Data supplement for Gray et al., Multimodal Abnormalities of Brain Structure and Function in Major Depressive Disorder: A Meta-Analysis of Neuroimaging Studies. Am J Psychiatry (doi: 10.1176/appi.ajp.2019.19050560)

CONTENTS

Appendix 1. Details of Literature Search

Neuroimaging experiments reporting gray matter atrophy (using MRI) or reporting increased or decreased resting-state function (using fMRI, PET, or SPECT) in patients with major depressive disorder (MDD) compared to controls and published between September 1992 and January 2018 were identified by PubMed, Google Scholar, and reference tracing of previous meta-analyses in MDD. Search terms included different combinations of: "voxel-based morphometry", "VBM", "gray matter", "gray matter atrophy", "gray matter volume", "gray matter concentration", "whole-brain", "resting-state", "brain function", "brain activity", "regional cerebral blood flow", "rCBF", "regional homogeneity", "ReHo", "amplitude of low frequency fluctuations", "ALFF/fALFF", "glucose metabolism", "arterial spin labeling", "ASL", "positron emission tomography", "PET", "FDG-PET", "O-15 PET", "single photon emission tomography", "SPECT", "major depressive disorder", "MDD", "major depression", "depression", and "unipolar depression".

The BrainMap voxel-based morphometry database was also queried for qualifying experiments demonstrating reduced gray matter volume in MDD patients relative to controls. Parameters for the BrainMap search included: "Experiments: Contrast is: Gray Matter", "Subjects: Diagnosis is: Major Depressive Disorder (MDD)", and "Experiments: Observed Changes is: Controls > Patients".

General exclusion criteria included: ROI-based or non voxel-wise whole-brain studies, functional or effective connectivity studies, or experiments which reported MDD patients in remission or any other contrast than acutely ill MDD patients vs. healthy controls. Included studies were peer-reviewed, English-language publications- though studies translated from original non-English publications were not excluded. Country of origin for each included study is tabulated in Supplemental Tables 1 & 2 within the Paper field. Distribution of countries of origin included in the present analysis are: 41.9% China, 15% United States, 6.5% Japan, 5.4% United Kingdom, 5.4% Germany, and less than 5% originating from Spain, France, Ireland, Australia, Taiwan, Canada, Israel, South Korea, Brazil, Netherlands, and Denmark.

Appendix 2. Details of ALE Analysis

B. Technical Details

(content adapted from brainmap.org and User Manual for GingerALE available at http://www.brainmap.org/ale/manual.pdf)

Activation/anatomical likelihood estimation (ALE) was employed through use of GingerALE 3.0 available through brainmap.org/ale. GingerALE utilizes input foci in either Talairach or MNI format. For the present study, all foci were converted to Talairach space using the Lancaster transform (www.talairach.org).

The ALE methods used in the present work represent the latest generation of CMBA methods, representing many years of progressive refinements and validations. The methods papers for ALE have been published in peer-reviewed journals and have been used in more than 800 peer-reviewed publications (brainmap.org/publications).

ALE (as implemented through GingerALE 3.0) models input foci as 3D images for each foci ("experiment") group. Foci are formatted as 3D Gaussian probability distributions, with the newest format of GingerALE utilizing the variable uncertainty of random effects method by Eickhoff et al 2009, the Full-Width Half-Maximum used to blur each foci group is based on the subject size of each group. This equates to larger subject groups being blurred with a taller, tighter Gaussian functions. This also results in sample size being the greatest determining factor in an individual study's contribution of overall ALE analysis. ALE generates

Upon computation of a P value image, the remaining step is to select a threshold for significance. The simplest thresholding method would be to use Uncorrected P, though as noted by Eickhoff et al 2012 uncorrected P thresholds are not optimal. For the present study, Cluster-Level Inference thresholding was used to simulate random data sets using the input data set's number of foci, number of foci groups, and subject sizes. In the case of cluster-level inference, simulated data is thresholded using a "cluster-forming threshold", in the present study this threshold was set to uncorrected P value of 0.001. GingerALE finds the contiguous volumes above this selected threshold ("clusters") and tracks the distribution of their volume. The cluster-level inference corrected threshold sets the cluster minimum volume such that only, for example, at a cluster-level inference threshold of 0.05 only 5% of the simulated data's clusters exceed this size.

C. Unified ALE Analysis

The following method was used to concatenate foci from different experimental contrasts performed on the same subject group. Examples of this method may be used for combining findings from voxel-based morphometry (*VBM*) and functional results (such as results from a regional homogeneity analysis, *ReHo*) or combining findings of both increased and decreased brain function as observed through glucose metabolism studies. As ALE operates independently of "sign" of observed effect, though standalone effects are also useful for analysis, this method is useful to evaluate all instances of effect in a unified analysis.

The following example demonstrates data from Qiu et al[37] is formatted for use with GingerALE 3.0

Qiu et al performed three experimental contrasts comparing 12 acute phase MDD patients to 12 healthy control subjects: *VBM* (MDD<HC), *ReHo* (MDD>HC), and *ReHo* (MDD<HC). The foci from each contrast (converted from MNI to Talairach space) are shown below as they would appear if retained for standalone effects analysis.

Contrast 1:

```
// Reference=Talairach
// Qiu H, 2016; GM volume decrease in MDD vs normals, VBM
// Subjects=12
12.36     -.93        43.14
```

Contrast 2:

        // Reference=Talairach
        // Qiu H, 2016: Decreased ReHo regions compared to controls, ReHo
        // Subjects=12
        -11.88   -41.02   -26.84
        7.49   -52.56   -24.9
        -6.86   -3.83   25.42
        4.84   -18.75   -24.44

Contrast 3:

        // Reference=Talairach
        // Qiu H, 2016: Increased ReHo regions compared to controls, ReHo
        // Subjects=12
        1.68   8.61   13.23
        54.16   -40.22   20.3
        -54.19   -42.97   23.61
        49.09   -.98   -5.8
        -59.4   -32.21   .22
        -31.3   -49.04   -30.63

To perform a unified all effects analysis utilizing data from all three types of experiments, the data need to be concatenated into a single foci group. The data may not be copied into a single ALE foci file as it appears above, as this would result in the same 12 MDD patients being reported three times (estimating a total of 36 patients instead of 12). The foci may be appended into a single group regardless of "sign" of effect. If desired, GingerALE allows for notes for each foci group as needed, illustrated below.

Unified Contrast:

        // Reference=Talairach
        // Qiu H, 2016; GM volume decrease in MDD vs normals, VBM (1)
        // Qiu H, 2016: Decreased ReHo regions compared to controls, ReHo (4)
        // Qiu H, 2016: Increased ReHo regions compared to controls, ReHo (6)
        // Subjects=12
        12.36   -.93   43.14
        -11.88   -41.02   -26.84
        7.49   -52.56   -24.9
        -6.86   -3.83   25.42
        4.84   -18.75   -24.44
        1.68   8.61   13.23
        54.16   -40.22   20.3
        -54.19   -42.97   23.61
        49.09   -.98   -5.8
        -59.4   -32.21   .22
        -31.3   -49.04   -30.63

Results from GingerALE will report experiments (foci groups) that contribute to any identified clusters; however, unless specific foci information is retained as in the example above, the type of effect contributing to the cluster will not be identifiable. This type of unified analysis is useful for preliminary investigations of effect across all types studies, and specific types of effect (such as increased versus decreased function) may be gleaned from subsequent analyses.

TABLE S1. Description of resting-state studies included in the present meta-analysis

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Aihara M et al.[1] 2007 *Japan*	24/23	52.4	DSM IV	SPM 99 software	Exclusion of any comorbid Axis I disorder	Medicated	FDG PET	Both
Bonte FJ et al.[2] 2001 *United States*	21/18	11-18	DSM III	SPM (version not cited) software	Not Specified	Drug naive	Tc99m HMPAO SPECT	Decrease
Brody AL et al.[3] 2006 *United States*	24/16	38.9	DSM IV	SPM 96 software	Exclusion of any comorbid Axis I disorder, substance abuse, neurological disorder, use of central nervous system medications, use of any psychotropic medication within 2 weeks of imaging	Drug washout	FDG PET	Both
Cao J et al.[4] 2016 *China*	53/47	21	DSM IV	Foam padding to minimize head motion, images reviewed by two experienced radiologists for quality, REST version 1.8	Exclusion of any comorbid Axis I disorder, neurological disease, substance or alcohol abuse, history of electroconvulsive therapy, history of head trauma, psychiatric disease or suicide among 1st degree relatives, other clinically relevant abnormalities	Majority medicated	ALFF	Both

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Chen G et al.[5] 2016 *China*	10/15	38.9	DSM IV	Foam padding to reduce head movement, SPM 8 software	Exclusion of comorbid severe mental illness, history of injury with unconsciousness >5 minutes, neurological disorder, serious physical illness, endocrine disease, pregnancy/lactating, current participation in other research study, MRI contraindications	Drug naive	ASL	Both
Chen JD et al.[6] 2012 *China*	46/37	24	DSM IV	Subjects' heads were fixed with foam pads and belt, SPM 8 software for motion correction	Exclusion of comorbid major psychiatric illness, major medical illness, neurological disorder, mental retardation, substance abuse, dementia, dementia, pregnancy, MRI abnormalities	Drug naive	ReHo	Both
Drevets WC et al.[7] 1992 *United States*	13/33	36	DSM III	Post hoc image comparisons found no significant difference in head placement	Exclusion of comorbid psychiatric disorders, medical or neurological illness, medications affecting cerebral blood flow, alcohol abuse	Drug washout	H2O-15 PET	Both

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Du L et al.[8] 2016 *China*	16/18	38.13	DSM IV	No subject with head motion >2mm or rotation >1 degree	Exclusion of comorbid Axis I or II disorder, alcohol/substance abuse, neurological disease, serious physical illness, morphological brain anomalies, MRI contraindications	Drug naive	ALFF	Increase
Duhameau B et al. [9] 2010 *France*	6/6	52.5	DSM IV	Over-artifacted images were excluded, SPM 2 software	Exclusion of comorbid Axis I disorder, personality disorder, suicide risk greater than 2 on item 3 of HDRS, neurological disease, history of significant head injury, severe intercurrent disease, active substance abuse/dependence, history of alcohol or cocaine abuse/dependence, circulatory conditions, MRI contraindications	Medicated	ASL	Increase

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Fang J et al.[10] 2015 *China*	20/18	59.2	DSM IV	Timing correction, head motion correction, spatial normalization and smoothing performed by SPM 8 and REST software	Exclusion of comorbid mental disorders, substance/alcohol abuse, severe physical illness, serious infection or surgeries	Untreated at baseline	ALFF	Decrease
Germain A et al.[11] 2007 *United States*	12/13	38.1	DSM IV	SPM 99 software	Exclusion of comorbid bipolar, schizophrenic, or psychotic disease, high risk for suicide, alcohol/substance abuse, serious physical illness, left handedness, pregnancy/breastfeeding, any current use of mood stabilizer medications, central nervous system stimulants, electroconvulsive therapy within 3 weeks of imaging	Drug washout	FDG PET	Both

