, sagittal T1-weighted (spin echo sequence, TR=9.7 msec, TE=2.1	5.3	1.5 GE: sagittal 1.5 Siemens: axial	Linux 2.6.37.1-1.2-desktop x86_64

		msec; FOV=25.0x25.0 cm2, voxel size=0.875 mm x0.875 mm x1.2 mm, 124-132 slices, flip angle=90°. #3: Siemens 1.5 Tesla, Vario, 3D MPRAGE, TR=11.6 msec; TE=4.9 msec; FOV 23x23 cm2; matrix 512x512; 126 axial slices; voxel site 0.45 mm x 0.45 mm x 1.5 mm. (only N=2 subjects)		
MMDP 3T	3T MRI Signa GE Excite	Axial T-1 weighted sequence; 3D SPGR pulse; fast IRP sequence; TR = 7.012 msec; TE = 2.1 msec; Ti=450 msec; flip angle= 12°; FOV = 240; slice thickness = 2 mm no skip; frequency matrix = 320; phase matrix = 192; frequency direction = A/P	5.3	Axial
MMDP 1.5T	1.5-T. Signa GE Genesis-based Echo-Speed scanner	Sagittal anatomic images were acquired by using a 3D/FSPGR/20 sequence. flip angle=20; TR=300 msec; inversion recovery=300 msec; matrix=512x256; FOV=24 cm; scan thickness=1.2 mm	5.3	Sagittal

3D: three-dimensional; TR: repetition time; TE: echo time; FOV: field of view

Supplementary Table S5: Full meta-analytic results for each mean structure for the first episode MDD patients versus Controls comparison controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

	Cohen's d [a] (First episode MDD - CTL)	Std. Err.	95% CI	% Difference	P-value	I^2	# Controls	# Patients
Lateral Ventricles	0.034	0.049	[-0.061 - 0.129]	0.601	0.485	<0.001	6922	567
Thalamus	-0.047	0.049	[-0.142 - 0.049]	-0.575	0.339	<0.001	6910	566
Caudate	-0.009	0.088	[-0.181 - 0.164]	-0.542	0.923	65.118	6898	573
Putamen	-0.032	0.061	[-0.151 - 0.088]	-0.652	0.605	27.697	6821	557
Pallidum	-0.008	0.049	[-0.104 - 0.089]	-0.286	0.876	<0.001	6882	558
Hippocampus	-0.073	0.074	[-0.219 - 0.073]	-0.762	0.325	51.155	6904	572
Amygdala	-0.041	0.057	[-0.153 - 0.072]	-0.317	0.478	20.999	6924	570
Accumbens	0.012	0.066	[-0.117 - 0.142]	-0.117	0.853	37.094	6831	550
ICV	-0.005	0.055	[-0.113 - 0.103]	-0.071	0.930	17.697	7063	583

[a] Included Samples: NESDA, Clinical Depression Dublin, CLING, SHIP, SHIP-trend, Sydney, QTIM, Rotterdam study, DepOx, MPIP, MMDP 3T, MMDP 1.5T.
ICV: Intracranial Volume; MDD: Major Depressive Disorder; CTL: Controls.

Supplementary Table S6: Full meta-analytic results for each mean structure for the recurrent MDD patients versus Controls comparison controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

	Cohen's d [a] (Recurrent MDD - CTL)	Std. Err.	95% CI	% Difference	P-value	I^2	# Controls	# Patients
Lateral Ventricles	0.067	0.040	[-0.01 - 0.145]	2.096	0.089	<0.001	6996	1096
Thalamus	0.001	0.040	[-0.078 - 0.079]	-0.042	0.990	<0.001	6984	1090
Caudate	0.015	0.052	[-0.086 - 0.117]	0.268	0.768	29.644	6972	1082
Putamen	0.045	0.043	[-0.039 - 0.128]	0.404	0.294	5.850	6895	1073
Pallidum	0.010	0.040	[-0.069 - 0.089]	0.114	0.799	<0.001	6956	1073
Hippocampus	-0.174	0.040	[-0.252 - -0.096]	-1.443	1.12E-05	<0.001	6978	1102
Amygdala	-0.070	0.040	[-0.148 - 0.008]	-0.814	0.077	<0.001	6998	1100
Accumbens	-0.043	0.040	[-0.121 - 0.036]	-0.612	0.288	<0.001	6905	1076
ICV	0.017	0.046	[-0.074 - 0.108]	0.135	0.712	18.621	7137	1119

[a] Included Samples: NESDA, Imaging Genetics Dublin, Clinical Depression Dublin, CODE, CLING, SHIP, SHIP-trend, Sydney, QTIM, Rotterdam study, DepOx, MPIP, MMDP 3T, MMDP 1.5T.
ICV: Intracranial Volume; MDD: Major Depressive Disorder; CTL: Controls.

Supplementary Table S7: Full meta-analytic results for each mean structure for the recurrent MDD patients versus first episode MDD patients comparison controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

	Cohen's d [a] (Recurrent MDD - First episode MDD)	Std. Err.	95% CI	% Difference	P-value	I^2	# First MDD	# Recur MDD
Lateral Ventricles	0.015	0.056	[-0.095 - 0.124]	1.262	0.795	<0.001	567	994
Thalamus	0.053	0.056	[-0.056 - 0.163]	0.488	0.341	<0.001	566	988
Caudate	-0.020	0.056	[-0.13 - 0.09]	-0.049	0.718	<0.001	573	980
Putamen	0.033	0.090	[-0.144 - 0.21]	0.980	0.715	52.590	557	971
Pallidum	-0.015	0.058	[-0.128 - 0.098]	0.026	0.795	1.968	558	971
Hippocampus	-0.069	0.079	[-0.223 - 0.085]	-0.701	0.379	39.712	572	1000
Amygdala	-0.035	0.056	[-0.145 - 0.075]	-0.528	0.531	<0.001	570	999
Accumbens	-0.093	0.066	[-0.222 - 0.037]	-0.865	0.160	17.638	550	975
ICV	0.030	0.055	[-0.079 - 0.138]	0.362	0.593	<0.001	583	1017

[a] Included Samples: NESDA, Clinical Depression Dublin, CLING, SHIP, SHIP-trend, Sydney, QTIM, Rotterdam study, DepOx, MPIP, MMDP 3T, MMDP 1.5T.
% Difference is difference between recurrent MDD patients and first episode MDD patients divided by the average volume in first episode MDD patients.
ICV: Intracranial Volume; MDD: Major Depressive Disorder; CTL: Controls.

