TECHNICAL COMMENTARY

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Magnetic resonance imaging

Introduction

The technology of structural magnetic resonance imaging (MRI) is based on the magnetisation properties of cellular protons. The application of a strong magnetic field causes the protons within cells to shift direction, which will return to their original position over time ("precession"). The rate of precession differs across tissue types (such as grey matter and white matter in the brain), which can be interpreted by specialised programs to represent a 3D image.

Studies have focused on individual regions but also whole brain investigations to identify differences between people with bipolar disorder and controls in regional volume or morphometry. For ease of description, the results reported in these studies are referred to as "volume" or "density" changes, though it is recognised that they are not exclusively representing alterations of regional volume.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, only the most recent and comprehensive version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis. Reviews were assigned a low, medium, or high possibility of reporting bias* depending on how many items were checked. Reviews rated as having less than 50% of items checked have now been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[1]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found 16 systematic reviews that met our inclusion criteria[2-17].

Compared to controls

Grey matter decreases

- High quality evidence shows small decreases in hippocampal volume across all subfields in people with bipolar disorder. Moderate quality evidence finds decreases in bilateral insula, superior temporal gyrus,

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superior and ventral medial prefrontal cortex, anterior cingulate cortex, left dorsalmedial prefrontal cortex, left ventrolateral prefrontal cortex, and right precentral gyrus. Moderate to low quality evidence finds decreases in left medial frontal, right inferior frontal, precentral frontal, left inferior longitudinal fasciculus, left insula, superior corona radiate, and the left limbic posterior cingulum.

- Moderate to high quality evidence finds grey matter reductions in bilateral anterior cingulate/paracingulate gyri in first episode mania compared to controls.
- In people with first-episode bipolar disorder, moderate to high quality evidence finds small decreases in whole brain grey matter. In youth with bipolar disorder, moderate quality evidence found decreases in the left orbitofrontal cortex, right claustrum, and right dorsolateral prefrontal cortex.
- In people with bipolar disorder and psychotic symptoms (not necessarily diagnosed with bipolar I disorder), moderate quality evidence finds decreases in bilateral superior frontal gyri, bilateral insula, bilateral median cingulated /paracingulate gyri, left anterior cingulate/paracingulate gyri, and right precentral gyrus (particularly in females). In people diagnosed with bipolar I disorder, decreases were also found in the right superior temporal gyrus, and the rolandic operculum.

Grey matter increases

- Moderate quality evidence finds increases in the cerebellum, bilateral middle frontal gyrus, right middle temporal gyrus, right inferior temporal gyrus, the right middle occipital gyrus, left putamen, and left posterior cingulate cortex. In people diagnosed with bipolar I disorder increases were also found in the left precuneus.
- In relatives of people with bipolar disorder, moderate to high quality evidence finds small increased intracerebral volume, with no differences in the thalamus, striatum, amygdala, hippocampus, pituitary, or frontal lobes compared to controls. Compared to people with bipolar disorder, relatives also show a small increase in grey matter volume.

White matter decreases

- Moderate to high quality evidence finds decreases in white matter volume in people with bipolar disorder in the posterior corpus callosum extending to the posterior cingulate cortex, with smaller reduced clusters in the left optic radiation and right frontal superior longitudinal tracts.
- In people with first-episode bipolar disorder, moderate to high quality evidence finds small decreases in total white matter.

White matter increases

- Moderate to high quality evidence finds small increased clusters of white matter volume in the cerebellum and the right lenticular nucleus.

Ventricular changes

- Moderate to high quality evidence finds small to medium-sized effects of increased volume in the lateral and third ventricles of people with bipolar disorder.
- Moderate to high quality finds a small to medium-sized effect of increased odds of having a cavum septum pellucidum of any size in people with bipolar disorder, with no increased risk of having a large cavum septum pellucidum.

Compared to people with schizophrenia

- Moderate quality evidence finds less grey matter reductions in people with bipolar disorder in the right dorsomedial frontal cortex, and the left dorsolateral prefrontal cortex, with studies balanced for gender. While grey matter reductions were more extensive in male-dominated schizophrenia samples, there was no effect of gender on the findings in bipolar disorder.
- Moderate to high quality evidence shows less reductions in people with bipolar disorder in the amygdala and in hippocampus regions; left cornu ammonis

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(CA)1, left CA2/3, left CA4/dentate gyrus, right presubiculum and right subiculum, with no differences in the left presubiculum or subiculum, or right CA1, CA2/3, or CA4/dentate gyrus.