Paper	Number of subjects: MDD/Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Gong Y et al.[12] 2014 *China*	15/16	15	DSM IV	Scanner artifacts and gross anatomical abnormalities evaluation through SPM 8 software	Exclusion of comorbid schizophrenia, bipolar disorder, personality disorder, or other mental disorder, neurological disease, organic mental disorder, dependence/abuse of psychoactive substances, serious physical illness, history of brain trauma, cerebrovascular disease, pregnancy, MRI contraindications	Drug naive	ALFF	Both
Guo W et al.[13] 2014 *China*	44/44	27.52	DSM IV	Foam padding to minimize head motion, structural images check for image artifacts, motion correction with DPARSF	Exclusion of comorbid Axis I disorders, substance abuse/dependence, acute physical illness, history of head injury	Not specified	ALFF	Decrease

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Guo WB et al. [14] 2011 *China*	24/19	27.88	DSM IV	Foam padding to minimize head movement, correction for head motion in SPM 8 software	Exclusion of comorbid neurological disease, family history of neurological disease, head injury, pregnancy, metallic implants	Drug washout	ReHo	Both
Guo WB et al.[15] 2012 *China*	45/19	27.5		Foam padding to minimize head movement, correction for head motion in SPM 8 software	Inclusion of 23 treatment resistant patients, 22 patients with remission after imaging and treatment Exclusion of comorbid psychiatric disorder, injury with loss of consciousness, serious medical illness, substance use disorder within 6 months of imaging, mental retardation, ages outside of 18-60	Some patients medicated	ReHo	Decrease

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Guo WB et al.[16] 2012 *China*	35/17	27	DSM IV	SPM 8 software for motion correction	Inclusion of 18 treatment resistant patients, 17 treatment sensitive patients Exclusion of comorbid bipolar disorder, other comorbid psychiatric disorders, serious medical or neurological illness, mental retardation, history of loss of consciousness, substance abuse within 6 months of scanning	Some patients medicated	ALFF	Both
Guo WB et al.[17] 2013 *China*	30/15	EOD 24, LOD 67.5	DSM IV	Subjects heads' were fixed with foam pads and belt, SPM 8 software for head motion correction	Inclusion of 15 early onset patients and 15 late onset patients Exclusion of other comorbid psychiatric disorders, substance abuse/dependence, primary medical illness, neurological disease, cardiovascular disease, dementia, organic brain disorder	Not specified	ALFF	Both

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Ho T et al.[18] 2013 *United States*	25/26	15.98	DSM IV	Motion correction through FSL and AFNI	Inclusion of adolescent population only Exclusion of comorbid psychiatric illness or disruptive disorder	Medicated	ASL	Both
Huang M et al.[19] 2017 *China*	25/16	31.4	DSM IV	SPM 8 correction for head motion	Exclusion of comorbid Axis I or II disorders, previous treatment for depression, significant medical illness, organic brain disease, cerebral trauma, seizure disorder, family history of bipolar disorder, alcohol/substance abuse, pregnancy/lactating, currently in menstrual period, MRI evidence of structural abnormalities, MRI contraindications	Drug naive	fALFF	Both
Ito H et al.[20] 1996 *Japan*	11/9	66.6		Anatomic standardization performed by HBA system	Exclusion of comorbid psychiatric illness, neurological illness, alcohol/substance abuse, use of any cerebral metabolic activator, vasodilator, dopamine agonist, electroconvulsive therapy within 6 months of imaging	Medicated	Tc99m HMPAO SPECT	Decrease

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Kaichi Y et al.[21] 2016 *Japan*	53/36	42.2	DSM IV	SPM 8 software	Exclusion of comorbid bipolar disorder, neurological illness, serious physical illness, alcohol/substance abuse, likely pregnancy, use of psychotropic medication within 4 weeks of imaging	Drug washout	ASL	Both
Kegeles LS et al.[22] 2003 *United States*	19/10	36	DSM III	Thermoplastic mask utilized to minimize head movement	Exclusion of comorbid DSM-IV disorder, body mass index outside of 20% of age average, recent exposure to antidepressant treatments (no exposure to electroconvulsive therapy within 3 months, fluoxetine within 8 weeks, or any other mood stabilizer within 4 weeks of imaging)	Drug washout	FDG PET	Decrease

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Kennedy SH et al.[23] 2001 *Canada*	13/24	36	DSM IV	Thermoplastic mask utilized to minimize head movement	Exclusion of comorbid bipolar disorder, major illness, cardiovascular illness, age outside of 18-50	Drug washout	FDG PET	Both
Kimbrell TA et al.[24] 2002 *United States*	38/37	43.3	DSM IV	Head movement restricted by with individually molded thermoplastic mask	Exclusion of psychosis, neurological illness, severe medical illness, history of head trauma, substance abuse, electroconvulsive therapy within 1 year of imaging	Drug washout	FDG PET	Both
Kohn Y et al.[25] 2007 *Israel*	33/25	53	DSV IV	Head immobilized	Inclusion of panic or anxiety disorder diagnosis if proceeding MDD diagnosis Exclusion of Axis I disorder diagnosis preceding MDD diagnosis, neurological illness, history of head injury, alcohol/substance abuse, electroconvulsive therapy within 6 months of imaging	Drug washout	Tc99m HMPAO SPECT	Decrease
Krausz Y et al.[26] 2007 *Israel*	10/10	49.1	DSM IV	SPM 99 software	Not specified	Drug washout	Tc99m HMPAO SPECT	Decrease

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Lai CH et al.[27] 2015 *Taiwan*	44/27	36.9	DSM IV	All subjects' head movements were less than 0.5mm in translation and one degree in rotation, no subject Demonstrated excessive motion, DPARSF for micro-motion correction	Exclusion of comorbid psychiatric or medical illness, previous CBT or other psychotherapies, alcohol/substance abuse, claustrophobia	Drug naive	fALFF	Both
Liang MJ et al.[28] 2013 *China*	16/16	36.06	DSM IV	Foam pads used to limit head motion, DPARSF for motion correction and spatial normalization	Exclusion of anxiety as a primary diagnosis, comorbid schizophrenia, schizoaffective disorder, substance dependence, serious medical illness, neurological illness, pregnancy/breastfeeding, metallic implants, MRI contraindications, use of caffeine or nicotine, positive urine toxicology, alcohol use within 1 week of imaging,	Medicated	ReHo	Both

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Liu CH et al.[29] 2013 *China*	22/26	36.8	DSM IV	SPM 8 software for head-motion correction	Not specified	Majority medicated	fAlFF	Both
Liu J et al.[30] 2014 *United States*	30/30	29.8	DSM IV	Head motion was minimized with restraining foam pads, SPM 8 and REST used for motion correction	Exclusion of comorbid Axis I disorders, history of psychopharmacotherapy, history of ECT or psychotherapy, history of head injury, neurological disease, concomitant medical disorders, MRI contraindications	Drug naive	ALFF	Both
Liu Y et al.[31] 2017 *China*	23/14	37.7	DSM IV	Foam pads to minimize head motion, head motion parameters for all participants less than 2.0 mm for translation and 2.0 degrees for rotation	Exclusion of comorbid psychiatric disorders, comorbid physical disease, alcohol/substance abuse, history of discomfort or claustrophobia while undergoing MRI	Drug naive	ReHo	Both

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Liu Z et al.[32] 2010 *China*	15/15	29.13	DSM IV	Foam pads to limit head motion, SPM 2 software for head motion correction	Exclusion of comorbid psychiatric disorder, neurological illness, systemic illness, major medical illness, history of head injury	Drug naive	ReHo	Both
Lui S et al.[33] 2009 *China*	61/42	34	DSM IV	Spatial normalization with SPM 2 software	Inclusion of 24 refectory depression patients and 37 non refractory depression patients Exclusion of comorbid bipolar disorder, previous psychiatric therapy, major medical illness, use of vasoactive medications, alcohol/substance abuse, age outside of 18-60	Drug naïve	ASL	Decrease
Monkul ES et al.[34] 2012 *United States*	20/21	37.2	DSM IV	Spatial normalization performed by Convex Hull Spatial Normalization tool and Spatial Normalization algorithm	Exclusion of neurological illness, major physical illness, substance abuse	Drug washout	H2O-15 PET	Both

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Oda K et al.[35] 2003 *Japan*	22/13	56	DSM IV	SPM 99 software	Inclusion of 12 patients exhibiting white matter hyperintensities and 11 patients without white matter hyperintensities Exclusion of stroke, neurological illness, dementia, psychosis, alcohol/substance abuse, organic brain disease, hyper/hypothyroidism, other significant pathology, previous electroconvulsive therapy	Medicated	Tc99m ECD SPECT	Decrease
Perico CA et al.[36] 2005 *Brazil*	15/15	34.5	DSM IV	SPM 99 software	Exclusion of neurological illness, cardiovascular illness, history of head trauma, ischemia, use of somatic medication, abnormal MRI results	Washout	Tc99m ECD SPECT	Increase
Qiu H et al.[37] 2016 *China*	12/15	34.4	DSM IV	Head motion correction with DPARSF	Exclusion of depression caused by or comorbid with somatic disease or other psychiatric disorders, neurological disease, severe somatic disease, substance abuse, pregnancy/lactating	Washout	ReHo	Both

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Shen T et al.[38] 2014 *China*	16/14	34/4	DSM IV	Subjects excluded if motion greater than 2.0mm or 2.0 degrees rotation	Exclusion of comorbid Axis I or II disorders, history of psychological treatment, medication within 4 weeks of scanning, medical illness, neurological disease, current suicide attempt, substance dependence aside from nicotine, alcohol consumption within one week of scanning, pregnancy or breastfeeding	Washout	fALFF	Decrease
Skaf C et al.[39] 2002 *Brazil*	21/12	39	DSM IV	SPM 96 software	Inclusion of 12 non-psychotic patients and 9 psychotic patients Exclusion of comorbid mental illness, pregnancy	Washout	Tc99m ECD SPECT	Decrease
Smith GS et al.[40] 2009 *United States*	16/13	65.3	DSM IV	SPM 5 software	Exclusion of comorbid Axis I disorder, neurological illness, or medically unstable	Washout	FDG PET	Both

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Tadayonnejad R et al.[41] 2015 *United States*	20/25	54.5	DSM IV	Artifact Detection Tool (ART) used to measure head motion artifacts, none exceeded more than 2m maximum displacement in x,y, or z axis or 2 degrees angular motion during fMRI scanning	Exclusion of comorbid bipolar disorder, schizophrenia, any psychotic disorder, history of anxiety disorder outside of major depressive episodes, history of head trauma or loss of consciousness, substance abuse, MRI contraindications	Washout	ALFF	Both
Vardi N et al.[42] 2011 *Israel*	37/27	55	DSM IV	SPM (version not cited) software	Exclusion of comorbid bipolar disorder, neurological illness, serious physical illness, potential pregnancy, alcohol/substance abuse, outside of 18-55 years old, use of psychotropic medication within 4 weeks of imaging	Washout	Tc99m HMPAO SPECT	Decrease

