Data supplement for Zhukovsky et al., Coordinate-Based Network Mapping of Brain Structure in Major Depressive Disorder in Younger and Older Adults: A Systematic Review and Meta-Analysis. Am J Psychiatry (doi: 10.1176/appi.ajp.2021.21010088)

CONTENTS

1. METHODS

1.1. Search Strategy

In separate searches of the PubMed database and the Web Of Science database covering publications in PubMed, MEDLINE, and Web of Science databases up until 27 October 2020, we screened for studies of cortical thickness or voxel-based morphometry differences in late-life depression and major depressive disorder. We did not restrict our search by date and screened the relevant articles to identify additional records. We used a regular search alongside MESH term searches in PubMed and also generated a data-driven set of search terms using the *litsearchr* package in RStudio (2). The precise search terms and dates are available in the Supplementary Information and more information on the meta-analytic protocol is available on Prospero (pre-registration ID: CRD42020187718). We also screened the references of pertinent review articles to identify studies that were potentially missed in the full search. Only articles in English were included.

1.2. Inclusion and Exclusion Criteria

We included studies that conducted a whole-brain analysis of structural differences between patients with a depression diagnosis (these were usually based on the Diagnostic Statistical Manual (DSM) or International Classification of Disorders (ICD) guidelines) and healthy controls using voxel-based-morphometry or surface-based analysis.

We focused on studies of MDD in adults aged 18 to 55 years old and on studies of late-life depression in elderly aged 55+ years old. In the studies analysed here, all but two LLD studies included participants who were on average over 60 years old. We include two late-life depression studies with an average age of 57 and 59 years since a reanalysis showed that exclusion of these studies from the LLD group did not impact the findings (Supplementary Information). One study (Yuan *et al*., 2008) was conducted in remitted LLD, but since depression episodes were relatively recent as it was a late onset study, this study was included as an exception. Re-analyzing the data without this study did not affect the results. One study (Kumar *et al*., 2014) was focusing on patients with minor depression, but was included since the participants showed moderate HDRS scores (8-14) and pronounced differences in cortical thickness.

Subthreshold depression studies or correlational studies of depressive symptoms were excluded. Quantitative ratings of depression symptoms were extracted from the Hamilton Depression Rating Scale (HDRS (3)), Montgomery Depression Rating Scale (MADRAS;(4)), and Center for Epidemiologic Studies Depression Scale (CES-D, (5)) where these were reported.

We include both medication-naïve and medicated participants. However, studies of patients with comorbid psychiatric conditions (such as panic disorder, psychosis, bipolar or borderline personality disorder) or severe medical conditions (such as stroke, cancer, traumatic brain injury or neurodegenerative diseases) were excluded given that these conditions could independently affect brain structure. Overall quality of the studies based on the above criteria was assessed using a modified version of the Newcastle-Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), an established measure of study quality in meta-analyses (6). The Newcastle-Ottawa scale is the standard tool to assess quality of observational studies in systematic reviews and meta-analyses (7). It is also

recommended by the Cochrane Collaboration, as reported in the Cochrane Handbook, Chapter 13.5.2.3 (8), because the Newcastle-Ottawa scale contains only eight items and is simpler to apply.

Common methodological exclusion reasons were: 1) focus on regions of interest rather than the whole brain; 2) correlational analyses or lack of a control group; 3) studies that reported no differences between patients and control participants since coordinate-based network mapping currently can not synthesize null-results (9); 4) case reports and reviews or meta-analyses (e.g. ENIGMA-meta-analysis); 5) non grey matter focused studies, e.g. studies of magnetization transfer ratio, single-photon emission computed tomography, positron emission tomography, gyrification and finally 6) studies that reported the results in a way that prevented the extraction of coordinates or a specific region of interest.

1.3. Data extraction

A full list of articles included in this meta-analysis can be found in Table S4. PZ, JA, and GC then extracted relevant information: authors, publication year, sample size, demographics (current age, sex), clinical information (proportion of participants using an antidepressant, depression severity (mild, moderate, or severe, see Supplementary information for precise cut-offs), and age at onset of the first major depressive episode), modality (voxel-based or surface-based morphometry), and the coordinates of significant group differences for all studies that passed the full-text screening. Talairach coordinates were converted to MNI coordinates using an online conversion algorithm (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html) that implements a nonlinear transformation (10). Some studies did not report MNI or Talairach coordinates. Whenever a study included a visualisation of the anatomical location of the difference and the name of the specific region such as “right middle frontal gyrus”, “left hippocampus” or “rostral anterior cingulate cortex”, the Harvard-Oxford atlas was used to threshold the relevant anatomical region (>60) and the resulting region was included in the study-specific seed. This applied to only 23 of 141 studies and exclusion of these studies did not affect the results (Supplementary Information). Several studies were excluded since no region of interest could be reliably determined from the reported data. More information on the extracted demographics can be found in Supplementary Information. The following variables were extracted from the studies:

Average Depression severity (based on HDRS and MADRAS)
Every study was assigned a depression severity rating, and this was computed from the average reported HDRS and MADRS scores. Each depressed group was classified as mild, moderate or severe. The HDRS standard cut-off score: mild depression (8-16); moderate depression (17-23); and severe depression (≥24). The MADRAS standard cut off scores: mild depression (7-19); moderate depression (20-34; and severe depression (>34).

Antidepressant medication
In order to assess the impact of medication on our outcome measures, we computed the proportion of individuals per study who were on an antidepressant. Medication-naïve and medicated depression groups were included (both MDD and LLD). In studies with non medication-naïve participants, the percentage of participants on antidepressants at the time of the MRI scan was recorded. The most commonly reported antidepressant medications included

selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors and tricyclic antidepressants. Among other less commonly reported medication was bupropion, a norepinephrine-dopamine reuptake inhibitor.

Average age
The average age of the MMD groups (and the control groups) was recorded in years.

Sex ratio
The ratio of females to total number of participants was recorded for each study and included as a covariate in downstream analysis.

Early vs late onset LLD
Late life depression studies were classified as either early onset, mixed or late onset. Five late onset studies reported age of onset of depression (average of 69 years), while two studies reported only including participants with age of onset greater than 50 (11) and 60 (12), respectively. Finally, another study classified as late onset (13) indicated that most depressed participants (12 of 16 patients) were never treated with antidepressants before. Two early onset studies reported the average onset age at 35 years of age. Mixed studies reported either a large range (20-60 years of age) in the age of onset or a proportion of patients with early and late onset.

Years since onset of depression in MDD
We used a continuous classification to determine years since onset of depression. In a case where 'years since onset of depression' was not reported, the average age was subtracted from the average age of depressive disorder onset.

MMSE/MOCA score
The average Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) scores were recorded for participants from the LLD studies. All LLD studies reached the threshold for normal cognition (average score of 24 and 26 respectively). That is, we did not include studies where a comorbid diagnosis of mild cognitive impairment or Alzheimer's might be determined.

1.4.Search terms

Several searches were conducted to retrieve all relevant articles. The search terms and dates are summarized in Table S1. Articles reporting results from multivariate analyses such as support vector machines were also excluded to ensure consistency in the underlying univariate analyses of VBM and cortical thickness.