Compared to people with major depression

- Moderate to low quality evidence finds increased grey matter volume in people with bipolar disorder in the right middle frontal gyrus, left hippocampus, right inferior temporal gyrus, left inferior parietal lobule, and right cerebellar vermis.

Compared to people with borderline personality disorder

- Moderate to low quality evidence finds different grey matter volume and density changes in bipolar disorder and borderline personality disorder. In bipolar disorder, grey matter is reduced in bilateral medial orbital frontal cortex, right insula, and right thalamus, and increased in the right putamen. In borderline personality disorder, grey matter is reduced in bilateral medial prefrontal cortex, bilateral amygdala, and right parahippocampal gyrus.

Medication effects

- Compared to bipolar patients not on lithium treatment, high quality evidence showed bipolar patients on lithium had small increased global grey matter volume. When comparing either group (lithium treated or lithium free) to controls, there were no differences in global grey matter volume. Lithium-treated patients showed fewer hippocampal reductions than patients treated with other medications.

Angelescu I, Brugger SP, Borgan F, Kaar SJ, Howes OD

The magnitude and variability of brain structural alterations in bipolar disorder: A double meta-analysis of 5534 patients and 6651 healthy controls

Journal of Affective Disorders 2021; 291: 171-6

View online review abstract

Comparison	**Brain structural alterations in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds small to medium-sized effects of increased volume in the lateral and third ventricles, and decreased volume in the hippocampus, total brain volume, total grey matter volume, and total white matter volume in bipolar disorder.**
Brain volume	
118 studies, N = 12,185 *Small to medium effects of greater volume in bipolar disorder in;* Lateral ventricle: *g* = -0.43, 95%CI -0.57 to -0.30, *p* = <0.0001 Third ventricle: *g* = -0.22, 95%CI -0.40 to -0.04, *p* = 0.01 *Small to medium effects of lower volume in bipolar disorder in;* Hippocampus: *g* = 0.41, 95%CI 0.14 to 0.66, *p* = 0.001 Total grey matter: *g* = 0.25, 95%CI 0.10 to 0.41, *p* = 0.001 White matter: *g* = 0.23, 95%CI 0.11 to 0.35, *p* = 0.0002 Total brain volume: *g* = 0.20, 95%CI 0.07 to 0.33, *p* = 0.003 A higher proportion of male subjects was associated with decreased mean volumes of the amygdala, hippocampus and thalamus and increased lateral ventricle volumes. There was higher volume variability in bipolar disorder in the amygdala and hippocampus.	
Consistency in results‡	Authors report data are inconsistent
Precision in results§	Precise
Directness of results‖	Direct

Beraldi GH, Prado KS, Amann BL, Radua J, Friedman L, Elkis H

Meta-analyses of cavum septum pellucidum in mood disorders in comparison with healthy controls or schizophrenia

European Neuropsychopharmacology 2018; 28: 1325-1338

View online review abstract

Comparison	**Cavum septum pellucidum in people with bipolar disorder vs. controls.** **Cavum septum pellucidum is defined as a cavity formed when the laminae of the septum pellucidum fail to fuse early in life.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, imprecise, direct) finds a small to medium-sized effect of increased odds of having a cavum septum pellucidum of any size in people with bipolar disorder, although there was no risk of having a large cavum septum pellucidum.**
Cavum septum pellucidum	
Small to medium-sized increased odds of having a cavum septum pellucidum of any size in people with bipolar disorder; 4 studies, N = 743, OR = 2.07, 95%CI 1.48 to 2.90, $p < 0.000$, $I^2 = 0\%$, $p = 0.731$ Prevalence in bipolar disorder = 50.20% *No significant differences for having a large cavum septum pellucidum;* 4 studies, N = 743, OR = 1.92, 95%CI 0.64 to 5.78, $p = 0.246$, $I^2 = 39.4\%$, $p = 0.176$ Prevalence in bipolar disorder = 9.14% Authors report no evidence of publication bias.	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Bora E, Fornito A, Yucel M, Pantelis C

The effects of gender on grey matter abnormalities in major psychoses: a comparative voxelwise meta-analysis of schizophrenia and bipolar disorder