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Wang L et al.[43] 2012 *China*	18/18	34	DSM IV	Head motion correction with DPARSF	Exclusion of comorbid bipolar disorder, schizophrenia, schizoaffective, delusional mental disorder, psychotic features coordinated or uncoordinated with mood, organic brain disorder, substance abuse, major physical illness, seizures, brain damage, nervous system disease, acutely suicidal or homicidal behaviors, pregnancy or breastfeeding	Drug naïve	ALFF	Both
Wang L et al.[44] 2014 *China*	14/14	32.9	DSM IV	Head motion correction with DPARSF, head motion of all subjects > 1.5 mm maximum displacement in any direction of x, y, and z and 1.5 degrees in any angular dimension	Exclusion of neurological illness, history of head trauma, serious medical illness, current or previous use of antidepressant/antipsychotic medication, previous electroconvulsive therapy, substance abuse within 1 year of imaging, acutely suicidal or homicidal, pregnancy/breastfeeding, age outside of 18-60 years, MRI contraindications	Drug Naïve	ReHo	Both

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Wang LJ et al.[45] 2014 *China*	56/33	34	DSM IV	All subjects with head movement exceeding 1.5 degrees (regardless of rotation) and translation exceeding 1.5 mm were excluded	Inclusion of 26 early treatment responsive patients and 30 early treatment nonresponsive patients Exclusion of comorbid Axis I disorders, organic brain disorder, neurological disease, cardiovascular disease, pregnancy, other physical illness, inability to undergo MRI	Drug naïve	ALFF	Both
Wu QZ et al.[46] 2011 *China*	44/26	35	DSM IV	9 subjects were excluded for excessive head motion of >1 mm of translation or 1 degree of rotation	Inclusion of 22 treatment resistant MDD patients and 22 non-refractory MDD patients Exclusion of comorbid bipolar disorder or other psychiatric illness, renal or major medical illness, cardiovascular illness, history of head trauma, left-handedness, age outside of 18-60 years, psychiatric treatment or substance misuse within 2 months of imaging	Not specified	ReHo	Both

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Xue S et al.[47] 2016 *China*	31/31	33.8	DSM IV	SPM 8 software for head motion correction	Exclusion of comorbid psychotic disorder, other type of personality disorder, brain lesions, substance/tobacco use	Some patients medicated	ReHo	Both
Yamaura T et al.[48] 2016 *Japan*	32/26	44	DSM IV	Subjects with excessive head motion >1.5 mm translation or 1.5 degrees rotation were excluded, motion correction with DPARSF	Inclusion of 16 treatment resistant patients and 16 non-treatment resistant patients, outpatient status only Exclusion of psychotic MDD, neurological illness, high risk for suicide, left handedness, (for non-TRD patients only): Exclusion of sufficient treatment and duration with one antidepressant to treat the current episode of depression, use of two separate antidepressants for current episode, use of mood stabilizers, antipsychotics or CNS stimulants, ECT within 6 months prior to scanning	Some patients medicated	fALFF	Both

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Yang X et al.[49] 2015 *China*	50/50	31.1	DSM IV	No participants with more than 2mm maximum displacement in x, y, or z and 2 degrees of angular motion during whole scan, SPM 8 software	Exclusion of comorbid bipolar disorder, schizophrenia, anxiety disorder, neurological disease, use of psychotropic medication within 3 months of scanning, history of loss of consciousness, mental retardation, cardiovascular disease, alcohol/substance abuse	Washout	ReHo	Both
Yang Y et al.[50] 2016 *China*	19/19	33.8	DSM IV	Foam padding to limit head motion, patients with movement >3 mm or 3 degrees and healthy subjects exceeding 2mm or 2 degrees excluded, SPM12 software	Exclusion of comorbid Axis I or II disorders, depressive patients with history of manic episode, concurrent serious medial illness, neurological disease, history of head injury resulting in loss of consciousness, alcohol/substance abuse, MRI contraindications	Not specified	ALFF	Both

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Yao Z et al.[51] 2009 *China*	22/22	38.2	DSM IV	Foam padding to reduce head motion, SPM 2 software for motion correction	Exclusion of comorbid psychiatric disorder, past electroconvulsive therapy, serious medical illness, family history of serious psychiatric or neurological illness, abnormal clinical labs, acutely suicidal or homicidal, substance abuse, current use of prescription medication, pregnancy/breastfeeding, age outside of 18-55	Washout	ReHo	Decrease
Yue Y et al.[52] 2013 *China*	22/22	67.5	DSM IV	Subjects' head fixed with belt and foam pads to minimize head motion, motion effects corrected with SPM 5 and REST software	Exclusion of comorbid major psychiatric disorders, neurodegenerative illness, severe physical or other medical illness causing impaired cognitive function, cardiac or pulmonary disease, substance abuse, MRI contraindications	Drug naïve	ReHo	Decrease

Paper	Number of subjects: MDD/ Controls	Mean MDD Patient age	Diagnostic criteria used	Technical details	Exclusion criteria for patients / special inclusion details	Patients medication status	Type of experiment	Reported changes w.r.t controls Increase and/or Decrease
Zhang K et al.[53] 2017 *China*	14/14	33.7	DSM IV	Foam pads to limit head motion, motion correction with Connectome Computation System (CCS)	Exclusion of neurological disease, other severe disease, left handedness, history of head injury	Drug naïve	fALFF	Decrease
Zhang X et al.[54] 2016 *China*	32/35	20.5	DSM IV	SPM 8 for head motion correction	Exclusion of current or previous psychiatric disorder (bipolar included), family history of psychotic disorders or personality disorders, previous head trauma with loss of consciousness, persistent headaches, current or previous ECT or psychotropic medications, neurological disease, alcohol/substance abuse	Drug naïve	ALFF	Both
Zhang X et al.[55] 2016 *China*	11/11	34.09	ICD 10	Pillows to minimize movement, DPARSF and SPM8 for motion correction	Exclusion for history of manic episode	Some patients medicated	ALFF	Both

TABLE S2. Description of gray matter volume studies included in the present meta-analysis

Paper	Number of subjects MDD/ Controls	Mean age of Patients	Diagnostic criteria used	Technical details	Exclusion/inclusion of psychiatric comorbidity	Patients medication status
Alemany S et al.[56] 2013 *Spain*	32/21	36.7	DSM IV	SPM 8 software	Exclusion of neurological illness, pregnancy, MRI contraindications	Some patients medicated
Arnone D et al.[57] 2013 *United Kingdom*	39/66	36.3	DSM IV	SPM 8 software	Exclusion of comorbid Axis I or II disorders, medically unstable, neurological illness, history of head trauma, alcohol/substance abuse, MRI contraindications	Drug Naïve
Arnone D et al.[58] 2009 *United Kingdom*	25/35	33.2	DSM IV	SPM 5 software	Not specified	Washout
Begouiganan L et al.[59] 2009 *France*	21/21	33.16	DSM IV	SPM 5 software	Exclusion of patients with manic episodes, psychotic features, neurological illness, major medical illness, use of medication likely to affect cognition, substance abuse, electroconvulsive therapy within 12 months of imaging	Patients scanned within 1st week of medication use
Cai Y et al.[60] 2015 *China*	23/23	30	DSM IV	SPM 8 software	Exclusion of personal or family history of psychiatric disorders, neurological illness, mental retardation, history of head injury, alcohol/substance abuse, smoking, HAMA>14, BRMS mania >5, MRI contraindications	Not specified
Chaney A et al.[61] 2014 *Ireland*	37/46	40.6	DSM IV	SPM 8 software	Exclusion of neurological disease, history of head injury, substance abuse	Majority medicated

Paper	Number of subjects MDD/ Controls	Mean age of Patients	Diagnostic criteria used	Technical details	Exclusion/inclusion of psychiatric comorbidity	Patients medication status
Cheng YQ et al.[62] 2010 *China*	68/68	29.9	DSM IV	Restraining pads used to minimize head motion, SPM 5 software	Exclusion of comorbid Axis I disorders, neurological disease, pregnancy, other major illness	
Fang J et al.[10] 2015 *China*	20/18	59.2	DSM IV	Timing correction, head motion correction, spatial normalization and smoothing performed by SPM 8 and REST software	Exclusion of comorbid mental disorders, substance/alcohol abuse, severe physical illness, serious infection or surgeries	Untreated at baseline
Frodl T et al.[63] 2008 *Ireland*	38/30	46.1	DSM IV	SPM 2 software	Exclusion of other comorbid mental or personality disorder, neurological disease, alcohol/substance abuse, history of head injury	Medicated
Gong Q et al.[64] 2011 *China*	61/42	40	DSM IV	SPM 8 software	Exclusion for previous psychiatric treatment, major physical illness, cardiovascular disease, use of vasoactive medication, alcohol/substance abuse, age outside of 18-60 year	Drug naïve
Grieve SM et al.[65] 2013 *Australia*	102/34	33.8	DSM IV	SPM 8 software	Exclusion for suicidal tendencies, history of: bipolar disorder, schizophrenia, schizoaffective disorder or psychosis, current anorexia, OCD, PTSD, substance abuse, history of brain injury, MRI contraindications	Washout

| Paper	Number of subjects MDD/ Controls	Mean age of Patients	Diagnostic criteria used	Technical details	Exclusion/inclusion of psychiatric comorbidity	Patients medication status
Guo W 2014 et al. [13]2014 *China*	44/44	27.5	DSM IV	Foam padding to minimize head motion, structural images checked for image artifacts, motion correction with Data Processing Assistant for Resting-State fMRI in Matlab	Exclusion of comorbid Axis I disorders, alcohol/substance abuse, acute physical illness, history of head injury	Drug naïve
Hwang JP et al.[66] 2010 *Taiwan*	70/26	79.4	DSM IV	SPM 2 software	Exclusion for onset before age 50, neurological disease	Not specified
Inkster B et al.[67] 2011 *United Kingdom*	96/96	50.4	DSM IV	Subjects excluded for excessive head motion, SPM 5 software	Exclusion for comorbid bipolar disorder, mood incongruent, neurological disease, history of head injury or epilepsy, alcohol/substance abuse	Medicated
Kim MJ et al.[68] 2008 *United States*	22/25	38.5	DSM IV	Excluded subjects with excessive head motion, SPM 2 software	Exclusion of comorbid bipolar disorder, social phobia, psychotic disorders, learning disability, history of head trauma, alcohol/substance abuse	Medicated
Lai, CH et al.[69] 2015 *Taiwan*	53/54	40	DSM IV	FSL and FSLVBM software	Exclusion of comorbid psychiatric or medical illness, previous CBT psychotherapy, alcohol/substance abuse, MRI contraindications	Drug naïve
Lee HY et al.[70] 2011 *South Korea*	47/51	46	DSM IV	SPM 2 software	Not specified	Medicated

