Supplementary methods

Meta-analysis

All analyses were conducted using the grey matter template included in AES-SDM using a voxel size of 1mm^3. We used a significance threshold of $p < .005$ with a peak Z value of >1 and cluster size of >10 voxels for all main analyses. We used a more conservative threshold of $p < .0005$ for meta-regressions as these are more susceptible to false positives, particularly when conducted on a small number of studies[1]. These thresholds have been found to provide the optimal balance of sensitivity and specificity in previous research[2]. As we had a large number of studies in each diagnostic group, we used a less conservative threshold of $p < .001$ for the comparison between MDD and BD. Regions where results were significant in both conditions were submitted to a conjunction analysis to identify regions that were robustly affected in both conditions, accounting for error in the estimation of p-values within individual meta-analyses[3].To protect against false positives in the conjunction analysis,the threshold was set at $p < .005$ for this analysis, without the correction described by Radua and others[3] in order to test against the conjunction null hypothesis (i.e. no significant difference in one or fewer disorders) rather than the global null (i.e. no significant difference in any disorder).

Supplementary results

Results of heterogeneity analysis in regions where there was significant heterogeneity but no main disorder effect – Bipolar Disorder

We found that studies with euthymic samples found greater volume reductions in the right caudate than those in other mood states (peak MNI = -4, 10, 4, Z = 2.21, p< .001, 120 voxels, Figure 2A). Although our overall analysis showed no differences between patients and controls here, we performed a subgroup analysis using only studies with euthymic patients and found a cluster of significant volume reductions in the caudate (peak MNI = -6, 14, 0, Z = -3.61, p< .001, 804 voxels), suggesting that this may be specific to the euthymic state.

Meta-regression analysis also revealed that the percentage of patients taking antipsychotic medication at the time of scanning was positively associated with effect size in the left fusiform gyrus and parahippocampal gyrus (peak MNI = -30, -28, -28, Z = --2.20, p< .001, 134 voxels), indicating that studies with higher numbers of patients receiving antipsychotic treatment found greater decreases in grey matter volume in this region (Figure 2B). Again, this region was not present in our main analysis but was present when we conducted a subgroup analysis using only studies with >50% of patients taking antipsychotic medication (peak MNI = -34, -28, -32, Z = 2.01, p = 0.001, 95 voxels).Meta-regression analyses with methodological variables showed that studies with higher strength scanners showed smaller volumes relative to controls in the right caudate (peak MNI = 10, 6, 6, Z = 3.19, p< .001, 597 voxels) and the right superior temporal gyrus (peak MNI = 62, -30, 2, Z = 2.57, p< .001, 269 voxels). Meta-regression analysis with spatial smoothing level revealed a negative relationship between smoothing level and effect size in the left inferior frontal gyrus (peak MNI = -44, 16, 4, Z = 4.14, p< .001, 101 voxels).

All other meta-regression results were non-significant, or did not overlap with regions of heterogeneity.