Psychological Medicine 2012; 42: 295-307

View online review abstract

Comparison	**Grey matter anomalies in people with bipolar disorder compared to controls vs. people with schizophrenia compared to controls, with studies balanced for gender.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) finds there is significantly greater grey matter reduction in people with schizophrenia compared to controls than in people with bipolar disorder compared to controls in the right dorsomedial frontal cortex, and the left dorsolateral prefrontal cortex, with studies balanced for gender. Grey matter reductions were more extensive in male-dominated schizophrenia samples but there was no effect of gender on the findings in bipolar disorder.**
Grey matter volume	
52 studies of schizophrenia, N = 4,374 24 studies of bipolar disorder, N = 1,648 *Greater reduction in grey matter was found in people with schizophrenia vs. controls in;* Right dorsomedial frontal cortex Left dorsolateral prefrontal cortex Authors report that grey matter reductions were more extensive in male-dominated samples in schizophrenia but there was no significant effect of gender on the findings in bipolar disorder.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported (CIs).
Directness of results	Direct

De Peri L, Crescini A, Deste G, Fusar-Poli P, Sacchetti E, Vita A

Brain structural abnormalities at the onset of schizophrenia and bipolar disorder: a meta-analysis of controlled magnetic resonance imaging studies

Current Pharmaceutical Design 2012; 18: 486-94

View online review abstract

Comparison	**Grey and white matter anomalies in people with first-episode bipolar disorder vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, precise, direct) finds small reductions in whole brain grey matter and total white matter in first-episode patients.**
Grey and white matter volume	
Significant, small reductions in people with first-episode bipolar disorder in; Intracranial: 7 studies, N = 458, *g* = -0.25, 95%CI -0.44 to -0.06, *p* = 0.009, I^2 = 4.5%, *p* = 0.60 Whole brain: 7 studies, N = 410, *g* = -0.35, 95%CI -0.61 to -0.10, *p* = 0.006, I^2 = 8%, *p* = 0.22 Total white matter: 5 studies, N = 211, *g* = -0.33, 95%CI -0.60 to -0.05, *p* = 0.017, I^2 = 7%, *p* = 0.20 There were no significant differences in total grey matter, or ventricle volume.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Fusar-Poli P, Howes O, Bechdolf A, Borgwardt S

Mapping vulnerability to bipolar disorder: a systematic review and meta-analysis of neuroimaging studies

Journal of Psychiatry & Neuroscience 2012; 37: 170-84

View online review abstract

Comparison 1	**Grey matter anomalies in people with a relative with bipolar disorder vs. controls.**

Summary of evidence	**Moderate to high quality evidence (medium-sized sample, consistent, precise, direct) finds a small increase in intracerebral volume in people with a relative with bipolar disorder.**
Grey matter volume	
Trend effect of a small increase in intracerebral volume in people with a relative with bipolar disorder; 3 studies, N = 337, SMD = -0.231, 95%CI -0.477 to 0.015, *p* = 0.066 The statistics show a decrease in controls. No significant differences were found in the analyses of the thalamus, striatum, amygdala, hippocampus, pituitary, or frontal lobe.	
Comparison 2	**Grey matter anomalies in people with a relative with bipolar disorder vs. people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (medium-sized sample, consistent, precise, direct) finds a small increase in grey matter volume in people with a relative with bipolar disorder.**
Grey matter volume	
Significant, small increase in grey matter volume in people with a relative with bipolar disorder; 5 studies, N = 264, SMD = -0.269, 95%CI -0.514 to -0.025, *p* = 0.031 The statistics show a decrease in people with bipolar disorder.	
Consistency in results	Authors report that results are consistent.
Precision in results	Precise
Directness of results	Direct

Ganzola R, Duchesne S

Voxel-based morphometry meta-analysis of gray and white matter finds significant areas of differences in bipolar patients from healthy controls

Bipolar Disorders 2017; 19: 74-83

View review abstract online

Comparison	**Grey and white matter anomalies in people with bipolar disorder**

	vs. controls.
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess precision or consistency) finds people with bipolar disorder showed increased grey matter concentrations in the left putamen and decreased grey matter concentrations in the left medial frontal, right inferior frontal, precentral frontal, left inferior longitudinal fasciculus, left insula superior corona radiate, and left limbic posterior cingulum. There were no differences in white matter concentrations.**
Grey and white matter volume	
People with bipolar disorder had higher grey matter concentrations in; Left lentiform nucleus putamen: 2 studies, N = unclear *People with bipolar disorder had reduced grey matter concentrations in;* Left medial frontal gyrus: 5 studies, N = unclear Right inferior frontal: 2 studies, N = unclear Precentral frontal: 4 studies, N = unclear Left temporal inferior longitudinal fasciculus: 2 studies, N = unclear Left insula superior corona radiate: 1 study, N = unclear Left limbic posterior cingulum: 1 study, N = unclear There were no significant differences in white matter concentrations.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported (CIs).
Directness of results	Direct