Paper	Number of subjects MDD/ Controls	Mean age of Patients	Diagnostic criteria used	Technical details	Exclusion/inclusion of psychiatric comorbidity	Patients medication status
Li CT at al.[71] 2010 *Taiwan*	48/25	44	DSM IV	SPM 2 software	Exclusion of comorbid psychiatric or personality disorder, alcohol/substance abuse	Not specified
Liu CH et al.[72] 2014 *China*	19/19	35	DSM IV	SPM 8 software	Exclusion of comorbid DSM-IV psychiatric disorders, neurological disease, patient in imminent danger, pregnancy/breastfeeding, MRI contraindications	Medicated
Machino A et al.[73] 2014 *Japan*	29/29	39.57	DSM IV	SPM 8 software	Exclusion of comorbid personality disorder, psychotic spectrum disorders, organic brain disorder, mental retardation, current high risk for suicide, severe somatic disease, substance abuse	Medicated
Mak AK et al.[74] 2009 *China*	17/17	45.5	ICD 10	SPM 2 software	Exclusion of comorbid psychiatric illness, neurological disease, mental retardation, alcohol abuse	Medicated
Peng J et al.[75] 2011 *China*	20/30	46.7	DSM IV	Foam padding to stabilize head position, SPM 2 software	Exclusion of comorbid psychiatric illness, neurological disease, history of head trauma	Majority unmediated
Perico CAM et al.[76] 2011 *Brazil*	20/94	29.9	DSM IV	Subjects excluded for excessive head motion, SPM 2 software	Exclusion of neurological or central nervous system disorders, history of head injury, MRI contraindications	Majority medicated
Qiu H et al.[37] 2016 *China*	12/15	34/4	DSM IV	Head motion correction with DPARSF	Exclusion of depression caused by or combined with somatic disease or other psychiatric disorders, neurological disease, severe somatic disease, pregnancy/lactating, substance abuse	Washout

Paper	Number of subjects MDD/ Controls	Mean age of Patients	Diagnostic criteria used	Technical details	Exclusion/inclusion of psychiatric comorbidity	Patients medication status
Redlich R et al.[77] 2014 *Germany*	58/58	37.6	DSM IV	VBM 8 software	Exclusion of comorbid lifetime mental disorders, dementia, psychotic episodes	Medicated
Salvadore G et al.[78] 2011 *United States*	58/107	38.8	DSM IV	Images visually checked for artifacts, SPM 5 software	Exclusion of suicidal ideation, neurological disease, exposure to psychotropic medication within 3 weeks of study, pregnancy/breastfeeding, alcohol/substance abuse	Washout
Scheuerecker J et al.[79] 2010 *Germany*	13/15	37.9	DSM IV	VBM 5 toolbox	Exclusion of comorbid mental or personality disorder, use of cortisol medication, neurological disease, pregnancy, history of head injury, alcohol/substance abuse	Washout
Serra-Blasco M et al.[80] 2013 *Spain*	22/32	49	DSM IV	SPM 8 software	Exclusion of comorbid Axis I disorder	Medicated
Shad MU et al.[81] 2012 *United States*	22/22	15	DSM IV	Subjects' heads immobilized with tightly-fitting foam pad with strap across forehead, SPM 5 software	Exclusion of current or prior history of mania, hypomania, schizophrenia, schizoaffective disorder, autism, family history of bipolar disorder, substance use disorder symptoms	Majority drug naïve, remaining washout
Shah PJ et al.[82] 1998 *United Kingdom*	20/20	48.9	DSM IV	SPM 96 software	Exclusion of history of manic episodes, neurological disease, hypothyroidism, use of steroids, history of head injury, alcohol/substance abuse	Medicated
Smith GS et al.[40] 2009 *United States*	16/13	65	DSM IV	SPM 5 software	Exclusion of comorbid Axis I disorder, neurological disease, medically unstable	Washout

Paper	Number of subjects MDD/ Controls	Mean age of Patients	Diagnostic criteria used	Technical details	Exclusion/inclusion of psychiatric comorbidity	Patients medication status
Soriano-Mas C et al.[83] 2011 *Spain*	70/40	61.5	DSM IV	SPM 2 software	Exclusion of present or past comorbid Axis I disorders, neurological disease, abnormal MRI results	Medicated
Stratmann M et al.[84] 2014 *Germany*	132/132	37.86	DSM IV	Images visually inspected for artifacts, SPM 8 software	Exclusion of comorbid Axis I or II disorder (other than anxiety disorder), neurological or neurodegenerative disease, serious medical illness, history of head injury, MRI contraindications	Medicated
Tang Y et al.[85] 2007 *China*	14/13	29.5	DSM IV	Head motion was minimized with restraining foam pads, SPM 5 software	Exclusion of major medical illness, neurological disease, history of head injury, alcohol/substance abuse	Drug naïve
van Eijndhoven P et al.[86] 2013 *Netherlands*	20/31	34.1	DSM IV	FreeSurfer software	Exclusion of comorbid Axis I disorder, postpartum depression, pregnancy/breastfeeding, menopause, history of traumatic brain injury, metal in body, claustrophobia, substance abuse	Drug naive
van Tol MJ et al.[87] 2010 *Netherlands*	68/65	37.1	DSM IV	SPM 5 software	Exclusion of known comorbid personality disorders (but not screened for), exposure to psychotropic medication within 48 hours of study, neurological disease, hypertension, alcohol/substance abuse, MRI contraindications	Washout
van Tol MJ et al.[88] 2014 *Netherlands*	20/20	38.25	ICD 10	CIVET processing	Exclusion of atypical depression, bipolar disorder, major medical illness, history of seizures, alcohol abuse, MRI contraindications	Medicated

Paper	Number of subjects MDD/ Controls	Mean age of Patients	Diagnostic criteria used	Technical details	Exclusion/inclusion of psychiatric comorbidity	Patients medication status
Vasic N et al.[89] 2008 *Germany*	15/14	37.4	DSM IV	SPM 5 software	Exclusion of comorbid Axis I disorders, neurological disease, family history of mood disorders, substance abuse	Medicated
Wagner G et al.[90] 2011 *Germany*	30/30	37	DSM IV	Head immobilization was established by pads, SPM 2 software	Exclusion of comorbid Axis I disorders, history of manic episodes, past or current neurological disease	Not specified
Yang X et al.[49] 2011 *China*	50/50	31.12	DSM IV	No participants with more than 2mm maximum displacement in x, y, or z and 2 degrees of angular motion during the whole MRI scan, SPM 8 software	Exclusion of use of psychotropic medication within 3 months of scanning, schizophrenia, bipolar disorder, neurological disease, history of loss of consciousness, mental retardation, cardiovascular disease, alcohol/substance abuse	Washout
Zhang X et al.[91] 2012 *China*	33/32	20.52	DSM IV	Foam pads used to reduce head motion, SPM 8 software	Exclusion of current or previous comorbid psychiatric disorder, comorbid personality disorder, neurological disease, history of head trauma, persistent headache, alcohol/substance abuse, current or previous electroconvulsive therapy or use of psychotropic medication	Drug naive
Zou K et al.[92] 2010 *United Kingdom*	23/23	31.1	DSM IV	SPM 2 software	Exclusion of comorbid Axis I or II disorders	Drug naïve

FIGURE S1. Render of coordinates included in each meta-analytic experiment class
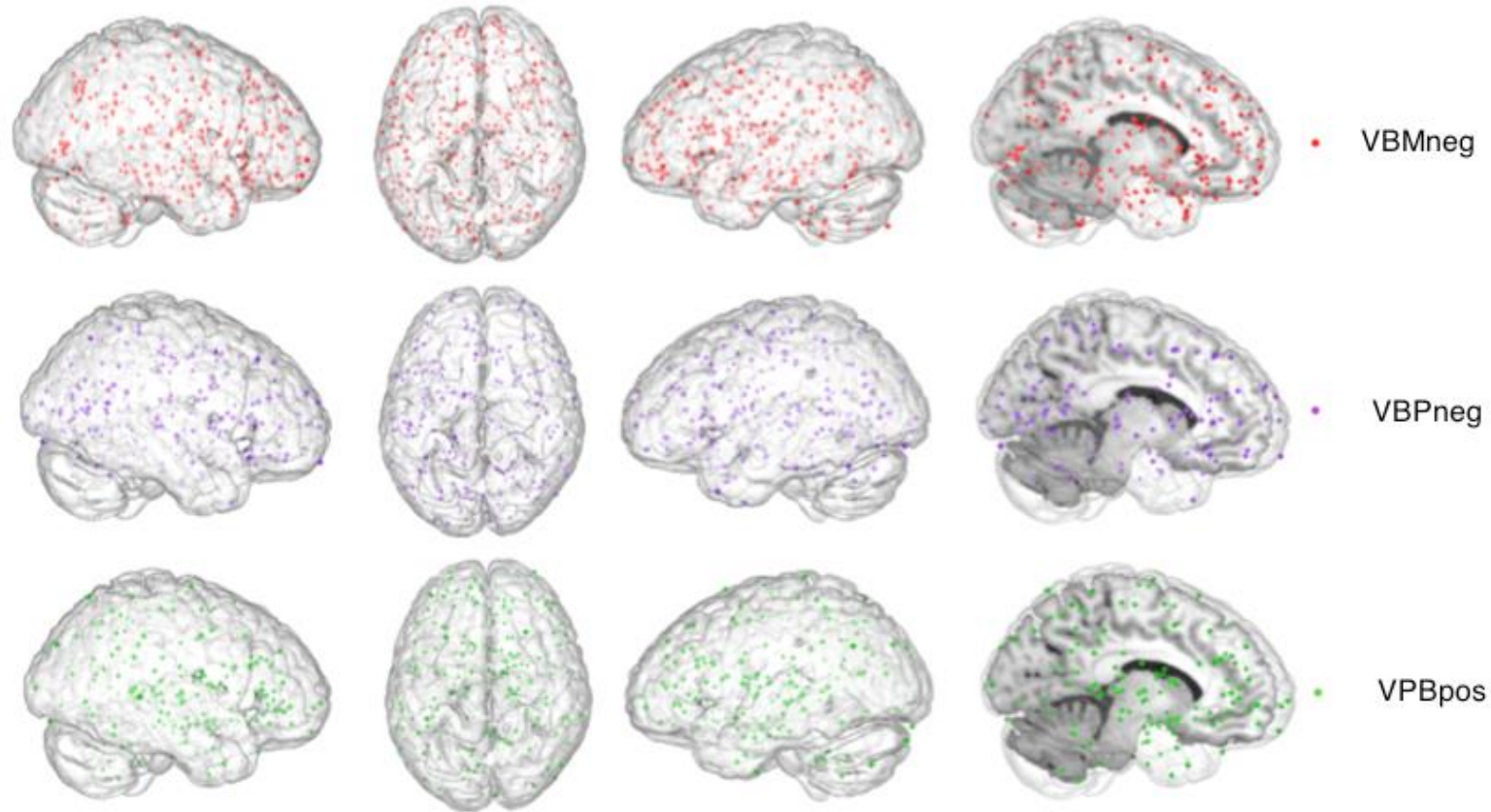
Major meta-analytic subgroupings for this study comprised decreased gray matter volume in patients compared to controls, increased and decreased function relative to controls. Red coordinates indicate reported locations of decreased gray matter volume (VBMneg) in major depressive disorder (MDD) patients, purple indicates reported locations of decreased function (VBPneg in MDD, and green indicates reported locations of increased function (VBPpos) in MDD. Color transparency indicates depth of coordinate with respect to cortical surface.