Supplementary Table S8: Full meta-analytic results for each mean structure for the early age of onset (≤ 21) MDD patients versus Controls comparison controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

	Cohen's d [a] (EAO MDD - CTL)	Std. Err.	95% CI	% Difference	P-value	I^2	# Controls	# Patients
Lateral Ventricles	0.145	0.055	[0.037 - 0.253]	5.107	8.50E-03	<0.001	2628	533
Thalamus	-0.067	0.055	[-0.175 - 0.042]	-0.678	0.228	0.003	2603	531
Caudate	0.020	0.073	[-0.123 - 0.163]	0.093	0.783	36.502	2597	529
Putamen	0.020	0.067	[-0.111 - 0.151]	0.075	0.763	24.492	2533	525
Pallidum	0.047	0.060	[-0.071 - 0.165]	0.538	0.434	10.892	2572	526
Hippocampus	-0.205	0.056	[-0.314 - -0.096]	-1.846	2.31E-04	0.579	2603	533
Amygdala	-0.117	0.055	[-0.225 - -0.01]	-1.228	0.033	<0.001	2612	537
Accumbens	-0.058	0.056	[-0.167 - 0.052]	-0.830	0.302	<0.001	2504	526
ICV	0.041	0.080	[-0.116 - 0.199]	-0.173	0.607	48.751	2717	541

[a] Included Samples: NESDA, Imaging Genetics Dublin, CLING, SHIP, SHIP-trend, Sydney, QTIM, DepOx, MPIP, MMDP 3T, MMDP 1.5T.
ICV: Intracranial Volume; EAO: Early Age of Onset; MDD: Major Depressive Disorder; CTL: Controls.

Supplementary Table S9: Full meta-analytic results for each mean structure for the late age of onset (> 21) MDD patients versus Controls comparison controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

	Cohen's d [a] (LAO MDD - CTL)	Std. Err.	95% CI	% Difference	P-value	I^2	# Controls	# Patients
Lateral Ventricles	-0.005	0.041	[-0.085 - 0.075]	-0.314	0.911	<0.001	2628	967
Thalamus	0.034	0.044	[-0.053 - 0.12]	0.262	0.447	7.019	2603	962
Caudate	-0.051	0.052	[-0.153 - 0.052]	-0.683	0.332	24.946	2597	965
Putamen	0.013	0.045	[-0.074 - 0.101]	0.039	0.766	7.080	2533	943
Pallidum	-0.032	0.041	[-0.113 - 0.05]	-0.373	0.446	0.009	2572	942
Hippocampus	-0.103	0.053	[-0.207 - 0.001]	-0.818	0.052	27.690	2603	978
Amygdala	-0.028	0.048	[-0.123 - 0.067]	-0.343	0.568	17.350	2612	971
Accumbens	-0.030	0.042	[-0.112 - 0.052]	-0.278	0.471	<0.001	2504	938
ICV	0.003	0.074	[-0.142 - 0.148]	0.213	0.968	61.068	2717	997

[a] Included Samples: NESDA, Imaging Genetics Dublin, Clinical Depression Dublin, CLING, SHIP, SHIP-trend, Sydney, DepOx, MPIP, MMDP 3T, MMDP 1.5T.
ICV: Intracranial Volume; MDD: LAO: Late Age of Onset; Major Depressive Disorder; CTL: Controls.

Supplementary Table S10: Full meta-analytic results for each mean structure for the late age of onset (> 21) MDD patients versus early age of onset (≤ 21) MDD patients comparison controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

	Cohen's d [a] (LAO MDD – EAO MDD)	Std. Err.	95% CI	% Difference	P-value	I^2	# Controls	# Patients
Lateral Ventricles	-0.133	0.062	[-0.254 - -0.011]	-7.101	0.032	<0.001	533	967
Thalamus	0.096	0.070	[-0.042 - 0.234]	1.554	0.173	15.429	531	962
Caudate	-0.059	0.077	[-0.21 - 0.092]	-1.209	0.442	26.757	529	965
Putamen	-0.028	0.070	[-0.164 - 0.109]	-0.625	0.691	13.196	525	943
Pallidum	-0.082	0.090	[-0.258 - 0.094]	-2.064	0.359	43.465	526	942
Hippocampus	0.143	0.066	[0.013 - 0.272]	2.228	0.031	8.355	533	978
Amygdala	0.120	0.065	[-0.008 - 0.247]	1.940	0.066	5.954	537	971
Accumbens	0.074	0.063	[-0.049 - 0.198]	1.079	0.238	<0.001	526	938
ICV	-0.074	0.096	[-0.262 - 0.114]	-0.609	0.439	52.258	541	997

[a] Included Samples: NESDA, Imaging Genetics Dublin, CLING, SHIP, SHIP-trend, Sydney, DepOx, MPIP, MMDP 3T, MMDP 1.5T.
% Difference is difference between late age of onset (> 21) MDD patients and early age of onset (≤ 21) MDD patients divided by the average volume in late age of onset (> 21) MDD patients.
ICV: Intracranial Volume; LAO: Late Age of Onset; EAO: Early Age of Onset; MDD: Major Depressive Disorder.

Supplementary Table S11: Full meta-analytic results for each mean structure for the association between symptom severity and brain volumes within MDD patients based on the HDRS-17 questionnaire controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

	Pearson's r [a]	Std. Err.	95% CI	P-value	I^2	# Patients
Lateral Ventricles	-0.013	0.066	[-0.142 - 0.117]	0.847	59.501	659
Thalamus	0.018	0.039	[-0.058 - 0.094]	0.640	0.003	658
Caudate	0.076	0.039	[-0.001 - 0.152]	0.053	<0.001	654
Putamen	0.005	0.039	[-0.072 - 0.081]	0.900	<0.001	657
Pallidum	-0.018	0.039	[-0.095 - 0.058]	0.639	<0.001	656
Hippocampus	0.109	0.068	[-0.024 - 0.241]	0.109	62.572	664
Amygdala	0.022	0.050	[-0.075 - 0.119]	0.659	29.854	667
Accumbens	0.017	0.039	[-0.059 - 0.093]	0.663	0.020	658
ICV	0.002	0.039	[-0.073 - 0.078]	0.956	<0.001	667

[a] Included samples: Imaging Genetics Dublin, Clinical Depression Dublin, CLING, Sydney, Bipolar Family Study, DepOx, MPIP, MMDP 3T, MMDP 1.5T.
HDRS-17: Hamilton Rating Scale for Depression 17 items; ICV: Intracranial Volume; MDD: Major Depressive Disorder.

Supplementary Table S12: Full meta-analytic results for each mean structure for the association between symptom severity and brain volumes within MDD patients based on the BDI-2 questionnaire controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

	Pearson's r [a]	Std. Err.	95% CI	P-value	I^2	# Patients
Lateral Ventricles	-0.020	0.076	[-0.168 - 0.128]	0.791	66.343	634
Thalamus	-0.048	0.056	[-0.157 - 0.062]	0.391	38.219	624
Caudate	-0.062	0.040	[-0.14 - 0.016]	0.120	<0.001	628
Putamen	-0.034	0.041	[-0.114 - 0.046]	0.408	<0.001	603
Pallidum	0.028	0.041	[-0.053 - 0.108]	0.500	<0.001	599
Hippocampus	-0.058	0.053	[-0.161 - 0.045]	0.271	34.161	646
Amygdala	-0.016	0.040	[-0.094 - 0.061]	0.677	0.059	639
Accumbens	-0.061	0.041	[-0.141 - 0.018]	0.130	0.008	599
ICV	-0.080	0.039	[-0.156 - -0.005]	0.037	0.496	667

[a] Included samples: Imaging Genetics Dublin, CLING, SHIP, SHIP-trend, MPIP.
BDI-2: Beck Depression Inventory second edition; ICV: Intracranial Volume; MDD: Major Depressive Disorder.