Supplementary tables

	Major Depression Patients							Healthy Controls			Methods	
Study	***n***	**Mean age**	**Sex (M/F)**	**Antidepressant %**	**Duration of illness (y)**	**State**	**HAMD-17**	***n***	**Mean age**	**Sex (M/F)**	**Field strength (Tesla)**	**Smoothing (mm)**
Abe (2010)[4]	21	48.1	11, 10	90	6	7 Depressed, 2 partially remitted, 12 fully remitted	9.2	42	48	22, 20	1.5	6
Amico (2011)[5]	33	32	19, 14	82	3.4	Depressed	18.6	64	30.4	36, 28	1.5	8
Arnone (2012a)[6]	39	36.3	12, 27	0	14.3	Depressed	21.8	66	32.1	20, 46	1.5	8
Arnone (2012b)[6]	25	34.5	5, 20	0	9.4	Remitted	0.3	66	32.1	20, 46	1.5	8
Bergouignan (2009)[7]	20	33.2	3, 17	100	8.5	Depressed	23.1	21	28.2	7, 14	1.5	8
Chaney (2014)[8]	37	-	-	-	-	Depressed	-	46	-	-	3	10
Cheng (2010)[9]	68	29.9	21, 47	0	11	Depressed	22.3	68	30.5	21, 47	1.5	10
de Azevedo-Marques Périco (2011)[10]	20	29.9	5, 15	55	0.7	-	19.6	94	30.2	41, 53	3	8
Grieve (2013)[11]	102	33.8	48, 54	0	11.3	Depressed	21	34	31.5	18, 16	3	8
Guo (2014)[12]	44	27.5	22, 22	0	1.6	Depressed	25.2	44	29.4	20, 24	1.5	10
Inkster (2011a)[13]	49	47.6	16, 33	-	14.1	-	-	183	48	73, 110	1.5	10
Inkster (2011b)[13]	96	50.4	35, 61	-	14.5	-	-	183	48	73, 110	3	6
Jia (2010a)[14]	36	34.7	20, 16	0	1.8	Depressed	22.3	52	37.1	24, 28	3	6
Jia (2010b)[14]	16	34.2	5, 11	0	6.7	Depressed	24.6	52	37.1	24, 28	1.5	8
Kim (2008)[15]	22	38.5	0, 22	45	17.4	Depressed	-	25	35.3	0, 25	1.5	8
Klauser (2015)[16]	56	34	16, 40	-	10.3	29 depressed, 27 remitted	-	33	34.7	12, 21	1.5	8
Kong (2014)[17]	28	34.4	11, 17	0	2.11	Depressed	21.7	28	32.1	14, 14	1.5	8
Kroes (2011)[18]	29	33.4	8, 21	76	-	Depressed	-	29	32.5	13, 16	3	3
Lai (2010)[19]	16	37.9	5, 11	0	0.4	Depressed	29.1	15	34.3	4, 11	3	3

Lai and Wu (2014)[20]	38	36.6	18, 20	0	0.4	Depressed	22.3	27	38.3	12, 15	1.5	8
Lee (2011)[21]	47	46	5, 42	62	3.9	Depressed	20.1	51	45.7	5, 46	1.5	12
Leung (2009)[22]	17	45.5	0, 17	-	7	Depressed	-	17	45.8	0, 17	1.5	8
Ma (2012a)[23]	18	27.4	11, 7	-	3	Depressed	23.9	17	24.2	10, 7	1.5	8
Ma (2012b)[23]	17	26.7	10, 7	0	0.22	Depressed	25.6	17	24.2	10, 7	1.5	NA
MacGregor Legge (2015)[24]†	67	50.5	28, 39	67	21.8	Depressed and remitted	-	67	26	23, 44	1.5	8
Machino (2014)[25]	29	39.6	16, 13	97	4.4	Depressed	13.9	29	38.7	16, 13	1.5	8
Modinos (2014)[26]	23	44.6	3, 20	-	-	-	-	46	25.3	32, 14	1.5	8
Nakano (2014)[27]	36	49	14, 22	-	5.6	Depressed & remitted	15.4	54	45.4	27, 27	3	8
Peng (2011)[28]	22	46.7	8, 14	23	0.7	Depressed	19.5	30	45.9	11, 19	3	8
Peng (2014a)[29]	18	31.1	6, 12	-	23.5	Depressed	24.1	28	28.6	15,13	3	12
Peng (2014b)[29]	20	27.8	7, 13	-	21.5	Depressed	25.6	28	28.6	15,13	1.5	8
Redlich (2014)[30]	58	37.6	22, 36	-	11	Depressed	22.4	58	37.7	21, 37	3	8
Rodríguez-Cano (2014)[31]	32	48.7	12, 20	88	11	Depressed	21.7	64	46	26, 38	1.5	4
Salvadore (2011a)[32]	58	38.8	21, 37	0	18.4	Depressed	20.8	107	36.2	47, 60	3	11
Salvadore (2011b)[32]	27	40.2	6, 21	0	15.1	Remitted	0	107	36.2	47, 60	3	11
Scheuerecker (2010)[33]	13	37.9	10, 3	0	4.4	Depressed	16.6	15	35.5	10, 5	3	8
Serra-Blasco (2013a)[34]	22	44	7, 15	-	0.5	Depressed	16.6	32	46	9, 23	3	8
Serra-Blasco (2013b)[34]	22	48	2, 20	-	17.9	Remitted	4	32	46	9, 23	3	8
Serra-Blasco (2013c)[34]	22	49	4, 18	-	22.7	Depressed	21	32	46	9, 23	3	8
Shah (1998a)[35]	20	47.7	13, 7	45	1.6	Remitted	2.6	20	49.3	13, 7	1	12
Shah (1998b)[35]	20	48.9	13, 7	100	5.5	Depressed	20.6	20	49.3	13, 7	1	12
Soriano-Mas (2011)[36]	70	61.6	29, 41	71	10.6	Depressed	28.6	40	59.2	17, 23	1.5	12
Sprengelmeyer (2011)[37]	17	45.6	8, 2	100	-	Depressed	23.2	21	42	9, 12	1.5	8