TABLE S3. Contributors to cluster #1 from All Effects analysis

Paper	Experiment type and reported changes (MDD relative to control subjects)
Arnone D et al.[57] 2013	VBM decreases
Germain A et al.[11] 2007	FDG-PET increases & decreases
Huang M et al.[19] 2017	fALFF increases & decreases
Lee HY et al.[70] 2011	VBM decreases
Shah PJ et al.[82] 1998	VBM decreases
Tadayonnejad R et al.[41] 2015	ALFF increases & decreases
Yang Y et al.[50] 2016	ALFF increases & decreases
Zou K et al.[92] 2010	VBM decreases

TABLE S4. List of studies included in VBPpos + VBMneg (All Patients) grouping

Paper/Experiment details	Number of depressed Subjects	Imaging Modality
Aihara M et al.[1] 2007	24	FDG-PET
Alemany S et al.[56] 2013	12	VBM
Arnone D et al.[58] 2009	25	VBM
Arnone D et al.[57] 2013	39	VBM
Begouiganan L et al.[59] 2009	21	VBM
Brody AL et al.[3] 2001	16	FDG-PET
Cai Y et al.[60] 2015	23	VBM
Cao J et al.[4] 2016 _(suicidal MDD)_	35	ALFF
Cao J et al.[4] 2016 _(non-suicidal MDD)_	18	ALFF
Chaney A et al.[61] 2014	10	VBM
Chen G et al.[5] 2016	10	ASL
Chen JD et al.[6] 2012 _(late onset MDD)_	15	ReHo
Chen JD et al.[6] 2012 _(early onset MDD)_	15	ReHo
Cheng YQ et al.[62] 2010	68	VBM
Drevets WC et al.[7] 1992	13	O-15 PET
Du L et al.[8] 2016	16	ALFF
Duhameau B et al.[9] 2010	6	ASL
Fang J et al.[10] 2015	20	VBM
Zou K et al.[92] 2010	30	VBM
Germain A et al.[11] 2007	12	FDG-PET
Gong Q et al.[64] 2011	23	VBM
Gong Y et al.[12] 2014	15	ALFF
Grieve SM et al.[65] 2013	34	VBM
Guo W et al.[13] 2014 _(first episode MDD)_	24	VBM
Guo W et al.[13] 2014 _(recurrent MDD)_	21	VBM
Guo WB et al.[14] 2011	24	ReHo
Guo WB et al.[16] 2012 _(treatment resistant MDD)_	18	ALFF
Guo WB et al.[16] 2012 _(treatment sensitive MDD)_	17	ALFF
Guo WB et al.[17] 2013 _(early onset MDD)_	15	ALFF
Guo WB et al.[17] 2013 _(late onset MDD)_	15	ALFF
Ho T et al.[18] 2013	25	ASL
Huang M et al.[19] 2017	25	fALFF
Hwang JP et al.[66] 2010	16	VBM
Inkster B et al.[67] 2011	49	VBM
Kaichi Y et al.[21] 2016	53	ASL
Kennedy SH et al.[23] 2001	13	FDG-PET
Kim MJ et al.[68] 2008	22	VBM

Paper/Experiment details	Number of depressed Subjects	Imaging Modality
Kimbrell TA et al.[24] 2002	37	FDG-PET
Lai CH et al.[27] 2015	44	fALFF
Lee HY et al.[70] 2011	47	VBM
Li CT et al.[71] 2010	25	VBM
Liang MJ et al.[28] 2013	16	ReHo
Liu CH et al.[29] 2013	22	fALFF
Liu CH et al.[72] 2014	19	VBM
Liu J et al.[30] 2014	30	ALFF
Liu Y et al.[31] 2017	23	ReHo
Liu Z et al.[32] 2010	45	ReHo
Lui S et al.[33] 2009	37	ASL
Machino A et al.[73] 2012	29	VBM
Mak AK et al.[74] 2009	17	VBM
Monkul ES et al.[34] 2011	20	O-15 PET
Peng J et al.[75] 2010	22	VBM
Perico CA et al.[36] 2005	15	Tc-99m SPECT
Perico CAM et al.[76] 2011	20	VBM
Qiu H et al.[37] 2016	12	ReHo
Redlich R et al.[77] 2014	58	VBM
Salvadore G et al.[78] 2011	58	VBM
Scheuerecker J et al.[79] 2010	13	VBM
Serra-Blasco M et al.[80] 2013	22	VBM
Shad MU et al.[81] 2012	22	VBM
Shah PJ et al.[82] 1998	20	VBM
Smith GS et al.[40] 2009	16	FDG-PET
Soriano-Mas C et al.[83] 2011	40	VBM
Stratmann M et al.[84] 2014	132	VBM
Tadayonnejad R et al.[41] 2015	20	ALFF
Tang Y et al.[85] 2007	14	VBM
van Eijndhoven P et al.[86] 2013	20	VBM
van Tol MJ et al.[87] 2010	65	VBM
van Tol MJ et al.[88] 2014	20	VBM
Vasic N et al.[89] 2008	15	VBM
Wagner G et al.[90] 2011	30	VBM
Wang L et al.[43] 2012	18	ALFF
Wang L et al.[44] 2014	14	ReHo
Wang LJ et al.[45] 2014 *(early treatment responsive MDD)*	26	ALFF
Wang LJ et al.[45] 2014 *(early treatment non-responsive MDD)*	30	ALFF
Wu QZ et al.[46] 2010 *(non-refractory MDD)*	22	ReHo
Wu QZ et al.[46] 2010 *(treatment resistant MDD)*	22	ReHo
Xue S et al.[47] 2016	31	ReHo
Yamaura T et al.[48] 2016 *(treatment resistant MDD)*	16	fALFF
Yamaura T et al.[48] 2016 *(non-treatment resistant MDD)*	16	fALFF
Yang X et al.[49] 2015	50	ReHo
Yang Y et al.[50] 2016	19	ALFF

Paper/Experiment details	Number of depressed Subjects	Imaging Modality
Zhang X et al.[91] 2012	32	VBM
Zhang X et al.[54] 2016 *(imbalanced spontaneous brain activity)*	32	ALFF
Zhang X et al.[54] 2016 *(females only)*	11	ALFF
Zou K et al.[92] 2010	23	VBM

Experiments: 86

Subjects: 2,254

Foci: 497

TABLE S5. List of studies included in VBPpos +VBMneg (Drug Naïve) grouping

Paper/Experiment details	Number of depressed Subjects	Imaging Modality
Arnone D et al.[58] 2009	25	VBM
Chen G et al.[5] 2016	10	ASL*
Chen JD et al.[6] 2012 *(late onset MDD)*	15	ReHo*
Chen JD et al.[6] 2012 *(early onset MDD)*	15	ReHo*
Cheng YQ et al.[62] 2010	68	VBM
Du L et al.[8] 2016	16	ALFF*
Gong Q et al.[64] 2011	23	VBM
Gong Y et al.[12] 2014	15	ALFF*
Grieve SM et al.[65] 2013	34	VBM
Guo W et al.[13] 2014 *(first episode MDD)*	24	VBM
Guo W et al.[13] 2014 *(recurrent MDD)*	21	VBM
Huang M et al.[19] 2017	25	fALFF*
Lai CH et al.[27] 2015	44	fALFF*
Liu J et al.[30] 2014	30	ALFF*
Liu Y et al.[31] 2017	23	ReHo*
Liu Z et al.[32] 2010	45	ReHo
Lui S et al.[33] 2009	37	ASL
Tang Y et al.[85] 2007	14	VBM
van Eijndhoven P et al.[86] 2013	20	VBM
Wang L et al.[43] 2012	18	ALFF*
Wang L et al.[44] 2014	14	ReHo*
Wang LJ et al.[45] 2014 *(early treatment responsive MDD)*	26	ALFF*
Wang LJ et al.[45] 2014 *(early treatment non-responsive MDD)*	30	ALFF*
Zhang X et al.[54] 2016 *(imbalanced spontaneous brain activity*	32	ALFF*
Zhang X et al.[54] 2016 *(females only)*	11	ALFF*
Zou K et al.[92] 2010	23	VBM*

Experiments: 26

Subjects: 693

Foci: 131

*= First Episode patient groups, n=16

TABLE S6. List of studies included in VBPpos +VBMneg (Only MDD) grouping

Paper/Experiment details	Number of depressed Subjects	Imaging Modality
Aihara M et al.[1] 2007	24	FDG-PET
Alemany S et al.[56] 2013	12	VBM
Brody AL et al.[3] 2001	16	FDG-PET
Cao J et al.[4] 2016 *(suicidal MDD)*	35	ALFF
Cao J et al.[4] 2016 *(non-suicidal MDD)*	18	ALFF
Chen G et al.[5] 2016	10	ASL
Cheng YQ et al.[62] 2010	68	VBM
Du L et al.[8] 2016	16	ALFF
Duhameau B et al.[9] 2010	6	ASL
Fang J et al.[10] 2015	20	VBM
Frodl T et al.[63] 2008	30	VBM
Germain A et al.[11] 2007	12	FDG-PET
Gong Y et al.[12] 2014	15	ALFF
Guo W et al.[13] 2014 *(first episode MDD)*	24	VBM
Guo W et al.[13] 2014 *(recurrent MDD)*	21	VBM
Guo WB et al.[17] 2013 *(early onset MDD)*	15	ALFF
Guo WB et al.[17] 2013 *(late onset MDD)*	15	ALFF
Ho T et al.[18] 2013	25	ASL
Huang M et al.[19] 2017	25	fALFF
Lai CH et al.[27] 2015	44	fALFF
Li CT et al.[71] 2010	25	VBM
Liu CH et al.[72] 2014	19	VBM
Liu J et al.[30] 2014	30	ALFF
Liu Y et al.[31] 2017	23	ReHo
Liu Z et al.[32] 2010	45	ReHo
Mak AK et al.[74] 2009	17	VBM
Peng J et al.[75] 2010	22	VBM
Redlich R et al.[77] 2014	58	VBM
Serra-Blasco M et al.[80] 2013	22	VBM
Smith GS et al.[40] 2009	16	FDG-PET
Soriano-Mas C et al.[83] 2011	40	VBM
Stratmann M et al.[84] 2014	132	VBM
Tadayonnejad R et al.[41] 2015	20	ALFF
van Eijndhoven P et al.[86] 2013	20	VBM
Vasic N et al.[89] 2008	15	VBM
Wagner G et al.[90] 2011	30	VBM
Wang LJ et al.[45] 2014 *(early treatment responsive MDD)*	26	ALFF
Wang LJ et al.[45] 2014 *(early treatment non-responsive MDD)*	30	ALFF