TABLE S1A. Details of initial literature searches conducted as part of the systematic meta-analysis

Date of Search	Search Terms	Database	Number of Articles Retrieved	Duplicates detected	Type of Search
26/02/2020	((((((geriatric OR elder OR elderly OR late-life OR old age OR old OR early-onset OR late-onset OR older))) AND (major depressive disorder OR depressive OR depressed OR depression))) AND (voxel-based morphometry OR voxel-based OR morphometry OR VBM))	PubMed	493	1	Fixed terms
09/03/2020	(((((((((geriatric) OR elder) OR elderly) OR old age) OR old) OR early-onset) OR late-onset) OR older) OR late-life) AND ((((major depressive disorder) OR depressive) OR depressed) OR depression) AND ((((voxel-based morphometry) OR voxel-based) OR VBM) OR cortical thickness)	PubMed	9	394	Fixed terms
09/03/2020	(((((((((geriatric) OR elder) OR elderly) OR old age) OR old) OR early-onset) OR late-onset) OR older) OR late-life) AND ((((major depressive disorder) OR depressive) OR depressed) OR depression) AND ((((voxel-based morphometry) OR voxel-based) OR VBM) OR cortical thickness)	PubMed	214	421	Fixed terms
27/04/2020	((((major depressive disorder) OR depressive) OR depressed) OR depression) AND ((((voxel-based morphometry) OR voxel-based) OR VBM) OR cortical thickness)	PubMed	489	636	Fixed terms
12/05/2020	((((major depressive disorder) OR depressive) OR depressed) OR depression) AND ((((voxel-based morphometry) OR voxel-based) OR VBM) OR cortical thickness)	Web of Science (all databases)	1,219	1035	Fixed terms
13/05/2020	(("voxel-bas* morphometri*" OR "cortic* region*" OR "cortic* thick*" OR "brain* structur*" OR "brain* volum*" OR "structur* brain* network*" OR "structur* covari* network*" OR "cerebellar* volum*" OR "cortic* thin*" OR "cortic* volum*" OR "high-resolut* structur*" OR "surface-bas* morphometri*" OR "structur* differ*" OR "volum* differ*" OR "cortic* surfac*" OR "structur* brain* correl*" OR "volum* increas*" OR "brain* morpholog*" OR "cortic* morpholog*" OR "brain* morphometri*" OR "comput* anatomi* toolbox*" OR "t1-weight* structur* magnet* reson* imag*" OR "cortic* gyrif*" OR "volum* reduct*" OR "volumetr* reduct*" OR "multi-mod* magnet* reson* imag*" OR "brain* structur* integr*" OR "voxel-bas* lesion-symptom* mapping" OR "gray-matt* volum*" OR "voxel* base* morphometri*" OR "smaller* hippocamp* volum*" OR "subcort* pattern*" OR "hippocamp* subfield* volum*" OR "matter* volum* chang*" OR "grey-matt* volum*" OR "reduc* hippocamp* volum*" OR "brain* atrophi*") AND ("depress* patient*" OR "major* depress*" OR "unipolar* depress*" OR "cognit* behavior* therapi*" OR "major* depress* disord*" OR "depress* compar*" OR "sever* depress*" OR "depress* suicid* attempt*" OR "hamilton* rate* scale*" OR "hamilton* depress* rate* scale*" OR "clinic* depress*" OR "antidepress* treatment*" OR "comorbid* depress*" OR "depress* inventori*" OR "depress* sever*" OR "depress* symptom*" OR "first-episod* medication-na* unipolar*" OR "first-episod* unipolar*") AND ("control* group*" OR "treatment* effect*" OR "treatment* group*" OR "match* control*" OR "patient* compar*"))	Web of Science (all databases)	200	90	litsearchr-generated terms
14/05/2020	(("late life depression") AND ("voxel based morphometry" OR "cortical thickness"))	PubMed	0	23	MESH-terms
14/05/2020	(("major depression") AND ("voxel based morphometry" OR "cortical thickness"))	PubMed	0	102	MESH-terms

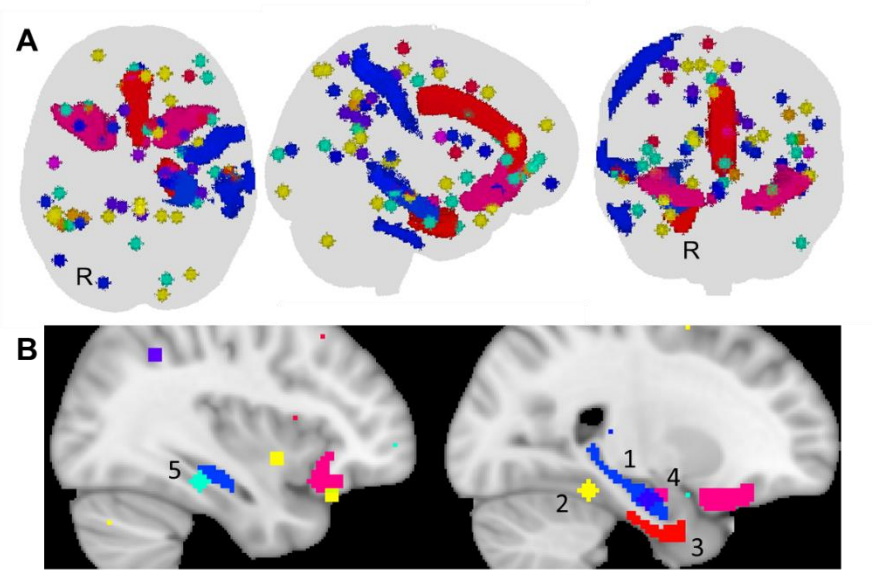
TABLE S1B. Details of updated literature searches conducted as part of the systematic meta-analysis

27/10/2020	((((((geriatric OR elder OR elderly OR late-life OR old age OR old OR early-onset OR late-onset OR older))) AND (major depressive disorder OR depressive OR depressed OR depression))) AND (voxel-based morphometry OR voxel-based OR morphometry OR VBM))	PubMed	67	1,785	Fixed terms
27/10/2020	(((((((((geriatric) OR elder) OR elderly) OR old age) OR old) OR early-onset) OR late-onset) OR older) OR late-life) AND ((((major depressive disorder) OR depressive) OR depressed) OR depression) AND ((((voxel-based morphometry) OR voxel-based) OR VBM) OR cortical thickness)	PubMed	6	274	Fixed terms
27/10/2020	(((((((((geriatric) OR elder) OR elderly) OR old age) OR old) OR early-onset) OR late-onset) OR older) OR late-life) AND ((((major depressive disorder) OR depressive) OR depressed) OR depression) AND ((((voxel-based morphometry) OR voxel-based) OR VBM) OR cortical thickness)	PubMed	8	487	Fixed terms
27/10/2020	((((major depressive disorder) OR depressive) OR depressed) OR depression) AND ((((voxel-based morphometry) OR voxel-based) OR VBM) OR cortical thickness)	PubMed	13	649	Fixed terms
27/10/2020	((((major depressive disorder) OR depressive) OR depressed) OR depression) AND ((((voxel-based morphometry) OR voxel-based) OR VBM) OR cortical thickness)	Web of Science (all databases)	76	1,141	Fixed terms
27/10/2020	(("voxel-bas* morphometri*" OR "cortic* region*" OR "cortic* thick*" OR "brain* structur*" OR "brain* volum*" OR "structur* brain* network*" OR "structur* covari* network*" OR "cerebellar* volum*" OR "cortic* thin*" OR "cortic* volum*" OR "high-resolut* structur*" OR "surface-bas* morphometri*" OR "structur* differ*" OR "volum* differ*" OR "cortic* surfac*" OR "structur* brain* correl*" OR "volum* increas*" OR "brain* morpholog*" OR "cortic* morpholog*" OR "brain* morphometri*" OR "comput* anatomi* toolbox*" OR "t1-weight* structur* magnet* reson* imag*" OR "cortic* gyrif*" OR "volum* reduct*" OR "volumetr* reduct*" OR "multi-mod* magnet* reson* imag*" OR "brain* structur* integr*" OR "voxel-bas* lesion-symptom* mapping" OR "gray-matt* volum*" OR "voxel* base* morphometri*" OR "smaller* hippocamp* volum*" OR "subcort* pattern*" OR "hippocamp* subfield* volum*" OR "matter* volum* chang*" OR "grey-matt* volum*" OR "reduc* hippocamp* volum*" OR "brain* atrophi*") AND ("depress* patient*" OR "major* depress*" OR "unipolar* depress*" OR "cognit* behavior* therapi*" OR "major* depress* disord*" OR "depress* compar*" OR "sever* depress*" OR "depress* suicid* attempt*" OR "hamilton* rate* scale*" OR "hamilton* depress* rate* scale*" OR "clinic* depress*" OR "antidepress* treatment*" OR "comorbid* depress*" OR "depress* inventori*" OR "depress* sever*" OR "depress* symptom*" OR "first-episod* medication-na* unipolar*" OR "first-episod* unipolar*") AND ("control* group*" OR "treatment* effect*" OR "treatment* group*" OR "match* control*" OR "patient* compar*"))	Web of Science (all databases)	0	662	litsearchr-generated terms
27/10/2020	(("late life depression") AND ("voxel based morphometry" OR "cortical thickness"))	PubMed	0	25	MESH-terms
27/10/2020	(("major depression") AND ("voxel based morphometry" OR "cortical thickness"))	PubMed	0	108	MESH-terms