Supplementary Table S13: Full meta-analytic results for each mean structure for the MDD patients versus Controls comparison (excluding remitted patients) controlling for age, sex, scan center and ICV. Adjusted Cohen's d is reported.

	Cohen's d [a] (MDD - CTL)	Std. Err.	95% CI	% Difference	P-value	I^2	# Controls	# Patients
Lateral Ventricles	0.081	0.060	[-0.036 - 0.198]	1.179	0.175	<0.001	4779	570
Thalamus	-0.108	0.075	[-0.256 - 0.04]	-1.040	0.152	33.014	4780	569
Caudate	-0.015	0.061	[-0.135 - 0.106]	-0.258	0.808	3.435	4782	563
Putamen	0.022	0.066	[-0.108 - 0.153]	0.146	0.737	15.933	4766	568
Pallidum	-0.011	0.060	[-0.128 - 0.107]	-0.174	0.855	<0.001	4788	567
Hippocampus	-0.189	0.060	[-0.306 - -0.072]	-1.534	0.002	<0.001	4787	575
Amygdala	-0.036	0.064	[-0.162 - 0.09]	-0.373	0.577	12.667	4798	576
Accumbens	-0.034	0.060	[-0.151 - 0.083]	-0.538	0.569	<0.001	4812	572
ICV	-0.046	0.061	[-0.165 - 0.073]	-0.446	0.449	3.571	4833	579

[a] Included samples: NESDA, Imaging Genetics Dublin, Clinical Depression Dublin, CODE, Rotterdam study, DepOx, MMDP 1.5T and MMDP 3T
ICV: Intracranial Volume; MDD: Major Depressive Disorder; CTL: Controls.

Supplementary Table 14: Adjusted means and standard errors for each site including the total number of subjects (N) for each structure and split into MDD patients and controls (CTL). Means are adjusted for age, sex, scan center, and ICV using the *lsmeans* package in R.

		Lateral Ventricles		Thalamus		Caudate		Putamen		Pallidum		Hippocampus		Amygdala		Accumbens		ICV	
		Mean (Std Err)	N	Mean (Std Err)	N	Mean (Std Err)	N	Mean (Std Err)	N	Mean (Std Err)	N	Mean (Std Err)	N	Mean (Std Err)	N	Mean (Std Err)	N	Mean (Std Err)	N
Bipolar Family Study	CTL	5889.994 (310.279)	62	6598.157 (61.08)	62	3761.069 (54.768)	62	5891.301 (76.594)	62	1893.376 (27.259)	62	3570.397 (42.926)	62	1878.994 (28.872)	62	709.989 (17.126)	62	1478595.321 (15147.359)	62
	MDD	5564.152 (565.765)	19	6407.857 (111.373)	19	3549.248 (99.865)	19	5635.256 (139.662)	19	1905.38 (49.703)	19	3454.205 (78.272)	19	1826.493 (52.646)	19	742.377 (31.227)	19	1429565.795 (27391.122)	19
CLING	CTL	6942.48 (211.514)	321	8169.268 (36.942)	321	4038.22 (23.439)	321	5694.382 (30.049)	321	1830.209 (10.654)	321	4320.772 (18.88)	321	1511.964 (7.769)	321	600.179 (4.461)	321	1591240.917 (8643.52)	321
	MDD	7237.454 (608.396)	49	8076.854 (106.259)	49	4037.733 (67.419)	49	5744.305 (86.431)	49	1828.344 (30.646)	49	4228.621 (54.308)	49	1545.63 (22.348)	49	585.005 (12.832)	49	1528713.378 (24731.27)	49
Clinical Depression Dublin	CTL	6988.118 (353.937)	93	8016.539 (53.974)	92	3811.332 (38.635)	94	5441.171 (48.265)	92	1660.76 (15.822)	94	4356.998 (31.401)	94	1579.756 (14.264)	94	549.138 (6.435)	94	1589222.261 (13006.95)	94
	MDD	6941.056 (572.299)	36	7899.126 (88.14)	35	3745.882 (62.793)	36	5371.409 (77.645)	36	1628.905 (25.715)	36	4353.172 (51.036)	36	1586.111 (23.183)	36	533.528 (10.458)	36	1607308.54 (21120.33)	36
CODE	CTL	7976.951 (344.051)	74	8184.291 (64.931)	74	3677.004 (43.3)	74	5090.771 (56.463)	74	1461.715 (19.857)	74	4504.577 (40.154)	74	1612.084 (18.493)	74	483.598 (8.869)	74	1548828.284 (15376.579)	74
	MDD	7739.908 (292.603)	102	8042.78 (55.221)	102	3661.025 (36.825)	102	5171.045 (48.019)	102	1466.824 (16.888)	102	4432.727 (34.149)	102	1599.804 (15.802)	101	496.076 (7.58)	101	1540359.872 (13078.319)	102
DepOx	CTL	6664.878 (534.892)	31	8675.676 (132.515)	30	4048.715 (81.239)	31	5478.909 (105.135)	31	1746.877 (32.757)	31	4124.748 (56.534)	31	1385.321 (25.847)	31	526.116 (15.71)	31	1362278.954 (29042.624)	31
	MDD	6999.747 (488.697)	37	8398.466 (117.587)	38	4144.386 (73.267)	38	5424.366 (94.818)	38	1741.563 (29.542)	38	4156.386 (51.682)	37	1396.384 (23.311)	38	527.716 (14.169)	38	1310535.09 (26227.952)	38
Imaging Genetics Dublin	CTL	6679.671 (332.052)	52	7813.388 (109.202)	41	3736.322 (53.219)	46	5615.651 (80.859)	46	1592.106 (22.241)	43	4442.311 (44.762)	51	1702.007 (24.781)	52	585.418 (12.733)	51	1474215.129 (27484.837)	52
	MDD	6445.497 (346.033)	48	7699.211 (105.262)	44	3767.299 (57.183)	40	5759.584 (81.777)	45	1595.575 (22.513)	42	4385.849 (44.762)	51	1734.793 (24.781)	52	581.516 (12.996)	49	1443020.948 (27484.837)	52
MMDP 1.5T	CTL	6791.453	44	7022.211	44	3695.889	44	5583.459	44	1641.016	44	3284.799	44	1218.104	44	566.467	44	1324071.785	44