Stratmann (2014)[38]	132	37.9	56, 76	94	7.8	Depressed	20.5	132	37.8	58, 74	3	8
Treadway (2009)[39]	19	35.2	9, 10	0	12.9	Depressed	21.5	19	30.3	9, 10	3	12
Wagner (2011)[40]	30	0	5, 25	-	6	Depressed	20.1	30	0	5, 25	1.5	12
Wang (2012)[41]	18	34	9, 9	0	0.4	Depressed	25	18	35	9, 9	3	6
Wang (2014)[42]	13	30.9	0, 13	-	-	Depressed	-	10	29.8	0, 10	3	4
Yoshikawa (2006)[43]	11	48.5	0, 11	0	-	Depressed	-	29	48.6	0, 29	1.5	8
Zou (2010)[44]	23	31.1	10, 13	0	0.6	Depressed	24.4	23	36.6	10, 13	3	10

Supplementary Table 1. Characteristics of major depression studies included in the meta-analysis. M = male, F = female, y = years, HAMD-17 = Hamilton Depression Rating Scale 17-item, † = unpublished voxel-based morphometry data from the sample reported in this study.

	Bipolar Disorder Patients										Healthy Controls			Methods	
Study	***N***	**Age**	**Sex (M,F)**	**Lithium (%)**	**Antipsychotic medication (%)**	**Duration of illness (y)**	**Subtype**	**State**	**HAMD -17**	**YMRS**	***N***	**Age**	**Sex (M/F)**	**Field strength (Tesla)**	**Smoothing (mm)**
Adler (2005)[45]	32	31.2	19, 13	-	-	8.7	BD-I	5 manic, 2 depressed, 25 euthymic	-	-	27	30.5	12, 15	3	12
Almeida (2009)[46]	27	**31.9**	10, 17	-	59.3	11.1	BD-I	17 euthymic, 10 depressed	-	-	28	30.8	13, 15	3	12
Ambrosi (2013)[47]	20	42	5, 15	35	50.0	12.6	BD-II	Euthymic	-	-	21	34.6	6, 15	1.5	8
Brown (2011)[48]	15	46.2	7, 8	-	20.0	19.1	BD-I	Depressed	7.9	-	21	45	10, 11	1.5	8
Bruno (2004)[49]	39	39.1	13, 26	59	23.1	13.2	28 BD-I, 11 BD-II	-	-	-	35	34.8	10, 25	1.5	8
Chen (2007)[50]	24	38.2	6, 18	50	0.0	14.2	BD-I	-	-	-	25	38.4	7, 18	1.5	12
Chen (2012)[51]	18	32	18, 0	83	16.7	4.2	-	Manic	3.2	24.8	27	31.3	27, 0	1.5	8
Cui (2011)[52]	24	28.4	15, 9	-	-	6.1	BD-I	Manic	-	25.9	23	24.8	16, 7	3	6
de Azevedo-Marques Périco (2011)[10]	26	29.9	5, 15	23.1	42.0	0.5	BD-I	-	7.5	7.4	94	30.2	41, 53	2	8
Doris (2004)[53]	11	40.5	6, 5	-	45.5	16.2	BD-I	Euthymic	8.3	-	16	39.1	7, 9	3	8
Eker (2014)[54]	28	36.4	16, 12	23	17.0	16.3	BD-I	Euthymic	2.3	1	30	34.7	10, 20	1.5	8
Emsell (2013)[55]	60	42	31, 29	77	56.7	13	BD-I	Euthymic	-	-	60	42	31, 29	1.5	8