Haukvik UK, Tamnes CK, Soderman E, Agartz I

Neuroimaging hippocampal subfields in schizophrenia and bipolar disorder: A systematic review and meta-analysis

Journal of Psychiatric Research 2018; 104: 217-26

View online review abstract

Comparison 1	**Hippocampal changes in people with bipolar disorder vs. controls.**

Summary of evidence	**High quality evidence (large sample, mostly consistent, precise, direct) shows small reductions in all hippocampal subfields in people with bipolar disorder.**
Hippocampal volume	
5 studies, N = 1,441 *Small, significant reductions in all hippocampal subfields in people with bipolar disorder;* <u>Left hemisphere</u> Cornu ammonis 1: *d* = -0.200, 95%CI -0.305 to -0.094, *p* < 0.001, Q*p* = 0.523 Cornu ammonis 2/3: *d* = -0.304, 95%CI -0.443 to -0.166, *p* < 0.0001, Q*p* = 0.859 Cornu ammonis 4 / dentate gyrus: *d* = -0.340, 95%CI -0.486 to -0.194, *p* < 0.00001, Q*p* = 0.191 Presubiculum: *d* = -0.285, 95%CI -0.405 to -0.166, *p* < 0.00001, Q*p* = 0.357 Subiculum: *d* = -0.354, 95%CI -0.540 to -0.168, *p* < 0.001, Q*p* = 0.048 <u>Right hemisphere</u> Cornu ammonis 1: *d* = -0.243, 95%CI -0.348 to -0.138, *p* < 0.00001, Q*p* = 0.534 Cornu ammonis 2/3: *d* = -0.349, 95%CI -0.467 to -0.231, *p* < 0.000001, Q*p* = 0.339 Cornu ammonis 4 / dentate gyrus: *d* = -0.328, 95%CI -0.434 to -0.223, *p* < 0.000001, Q*p* = 0.880 Presubiculum: *d* = -0.219, 95%CI -0.327 to -0.111, *p* < 0.0001, Q*p* = 0.624 Subiculum: *d* = -0.284, 95%CI -0.420 to -0.149, *p* < 0.0001, Q*p* = 0.248	
Comparison 2	**Hippocampal changes in people with bipolar disorder vs. people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) shows small reductions in left cornu ammonis (CA)1, left CA2/3, left CA4/dentate gyrus, right presubiculum, and right subiculum in people with schizophrenia, with no differences in left presubiculum or subiculum, or right CA1, CA2/3, or CA4/dentate gyrus.**
Hippocampal volume	
2 studies, N = 809 *Small, significant reductions in the following hippocampal subfields in people with schizophrenia;* <u>Left hemisphere</u> Cornu ammonis 1: *d* = -0.105, 95%CI -0.197 to -0.012, *p* = 0.028, Q*p* = 0.027 Cornu ammonis 2/3: *d* = -0.145, 95%CI -0.254 to -0.037, *p* = 0.0086, Q*p* = 0.009 Cornu ammonis 4 / dentate gyrus: *d* = -0.153, 95%CI -0.274 to -0.032, *p* = 0.013, Q*p* = 0.013	

Right hemisphere Presubiculum: *d* = -0.130, 95%CI -0.210 to -0.050, *p* = 0.0014, Q*p* = 0.001 Subiculum: *d* = -0.091, 95%CI -0.166 to -0.015, *p* = 0.018, Q*p* = 0.018 *No significant differences in;* Left hemisphere Presubiculum: *d* = -0.001, 95%CI -0.085 to 0.084, *p* > 0.05, Q*p* = 0.987 Subiculum: *d* = -0.040, 95%CI -0.122 to 0.042, *p* > 0.05, Q*p* = 0.339 Right hemisphere Cornu ammonis 1: *d* = -0.039, 95%CI -0.115 to 0.037, *p* > 0.05, Q*p* = 0.314 Cornu ammonis 2/3: *d* = 0.021, 95%CI -0.066 to 0.108, *p* > 0.05, Q*p* = 0.633 Cornu ammonis 4 / dentate gyrus: *d* = -0.035, 95%CI -0.111 to 0.041, *p* > 0.05, Q*p* = 0.367

Consistency in results	Consistent for comparison 1, apart from the left subiculum. Consistent for comparison 2, apart from the presubiculum, subiculum, cornu ammonis 1, 2/3 and 4 / dentate gyrus.
Precision in results	Precise
Directness of results	Direct