1.5. Coordinate-based network mapping methods

To illustrate the methodology underlying coordinate-based network mapping, Figure S1 shows seeds derived for each of the 17 LLD studies.

FIGURE S1. Study-specific seeds for 17 LLD studies. Whole-brain view (A) and a more detailed view of the hippocampus (B). Five studies specified significant differences in a region of interest such as the hippocampus, or OFC, while the remaining 12 studies reported coordinates of significant differences.



These seed maps were then used in a seed-based analyses of resting-state connectivity and morphometric similarity in unrelated Human Connectome Project (HCP1200) participants. The study-specific connectivity maps derived using the seeds above are shown in Figure S2.

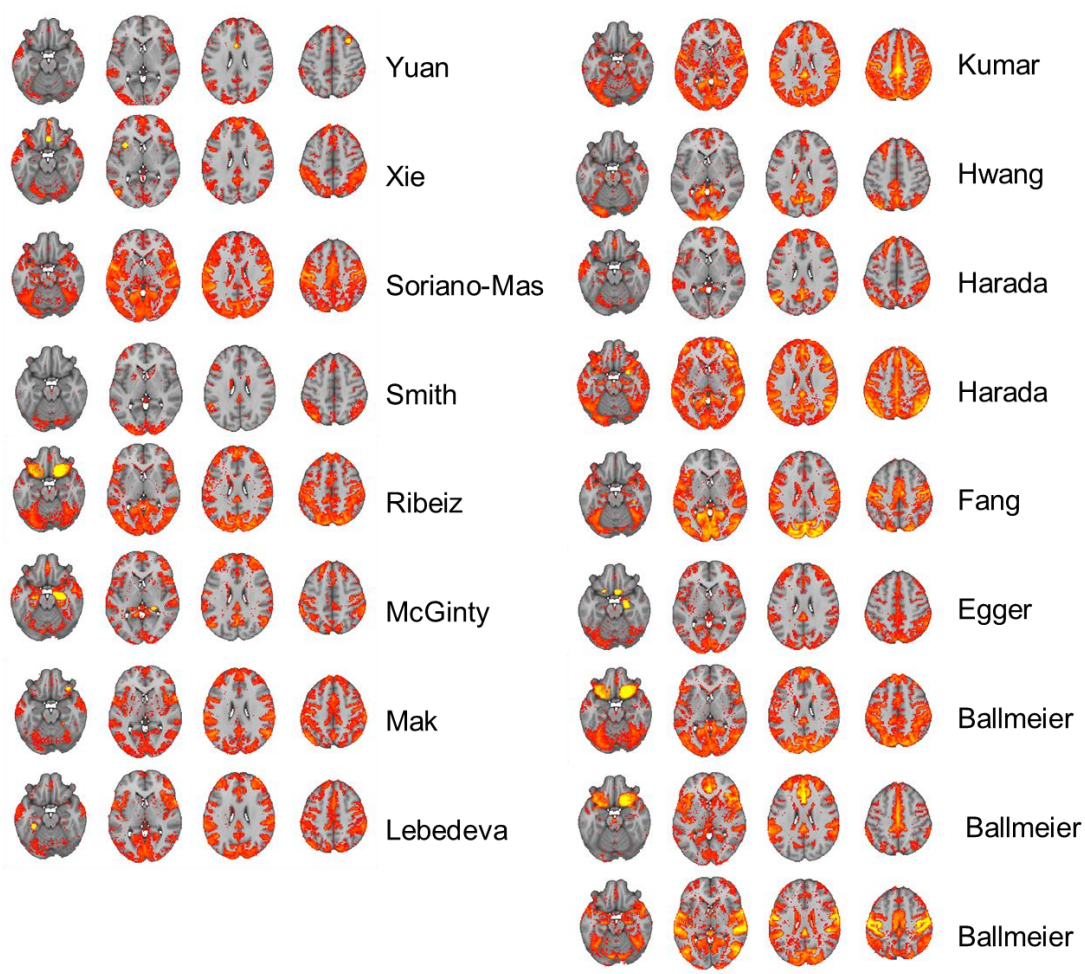
Resting state connectivity analyses were run using the dual regression tool in FSL (14,15). Study-specific network maps were derived by generating group t-statistics for healthy, young participants from HCP1200 and thresholding study-specific t-statistic map at $t > 3$ (voxelwise $p<0.0029$). Notably we did not use any MRI image smoothing which is known to boost correlations. Following previous implementations of coordinate-based network mapping, we used the absolute connectivity maps that were binarized for each study and added together to be able to assess which brain networks are affected in most studies investigating MDD and LLD. For subsequent analyses including demographic and clinical information, t-statistics were converted to z-statistics using AFNI 3dcalc (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dcalc.html). Group mean maps were transformed from voxel space to surface space to obtain the average z-values for each of the Yeo 7 networks (16).

We developed a novel extension to map out networks derived from each study's seed maps using morphometric similarity (17) instead of resting-state connectivity. The morphometric similarity analyses closely followed the resting-state network construction. The two approaches differed in that morphometric similarity networks were built in *fsaverage* surface-space using 360 regions of interest as network nodes (18), while resting state networks were conducted in *MNI152* voxel space, estimating voxelwise rather than ROI-wise correlations. More specifically, Glasser ROIs

with a significant difference were identified for each study to form a study-specific seed map. Some studies reported coordinates located in white matter, likely due to the excessive amount of smoothing applied to the data. In this case, if a cortical grey matter region was found close to the reported coordinate, then that grey matter region was included in the seed map. Subcortical seeds were not included since morphometric similarity relies on cortical curvature and folding information that is not applicable to subcortical ROIs.