Ha (2009a)[56]	23	35.2	8, 15	30	34.8	10.5	BD-II	7 depressed, 16 euthymic	13.1	-	23	36	8,15	1.5	8
Ha (2009b)[56]	23	35.6	8,15	35	43.5	10.4	BD-I	4 depressed, 19 euthymic	8.8	-	23	36	8,15	1.5	5
Haldane (2008)[57]	44	42.7	20, 24	-	50.0	16.3	BD-I	Euthymic	4	1.2	44	43.1	20, 24	1.5	8
Kempton (Unpublished)[58]	26	42.1	9, 17	35	15.0	16.1	24 BD-I, 2 BD-II	Euthymic	-	-	23	41.2	7, 16	3	8
Li (2011)[59]	24	28.4	15, 9	83	-	6	BD-I	7 depressed, 17 manic	20	25.9	36	26.6	21, 15	1.5	12
Lochhead (2004)[60]	11	38.2	6, 5	-	-	13.9	7 BD-I, 4 BD-II	11 depressed	18	-	31	36	16, 15	1.5	8
Lyoo (2004)[61]	39	38.3	16, 23	26	-	19.7	BD-I	22 depressed, 17 manic	-	-	43	35.7	19, 24	1.5	8
McDonald (2005)[62]	37	40.7	15, 22	59	24.3	17.8	BD-I	-	-	-	52	39.3	24, 28	1.5	8
McIntosh (2004a)[63]	26	40.5	14, 12	-	-	-	BD-I	-	-	-	54	35.3	23, 26	1.5	8
McIntosh (2004b)[63]	19	39.7	7, 12	-	-	-	BD-I	-	-	-	54	35.3	23, 26	1.5	8

Molina (2011)[64]	19	38.3	12, 7	84	5.3	12	BD-I	Euthymic	-	-	24	34.6	16, 8	1.5	12
Narita (2011a)[65]	17	41.4	9, 8	65	11.8	6.2	BD-II	6 euthymic, 9 depressed, 2 manic	-	-	84	41.1	48, 36	1.5	12
Narita (2011b)[65]	14	40.2	8, 6	76	21.4	8.6	BD-II	2 euthymic, 10 depressed, 2 manic	-	-	84	41.1	48, 36	3	8
Nugent (2006a)[66]	16	37	5, 11	0	0.0	17	-	Depressed	-	-	65	38	19, 46	3	8
Nugent (2006b)[66]	20	41	5, 15	31	2.8	23	-	Depressed	-	-	65	38	19, 46	1.5	8
Redlich (2014)[30]	58	37.5	21, 37	26	64.0	14.2	BD-I	Depressed	21	3.0	58	37.7	21, 37	3	8
Rocha-Rego (2013a)[67]	26	41.5	12, 14	38	30.8	15.8	BD-I	Euthymic	6.6	1.8	26	41.3	12, 14	1.5	8
Rocha-Rego (2013b)[67]	14	37.6	6. 8	-	0.0	18.8	BD-I	Euthymic	4.2	1.7	14	37.4	6, 8	1.5	8
Scherk (2008)[68]	35	43.3	18, 17	34	51.4	14.4	BD-I	Euthymic	2.5	2.6	32	33.7	12, 20	1.5	8
Shepherd (2014)[69]	30	39.1	12, 18	-	-	13.5	BD-I	-	-	6.7	34	32.6	16, 18	3	8
Stanfield (2009)[70]	66	36.4	30, 36	-	47.0	15.4	BD-I	Euthymic	-	-	66	39	31, 35	1.5	12
Tang (2014)[71]	27	32	10, 17	33	-	4.2	-	Depressed	19.7	1	27	32.6	11, 16	3	8
Yatham (2007)[72]	15	36	6, 9	-	0.0	3.9	BD-I	Manic	-	27	15	36	6, 9	1.5	8
Yüksel (2012)[73]	27	32.9	17, 10	48	0.0	-	BD-I	18 manic, 5 mixed, 4 euthymic	7.2	22.8	43	36.4	-	3	12