Ho NF, Chong PLH, Lee DR, Chew QH, Chen G, Sim K

The Amygdala in Schizophrenia and Bipolar Disorder: A Synthesis of Structural MRI, Diffusion Tensor Imaging, and Resting-State Functional Connectivity Findings

Harvard Review of Psychiatry 2019; 27: 150-64

View review abstract online

Comparison	**Amygdala volume in people with bipolar disorder vs. controls or people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (unclear sample size, inconsistent, precise, direct) finds a medium-sized reduction in amygdala volume in people with schizophrenia compared to people with bipolar disorder. There were no differences between bipolar disorder and controls.**
Amygdala volume	

No differences compared to controls; 17 studies, N not reported, g = -0.005, 95%CI -0.24 to 0.23, p = 0.97, I^2 = 79% *A medium-sized effect of reduced amygdala volume in people with schizophrenia vs. bipolar disorder;* 6 studies, N not reported, g = -0.47, 95%CI -0.91 to -0.03, p = 0.04, I^2 = 78%	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Keramatian K, Chakrabarty T, Saraf G, Pinto JV, Yatham LN

Grey matter abnormalities in first-episode mania: A systematic review and meta-analysis of voxel-based morphometry studies

Bipolar Disorders 2021; 23: 228-40

View online review abstract

Comparison	**Grey matter alterations in people with first-episode mania vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, unable to assess precision, direct) finds grey matter reduction in bilateral anterior cingulate/paracingulate gyri in first episode mania.**
Grey matter volume	
15 studies, N = 901 *There was a single cluster of grey matter volume reduction in;* Bilateral anterior cingulate/paracingulate gyri: 339 voxels, MNI = -4, 44, 6, p < 0.001, I^2 = 13% There were no moderating effects of age sex, use of lithium, or study quality.	
Consistency in results	Consistent
Precision in results	Unable to assess; no CIs are reported
Directness of results	Direct

Lu X, Zhong Y, Ma Z, Wu Y, Fox PT, Zhang N, Wang C

Structural imaging biomarkers for bipolar disorder: Meta-analyses of whole-brain voxel-based morphometry studies

Depression and Anxiety 2019; 36(4): 353-364

View online review abstract

Comparison	**Grey matter volume in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to assess precision or consistency) finds people with bipolar disorder show decreased grey matter volume in the left dorsalmedial prefrontal cortex, left ventrolateral prefrontal cortex, and right precentral gyrus.** **In subgroup analysis of bipolar I disorder patients, the right superior temporal gyrus showed reductions. In the subgroup analysis of youth with bipolar disorder, the left orbitofrontal cortex, right claustrum, and right dorsolateral prefrontal cortex showed reductions.** **Increases were found in the left putamen, left posterior cingulate cortex and left precuneus (bipolar I disorder subgroup analysis).**

Grey matter volume

46 studies, N = 1,720

People with bipolar disorder had decreased grey matter volume in;

Left dorsalmedial prefrontal cortex

Left ventrolateral prefrontal cortex

Right precentral gyrus

Right superior temporal gyrus (bipolar I disorder subgroup)

Left orbitofrontal cortex (youth with bipolar disorder subgroup)

Right claustrum (youth with bipolar disorder subgroup)

Right dorsolateral prefrontal cortex (youth with bipolar disorder subgroup)

People with bipolar disorder had increased grey matter volume in;

Left putamen

Left posterior cingulate cortex

Left precuneus (bipolar I disorder subgroup)

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported (CIs).
Directness of results	Direct

Otten M, Meeter M

Hippocampal structure and function in individuals with bipolar disorder: a systematic review

Journal of Affective Disorders 2015; 174: 113-25

View online review abstract

Comparison	**Hippocampal volume in people with bipolar disorder vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) shows small reductions in hippocampal volume in people with bipolar disorder. Lithium treatment was associated with smaller reductions.**
Hippocampal volume	
A small, significant effect of reduced hippocampal volume in people with bipolar disorder; 23 studies, N = 1,043, *d* = 0.22, 95%CI 0.134 to 0.309, *p* < 0.001, Q*p* = 0.979 Lithium treatment was associated with larger hippocampal volumes in patients, and smaller effect sizes. There was no evidence of publication bias.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Pezzoli S, Emsell L, Yip SW, Dima D, Giannakopoulos P, Zarei M