		(410.328)		(92.464)		(62.307)		(96.093)		(31.318)		(57.458)		(33.778)		(14.881)		(16810.368)	
	MDD	6956.363 (376.762)	52	7170.824 (84.073)	53	3642.837 (56.653)	53	5768.374 (87.373)	53	1595.806 (28.476)	53	3309.866 (52.244)	53	1274.021 (30.713)	53	580.716 (13.531)	53	1318317.763 (15285.375)	53
MMDP 3T	CTL	6896.163 (551.065)	63	7190.513 (84.787)	64	3773.774 (63.633)	64	5701.727 (97.508)	63	1586.822 (34.388)	64	4101.055 (74.291)	64	1552.397 (31.698)	63	687.643 (24.293)	63	1334270.65 (20454.624)	64
	MDD	7094.725 (518.085)	71	7287.834 (79.224)	73	3676.387 (59.89)	72	5799.168 (91.698)	71	1621.507 (32.365)	72	3915.255 (69.416)	73	1489.517 (29.377)	73	672.536 (22.841)	71	1317098.334 (19114.304)	73
MPIP	CTL	8818.892 (307.642)	222	7073.492 (38.931)	222	3523.561 (24.625)	222	4799.981 (35.187)	222	1424.726 (12.855)	222	4157.692 (24.707)	222	1300.625 (9.879)	222	536.087 (5.525)	222	1488615.256 (9114.622)	222
	MDD	9038.434 (233.636)	368	7134.62 (29.566)	368	3566.813 (18.701)	368	4854.76 (26.723)	368	1435.139 (9.762)	368	4069.651 (18.793)	367	1304.765 (7.502)	368	534.338 (4.196)	368	1519925.444 (6932.068)	368
NESDA	CTL	7603.141 (424.098)	66	7128.616 (77.535)	66	3726.262 (46.938)	66	5427.6 (59.58)	66	1656.268 (20.11)	66	3977.239 (43.535)	66	1671.812 (20.174)	66	534.181 (10.025)	66	1403332.576 (21205.533)	66
	MDD	7737.325 (272.951)	156	7140.999 (49.902)	156	3645.383 (30.21)	156	5314.881 (38.346)	156	1663.002 (12.943)	156	3869.517 (28.118)	155	1623.787 (13.03)	155	515.112 (6.452)	156	1447890.846 (13687.025)	156
QTIM	CTL	5953.172 (162.994)	262	7369.803 (44.326)	259	3998.126 (25.534)	260	6304.493 (33.373)	258	1706.745 (12.131)	258	4064.651 (20.285)	259	1767.142 (13.887)	260	771.597 (6.508)	260	1250942.494 (12205.945)	262
	MDD	6156.33 (430.333)	38	7296.289 (116.389)	38	3883.602 (68.022)	37	6244.967 (87.457)	38	1686.245 (31.779)	38	4034.612 (54.739)	36	1742.808 (36.519)	38	770.1 (17.118)	38	1208587.409 (32164.565)	38
Rotterdam study	CTL	12852.092 (91.357)	4356	6410.049 (6.77)	4369	3444.598 (6.641)	4363	4740.189 (7.24)	4350	1540.048 (2.721)	4372	4067.812 (5.103)	4363	1403.836 (2.045)	4374	548.964 (1.117)	4389	1489885.576 (1945.914)	4408
	MDD	14864.288 (732.799)	68	6300.27 (54.405)	68	3557.156 (54.109)	66	4717.23 (58.48)	67	1540.473 (21.865)	68	3977.368 (40.966)	68	1405.81 (16.436)	68	549.663 (8.994)	68	1467863.014 (15585.051)	69
SHIP	CTL	9728.093 (209.644)	422	7102.279 (24.194)	411	3578.507 (16.767)	408	4855.628 (21.313)	384	1552.076 (7.773)	397	3904.607 (16.157)	408	1480.362 (6.219)	408	457.687 (2.855)	386	1571014.869 (6143.991)	441
	MDD	9768.208 (385.635)	129	7091.613 (44.867)	123	3538.137 (30.413)	128	4901.653 (39.029)	117	1542.359 (14.463)	119	3922.065 (28.503)	135	1466.248 (11.229)	129	459.48 (5.312)	115	1590808.94 (11103.52)	139
SHIP-trend	CTL	8821.668 (139.014)	884	7254.004 (18.827)	885	3622.718 (12.413)	873	4929.271 (15.066)	838	1576.587 (5.581)	865	3979.707 (10.353)	875	1498.57 (4.288)	883	472.71 (2.086)	798	1586377.419 (3941.202)	952
	MDD	8701.92 (239.646)	303	7252.366 (32.491)	303	3599.847 (21.191)	305	4907.621 (26.098)	285	1575.163 (9.843)	284	3973.491 (17.664)	306	1480.291 (7.372)	304	473.698 (3.54)	282	1586590.378 (6829.382)	323

Sydney	CTL	7747.358 (463.926)	106	7146.326 (61.633)	106	4168.19 (58.437)	106	6393.662 (72.337)	106	1635.336 (18.616)	105	4208.748 (39.453)	106	1577.017 (17.808)	106	532.778 (8.548)	106	1499287.583 (12294.367)	106
	MDD	9079.575 (323.319)	214	7173.986 (42.953)	214	4332.366 (40.806)	213	6379.102 (50.525)	213	1649.354 (12.911)	214	4110.809 (27.496)	214	1549.776 (12.41)	214	524.398 (6.006)	210	1500726.805 (8568.216)	214

Supplementary Table 15: Full results from the moderator analyses of mean age, field strength of scanner, percent of acute patients, percent of patients with anxiety, FreeSurfer version used for processing, percent of patients taking antidepressants, and percent of patients taking antipsychotics. Effect sizes for the meta-regression models were available from all 15 sites (percent of patients taking antipsychotics was not available in MMDP 1.5T and MMDP 3T). Table is split into two parts to fit on a single page for easier comparison.

A)

	Mean Age			Field Strength			Percent Acute			Percent with Anxiety		
	Beta	Std Err	P-value	Beta	Std Err	P-value	Beta	Std Err	P-value	Beta	Std Err	P-value
Lateral Ventricles	2.62E-03	3.41E-03	0.441	-3.01E-02	7.72E-02	0.697	-1.79E-03	1.42E-03	0.206	1.07E-04	2.59E-03	0.967
Thalamus	6.67E-04	3.51E-03	0.849	4.34E-02	8.01E-02	0.587	-1.10E-03	1.75E-03	0.530	5.05E-03	2.85E-03	0.076
Caudate	7.46E-03	4.07E-03	0.067	-8.47E-03	1.04E-01	0.935	-1.00E-03	2.00E-03	0.616	-3.92E-03	3.26E-03	0.229
Putamen	1.28E-03	3.20E-03	0.690	1.80E-03	7.35E-02	0.981	1.01E-03	1.40E-03	0.469	-2.01E-03	2.48E-03	0.417
Pallidum	8.92E-04	3.09E-03	0.773	-4.59E-02	7.07E-02	0.516	-2.91E-04	1.40E-03	0.835	-5.66E-04	2.48E-03	0.819
Hippocampus	1.36E-03	3.61E-03	0.707	1.19E-01	7.87E-02	0.130	-4.43E-06	1.40E-03	0.997	1.25E-03	2.64E-03	0.638
Amygdala	-1.52E-03	3.33E-03	0.647	2.81E-02	7.88E-02	0.722	1.59E-03	1.44E-03	0.270	-4.45E-03	2.45E-03	0.070
Accumbens	2.41E-03	3.10E-03	0.436	7.70E-02	7.06E-02	0.276	3.47E-04	1.40E-03	0.804	-2.41E-03	2.48E-03	0.330
ICV	6.63E-03	4.24E-03	0.118	1.28E-01	1.00E-01	0.201	2.08E-04	2.15E-03	0.923	5.72E-03	3.35E-03	0.088

B)