More specifically, 7 regional metrics (gray matter volume, surface area, cortical thickness, intrinsic (Gaussian) curvature; mean curvature, curved index, folding index) were estimated using Freesurfer and ROI-to-ROI correlation between these metrics was computed for each HCP1200 participant. An average of these 7 regional metrics was calculated for the regions included in the study-specific seed map and this morphometric similarity seed was then correlated with each of the 360 Glasser ROIs to produce a subject-specific morphometric similarity network for each HCP1200 participant. For each study, Z-maps were computed based on all 428 participants' seed connectivity maps. Absolute connectivity maps were thresholded at $z>1.96$ ($p<0.05$) and binarized for each study and added together to assess which brain networks are affected in most studies investigating MDD and LLD. Non-thresholded Z-scores were used for subsequent analyses including demographic and clinical information. Average z-values were then analysed in a mixed effect ANOVA using a "between" factor of group (LLD, MDD) and a "within" factor of Yeo network as well as a "within" factor of modality (resting state, morphometric similarity, Figure 2, Table S3).

FIGURE S2. Study-specific network maps for 17 LLD studies derived using resting-state connectivity.



2. RESULTS

2.1. ALE group mean maps

Twelve late-life depression (754 subjects, 51 unique foci) studies, and 107 major-depression (11,008 subjects, 760 unique foci) studies were included in the first and second ALE analysis, respectively. Some studies did not report any coordinates since they focused on anatomical regions of interest and were thus not suitable for the ALE approach.

ALE analyses identified two significant clusters in MDD studies, involving the medial prefrontal cortex and bilateral temporal lobes (see Figure S3A and Table S2A). A single significant cluster was identified for the LLD studies involving the medial frontal cortex Figure S3B). To illustrate trend results, uncorrected z-scores from the ALE meta-analysis were thresholded at z>2 and presented with the significant clusters (in green). More details about which regions contributed to this pattern can be found in Table S2B. Finally, a contrast analysis (Figure S3C) was used to evaluate the uniqueness of the affected areas. Regions common to both LLD and MDD were the bilateral anterior cingulate gyrus and the right subcallosal gyrus. In contrast, LLD was more associated with regions just anterior to this in the bilateral medial frontal gyrus, superior frontal gyrus, and the anterior cingulate cortex. There were no regions where MDD was associated with a higher likelihood than LLD (for more details, see Table S2C).

FIGURE S3. Activation likelihood estimation results. In green are clusters that survived family-wise error correction (PFWE<0.05), and in red are shown the uncorrected z-scores thresholded at z>2. Panel A) shows ALE results for MDD studies, panel B) shows results for LLD studies, and panel C) shows the results of the contrast analysis.

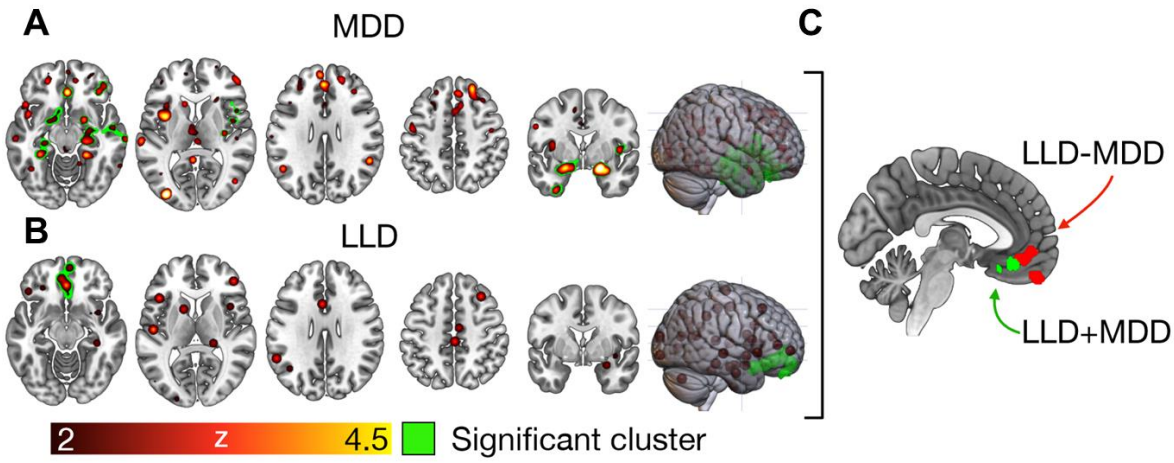


TABLE S2A. Significant clusters identified for MDD studies using ALE meta-analysis. X, Y, Z: MNI X,Y,Z, coordinates; ALE: Activation likelihood estimation probability; PFWE: familywise-error corrected p-value; BA: Brodmann Area.

Cluster	X	Y	Z	Z-score	ALE	P_{FWE}	Hemisphere	Gray matter region	BA
1	20	0	-18	5.2	0.04	8.40E-08	Right	Parahippocampal Gyrus	34
1	26	22	-24	4.8	0.03	8.01E-07	Right	Inferior Frontal Gyrus	47
1	36	22	-4	4.2	0.03	1.53E-05	Right	Insula	
1	14	-6	-26	3.9	0.03	5.32E-05	Right	Parahippocampal Gyrus	34
1	48	10	2	3.8	0.02	7.10E-05	Right	Precentral Gyrus	44
1	36	-20	-28	3.7	0.02	9.13E-05	Right	Parahippocampal Gyrus	36
1	44	40	-16	3.7	0.02	1.21E-04	Right	Middle Frontal Gyrus	47
1	24	-24	-14	3.6	0.02	1.57E-04	Right	Parahippocampal Gyrus	35
1	48	-6	-6	3.4	0.02	3.20E-04	Right	Insula	13
1	38	34	-12	3.2	0.02	8.13E-04	Right	Inferior Frontal Gyrus	47
1	30	18	-40	3.1	0.02	9.99E-04	Right	Superior Temporal Gyrus	38
1	42	0	4	3.1	0.02	0.001003205	Right	Claustrum	
1	70	-22	-14	3.0	0.02	0.001226654	Right	Middle Temporal Gyrus	21
1	20	14	-34	3.0	0.02	0.001425992	Right	Inferior Frontal Gyrus	47
1	34	-14	6	3.0	0.02	0.001457851	Right	Putamen	
1	34	28	-22	2.8	0.02	0.00232136	Right	Inferior Frontal Gyrus	47
1	56	-16	-6	2.8	0.02	0.002697906	Right	Superior Temporal Gyrus	22
1	54	-8	-22	2.3	0.01	0.010594586	Right	Middle Temporal Gyrus	21
1	60	-24	-6	2.1	0.01	0.017787304	Right	Superior Temporal Gyrus	21
1	42	22	12	2.1	0.01	0.019114463	Right	Insula	13
1	50	14	18	2.0	0.01	0.020386685	Right	Inferior Frontal Gyrus	9
1	44	-12	-14	2.0	0.01	0.020619739	Right	Sub-Gyral Gray Matter	21
1	36	-10	-2	2.0	0.01	0.021013288	Right	Putamen	
1	48	52	-14	2.0	0.01	0.022843895	Right	Middle Frontal Gyrus	10
1	28	10	-30	2.0	0.01	0.024468813	Right	Superior Temporal Gyrus	38
2	0	34	-14	4.5	0.03	2.75E-06	Left	Anterior Cingulate	32
2	-22	-2	-18	4.3	0.03	8.72E-06	Left	Parahippocampal Gyrus	34
2	-20	-16	-26	4.2	0.03	1.14E-05	Left	Parahippocampal Gyrus	28
2	-32	-40	-10	3.8	0.02	6.18E-05	Left	Parahippocampal Gyrus	37
2	2	32	2	3.7	0.02	1.03E-04	Left	Anterior Cingulate	24
2	6	18	-26	3.6	0.02	1.41E-04	Right	Medial Frontal Gyrus	25
2	-32	0	-44	3.3	0.02	5.76E-04	Left	Uncus	20
2	-2	36	-24	3.2	0.02	7.02E-04	Left	Medial Frontal Gyrus	11
2	-30	-18	-18	3.1	0.02	0.001072651	Left	Hippocampus	
2	-4	20	-20	3.0	0.02	0.00131098	Left	Sub-Gyral Gray Matter	25
2	-36	-14	-32	3.0	0.02	0.001419705	Left	Uncus	20