Meta-analysis of regional white matter volume in bipolar disorder with replication in an independent sample using coordinates, T-maps, and

individual MRI data

Neuroscience and Biobehavioral Reviews 2018; 84: 162-70

View online review abstract

Comparison	**White matter anomalies in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, unable to assess precision, direct) finds decreased white matter volume in people with bipolar disorder in posterior corpus callosum extending to the posterior cingulate cortex, with smaller clusters in the left optic radiation and right frontal superior longitudinal tracts. There were small clusters of increased white matter volume in people with bipolar disorder in the cerebellum and the right lenticular nucleus.**
White matter volume	
18 studies, N = 1,820 *Decreased white matter volume in people with bipolar disorder;* Posterior corpus callosum extending to the posterior cingulate cortex Smaller clusters in the left optic radiation and right frontal superior longitudinal tracts *Increased white matter volume in people with bipolar disorder;* Small clusters within the cerebellum, and the right lenticular nucleus	
Consistency in results	Authors report the data are consistent.
Precision in results	Unable to assess; no measure of precision is reported (CIs).
Directness of results	Direct

Sun YR, Herrmann N, Scott CJM, Black SE, Khan MM, Lanctot KL

Global grey matter volume in adult bipolar patients with and without lithium treatment: A meta-analysis

Journal of Affective Disorders 2018; 225: 599-606

View online review abstract

Comparison	**Grey matter volume in people with bipolar disorder on lithium vs. people with bipolar disorder not on lithium.**

Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) finds small increased global grey matter volume in lithium-treated patients compared to lithium-free patients.**
Grey matter volume	
Significant, small effect of increased global grey matter volume in lithium-treated bipolar patients; 15 studies, N = 854, SMD = 0.17, 95%CI 0.01 to 0.33, p = 0.035, I^2 = 12%, ^{p} = 0.317 Subgroup analysis of studies that employed semi-automated segmentation methods showed larger effects than studies that used fully automated segmentation. There were no moderating effects of age, sex, age of onset of disease, duration of illness, length of lithium treatment, dose of lithium treatment, or date of publication. Authors report no evidence of publication bias.	
Comparison 2	**Grey matter volume in people with bipolar disorder on and not on lithium vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, unable to assess consistency, precise, direct) finds no significant differences in global grey matter volume between patients on lithium or not on lithium when compared to controls.**
Grey matter volume	
There were no significant differences in global grey matter volume between lithium-medicated bipolar patients and healthy controls; 8 studies, N = 529, SMD = 0.20, 95%CI -0.12 to 0.52, p = 0.22 *There were no significant differences in global grey matter volume between lithium-free bipolar patients and healthy controls;* 8 studies, N = 481, SMD = -0.08, 95%CI 0.30 to 0.14, p = 0.50	
Consistency in results	Consistent where reported (comparison 1).
Precision in results	Precise
Directness of results	Direct

Wang X, Tian F, Wang S, Cheng B, Qiu L, He M, Wang H, Duan M, Dai J, Jia Z

Gray matter bases of psychotic features in adult bipolar disorder: A systematic review and voxel-based meta-analysis of neuroimaging studies

Human Brain Mapping 2018; 39: 4707-23 View online review abstract	
Comparison	**Grey matter volume in people with bipolar disorder and psychotic symptoms vs. controls people with bipolar disorder and no psychotic symptoms.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, unable to assess precision, direct) finds decreased grey-matter volume in bipolar patients with psychotic symptoms in bilateral superior frontal gyri, bilateral insula, bilateral median cingulated /paracingulate gyri, left anterior cingulate/paracingulate gyri, right superior temporal gyrus, and right precentral gyrus (particularly in females).** **In subgroup analysis of patients with bipolar I disorder and psychotic symptoms, the rolandic operculum also showed reductions.**
Grey matter volume	
14 studies, N = 1,518 *Reduced grey matter volume was found in people with bipolar disorder and psychotic symptoms in;* Bilateral superior frontal gyri Bilateral insula Bilateral median cingulate/paracingulate gyri Left anterior cingulate/paracingulate gyri Right precentral gyrus Right superior temporal gyrus *Reduced grey matter volume was found in patients with bipolar I disorder and psychotic symptoms;* Bilateral superior frontal gyri Bilateral insula Bilateral median cingulate/paracingulate gyri Right precentral gyrus Rolandic operculum Meta-regression analyses indicated that studies with a greater proportion of female patients were associated with lower grey matter volumes in the right precentral gyrus. Studies with greater proportions of patients taking psychotropic medications were associated with lower grey matter volumes in the right insula. There were no moderating effects of age, mania symptom scores, lithium use, antipsychotic use, or study methods (MRI field strength and image smoothing levels)	