	FreeSurfer Version			Percent on Antidepressants			Percent on Antipsychotics		
	Beta	**Std Err**	**P-value**	**Beta**	**Std Err**	**P-value**	**Beta**	**Std Err**	**P-value**
Lateral Ventricles	-0.294	0.194	0.128	7.02E-04	1.24E-03	0.571	1.06E-02	5.52E-03	0.055
Thalamus	0.265	0.197	0.366	1.42E-03	1.24E-03	0.253	8.30E-03	6.05E-03	0.170
Caudate	-0.470	0.257	0.285	1.48E-03	1.60E-03	0.355	1.61E-02	5.95E-03	6.71E-03
Putamen	-0.187	0.192	0.135	9.53E-04	1.11E-03	0.392	1.67E-03	5.54E-03	0.763
Pallidum	0.039	0.191	0.979	5.70E-04	1.11E-03	0.608	4.57E-03	5.40E-03	0.397
Hippocampus	-0.039	0.192	0.054	-2.31E-03	1.12E-03	0.038	-6.13E-03	6.25E-03	0.327
Amygdala	-0.310	0.192	0.049	2.07E-03	1.10E-03	0.061	6.64E-04	5.78E-03	0.909
Accumbens	-0.246	0.191	0.505	-1.96E-03	1.11E-03	0.078	-4.19E-03	5.39E-03	0.438
ICV	0.043	0.245	0.862	9.11E-04	1.75E-03	0.603	-2.96E-04	8.71E-03	0.973

Supplementary Table S16: Meta-analytic results for each mean structure for the diagnosis * sex interactive effect in the full sample of MDD patients and Controls while controlling for age, sex, diagnosis, scan center and ICV. Adjusted Cohen's d is reported.

	Cohen's d (Diagnosis * Sex)	Std. Err.	95% CI	P-value	I^2	# Controls	# Patients
Lateral Ventricles	-0.029	0.0378	[-0.103 - 0.045]	0.437	14.275	7058	1689
Thalamus	-0.002	0.0463	[-0.093 - 0.088]	0.962	37.700	7046	1682
Caudate	0.029	0.0361	[-0.042 - 0.099]	0.428	8.460	7034	1681
Putamen	-0.005	0.0338	[-0.071 - 0.062]	0.891	0.033	6957	1656
Pallidum	0.023	0.0484	[-0.071 - 0.118]	0.627	42.117	7018	1657
Hippocampus	-0.008	0.0332	[-0.073 - 0.057]	0.809	<0.001	7040	1700
Amygdala	0.027	0.0333	[-0.038 - 0.092]	0.413	0.017	7060	1696
Accumbens	0.029	0.0338	[-0.037 - 0.095]	0.394	<0.001	6967	1652
ICV	0.002	0.0579	[-0.111 - 0.116]	0.971	61.128	7199	1728

Supplemental Figures

Supplemental Figure S1: Overview of research institutes participating in the ENIGMA-Major Depressive Disorder Working Group, displayed on a world map.

Supplemental Figure S2: Forest plot of meta-analytic effect size hippocampus with $p<0.05$: MDD patients versus controls

Supplemental Figure S3: Forest plot of meta-analytic effect size hippocampus with $p<0.05$: Recurrent MDD patients versus controls

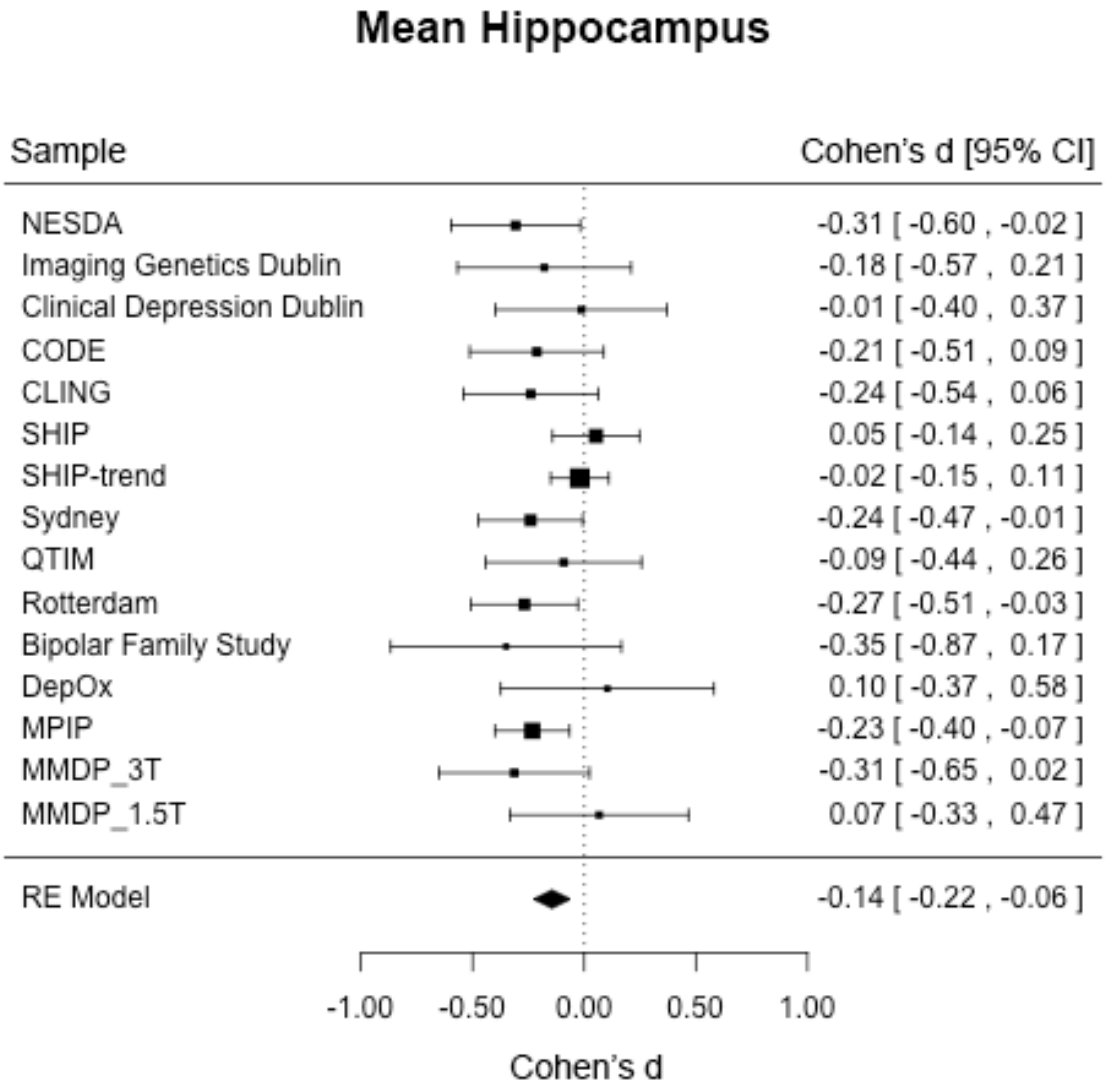
Supplemental Figure S4: Forest plot of meta-analytic effect size hippocampus with $p<0.05$: Early age of onset ($\leq$ 21) MDD patients versus controls