Paper/Experiment details	Number of depressed Subjects	Imaging Modality
Wu QZ et al.[46] 2010 *(non-refractory MDD)*	22	ReHo
Wu QZ et al.[46]2010 *(treatment resistant MDD)*	22	ReHo
Yang Y et al.[50] 2016	19	ALFF
Zhang X et al.[91] 2012	32	VBM
Zou K et al.[92] 2010	23	VBM

Experiments: 43

Subjects: 1,186

Foci: 271

TABLE S7. List of studies included in VBPpos +VBMneg (Naïve+Washout) grouping

Paper/Experiment details	Number of depressed Subjects	Imaging Modality
Arnone D et al.[57] 2013	39	VBM
Brody AL et al.[3] 2001	16	FDG-PET
Chen G et al.[5] 2016	10	ASL
Chen JD et al.[6] 2012 (late onset MDD)	15	ReHo
Chen JD et al.[6] 2012 (early onset MDD)	15	ReHo
Cheng YQ et al.[62] 2010	68	VBM
Drevets WC et al.[7] 1992	13	O-15 PET
Du L et al.[8] 2016	16	ALFF
Fang J et al.[10] 2015	20	VBM
Germain A et al.[11] 2007	12	FDG-PET
Gong Q et al.[64] 2011	23	VBM
Gong Y et al.[12] 2014	15	ALFF
Grieve SM et al.[65] 2013	34	VBM
Guo W et al.[13] 2014 (first episode MDD)	24	VBM
Guo W et al.[13] 2014 (recurrent MDD)	21	VBM
Huang M et al.[19] 2017	25	fALFF
Kaichi Y et al.[21] 2016	53	ASL
Kennedy SH et al.[23] 2001	13	FDG-PET
Kimbrell TA et al.[24] 2002	37	FDG-PET
Lai CH et al.[27] 2015	44	fALFF
Liang MJ et al.[28] 2013	16	ReHo
Liu J et al.[30] 2014	30	ALFF
Liu Y et al.[31] 2017	23	ReHo
Liu Z et al.[32] 2010	45	ReHo
Lui S et al.[33] 2009	37	ASL
Monkul ES et al.[34] 2011	20	O-15 PET
Perico CA et al.[36] 2005	15	Tc-99m SPECT
Qiu H et al.[37] 2016	12	ReHo
Salvadore G et al.[78] 2011	58	VBM
Scheuerecker J et al.[79] 2010	13	VBM
Smith GS et al.[40] 2009	16	FDG-PET
Tang Y et al.[85] 2007	14	VBM
van Eijndhoven P et al.[86] 2013	20	VBM
van Tol MJ et al.[87] 2010	65	VBM
Wang L et al.[43] 2012	18	ALFF
Wang L et al.[44] 2014	14	ReHo
Wang LJ et al.[45] 2014 (early treatment responsive MDD)	26	ALFF
Wang LJ et al.[45] 2014 (early treatment non-responsive MDD)	30	ALFF
Yang X et al.[49] 2015	50	ReHo
Zhang X et al.[91] 2012	32	VBM

Paper/Experiment details	Number of depressed Subjects	Imaging Modality
Zhang X et al.[54] 2016 *(imbalanced spontaneous brain activity*	32	ALFF
Zou K et al.[92] 2010	23	VBM

Experiments: 42

Subjects: 1,122

Foci: 212

TABLE S8. List of studies included in VBPneg (Drug Naïve) grouping

Paper/Experiment details	Number of depressed Subjects	Imaging Modality
Bonte FJ et al.[2] 2001 (with frontal deficits)	13	FDG-PET
Bonte FJ et al.[2] 2001 (with occipital deficits)	8	FDG-PET
Chen G et al.[5] 2016	10	ASL*
Chen JD et al.[6] 2012 (late onset MDD)	15	ReHo*
Chen JD et al.[6] 2012 (early onset MDD)	15	ReHo*
Gong Y et al.[12] 2014	15	ALFF*
Huang M et al.[19] 2017	25	fALFF*
Lai CH et al.[27] 2015	44	fALFF
Liu J et al.[30] 2014	30	ALFF
Liu Y et al.[31] 2017	23	ReHo*
Liu Z et al.[32] 2010	45	ReHo*
Lui S et al.[33] 2009 (non-refractory MDD)	37	ASL
Lui S et al.[33] 2009 (refractory MDD)	24	ASL
Wang L et al.[43] 2012	18	ALFF*
Wang L et al.[44] 2014	14	ReHo*
Wang LJ et al.[45] 2014 (early treatment responsive MDD)	26	ALFF*
Wang LJ et al.[45] 2014 (early treatment non-responsive MDD)	30	ALFF*
Yue Y et al.[52] 2013 (late onset MDD)	22	ReHo
Zhang K et al.[53] 2017	14	fALFF*
Zhang X et al.[54] 2016 (imbalanced spontaneous brain activity	32	ALFF*

Experiments: 20

Subjects: 460

Foci: 67

*= First episode patient groups, n=12

TABLE S9. List of studies included in VBPneg (Only MDD) grouping

Paper/Experiment details	Number of depressed Subjects	Imaging Modality
Aihara M et al.[1] 2007	24	FDG-PET
Brody AL et al.[3] 2001	16	FDG-PET
Cao J et al.[4] 2016 *(suicidal MDD)*	35	ALFF
Cao J et al.[4] 2016 *(non-suicidal MDD)*	18	ALFF
Chen G et al.[5] 2016	10	ASL
Fang J et al.[10] 2015	20	ALFF
Germain A et al.[11] 2007	12	FDG-PET
Gong Y et al.[12] 2014	15	ALFF
Guo W et al.[13] 2014	44	ALFF
Ho T et al.[18] 2013	25	ASL
Huang M et al.[19] 2017	25	fALFF
Ito H et al.[20] 1996	11	Tc99m HMPAO SPECT
Kohn Y et al. [25] 2007	33	Tc99m HMPAO SPECT
Lai CH et al.[27] 2015	44	fALFF
Liu J et al.[30] 2014	30	ALFF
Liu Y et al.[31] 2017	23	ReHo
Liu Z et al.[32] 2010	45	ReHo
Shen T et al.[38] 2014	16	fALFF
Smith GS et al.[40] 2009	16	FDG-PET
Tadayonnejad R et al.[41] 2015	20	ALFF
Wang LJ et al.[45] 2014 *(early treatment responsive MDD)*	26	ALFF
Wang LJ et al.[45] 2014 *(early treatment non-responsive MDD)*	30	ALFF
Wu QZ et al.[46] 2010 *(non-refractory MDD)*	22	ReHo
Wu QZ et al.[46]2010 *(treatment resistant MDD)*	22	ReHo
Yang Y et al.[50] 2016	19	ALFF
Yao Z et al.[51] 2009	22	ReHo
Yue Y et al.[52] 2013 *(late onset MDD)*	22	ReHo

Experiments: 27

Subjects: 710

Foci: 118

TABLE S10. Experiment classes contributing to each grouping tested* **

Grouping tested	% contribution to each grouping					
	VBM	ALFF	fALFF	Glucose Metabolism	rCBF	ReHo
VBPpos + VBMneg (all patients)	45.45%	18.6%	5.81%	6.98%	9.3%	13.95%
VBPpos + VBMneg (drug naive)	34.62%	30.77%	7.69%	0%	7.69%	19.23%
VBPpos + VBMneg (only MDD)	44.19%	25.58%	4.65%	9.3%	6.98%	9.3%
VBPpos + VBMneg (naïve+washout)	33.33%	16.67%	4.76%	11.9%	14.29%	19.05%
VBPneg (drug naïve)	-	30%	15%	10%	15%	30%
VBPneg (only MDD)	-	37.1%	11.1%	14.8%	14.8%	22.2%

*only groupings which yielded significant clusters from ALE analysis are shown
**All Effects grouping is not shown as multi-modality data was pooled into shared categories

TABLE S11. Experiment classes contributing to each cluster

Brain region	Identified from	% contribution to cluster					
		VBM	ALFF	fALFF	Glucose metabolism	rCBF	ReHo
L Hippocampus	All Effects	50%	25%	12.5%	12.5%	0%	0%
L Hippocampus	VBPpos + VBMneg (all patients)	66.67%	0%	16.7%	16.67%	0%	0%
Subgenual Cingulate	VBPpos + VBMneg (all patients)	75%	25%	0%	0%	0%	0%
R Amygdala/ Putamen	VBPpos + VBMneg (drug naive)	20%	40%	20%	0%	20%	0%
L Hippocampus	VBPpos + VBMneg (only MDD)	66.67%	0%	16.67%	16.67%	0%	0%
R Amygdala/ Putamen	VBPpos + VBMneg (naïve+washout)	25%	50%	25%	0%	0%	0%
L Hippocampus	VBPpos + VBMneg (naïve+washout)	50%	0%	25%	25%	0%	0%
R Middle Occipital/ Inferior frontal	VBPneg (drug naïve)	-	33.3%	0%	0%	0%	66.7%
L Retrosplenial Cortex	VBPneg (only MDD)	-	100%	0%	0%	0%	0%
R Putamen	VBPneg (only MDD)	-	33.3%	33.3%	0%	0%	33.3%

