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.

Schizophrenia has been associated with structural alterations in many brain regions. Understanding of any alterations of brain structure in people with schizophrenia may provide insight changes in brain development associated with the illness onset or progression and may also help to inform future treatment strategies. Studies have focused on individual regions but also whole brain investigations to identify differences between schizophrenia patients and controls in regional volume or morphometry. For ease of description, the results reported in these studies are referred to here 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 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first-episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are given priority for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have 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)[2]. 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).

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Results

We found 67 systematic reviews that met our inclusion criteria[3-69].

In chronic patients

- Moderate to high quality evidence found reductions in whole brain and bilateral frontal lobe grey and white matter volume. There were grey matter reductions in the anterior and posterior cingulate gyri, superior and medial temporal gyrus, inferior parietal gyrus, corpus callosum, cerebellum, thalamus (particularly mediodorsal, and an absent adhesio interthalamica), insula, amygdala, hippocampus, and parahippocampus in people with schizophrenia compared to controls. Volume increases were found in the caudate, putamen, right globus pallidus, cerebrospinal fluid, and ventricles (lateral, third, and fourth, and a large cavum septum pellucidum). There were white matter reductions in the anterior commissure, corpus callosum, fornix, internal capsule, bilateral anterior segment of the arcuate fasciculus, left long segment of the arcuate fasciculus, bilateral arcuate fasciculus, bilateral cingulum, bilateral cortico-ponto-cerebellum tract, bilateral cortico spinal tract, bilateral inferior fronto-occipital fasciculus, bilateral inferior longitudinal fasciculus, bilateral inferior cerebellar penduculus, bilateral optic radiation, bilateral posterior segment of the arcuate fasciculus, bilateral superior longitudinal fasciculus 1, 2 and 3, bilateral superior cerebellar penduculus and bilateral uncinate fasciculus.
- Moderate to low quality evidence found an absence of normal leftward asymmetry in the planum temporale and Sylvian fissure, and an excess rightward asymmetry in the superior temporal gyrus (particularly posterior). There was also a higher frequency of abnormal (reversed) asymmetry in the frontal and occipital lobes in people with schizophrenia compared to controls.
- Moderate to low quality evidence found schizophrenia patients with persistent negative symptoms showed reductions in bilateral medial frontal gyrus, the left precentral gyrus, the left middle frontal gyrus, the left caudate nucleus (caudate head), the bilateral parahippocampal gyri, the left anterior cingulate, the thalamus and the insula.
- Moderate quality evidence found antipsychotic use was associated with reduced left lateral temporal cortex, left inferior frontal gyrus, superior frontal gyrus extending to the left middle frontal gyrus, and the right rectal gyrus. Antipsychotic use was associated with volume increases in the left dorsal/anterior cingulate cortex, left ventral/anterior cingulate cortex and right putamen. Increased antipsychotic use over time (>2 years) was associated with small decreases in parietal and occipital lobe volume, and small increases in basal ganglia volume. There were no associations with total brain, frontal, temporal, cerebellum, or CSF/ventricle volume.
- Moderate to high quality evidence found a small association between increased hippocampal volume and better verbal learning. Moderate quality evidence found increased severity of auditory hallucinations was associated with grey matter volume reductions in the left superior temporal gyri, (including the rolandic operculum and Heschl's gyri), and a trend effect for the right superior temporal gyri (including the medial temporal gyrus and Heschl's gyri). Moderate to low quality evidence also found associations with reductions in insula grey matter volume.
- Moderate quality evidence found increased severity of neurological soft signs was associated with reduced grey matter volume in the precentral/inferior frontal gyri, left postcentral/inferior parietal lobe and thalamus and reduced white matter volume in the middle temporal and cerebellum.

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Magnetic resonance imaging

- Moderate to low quality evidence found overlapping grey matter volume decreases in autism spectrum disorder and schizophrenia in the right posterior cingulate cortex, right parahippocampus, and right putamen, and to a lesser extent, in the right insula and left thalamus.
- Moderate to high quality evidence shows small reductions in amygdala, left insula, and left hippocampal regions (CA1, CA2/3, and CA4/dentate gyrus), and right hippocampal regions (presubiculum and subiculum) in people with schizophrenia compared to people with bipolar disorder. There was a distinct region of the pregenual cingulate cortex (anterior Brodmann area 24) where grey matter reduction was detected in bipolar disorder and not schizophrenia.
- Moderate to low quality evidence found volume reductions in the temporal lobe, thalamus, and amygdala, and increased volume in the basal ganglia and ventricles in child-onset schizophrenia compared to controls.
- Moderate to high quality evidence found better overall functioning was associated with larger volumes in whole brain, frontal lobe, parietal lobe, occipital lobe, cerebellum, and limbic regions. Better functioning was also associated with smaller ventricle volumes. There were no associations with the temporal lobe or white matter tracts.
- Moderate to high quality evidence finds greater variability in intracranial volume, bilateral lateral ventricle, and third ventricle volume of people with schizophrenia than in these regions in controls. No other brain region showed differences in variability.
- Moderate to low quality evidence suggests no differences in rates of cavum septum pellucidum in people with schizophrenia compared to controls.