Supplemental Figure S5: Forest plot of meta-analytic effect size amygdala with $p<0.05$: Early age of onset ($\leq$ 21) MDD patients versus controls

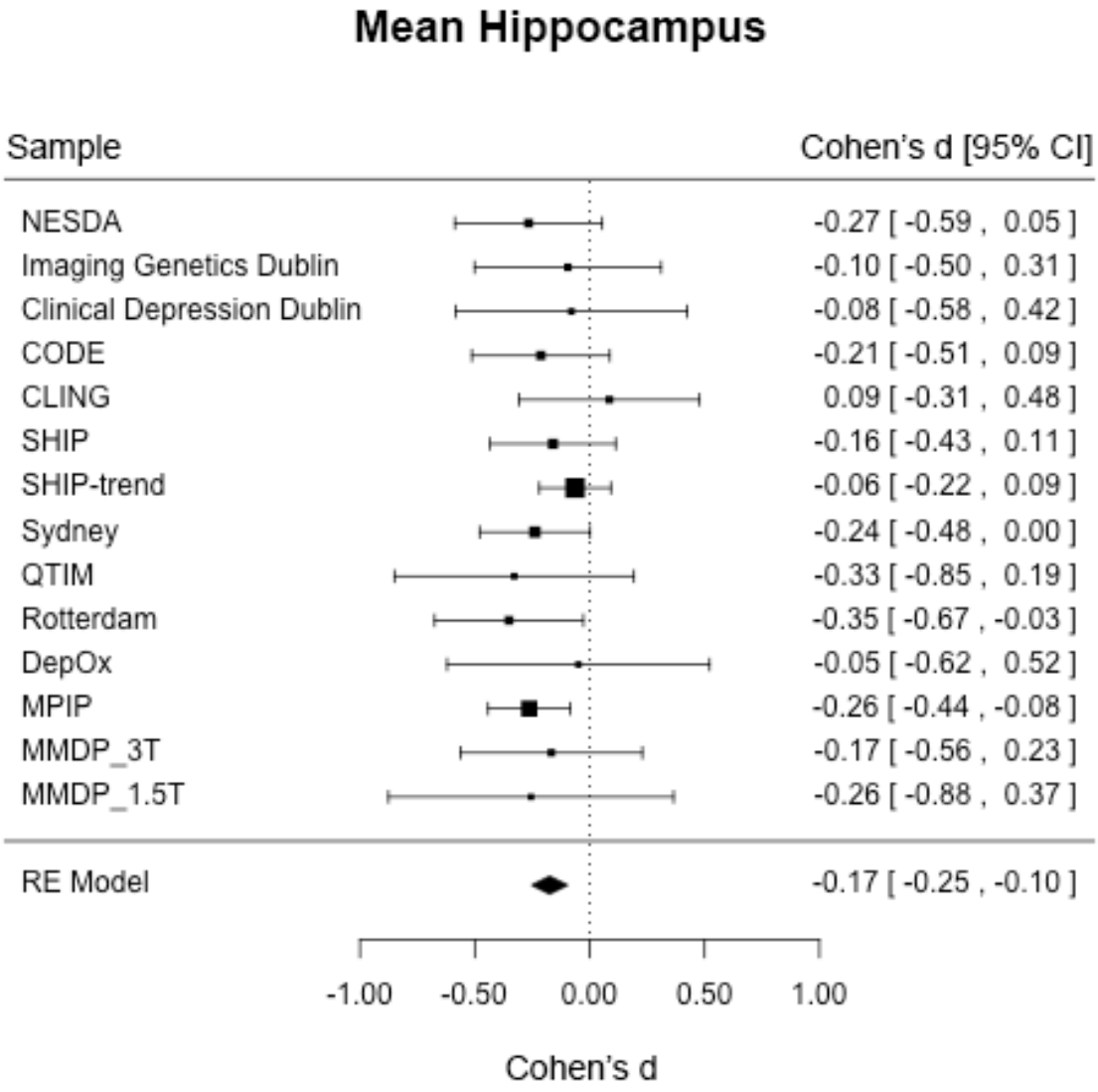
Supplemental Figure S6: Forest plot of meta-analytic effect size lateral ventricles with $p<0.05$: Early age of onset ($\leq$ 21) MDD patients versus controls

Supplemental Figure S7: Scatterplots of the percentage of patients taking antipsychotic medication versus the effect size for the caudate at each site

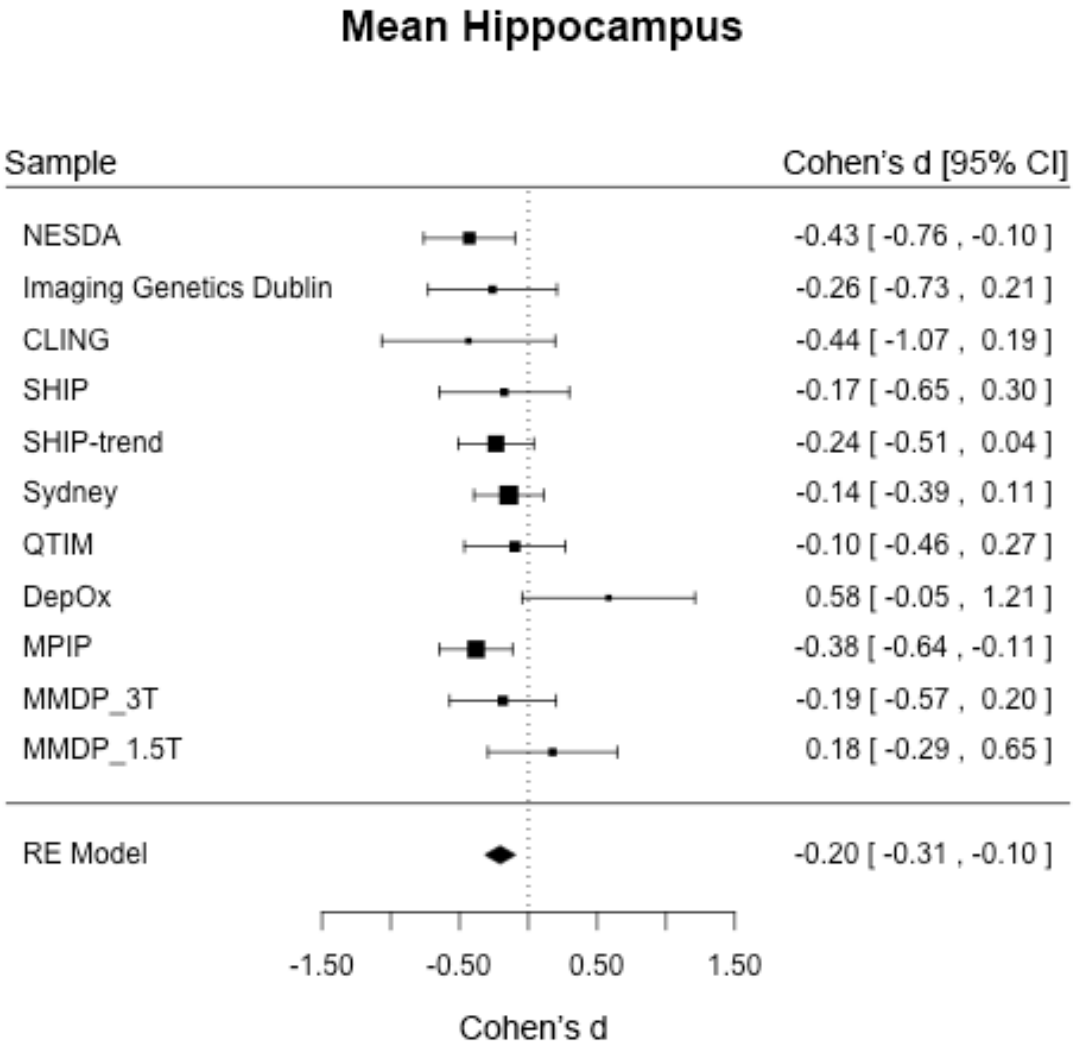
Supplemental Figure S1: Overview of research institutes participating in the ENIGMA-Major Depressive Disorder Working Group, displayed on a world map.