TABLE S12. List of experiments contributing to each cluster

Brain region	Identified from	Experiment, Imaging Modality
L Hippocampus	All Effects: All Patients	Arnone D et al.[57] 2013, [VBM] Germain A et al.[11] 2007, [FDG-PET] Huang M et al.[19] 2017, [fALFF] Lee HY et al.[70] 2011, [VBM] Shah PJ et al.[82] 1998, [VBM] Tadayonnejad R et al.[41] 2015, [ALFF] Yang Y et al.[50] 2016, [ALFF] Zou K et al.[92] 2010, [VBM]
L Hippocampus	VBPpos + VBMneg (all patients)	Arnone D et al.[57] 2013, [VBM] Germain A et al.[11] 2007, [FDG-PET] Huang M et al.[19] 2017, [fALFF] Lee HY et al.[70] 2011, [VBM] Shah PJ et al.[82] 1998, [VBM] Zou K et al.[92] 2010, [VBM]
Subgenual Cingulate Gyrus	VBPpos + VBMneg (all patients)	Frodl T et al.[63] 2008, [VBM] Guo WB et al.[16] 2012, TRD>HC, [ALFF] Lee HY et al.[70] 2011, [VBM] Machino A et al.[73] 2012, [VBM]
R Amygdala/Putamen	VBPpos + VBMneg (drug naive)	Du L et al.[8] 2016, [ALFF] Lai CH et al.[27] 2015, [fALFF] Liu J et al.[30] 2014, [ALFF] Lui S et al.[33] 2009, [ASL] Tang Y et al.[85] 2007, [VBM]
L Hippocampus	VBPpos + VBMneg (only MDD)	Arnone D et al.[57] 2013, [VBM] Frodl T et al.[63] 2008, [VBM] Germain A et al.[11] 2007, [FDG-PET] Huang M et al.[19] 2017, [fALFF] Stratmann M et al.[84] 2014, [VBM] Zou K et al.[92] 2010, [VBM]
R Amygdala/Putamen	VBPpos + VBMneg (naïve+washout)	Du L et al.[8] 2016, [ALFF] Lai CH et al.[27] 2015, [fALFF] Liu J et al.[30] 2014, [ALFF] Tang Y et al.[85] 2007, [VBM]
L Hippocampus	VBPpos + VBMneg (naïve+washout)	Arnone D et al.[57] 2013, [VBM] Germain A et al.[11] 2007, [FDG-PET] Huang M et al.[19] 2017, [fALFF] Zou K et al.[92] 2010, [VBM]
R Middle Occipital/ Inferior Temporal	VBPneg (drug naïve)	Liu J et al.[30] 2014, [ALFF] Liu Y et al.[31] 2017, [ReHo] Wang L et al.[44] 2014, [ReHo]
L Retrosplenial Cortex	VBPneg (only MDD)	Fang J et al.[10] 2015, [ALFF] Wang LJ et al.[45] 2014, ERD<HC, [ALFF] Wang LJ et al.[45] 2014, END<HC, [ALFF]
R Putamen	VBPneg (only MDD)	Liu Z et al.[32] 2010, [ReHo] Shen T et al.[38] 2014, [fALFF] Yang Y et al.[50] 2016, [ALFF]

References

1. Aihara M, Ida I, Yuuki N, et al. HPA axis dysfunction in unmediated major depressive disorder and its normalization by pharmacotherapy correlates with alteration of neural activity in prefrontal cortex and limbic/paralimbic regions. *Psychiatry Res.* 2007;155(3):245-256.
2. Bonte FJ, Trivedi MH, Devous MD Sr, et al. Occipital brain perfusion deficits in children with major depressive disorder. *J Nucl Med.* 2000;42(7):1059-1061.
3. Brody AL, Saxena S, Stoessei P, et al. Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: preliminary findings. *Arch Gen Psychiatry.* 2001;58(7):631-640.
4. Cao J, Chen X, Chen J, et al. Resting-state functional MRI of abnormal baseline brain activity in young depressed patients with and without suicidal behavior. *J Affect Disord.* 2016;205:252-263.
5. Chen G, Bian H, Jiang D, et al. Pseudo-continuous arterial spin labeling imaging of cerebral blood perfusion asymmetry in drug-naïve patients with first-episode major depression. *Biomed Rep.* 2016;5(6):675-680.
6. Chen JD, Liu F, Xun GL, et al. Early and late onset, first-episode, treatment-naïve depression: same clinical symptoms, different regional neural activities. *J Affect Disord.* 2012;143(1-3):56-63.
7. Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichie ME. A functional anatomical study of unipolar depression. *J Neurosci.* 1992;12(9):3628-3641.
8. Du L, Wang J, Meng B, et al. Early life stress affects limited regional brain activity in depression. *Sci Rep.* 2016;6:25338.
9. Duhameau B, Ferré JC, Jannin P, et al. Chronic and treatment-resistant depression: a study using arterial spin labeling perfusion MRI at 3Tesla. *Psychiarty Res*. 2010;182(2):111-116.
10. Fang J, Mao N, Jiang X, Li X, Wang B, Wang Q. Functional and Anatomical Brain Abnormalities and Effects of Antidepressant in Major Depressive Disorder: Combined Application of Voxel-Based Morphometry and Amplitude of Frequency Fluctuation in Resting State. *J Comput Assist Tomogr.* 2015;39(5):766-773.
11. Germain A, Nofzinger EA, Meltzer CC, et al. Diurnal variation in regional brain glucose metabolism in depression. *Biol Psychiatry.* 2007;62(5):438-445.
12. Gong Y, Hao L, Zhang X, et al. Case-control resting-state fMRI study of brain functioning among adolescents with first-episode major depressive disorder. *Shanghai Arch Psychiatry.* 2014;26(4):207-215.
13. Guo W, Liu F, Yu M, et al. Functional and anatomical brain deficits in drug-naïve major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry.* 2014;54:1-6.
14. Guo WB, Sun XL, Liu L, et al. Disrupted regional homogeneity in treatment-resistant depression: a resting-state fMRI study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(5):1297-1302.
15. Guo WB, Liu F, Chen JD, et al. Abnormal neural activity of brain regions in treatment-resistant and treatment-sensitive major depressive disorder: a resting-state fMRI study. *J Psychiatry Res*. 2012;46(10):1366-1373.
16. Guo WB, Liu F, Xue ZM, et al. Alterations of amplitude of low-frequency fluctuations in treatment-resistant and treatment-response depression: a resting-state fMRI study. *Prog Neuropsychopharmacol Biol Psychiatry.* 2012;37(10:153-160.

17. Guo WB, Liu F, Xun GL, et al. Reversal alterations of amplitude of low-frequency fluctuations in early and late onset, first-episode, drug-naïve depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2013;40:153-159.
18. Ho TC, Wu J, Shin DD, et al. Altered cerebral perfusion in executive, affective, and motor networks during adolescent depression. *J Am Acad Child Adolesc Psychiatry.* 2013;52(10):1076-1091.
19. Huang M, Lu S, Yu L, et al. Altered fractional amplitude of low frequency fluctuation associated with cognitive dysfunction in first-episode drug-naïve major depressive disorder patients. *BMC Psychiatry.* 2017;17(1):11.
20. Ito H, Kawashima R, Awata S, et al. Hypoperfusion in the limbic system and prefrontal cortex in depression: SPECT with anatomic standardization technique. *J Nucl Med.* 1996;37(3):410-414.
21. Kaichi Y, Okada G, Takamura M, et al. Changes in the regional cerebral blood flow detected by arterial spin labeling after 6-week escitalopram treatment for major depressive disorder. *J Affect Disord.* 2016;194:135-143.
22. Kegeles LS, Malone KM, Slifstein M, et al. Response of cortical metabolic deficits to serotonergic challenge in familial mood disorders. *Am J Psychiatry.* 2003;160(1):76-82.
23. Kennedy SH, Evans KR, Krüger S, et al. Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. *Am J Psychiatry.* 2001;158(6):899-905.
24. Kimbrell TA, Ketter TA, George MS, et al. Regional cerebral glucose utilization in patients with a range of severities in unipolar depression. *Biol Psychiatry.* 2002;51(3):237-252.
25. Kohn Y, Freedman N, Lester H, et al. 99mTc-HMPAO SPECT study of cerebral perfusion after treatment with medication and electroconvulsive therapy in major depression. *J Nucl Med.* 2007;48(8):1273-1278.
26. Krausz Y, Freedman N, Lester H, et al. Brain SPECT study of common ground between hypothyroidism and depression. *Int J Neuropsychopharmacol.* 2007;10(1):99-106.
27. Lai CH, Wu YT. The patterns of fractional amplitude of low-frequency fluctuations in depression patients: the dissociation between temporal regions and fronto-parietal regions. *J Affect Disord.* 2015;175:441-445.
28. Liang MJ, Zhou Q, Yang KR, et al. Identify Changes of Brain Regional Homogeneity in Bipolar Disorder and Unipolar Depression Using Resting-State fMRI. *PLoS One.* 2013;8(12):e79999.
29. Liu CH, Ma X, Wu X, et al. Resting-state brain activity in major depressive disorder patients and their siblings. *J Affect Disord.* 2013;149(1-3):299-306.
30. Liu J, Ren L, Womer FY, et al. Alterations in amplitude of low frequency fluctuation in treatment-naïve major depressive disorder measured with resting-state fMRI. *Hum Brain Mapp.* 2014;35(10):4979-4988.
31. Liu Y, Zhao X, Cheng Z, et al. Regional homogeneity associated with overgeneral autobiographical memory of first-episode treatment-naïve patients with major depressive disorder in the orbitofrontal cortex: A resting-state fMRI study. *J Affect Disord.* 2017;209:163-168.
32. Liu Z, Xu C, Xu Y, et al. Decreased regional homogeneity in insula and cerebellum: a resting-state fMRI study in patients with major depression and subjects at high risk for major depression. *Psychiatry Res.* 2010;182(3):211-215.

33. Lui S, Parkes LM, Huang X, et al. Depressive disorders: focally altered cerebral perfusion measured with arterial spin-labeling MR imaging. *Radiology.* 2009;251(2):476-484.
34. Monkul ES, Silva LAP, Narayana S, et al. Abnormal Resting State Corticolimbic Blood Flow in Depressed Unmedicated Patients With Major Depression: A 15O-H2O PET Study. *Hum Brain Mapp.* 2012;33(2):272-279.
35. Oda K, Okubo Y, Ishida R, et al. Regional cerebral blood flow in depressed patients with white matter magnetic resonance hyperintensity. *Biol Psychiatry.* 2003;52(2):150-156.
36. Perico CA, Skaf CR, Yamada A, et al. Relationship between regional cerebral blood flow and separate symptom clusters of major depression: a single photon emission computed tomography study using statistical parametric mapping. *Neurosci Lett.* 2005;384(3):265-270.
37. Qiu H, Li X, Zhao W, et al. Electroconvulsive Therapy-Induced Brain Structural and Functional Changes in Major Depressive Disorders: A Longitudinal Study. *Med Sci Monit.* 2016;22:4577-4586.
38. Shen T, Qiu M, Li C, et al. Altered spontaneous neural activity in first-episode, unmedicated patients with major depressive disorder. *Neuroreport.* 2014;25(16):1302-1307.
39. Skaf CR, Yamada A, Garrido GE, et al. Psychotic symptoms in major depressive disorder are associated with reduced regional cerebral blood flow in the subgenual anterior cingulated cortex: a voxel-based single photon emission computed tomography (SPECT) study. *J Affect Disord.* 2002;68(2-3):295-305.
40. Smith GS, Kramer E, Ma Y, et al. The functional neuroanatomy of geriatric depression. *Int J Geriatr Psychiatry.* 2009;24(8):798-808.
41. Tadayonnejad F, Yang S, Kumar A, Ajilore O. Clinical, cognitive, and functional connectivity correlations of resting-state intrinsic brain activity alterations in unmedicated depression. *J Affect Disord.* 2015;172:241-250.
42. Vardi N, Freedman N, Lester H, et al. Hyperintensities on T2-weighted imaged in the basal ganglia of patients with major depression: cerebral perfusion and clinical implications. *Psychiatry Res.* 2011;192(2):125-130.
43. Wang L, Dai W, Su Y, et al. Amplitude of Low-Frequency Oscillations in First-Episode, Treatment-Naïve Patients with Major Depressive Disorder: A Resting-State Functional MRI Study. *PLoS One.* 2012;7(10):e48658.
44. Wang L, Li K, Zhang Q, et al. Short-term effects of escitalopram on regional brain function in first-episode drug-naïve patients with major depressive disorder assessed by resting-state functional magnetic resonance imaging. *Psychol Med.* 2014;44(7):1417-1426.
45. Wang LJ, Kuang WH, Xu JJ, Lei D, Yang YC. Resting-state brain activation correlates with short-time antidepressant treatment outcome in drug-naïve patients with major depressive disorder. *J Int Med Res.* 2014;42(4):966-975.
46. Wu QZ, Li DM, Kuang WH, et al. Abnormal regional spontaneous neural activity in treatment-refractory depression revealed by resting-state fMRI. *Hum Brain Mapp.* 2011;32(8):1290-1299.
47. Xue S, Wang X, Wang W, Liu J, Qiu J. Frequency-dependent alterations in regional homogeneity in major depression. *Behav Brain Res.* 2016;306:13-19.
48. Yamaura T, Okamoto Y, Okada G, et al. Association of thalamic hyperactivity with treatment-resistant depression and poor response in early treatment for major depression: a resting-state fMRI study using fractional amplitude of low-frequency fluctuations. *Transl Psychiatry.* 2016;6:e754.