2	-24	-28	-20	2.9	0.02	0.001826203	Left	Parahippocampal Gyrus	35
2	-10	10	-8	2.6	0.02	0.004113356	Left	Caudate Head	
2	-26	-26	-12	2.6	0.01	0.005198211	Left	Parahippocampal Gyrus	28
2	-10	24	-4	2.3	0.01	0.010433223	Left	Caudate Head	
2	8	32	-26	2.2	0.01	0.012782307	Right	Medial Frontal Gyrus	11
2	-6	0	-8	1.8	0.01	0.035651743	Left	Lentiform Nucleus	

TABLE S2B. Significant clusters identified for LLD studies using ALE meta-analysis. X, Y, Z: MNI X,Y,Z, coordinates; ALE: Activation likelihood estimation probability; PFWE: familywise-error corrected p-value; BA: Brodmann Area.

Cluster	x	y	z	Z	ALE	P_{FWE}	Hemisphere	Gray matter region	BA
1	2	26	-18	3.71	0.01	1.05E-04	Right	Medial Frontal Gyrus	11
1	4	58	-16	3.66	0.01	1.24E-04	Right	Medial Frontal Gyrus	10
1	-2	52	-4	3.63	0.01	1.40E-04	Left	Anterior Cingulate	32
1	0	38	-12	3.60	0.01	1.56E-04	Left	Anterior Cingulate	32
1	-6	46	-8	3.40	0.01	3.41E-04	Left	Anterior Cingulate	32
1	-4	52	-28	3.23	0.01	6.14E-04	Left	Medial Frontal Gyrus	11
1	6	14	-20	3.16	0.01	7.88E-04	Right	Subcallosal Gyrus	25

TABLE S2C. Significant clusters identified for Contrast between LLD and MDD studies using ALE meta-analysis. X, Y, Z: MNI X,Y,Z, coordinates; ALE: Activation likelihood estimation probability; P_{FWE}: familywise-error corrected p-value; BA: Brodmann Area.

Contrast	Cluster	x	y	z	Z	ALE	P_{FWE}	Hemisphere	Gray Matter Region	BA
LLD - MDD	1	-6	40	-12	2.65	NA	0.004	Left	Anterior Cingulate	32
LLD - MDD	1	-2	42	-12	2.58	NA	0.005	Left	Anterior Cingulate	32
LLD - MDD	1	-2	40	-8	2.46	NA	0.007	Left	Anterior Cingulate	24
LLD - MDD	1	-2	48	-4	2.26	NA	0.012	Left	Anterior Cingulate	32
LLD - MDD	1	-2	49	-8	2.23	NA	0.013	Left	Anterior Cingulate	32
LLD - MDD	1	4	58	-2	1.76	NA	0.039	Right	Medial Frontal Gyrus	10
LLD - MDD	2	0	52	-22	2.33	NA	0.01	Left	Medial Frontal Gyrus	10
LLD - MDD	2	-3	57	-25	2.17	NA	0.015	Left	Medial Frontal Gyrus	11
LLD - MDD	2	2	52	-28	1.98	NA	0.024	Right	Medial Frontal Gyrus	11
LLD - MDD	2	4	62	-14	1.93	NA	0.027	Right	Medial Frontal Gyrus	10
LLD - MDD	2	4	58	-20	1.81	NA	0.035	Right	Medial Frontal Gyrus	10
LLD - MDD	2	8	60	-14	1.7	NA	0.045	Right	Medial Frontal Gyrus	10
LLD - MDD	3	6	22	-16	1.88	NA	0.03	Right	Anterior Cingulate	32
LLD - MDD	3	2	26	-14	1.8	NA	0.036	Right	Anterior Cingulate	24
LLD + MDD	1	0	38	-12		0.0101	NA	Left	Anterior Cingulate	32
LLD + MDD	1	6	14	-20		0.0088	NA	Right	Subcallosal Gyrus	25

LLD + MDD	1	2	28	-16	0.0079	NA	Right	Anterior Cingulate	24
LLD + MDD	1	0	24	-18	0.0077	NA	Left	Anterior Cingulate	32

2.2. Robustness analyses

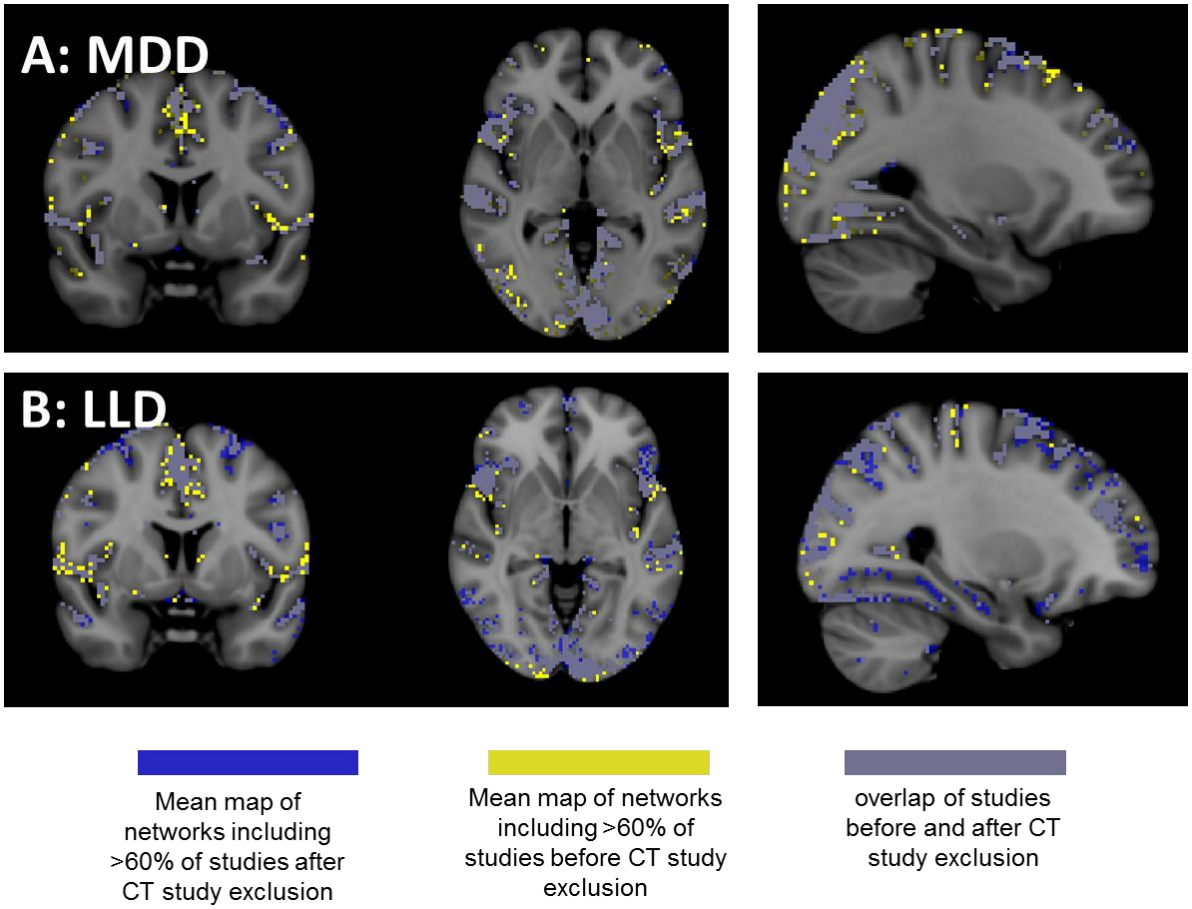
We reanalysed the data three times: firstly, excluding one LLD study of remitted geriatric depression patients; secondly, excluding two LLD studies of participants 57 and 59 years old, respectively; thirdly, excluding five LLD studies and 21 MDD studies that reported their results in regions of interest rather than in coordinates. The cut-off score for LLD is somewhat arbitrary and is often considered to be 60 years of age (19,20). In the main text we provide the most inclusive analysis (whereby we include two studies of patients with late-life depression with a mean age of 56 and 59 years), but also present the results of a more stringent reanalysis (studies with average age greater than 60 years) here. Briefly, the results of the main analysis replicated in all of the re-analyses as shown in the summary of three-way ANOVA results in in Table S3.