There was no evidence of publication bias.	
Consistency in results	Authors report many of the region results were inconsistent.
Precision in results	Unable to assess; no measure of precision is reported (CIs).
Directness of results	Direct

Wise T, Radua J, Via E, Cardoner N, Abe O, Adams TM, Amico F, Cheng Y, Cole JH, de Azevedo Marques Perico C, Dickstein DP, Farrow TFD, Frodl T, Wagner G, Gotlib IH, Gruber O, Ham BJ, Job DE, Kempton MJ, Kim MJ, Koolschijn PCMP, Malhi GS, Mataix-Cols D, McIntosh AM, Nugent AC, O'Brien JT, Pezzoli S, Phillips ML, Sachdev PS, Salvadore G, Selvaraj S, Stanfield AC, Thomas AJ, van Tol MJ, van der Wee NJA, Veltman DJ, Young AH, Fu CH, Cleare AJ, Arnone D

Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis

Molecular Psychiatry 2016; 22(10): 1455-1463

View online review abstract

Comparison 1	**Grey matter volume in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) finds decreased grey-matter volume in bipolar patients in bilateral insula, superior temporal gyrus, superior and ventral medial prefrontal cortex, and bilateral anterior cingulate cortex. There was increased grey-matter volume in bipolar patients in the cerebellum, bilateral middle frontal gyrus, right middle temporal gyrus, right inferior temporal gyrus, and the right middle occipital gyrus.**
Grey matter volume	
36 studies, N = 2,407 *Significant effects of decreased grey-matter volume in bipolar patients was found in;* Bilateral insula Superior temporal gyrus Superior and ventral medial prefrontal cortex Bilateral anterior cingulate cortex	

Significant effects of increased grey-matter volume in bipolar patients was found in; Cerebellar vermis Middle cerebellar peduncles Bilateral middle frontal gyrus Right middle temporal gyrus Right inferior temporal gyrus Right middle occipital gyrus	
Comparison 2	**Grey matter volume in people with bipolar disorder compared to controls vs. people with major depression compared to controls.**
Summary of evidence	**Moderate to low quality evidence (large sample, unable to assess consistency or precision, in direct) finds increased grey matter volume in people with bipolar disorder in the right middle frontal gyrus, left hippocampus, right inferior temporal gyrus, left inferior parietal lobule, and right cerebellar vermis.**
Grey matter volume	
86 studies, N = 6,508 *Significant effects of increased grey matter volume in people with bipolar disorder in;* Right middle frontal gyrus Left hippocampus Right inferior temporal gyrus Left inferior parietal lobule Right cerebellar vermis	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported (CIs).
Directness of results	Direct for comparison 1, indirect for comparison 2.

Yu H, Meng YJ, Li XJ, Zhang C, Liang S, Li ML, Li Z, Guo W, Wang Q, Deng W, Ma X, Coid J, Li T

Common and distinct patterns of grey matter alterations in borderline personality disorder and bipolar disorder: Voxel-based meta-analysis

British Journal of Psychiatry 2019; 215: 395-403 View online review abstract	
Comparison	**Grey matter volume and density in people with bipolar disorder vs. borderline personality disorder.**
Summary of evidence	**Moderate to low quality evidence (large samples, unable to assess consistency or precision, indirect) finds different grey matter volume and density changes in bipolar disorder and borderline personality disorder. In bipolar disorder, grey matter volume and density is reduced in bilateral medial orbital frontal cortex, right insula, and right thalamus, and increased in the right putamen. In borderline personality disorder, grey matter volume and density is reduced in bilateral medial prefrontal cortex network, bilateral amygdala, and right parahippocampal gyrus.**
Grey matter volume and density	
47 bipolar disorder studies (vs. controls), N = 5,372 *Reduced grey matter volume and density was found in people with bipolar disorder in;* Bilateral medial orbital frontal cortex Right insula Right thalamus *Increased grey matter volume and density was found in people with bipolar disorder in;* Right putamen 13 borderline personality disorder studies (vs. controls), N = 810 *Reduced grey matter volume and density was found in people with borderline personality disorder in;* Bilateral medial prefrontal cortex network Bilateral amygdala Right parahippocampal gyrus	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Indirect comparison of bipolar disorder vs. borderline personality disorder.

Explanation of acronyms

CI = confidence interval, CVR = coefficient of variability ratio, *d* or *g* = Cohen's d or Hedges' g standardised mean differences, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MNI = Montreal Neurological Institute, N = number of participants, *p* = probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = test for heterogeneity, SMD = standardised mean difference, VR = variability ratio, vs. = versus.