49. Yang X, Ma X, Li M, et al. Anatomical and functional brain abnormalities in unmedicated major depressive disorder. *Neuropsychiatr Dis Treat.* 2015;11:2415-2423.
50. Yang Y, Zhong N, Imamura K, et al. Task and Resting-State fMRI Reveal Altered Salience Response to Positive Stimuli in Patients with Major Depressive Disorder. *PLoS One.* 2016;11(5):e0155092.
51. Yao Z, Wang L, Lu Q, Liu H, Teng G. Regional homogeneity in depression and its relationship with separate depressive symptom clusters: a resting-state fMRI study. *J Affect Disord.* 2009;115(3):430-438.
52. Yue Y, Yuan Y, Hou Z, Jiang W, Bai F, Zhang Z. Abnormal functional connectivity of amygdala in late-onset depression was associated with cognitive deficits. *PLoS One.* 2013;8(9):e75058.
53. Zhang K, Liu Z, Cao X, et al. Amplitude of low-frequency fluctuations in first-episode, drug-naïve depressive patients: A 5-year retrospective study. *PLoS One.* 2017;12(4):e0174564.
54. Zhang X, Di X, Lei H, et al. Imbalanced spontaneous brain activity in orbitofrontal-insular circuits in individuals with cognitive vulnerability to depression. *J Affect Disord.* 2016;198:56-63.
55. Zhang X, Tang Y, Maletic-Savatic M, et al. Altered neuronal spontaneous activity correlated with glutamate concentration in medial prefrontal cortex of major depressed females: An fMRI-MRS study. *J Affect Disord.* 2016;201:153-161.
56. Alemany S, Mas A, Goldberg X, et al. Regional gray matter reductions are associated with genetic liability for anxiety and depression: an MRI twin study. *J Affect Disord.* 2013;149(1-3):175-181.
57. Arnone D, McKie S, Elliott R, et al. State-dependent changes in hippocampal grey matter in depression. *Mol Psychiatry.* 2013;18(12):1265-1272.
58. Arnone D, Pegg EJ, McKie S, et al. Decreased fronto-limbic gray matter volume associated with recurrent major depressive disorder. *European Neuropsychopharmacology.* 2009;19:s371.
59. Bergouignan L, Chupin M, Czechowska Y, et al. Can voxel based morphometry, manual segmentation and automated segmentation equally detect hippocampal volume differences in acute depression? *Neuroimage.* 2009;45(1):29-37.
60. Cai Y, Liu J, Zhang L, et al. Gray matter volume abnormalities in patients with bipolar I depressive disorder and unipolar depressive disorder: a voxel-based morphometry study. *Neurosci Bull.* 2015;31(1):4-12.
61. Chaney A, Carballedo A, Amico F, et al. Effect of childhood maltreatment on brain structure in adult patients with major depressive disorder and healthy participants. *J Psychiatry Neurosci.* 2014;39(1):50-59.
62. Cheng YQ, Xu J, Chai P, et al. Brain volume alteration and the correlations with the clinical characteristics in drug-naïve first-episode MDD patients: a voxel-based morphometry study. *Neurosci Lett.* 2010;480(1):30-34.
63. Frodl TS, Koutsouleris N, Bottlender R, et al. Depression-related variation in brain morphology over 3 years: effects of stress? *Arch Gen Psychiatry.* 2008:65(10):1156-1165.
64. Gong Q, Wu Q, Scarpazza C, et al. Prognostic predication of therapeutic response in depression using high-field MR imaging. *Neuroimage.* 2011;55(4):1497-1503.
65. Grieve SM, Korgaonkar MS, Koslow SH, Gordon E, Williams LM. Widespread reductions in gray matter volume in depression. *Neuroimage Clin.* 2013;3:332-339.

66. Hwang JP, Lee TW, Tsai SJ, et al. Cortical and subcortical abnormalities in late-onset depression with history of suicide attempts investigated with MRI and voxel-based morphometry. *J Geriatr Psychiatry Neurol.* 2010;23(3):171-184.

67. Inkster B, Rao AW, Ridler K, et al. Structural brain changes in patients with recurrent major depressive disorder presenting with anxiety symptoms. *J Neuroimaging.* 2011;21(4):375-382.

68. Kim MJ, Hamilton JP, Gotlib IH. Reduced Caudate gray Matter Volume in Women with Major Depressive Disorder. *Psychiatry Res.* 2008;164(2):114-122.

69. Lai CH, Wu YT. The gray matter alterations in major depressive disorder and panic disorder: Putative differences in the pathogenesis. *J Affect Disord.* 2015;186:1-6.

70. Lee HY, Tae WS, Yoon HK, et al. Demonstration of decreased gray matter concentration in the midbrain encompassing the dorsal raphe nucleus and the limbic subcortical regions in major depressive disorder: an optimized voxel-based morphometry study. *J Affect Disord.* 2011;133(1-2):128-136.

71. Li CT, Lin CP, Chou KH, et al. Structural and cognitive deficits in remitting and non-remitting recurrent depression: a voxel-based morphometric study. *Neuroimage.* 2010;50(1);347-356.

72. Liu CH, Jing B, Ma X, et al. Voxel-based morphometry study of the insular cortex in female patients with current and remitted depression. *Neuroscience.* 2014;262:190-199.

73. Machino A, Kunisato Y, Matsumoto T, et al. Possible involvement of rumination in gray matter abnormalities in persistent symptoms of major depression: an exploratory magnetic resonance imaging voxel-based morphometry study. *J Affect Disord.* 2014;168:229-35.

74. Mak AK, Wong MM, Han SH, Lee TM. Gray matter reduction associated with emotion regulation in female outpatients with major depressive disorder: a voxel-based morphometry study. *Prog Neuropsychopharmacol Biol Psychiatry.* 2009;33(7):1184-1190.

75. Peng J, Liu J, Nie B, et al. Cerebral and cerebellar gray matter reduction in first-episode patients with major depressive disorder: a voxel-based morphometry study. *Eur J Radiol.* 2011;80(2):395-399.

76. Perico CAM, Duran FL, Zanetti MV, et al. A population-based morphometric MRI study in patients with first-episode psychotic bipolar disorder: comparison with geographically matched healthy controls and major depressive disorder subjects. *Bipolar Disord.* 2011;13(1):28-40.

77. Redlich R, Almeida JJ, Grotegerd D, et al. Brain morphometric biomarkers distinguishing unipolar and bipolar depression. A voxel-based morphometry-pattern classification approach. *JAMA Psychiatry.* 2014;71(11):1222-1230.

78. Salvadore G, Nugent AC, Lemaitre H, et al. Prefrontal cortical abnormalities in currently depressed versus currently remitted patients with major depressive disorder. *Neuroimage.* 2011;54(4):2643-2651.

79. Scheuerecker J, Meisenzahl EM, Koutsouleris N, et al. Orbitofrontal volume reductions during emotion recognition in patients with major depression. *J Psychiatry Neurosci.* 2010;35(5);311-320.

80. Serra-Blasco M, Portella MJ, Gomez-Anson B, et al. Effects of illness duration and treatment resistance on gray matter abnormalities in major depression. *Br J Psychiatry.* 2013;202:434-440.

81. Shad MU, Muddasani S, Rao U. Gray Matter Differences Between Healthy and Depressed Adolescents: A Voxel-Based Morphometry Study. *J Child Adolesc Psychopharmacol.* 2012;22(3);190-197.
82. Shah PJ, Ebmeier KP, Glabus MF, Goodwin GM. Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression. Controlled magnetic resonance imaging study. *Br J Psychiatry.* 1998;172:527-532.
83. Soriano-Mas C, Hernandez-Ribas R, Pujol J, et al. Cross-sectional and longitudinal assessment of structural brain alterations in melancholic depression. *Biol Psychiatry.* 2011;69(4):318-325.
84. Stratmann M, Konrad C, Kugel H, et al. Insular and hippocampal gray matter volume reductions in patients with major depressive disorder. *PLoS One.* 2014;9(7):e102692.
85. Tang Y, Wang F, Xie G, et al. Reduced ventral anterior cingulate and amygdala volumes in medication-naïve females with major depressive disorder: A voxel-based morphometric magnetic resonance imaging study. *Psychiatry Research: Neuroimaging.* 2007;156(1):83-86.
86. van Eijndhoven P, van Wingen G, Katzenbauer M, et al. Paralimbic cortical thickness in first-episode depression: evidence for trait-related differences in mood regulation. *Am J Psychiatry.* 2013;170(12):1477-1486.
87. van Tol MJ, van der Wee NJ, van den Heuvel OA, et al. Regional brain volume in depression and anxiety disorders. *Arch Gen Psychiatry.* 2010;67(20):1002-1011.
88. van Tol MJ, Li M, Metzger CD, et al. Local cortical thinning links to resting-state disconnectivity in major depressive disorder. *Psychol Med.* 2014;44(10):2053-2065.
89. Vasic N, Walter H, Höse A, Wolf RC. Gray matter reduction associated with psychopathology and cognitive dysfunction in unipolar depression: a voxel-based morphometry study. *J Affect Disord.* 2008;109(1-2):107-116.
90. Wagner G, Koch K, Schachtzabel C, Schultz CC, Sauer H, Schlösser RG. Structural brain alterations in patients with major depressive disorder and high risk for suicide: evidence for a distinct neurobiological entity? *Neuroimage.* 2011;54(2):1607-1614.
91. Zhang X, Yao S, Zhu X, Wang x, Zhu X, Zhong M. Gray matter volume abnormalities in individuals with cognitive vulnerability to depression: A voxel-based morphometry study. *J Affect Disord.* 2012;136(3):443-452.
92. Zou K, Deng W, Li T, et al. Changes of brain morphometry in first-episode, drug-naïve, non-late-life adult patients with major depression: an optimized voxel-based morphometry study. *Biol Psychiatry.* 2010;67(2):186-188.