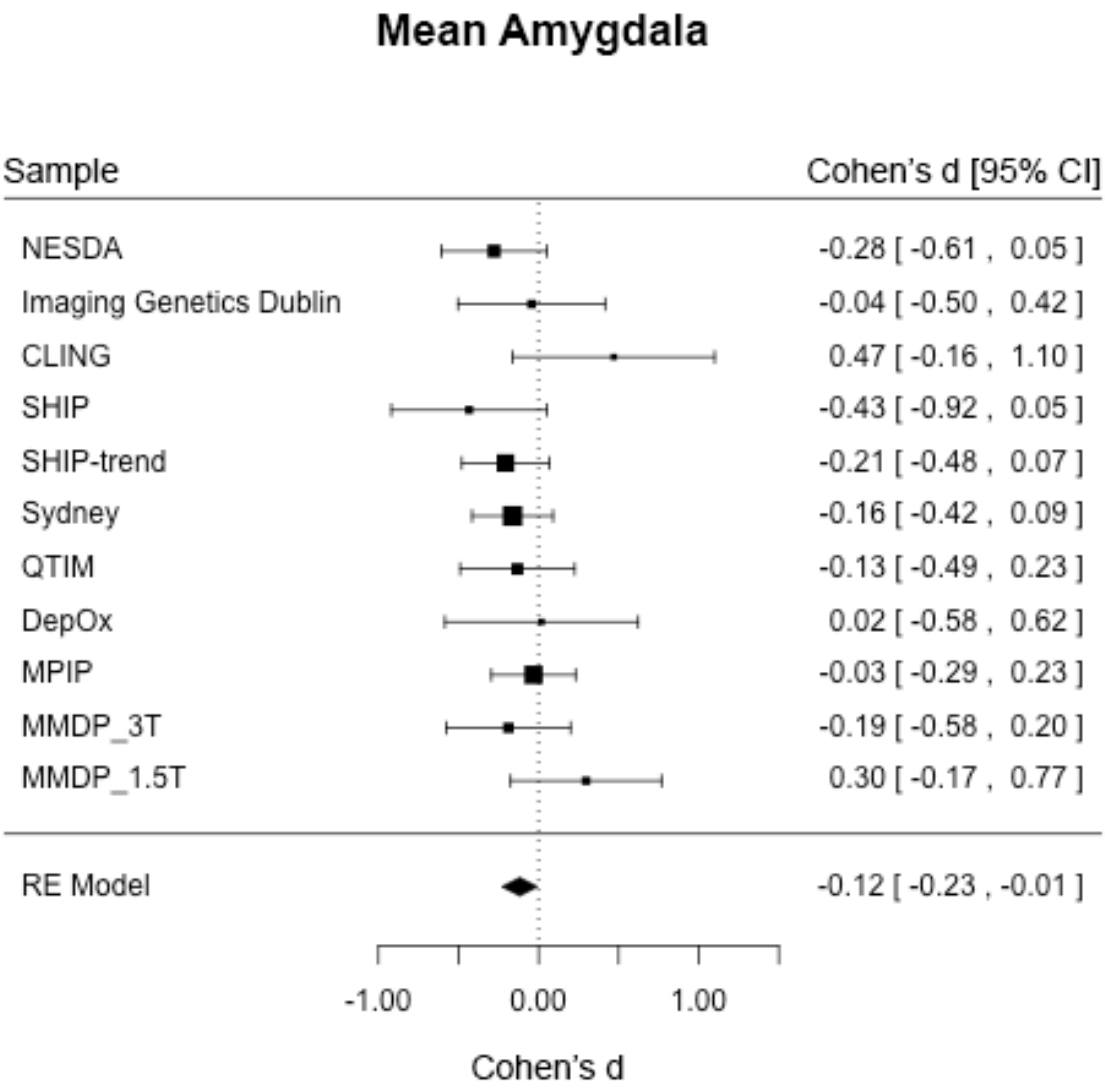
Supplemental Figure S2: Forest plot of meta-analytic effect size hippocampus with $p<0.05$: MDD patients versus controls



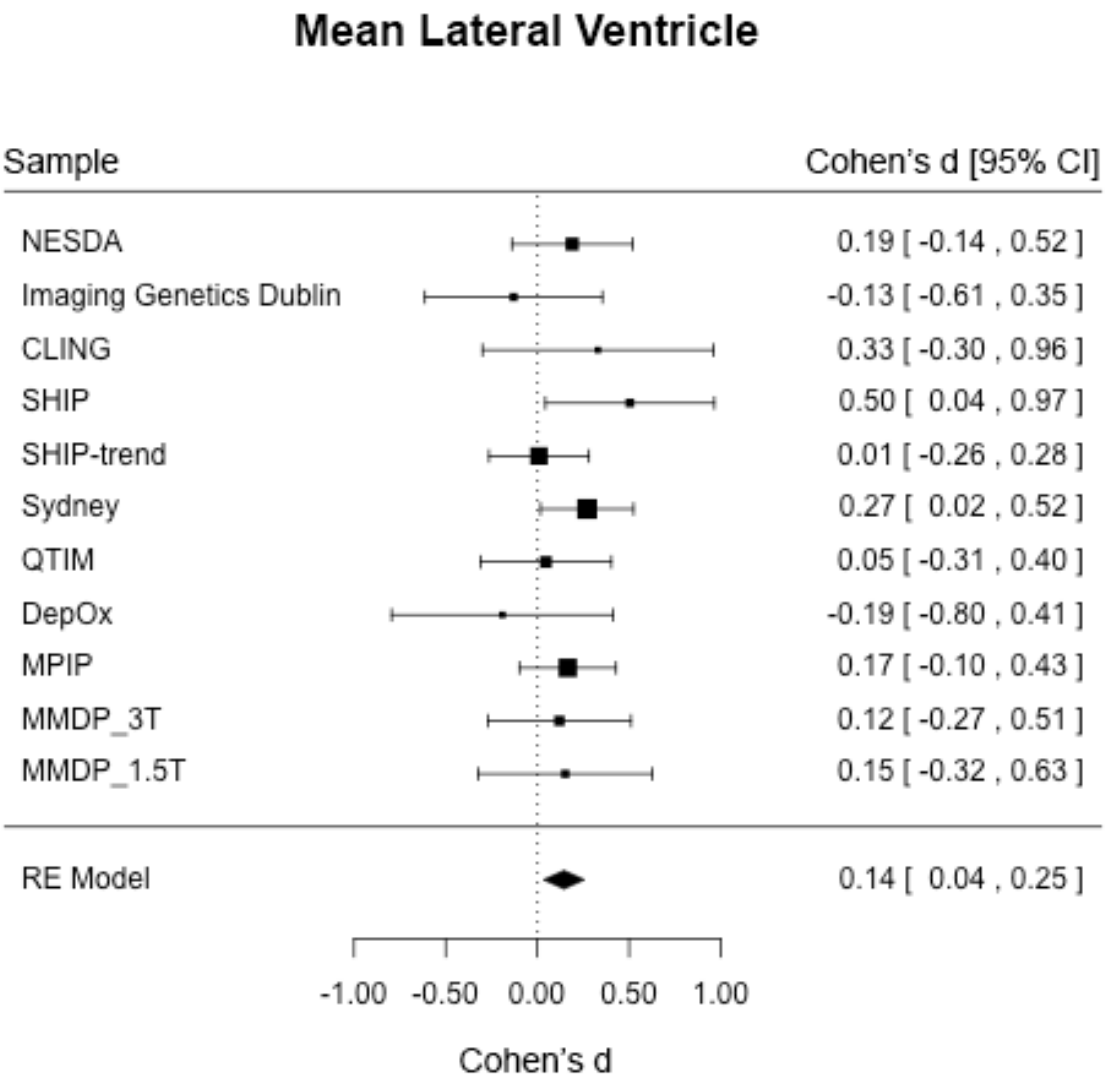
Supplemental Figure S3: Forest plot of meta-analytic effect size hippocampus with $p<0.05$: Recurrent MDD patients versus controls