Supplementary Table 2. Characteristics of bipolar disorder studies included in the meta-analysis. M = male, F = female, y = years, HAMD-17 = Hamilton Depression Rating Scale 17-item, BD-I = bipolar disorder type I, BD-II = bipolar disorder type II, YMRS = Young Mania Rating Scale

Peak MNI coordinate	*Z*	P	Voxels	Brodmann areas	Regions
Major Depression<Healthy Controls					
-66,-16,-12	2.64	0.002	19	21	Left middle temporal gyrus
-30,-72,44	2.51	0.003	18	7	Left inferior parietal lobule
-36,-34,-18	2.74	0.001	13	37	Left fusiform gyrus
-4,-44,-22	2.46	0.004	13	-	Cerebellar vermis
Major Depression > Healthy Controls					
-10,-72,0	-1.04	<0.001	207	18	Left lingual gyrus
-8,-52,18	-1.06	<0.001	197	30	Left precuneus
-48,-50,-40	-1.01	<0.001	129	-	Left cerebellum, crus I

Table S3. Clusters showing differences between major depression and controls that did not meet our criteria for robustness

Peak MNI coordinate	*Z*	P	Voxels	Brodmann areas	Regions
-46,4,4	1.82	<0.001	436	48	Left insula
2,34,-16	1.33	<0.001	248	11	Left gyrus rectus, medial orbitofrontal cortex
4,-2,42	1.15	<0.001	203	23, 24	Right midcingulate area
22,2,-18	1.33	<0.001	207	34	Right amygdala
52,6,-20	1.23	<0.001	173	21	Right temporal pole, middle temporal gyrus
-22,-16,-14	1.50	<0.001	51	35	Left hippocampus
-26,20,60	1.18	<0.001	42	8	Left middle frontal gyrus

Table S4. Clusters showing significant between study heterogeneity in major depression

Peak MNI coordinate	*Z*	P	Voxels	Brodmann areas	Regions
Bipolar Disorder<Healthy Controls					
-62,-60,-10	2.71	0.002	20	37	Left inferior temporal gyrus
36,60,6	2.64	0.002	13	10	Right middle frontal gyrus
Bipolar Disorder>Healthy Controls					
-14,-60,-44	-1.21	0.003	23	-	Left cerebellum, hemispheric lobule VIII
4,-14,-22	-1.33	0.002	16	-	Right pons
-14,-30,-34	-1.39	0.001	19	-	Middle cerebellar peduncles
4,-38,-18	-1.17	0.003	20	-	Cerebellar vermis
42,-56,6	-1.34	0.002	20	37	Right middle temporal gyrus
-10,46,-30	-1.38	0.001	11	11	Left orbitofrontal cortex
-32,-54,38	-1.22	0.003	11	40	Left inferior parietal gyrus

Table S5. Clusters showing differences between bipolar disorder and controls did not meet our criteria for robustness