TABLE S3. ANOVA results from the analysis of the full sample and three additional reanalyses. When the sphericity assumption was violated (assessed by the presence of a significant Mauchly's test result), we used Greenhouse-Geisser correction to the degrees of freedom of the mixed-effect ANOVA, which reduces the degrees of freedom to correct for the lack of sphericity. SPSS v25 was used for these comparisons.

Main Effects						**2-Way Interactions**						**3-Way Interaction**	
Analysis of the full sample													
Group (LLD vs MDD)		Network (Yeo 7)		Modality		Group by Network		Group by Modality		Modality by Network		Group by Modality by Network	
$F_{1,143}$=0.3	p=.85	$F_{3,430}$=42.8	p<.001	$F_{1,143}$=4.7	p=.03	$F_{3,430}$=0.4	p=.75	$F_{1,143}$=1.0	p=.32	$F_{3,426}$=2.3	p=.08	$F_{3,426}$=1.2	p=.29
Group (Late- vs Mixed-onset LLD)		Network (Yeo 7)		Modality		Group by Network		Group by Modality		Modality by Network		Group by Modality by Network	
$F_{1,15}$=1.2	p=.30	$F_{2.5,38}$=14.9	p<.001	$F_{1,15}$=0.1	p=.75	$F_{2.5,38}$=1.8	p=.16	$F_{1,15}$=4.9	p=.04	$F_{2.7,40}$=1.0	p=.39	$F_{2.7,40}$=1.2	p=.33
Reanalysis excluding Yuan et al (remitted LLD)													
Group (LLD vs MDD)		Network (Yeo 7)		Modality		Group by Network		Group by Modality		Modality by Network		Group by Modality by Network	
$F_{1,142}$=0.29	p=.59	$F_{3,426}$=41.8	p<.001	$F_{1,142}$=4.6	p=.03	$F_{3,426}$=0.4	p=.77	$F_{1,142}$=0.9	p=.35	$F_{3,422}$=2.2	p=.09	$F_{3,422}$=1.2	p=.29
Group (Late- vs Mixed-onset LLD)		Network (Yeo 7)		Modality		Group by Network		Group by Modality		Modality by Network		Group by Modality by Network	
$F_{1,14}$=3.2	p=.09	$F_{2.6,36}$=15.8	p<.001	$F_{1,14}$=0.03	p=.88	$F_{2.6,36}$=2.4	p=.09	$F_{1,14}$=4.8	p=.04	$F_{2.6,37}$=1.2	p=.32	$F_{2.6,37}$=1.4	p=.27
Reanalysis excluding Fang et la 2015 and Harada et al 2018 with strict age inclusion criteria (>60 years old) for LLD													
Group (LLD vs MDD)		Network (Yeo 7)		Modality		Group by Network		Group by Modality		Modality by Network		Group by Modality by Network	
$F_{1,141}$=0.01	p=.91	$F_{3,429}$=36.4	p<.001	$F_{1,141}$=5.5	p=.02	$F_{3,429}$=0.6	p=.60	$F_{1,141}$=0.42	p=.52	$F_{3,424}$=1.9	p=.12	$F_{3,424}$=1.0	p=.40
Group (Late- vs Mixed-onset LLD)		Network (Yeo 7)		Modality		Group by Network		Group by Modality		Modality by Network		Group by Modality by Network	
$F_{1,13}$=0.2	p=.65	$F_{2.6,33}$=12.3	p<.001	$F_{1,13}$=0.3	p=.59	$F_{2.6,33}$=0.6	p=.57	$F_{1,13}$=4.7	p=.04	$F_{2.9,38}$=0.6	p=.62	$F_{2.9,38}$=0.8	p=.49
Reanalysis excluding studies that reported results as ROIs instead of coordinates													
Group (LLD vs MDD)		Network (Yeo 7)		Modality		Group by Network		Group by Modality		Modality by Network		Group by Modality by Network	
$F_{1,117}$=0.08	p=.77	$F_{2.9,334}$=33.2	p<.001	$F_{1,117}$=1.1	p=.30	$F_{2.9,334}$=0.4	p=.73	$F_{1,117}$=0.9	p=.33	$F_{2.9,338}$=1.7	p=.17	$F_{2.9,338}$=0.8	p=.47
Group (Late- vs Mixed-onset LLD)		Network (Yeo 7)		Modality		Group by Network		Group by Modality		Modality by Network		Group by Modality by Network	
$F_{1,10}$=0.8	p=.38	$F_{2.3,23}$=11.5	p<.001	$F_{1,10}$=0.01	p=.96	$F_{2.3,23}$=1.2	p=.34	$F_{1,10}$=6.1	p=.03	$F_{2.2,22}$=0.3	p=.74	$F_{2.2,22}$=0.9	p=.44

We also re-created the group mean maps for LLD and MDD before and after the inclusion of cortical thickness studies. As shown in Figure S3, these maps were very similar to each other. No striatal voxels and only very few hippocampal voxels were shared in LLD and in MDD regardless of the cortical thickness study inclusion. This is likely due to the connectivity profiles from the resting state functional and morphometric similarity analyses.

FIGURE S3. Group mean maps for MDD (A) and LLD (B) before and after exclusion of cortical thickness studies. 128 MDD studies before and 91 MDD studies after the exclusion of cortical thickness studies were combined to create group mean maps in (A). 17 LLD studies before and 11 LLD studies after the exclusion of cortical thickness studies were combined to create group mean maps in (B). CT: cortical thickness



2.3 Sensitivity analysis

To assess the stability of the antidepressant effects on networks derived using resting state network mapping, we reanalysed a subset of studies comprising only first episode MDD in younger adults (5 studies of first-episode MDD patients taking antidepressants and 29 studies of unmedicated first episode MDD). Using multiple comparison correction ($P_{FDR} < 0.05$, *mafdr* function in MATLAB R2016a), no significant associations with antidepressant medication were detected (using *fitlm* function in MATLAB R2016a). However, when the threshold was relaxed to $P_{UNCORRECTED} < 0.05$, some of the results reported in the main analysis were replicated, with the ACC (left BA32, $t_{1,27}=2.14$, $P_{UNCORRECTED}=0.04$) showing greater involvement in medicated studies (Figure S4). No regions showed greater involvement in unmedicated studies compared with studies of patients on antidepressants even at the uncorrected thresholding level. Compared to the main analysis, notable overlap was found in the anterior cingulate (BA32). Occipito-temporal associations with lower proportion of medicated participants did not replicate in this sensitivity analysis of first episode MDD, possibly due to the lower number of studies available.