Supplemental Figure S4: Forest plot of meta-analytic effect size hippocampus with $p<0.05$: Early age of onset ($\leq$ 21) MDD patients versus controls



Supplemental Figure S5: Forest plot of meta-analytic effect size amygdala with $p<0.05$: Early age of onset ($\leq$ 21) MDD patients versus controls



Supplemental Figure S6: Forest plot of meta-analytic effect size lateral ventricles with $p<0.05$: Early age of onset (≤ 21) MDD patients versus controls

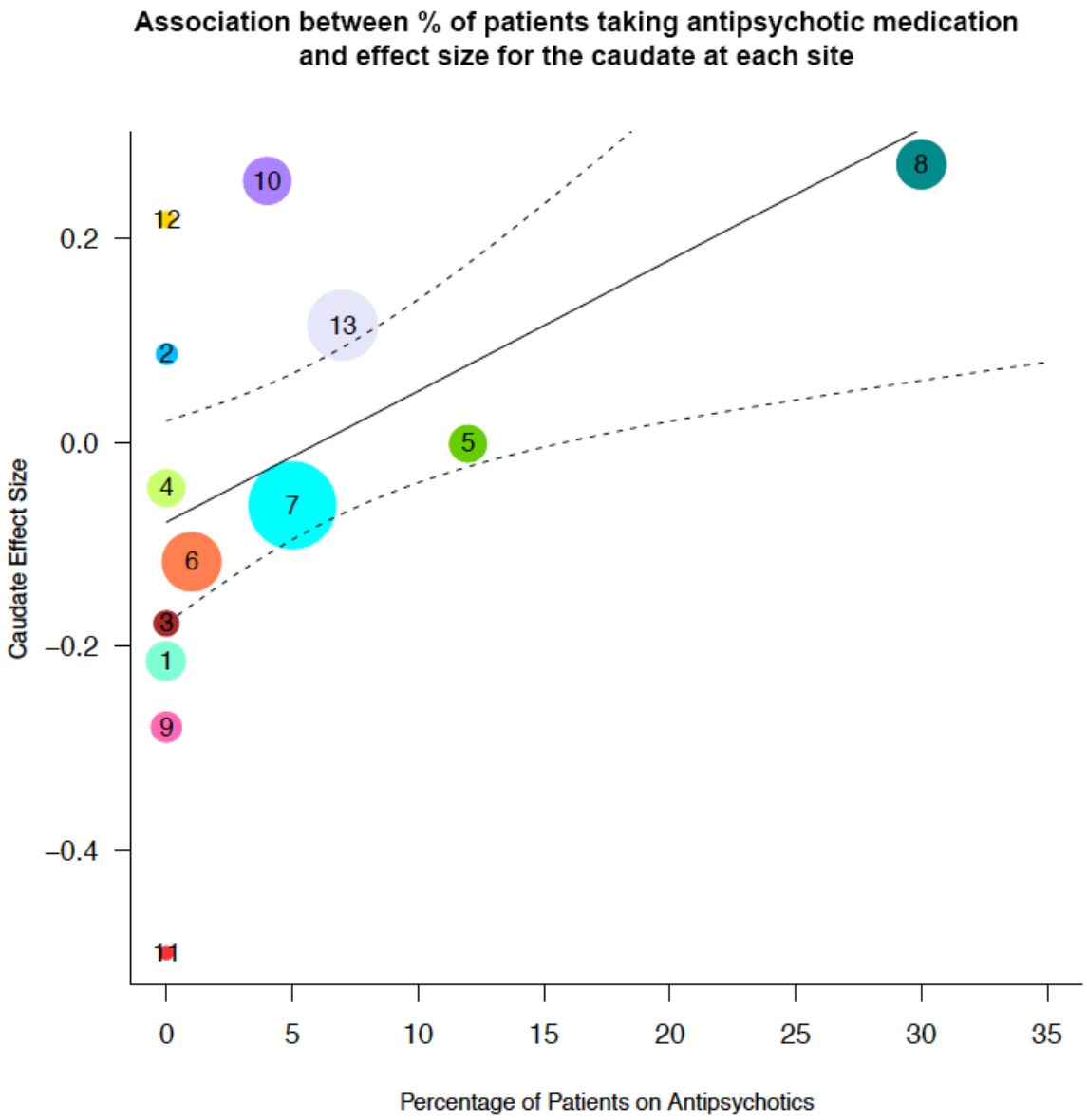


Figure S7. Scatterplots of the percentage of patients taking antipsychotic medication versus the effect size for the caudate at each site. Points are numbered according to the order of study sites listed in Table 1 (note: MMDP 3T and MMDP 1.5T studies were excluded from this analysis due to missing data on antipsychotic use). The size of each point corresponds to the inverse of the standard error for the effect size at each site (i.e., sites with larger samples have bigger points). The solid black line represents the effect of the percentage of patients taking antipsychotics on the effect size (the result of the moderator analysis) weighted by the inverse of the standard error in each sample. A positive association of the percentage of patients using antipsychotics on the caudate effect size was observed using a Bonferroni significance threshold for comparisons of 9 brain regions ($P^* = 0.05/9 \sim 5.6 \times 10^{-3}$), i.e. caudate volume of MDD patients more strongly increased relative to controls as the percentage of patients taking antipsychotic medication increased.