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[18].

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† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment effect[18].

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[19]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship

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between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[20].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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References

1. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
2. Bora E, Fornito A, Yucel M, Pantelis C (2012): The effects of gender on grey matter abnormalities in major psychoses: a comparative voxelwise meta-analysis of schizophrenia and bipolar disorder. *Psychological Medicine* 42: 295-307.
3. De Peri L, Crescini A, Deste G, Fusar-Poli P, Sacchetti E, Vita A (2012): Brain structural abnormalities at the onset of schizophrenia and bipolar disorder: a meta-analysis of controlled magnetic resonance imaging studies. *Current Pharmaceutical Design* 18: 486-94.
4. Fusar-Poli P, Howes O, Bechdolf A, Borgwardt S (2012): Mapping vulnerability to bipolar disorder: a systematic review and meta-analysis of neuroimaging studies. *Journal of Psychiatry & Neuroscience* 37: 170-84.
5. Ganzola R, Duchesne S (2017): Voxel-based morphometry meta-analysis of gray and white matter finds significant areas of differences in bipolar patients from healthy controls. *Bipolar Disorders* 19: 74-83.
6. Otten M, Meeter M (2015): Hippocampal structure and function in individuals with bipolar disorder: a systematic review. *Journal of Affective Disorders* 174: 113-25.
7. Pezzoli S, Emsell L, Yip SW, Dima D, Giannakopoulos P, Zarei M*, et al.* (2018): Meta-analysis of regional white matter volume in bipolar disorder with replication in an independent sample using coordinates, T-maps, and individual MRI data. *Neuroscience and Biobehavioral Reviews* 84: 162-70.
8. Sun YR, Herrmann N, Scott CJM, Black SE, Khan MM, Lanctot KL (2018): Global grey matter volume in adult bipolar patients with and without lithium treatment: A meta-analysis. *Journal of Affective Disorders* 225: 599-606.
9. Wise T, Radua J, Via E, Cardoner N, Abe O, Adams TM*, et al.* (2016): Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis. *Molecular Psychiatry* 22: 1455-63.
10. Beraldi GH, Prado KS, Amann BL, Radua J, Friedman L, Elkis H (2018): Meta-analyses of cavum septum pellucidum in mood disorders in comparison with healthy controls or schizophrenia. *European Neuropsychopharmacology* 28: 1325-138.
11. Haukvik UK, Tamnes CK, Soderman E, Agartz I (2018): Neuroimaging hippocampal subfields in schizophrenia and bipolar disorder: A systematic review and meta-analysis. *Journal of Psychiatric Research* 104: 217-26.
12. Wang X, Tian F, Wang S, Cheng B, Qiu L, He M*, et al.* (2018): Gray matter bases of psychotic features in adult bipolar disorder: A systematic review and voxel-based meta-analysis of neuroimaging studies. *Human brain mapping* 39: 4707-23.
13. Lu X, Zhong Y, Ma Z, Wu Y, Fox PT, Zhang N*, et al.* (2019): Structural imaging biomarkers for bipolar disorder: Meta-analyses of whole-brain voxel-based morphometry studies. *Depression and Anxiety* 36: 353-64.
14. Yu H, Meng YJ, Li XJ, Zhang C, Liang S, Li ML*, et al.* (2019): Common and distinct patterns of grey matter alterations in borderline personality disorder and bipolar disorder: Voxel-based meta-analysis. *British Journal of Psychiatry* 215: 395-403.
15. Ho NF, Chong PLH, Lee DR, Chew QH, Chen G, Sim K (2019): The Amygdala in Schizophrenia and Bipolar Disorder: A Synthesis of Structural MRI, Diffusion Tensor Imaging, and Resting-State Functional Connectivity Findings. *Harvard Review of Psychiatry* 27: 150-64.
16. Angelescu I, Brugger SP, Borgan F, Kaar SJ, Howes OD (2021): The magnitude and variability of brain structural alterations in bipolar disorder: A double meta-analysis of 5534 patients and 6651 healthy controls. *Journal of Affective Disorders* 291: 171-6.
17. Keramatian K, Chakrabarty T, Saraf G, Pinto JV, Yatham LN (2021): Grey matter abnormalities in first-episode mania: A systematic review and meta-analysis of voxel-based morphometry studies. *Bipolar Disorders* 23: 228-40.

18. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
19. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
20. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*