Peak MNI coordinate	*Z*	P	Voxels	Brodmann areas	Regions
8, 12, 12	5.88	<0.001	657	25	Right caudate nucleus
-46,38,-14	4.42	<0.001	425	47	Left inferior frontal gyrus
30,-36,-18	3.297	0.001	169	37	Right fusiform gyrus
48,36,-12	3.94	<0.001	119	47	Right inferior frontal gyrus
-58,-66,-12	3.33	<0.001	61	37	Left inferior occipital gyrus
6,18,22	2.82	0.002	55	24	Right anterior cingulate cortex
50,16,2	2.77	0.002	33	45, 48	Right inferior frontal gyrus
62,-20,-4	2.72	0.003	30	21, 22	Right superior temporal gyrus, middle temporal gyrus
6,-14,10	3.03	0.002	30	-	Right thalamus
-20, -22, -22	2.89	0.002	28	30	Left parahippocampal gyrus
-42, -46, 46	2.60	0.003	24	40	Left inferior parietal gyrus
-52, 34, 24	3.39	0.001	18	45	Left inferior frontal gyrus, pars triangularis

Table S6. Clusters showing significant between study heterogeneity in bipolar disorder

Supplementary figures

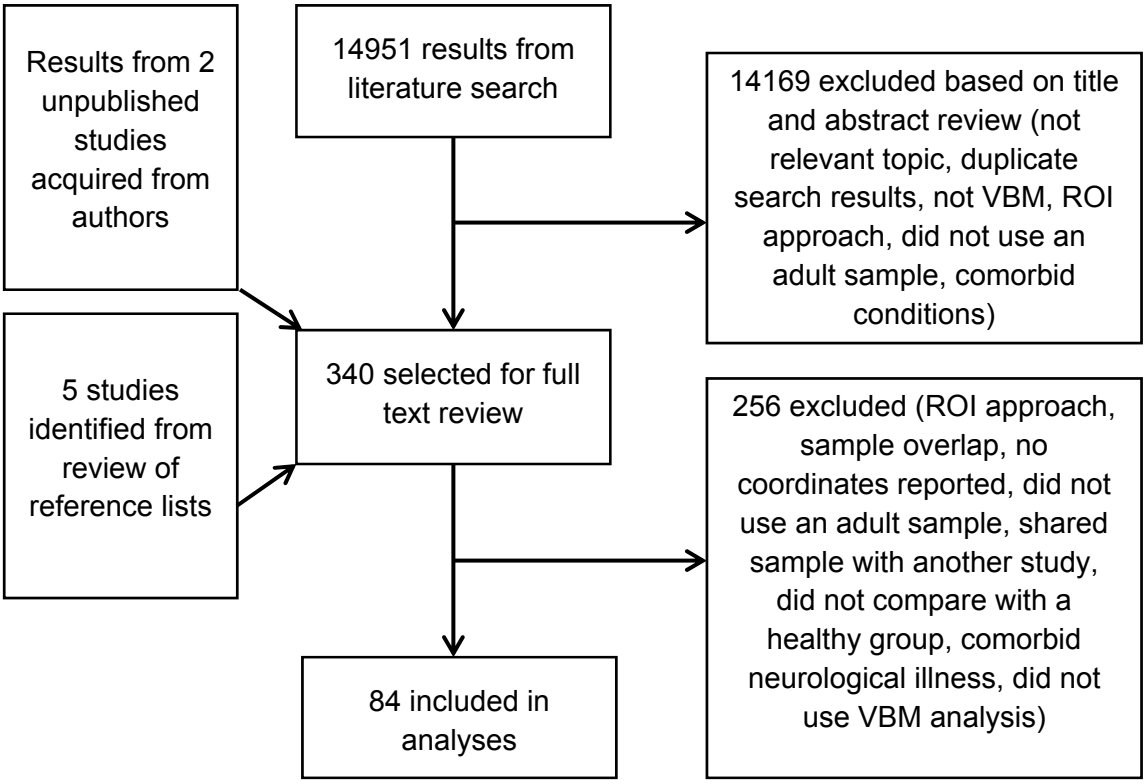

Figure S1. Literature search

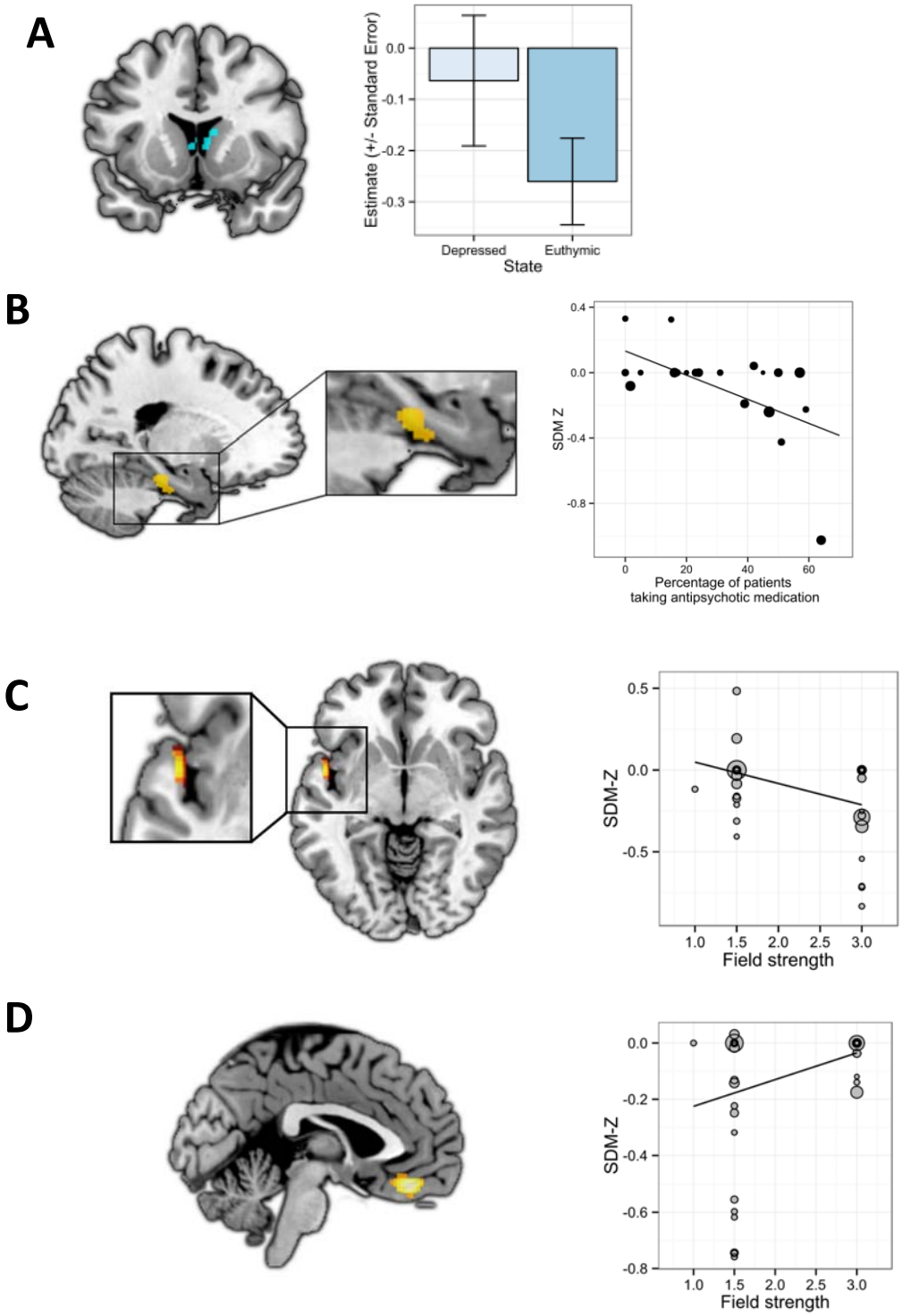

Figure S2. A) Results of mood state comparison in bipolar disorder.B) Results of meta-regression with antipsychotic medication load in bipolar disorder. C & D) Results of meta-regression with scanner field strength in major depression.

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