FIGURE S4. First-episode major depressive disorder (MDD) studies with more participants did not differ in their age (A). They showed more involvement of ACC and frontal operculum (FOP) highlighted in red (B) at $P_{UNCORRECTED}<0.05$ level. BA: Brodmann Area

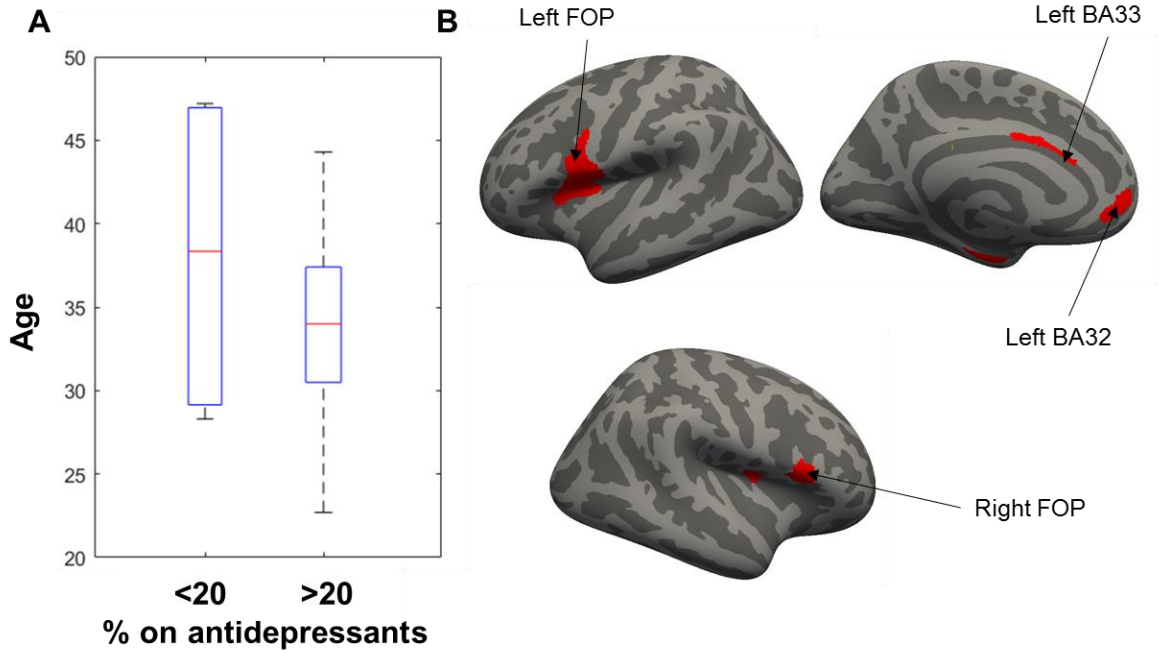


TABLE S4. Complete list of studies

Study MRI-ID	Study Reference-ID
1. Abe	(21)
2. Ahdidan	(22)
3. Ahn	(23)
4. Arnone	(24)
5. Ballmeier	(25)
6. Ballmeier04b	(26)
7. Ballmeier04c	(27)
8. Bergouignan	(28)
9. Cai	(29)
10. Camilleri	(30)
11. Canu	(31)
12. Chaney	(32)
13. Chen15	(33)
14. Chen16	(34)
15. Chen16a	(35)
16. Chen18	(36)
17. Chen20	(37)
18. Cheng20	(38)
19. Cheng	(39)
20. Cui20	(40)
21. Dannlowski	(41)
22. Depping	(42)
23. Egger	(12)
24. Eindhoven13	(43)
25. Fang15	(44)
26. Frodl08	(45)
27. Fung15	(46)
28. Gong19	(47)
29. Grieve	(48)
30. Guo	(49)
31. Han	(50)
32. Han20	(51)
33. Harada16	(52)
34. Harada18	(53)
35. Hellewell	(54)
36. HellewellRep	(54)
37. Hwang	(11)
38. Inkster	(55)
39. Jarnum	(56)
40. Jiang	(57)
41. Johnston15	(58)
42. Jung	(59)
43. Kakeda	(60)
44. Kandarilova	(61)
45. Katsuki19	(62)
46. Kim	(63)
47. Kong13	(64)
48. Kong14	(65)
49. Kumar	(66)
50. Lai	(67)
51. Lai14	(68)
52. Lai15	(69)
53. Lai16	(70)
54. Lan	(71)
55. Lebedeva15	(72)
56. Lee11	(73)
57. Lee20	(74)
58. Lener16	(75)
59. Leung	(76)
60. Li	(77)
61. Li19	(78)
62. Liao13	(79)
63. Liu	(80)
64. Liu20	(81)
65. Lu18	(82)
66. Lu19	(83)
67. Ma12	(84)
68. Machino	(85)
69. Maggioni	(86)
70. Mak	(87)
71. Mak09	(88)
72. Matsubara	(89)
73. McGinty	(90)
74. Meng20	(91)
75. Mwangi12	(92)
76. Na14	(93)
77. Na16	(94)
78. Nakano	(95)
79. Nan20	(96)
80. Niu17	(97)
81. Opel	(98)
82. Opel19	(99)
83. Ozalay	(100)
84. Peng	(101)
85. Peng14	(102)

86. Peng15 (103)
87. Perico (104)
88. Qi14 (105)
89. Qiu (106)
90. Qiu16 (107)
91. Radoman19 (108)
92. Ribeiz (109)
93. RodriguezCano (110)
94. Salvadore (111)
95. Sandu (112)\
96. Scheinost (113)
97. Scheuerecker (114)
98. SerraBlasco (115)
99. Shah (116)
100. Shah02 (117)
101. Shen (118)
102. Shen19 (119)
103. Shen20 (120)
104. Smith (13)
105. SorianoMas (121)
106. Spaeti (122)
107. Sprengelmeyer11 (123)
108. Stratmann (124)
109. Suh20 (125)
110. Tae15 (126)
111. Tang (127)
112. Treadway (128)
113. Treadway15 (129)
114. Tu (130)
115. Ueda (131)
116. VanTol (132)
117. VanTol14 (133)
118. Vasic (134)
119. Vasic15 (135)
120. Wagner (136)
121. Wagner07 (137)
122. Watanabe (138)
123. Wolf16 (139)
124. Xie (140)
125. Xiong19 (141)
126. Xu19 (142)
127. Yang15 (143)
128. Yang15a (144)
129. Yang15b (145)
130. Yang17 (146)
131. Yang17a (147)
132. Yang20 (148)
133. Ye17old (149)
134. Ye17young (149)
135. Yuan (1)
136. Zaremba (150)
137. Zhang (151)
138. Zhang19 (152)
139. Zhang20 (153)
140. Zhao17 (154)
141. Zhao17a (155)
142. Zhou18 (156)
143. Zhuo17 (157)
144. Zou (158)
145. Zuo18 (159)

3. Discussion

3.1. Age and sex effects

No age or sex effects were found on study-specific networks. Given that age and sex distributions were relatively heterogeneous within studies, it is likely that meta-regressions at the study level would not be sensitive to age and sex effects if those are present. Ethnicity is crucial demographic variable that was rarely recorded and thus could not be included in this analysis. Future studies need to report more information on ethnic characteristics of their samples in order to assess ethnicity-specific brain structure differences in MDD and LLD.

3.2. Similarities and differences between ALE and network mapping results

While coordinate-based network mapping is able to capture large-scale networks involved in major depression, these networks are more reminiscent of functional connectivity findings (160) and in contrast to traditional ALE methods, network mapping does not capture the medial temporal regions and the striatal nuclei as key loci of structural brain change. Functional connectivity network maps are less likely to include medial temporal lobe and ventral PFC regions due to BOLD signal dropout (161–163) in BOLD imaging.

To illustrate the differences between network mapping and ALE, we propose a synthetic example including four studies, each of which reports a coordinate of case-control differences falling onto the frontoparietal network. Each study reports a coordinate in the anterior left, anterior right, posterior left and posterior right part of the frontoparietal network. ALE would not identify any overlap between these studies since the coordinates not located close to each other. However, coordinate based network mapping leverages the coordinates reported in each study to a connectivity map. Each of these four connectivity maps taps into the frontoparietal network as each of the studies is reporting coordinates in the anterior, posterior, left or right parts of the network. Coordinate-based network mapping is thus able to capture this relationship between studies.

3.3. Similarities and differences between morphometric similarity and functional connectivity network mapping results

Overall, we see highly consistent morphometric similarity and functional connectivity network mapping results for the group mean maps (Figure 2). However, we see some divergence between morphometric similarity and functional connectivity in the secondary analyses. We report differences between early and late onset LLD only using morphometric similarity and we report effects of medication only using functional connectivity. This pattern of results may have several methodological and conceptual explanations.

Methodologically, morphometric similarity and functional connectivity network mapping follow a separate processing and pipeline once the coordinates are extracted. More specifically, we use FSL to create seed maps for functional connectivity analyses from the extracted coordinates and those seeds are then used in a whole-brain voxel-wise correlation analysis. On the other hand, we used manual mapping of the extracted coordinates onto regions of the HCP parcellation, and the resulting seeds are then used to generate whole-cortex similarity maps based on region-wise similarity to the seed. This means that we could not include subcortical coordinates in

morphometric similarity analyses. These nuanced differences in methods may affect our secondary analyses. Nevertheless, the group mean maps were highly consistent despite any methodological differences.

Conceptually, morphometric similarity aims to capture the similarity of cortical folding patterns and other features of cortical morphology between parts of the brain. Resting state connectivity aims to capture the similarity of blood oxygen level-dependent signal variation between parts of the brain. Therefore, patterns of functional connectivity do not necessarily follow patterns of morphometric similarity. A thorough analysis of the relationship between these two network mapping approaches is beyond the scope of this meta-analysis, however. We propose that the effects of late onset depression are more prominent in structural networks, while the effects of medication are more prominent in functional networks, possibly due to the neurobiological characteristics of structural and functional networks.

3.4. Effects of the age of onset of depression on brain structure

To our knowledge, no meta-analyses of the effects of age of onset on brain structure exist to date. Kempton et al (164) investigated the effects of the age at onset in 23 studies of MDD but did not find significant associations between age at onset and hippocampal volume. Individual studies have reported a negative correlation between years since onset of the first episode of depression with the volumes of the hippocampus (90). Early-onset LLD is associated with smaller hippocampal volumes (165,166), while no significant differences between controls and late-onset LLD or late and early onset LLD were found (166).

Late-onset depression has also been associated with reduced prefrontal volumes (167,168), and increased white matter hyperintensities (169). Neuropsychological evidence also shows frontostriatal-mediated executive dysfunction in late-onset LLD and episodic memory deficits in early-onset depression (170), consistent with the neuroimaging findings. These findings have stimulated the hypothesis that a hippocampal stress-mediated pathway underlies early-onset LLD, while frontostriatal abnormalities driven by cerebrovascular disease underlie late-onset depression (171,172).

Our results from network mapping show a greater degree of impairment in attention/salience and frontoparietal networks in late onset compared to early onset LLD. This evidence is consistent with the argument that there is a greater disease burden in late- onset compared to early-onset LLD. We do not report a hippocampal vs frontostriatal dissociation between early and late onset LLD, but this may be due to the connectivity profiles inherent to the coordinate-based network mapping approach, since it appears to be most sensitive to cortical connectivity patterns as discussed in section 3.2 above.

3.5. Effects of medication

Our coordinate-based network mapping approach revealed that studies that included more participants taking antidepressants found greater involvement of rostral ACC, dorsal ACC, and dlPFC regions. Greater volume or thickness in several regions affected in MDD (notably cingulate, medial prefrontal and orbitofrontal cortices as well as dorsolateral prefrontal cortex) are associated with remission after antidepressant treatment (173). Convergent evidence from nonhuman primates also suggests that antidepressants increase anterior cingulate volume in

animal models of depression (174). Similarly, increased hippocampal volumes may modulate the response to antidepressants (173).

Our finding of increased involvement of the ACC and dlPFC in studies of patients taking antidepressants is consistent with two explanatory hypotheses: first, it is possible that these studies are reporting reduced ACC volume due to greater depression severity. Second, it is possible that these studies are reporting greater volumes of the ACC as a result of antidepressant medication. We therefore checked the direction of the case-control differences in each study that included MDD participants on antidepressant medication. Among 47 studies with over 50% of participants taking antidepressants, 30 studies showed a reduction in the prefrontal regions including ACC or dlPFC, while 26 studies showed a reduction in gray matter in other regions and one study (Johnston et al (58)) showed a gray matter increase in the middle frontal gyrus. Therefore, we argue it is plausible that the ACC involvement in medicated studies is due to greater disease burden since those participants are actively depressed despite taking antidepressants. On the other hand, studies of medicated patients reported fewer differences in medial temporal and visual regions compared to studies of unmedicated actively depressed patients. This may be due to beneficial effects of antidepressant medication that is known to increase neurogenesis (175). Antidepressant treatment may therefore protect against gray matter loss in the medial temporal lobe, though this may not be sufficient for remission in absence of beneficial effects on the structural integrity of the prefrontal cortex.

3.6. Methodological considerations and limitations

While this meta-analysis focused on changes in brain structure in MDD in adults and elderly, it will be crucial to extend these findings to resting-state functional connectivity studies (ReHo, ALFF, seed-based connectivity) in the future. Meta-analytic results we obtained using traditional ALE methods are consistent with other meta-analyses of brain structure in depression in identifying the ACC and medial temporal lobes as key loci of structural impairment in depression. Results from the novel coordinate-based network mapping approach provide a more consistent and wholistic picture of the networks affected in adult MDD and LLD. However, it does not implicate striatal and hippocampal regions and thus provides a complimentary way of synthesizing existing literature to traditional ALE methods. Further, a related limitation is our inclusion of both cortical thickness studies that focus exclusively on the cortical mantle as well as VBM studies that focus on all grey matter regions. While this very inclusive approach aimed to synthesize as many findings of cortical structural changes as possible, it is also likely to miss subcortical structural changes.

Although leveraging coordinate-based information obtained from individual studies to study-specific networks achieves greater consistency, it also introduces biases inherent to connectivity profiles such as high connectivity of occipital and parietal areas. We argue it is valuable to employ different approaches to constructing study-specific networks using morphometric similarity and resting-state connectivity since these approaches allow us to detect network differences in groups stratified according to their clinical profiles.

Finally, as in previous meta-analyses of whole-brain structural differences, we only provide a synthesis of significant findings rather since a complete account of non-significant findings, many of which were not published, was not possible. Direction of the case-control differences in

brain structure was also not considered in this meta-analysis to achieve the greatest inclusivity. A separate focus on increases and decreases may provide a more nuanced network mapping for MDD and LLD. Although we conducted a thorough and comprehensive search, the search tools available may not have been sensitive to all relevant studies.

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