In first-episode patients

- High quality evidence found significant reductions in grey matter volume of the whole brain, corpus callosum, hippocampus, thalamus, and increases in the ventricles (right and left lateral ventricles, and third ventricle).
- Moderate to high quality evidence found medium-sized reductions in the amygdala and small reductions in the temporal lobe, anterior cingulate cortex, and frontal lobe.
- Moderate quality evidence found grey matter reductions in the bilateral caudate head, left putamen, bilateral insula, and cerebellum. White matter reductions were found in the temporal lobe.
- Moderate quality evidence found grey matter reductions in the left anterior cingulate, right precuneus, left cerebellum and right superior temporal gyrus in people with first-episode psychosis compared to people at high-risk of psychosis.
- Moderate quality evidence found common patterns of grey matter abnormalities in frontal (gyrus rectus), superior temporal, left hippocampal, and insula cortex of antipsychotic-naïve and treated first-episode patients. Grey matter in the left supramarginal gyrus and left middle temporal gyrus were increased in antipsychotic-naive patients, but decreased in treated patients, while left median cingulate/paracingulate gyri and right hippocampus grey matter was decreased in antipsychotic-naive patients but increased in treated patients. There was also reduced grey matter volume in the cerebellar vermic lobule IV/V/VII, left cerebellar lobule IV/V, and left cerebellar Crus I in antipsychotic-naïve patients.
- Moderate quality evidence found regions of overlap between structural and functional abnormalities in first-episode patients of mixed medication status in the medial frontal/anterior cingulate cortex. In drug-free patients, there was decreased grey matter volume and decreased functional activity in the left medial posterior

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cingulate/paracingulate gyrus, right temporal pole/superior temporal gyrus, left fusiform gyrus, left inferior parietal gyrus, and left caudate nucleus in drug-free patients. There was decreased grey matter volume and increased functional activity in the left superior temporal gyrus, right superior temporal gyrus, left fusiform gyrus, and right lingual gyrus. There was increased grey matter volume and decreased functional activity in the left cerebellum, right gyrus rectus, and right inferior parietal gyrus. There was increased grey matter volume and increased functional activity in the left insula and left cerebellum (lobule IX).

In high-risk individuals

- Moderate quality evidence found individuals at either clinical or genetic high risk have greater pituitary volume than controls, particularly high-risk individuals who transition to psychosis. They also show grey matter reductions in the anterior cingulate gyrus, right superior temporal gyrus, left precuneus, left medial frontal gyrus, right middle frontal gyrus, left inferior frontal gyrus, parahippocampal and hippocampal regions, right insula, left amygdala, and left subcallosal gyrus when compared to controls.
- People at high clinical risk showed increased grey matter volume in bilateral median cingulate, right fusiform gyrus, left superior temporal gyrus, and right thalamus, and decreased grey matter volume in the right gyrus rectus, right superior frontal gyrus, and left superior frontal gyrus when compared to controls.
- People at high genetic risk have reduced hippocampus, anterior cingulate, left basal ganglia/claustrum, left thalamus/putamen, right superior frontal gyrus, left insula, left inferior temporal gyrus, and right inferior network compared to controls. They also showed increased grey matter in the left medial frontal gyrus and increased third ventricle volume. People at high clinical risk show decreases in the parahippocampus and hippocampus, right anterior cingulate, insula, right middle/superior temporal gyrus, right inferior frontal gyrus, and right frontal gyrus compared to controls.
- People at high clinical risk showed decreases in the bilateral anterior cingulate compared to people at high genetic risk. People at high genetic risk showed decreases in the left parahippocampus, insula and right superior temporal gyrus compared to people at high clinical risk.
- Compared to people with schizophrenia, moderate quality evidence found people at high genetic risk had decreased grey matter in the left putamen and increased grey matter in the left insula and right inferior frontal gyrus. Compared to people with psychosis in general, moderate quality evidence found people at high-risk show increases in the amygdala, medial frontal gyrus, middle temporal gyrus and the right precuneus. There were also increases in the right superior temporal gyrus, left insula, and left cerebellum.
- Moderate quality evidence found high risk individuals who transitioned to psychosis had greater whole brain volume than high risk individuals who did not transition to psychosis and also when compared to controls and people with first-episode psychosis. Moderate to low quality evidence found high risk individuals who transitioned to psychosis had reduced grey matter in the insula, cingulate cortex, superior temporal gyrus, prefrontal cortex, and cerebellum compared to non-transitioners.
- Moderate to high quality evidence suggests a small association between increased left hippocampal volume and better immediate recall in people at genetic risk of schizophrenia, with no associations with the right hemisphere or the left hemisphere and delayed recall.

Adriano F, Spoletini I, Caltagirone C, Spalletta G

Updated meta-analyses reveal thalamus volume reduction in patients with first episode and chronic schizophrenia

Schizophrenia Research 2010; 123(1): 1-4

View review abstract online

Comparison	**Thalamic grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests reduced thalamic grey matter volume bilaterally in people with schizophrenia, of slightly larger magnitude in first episode compared to chronic schizophrenia.**

Thalamic volume

All patients

Small to medium effect size shows significantly reduced bilateral thalamus;

Right thalamus: 15 studies, N = 957, *d* = -0.38, 95%CI -0.52 to -0.25, *p* = 0.00001, Q = 13.16, *p* = 0.51, I^2 = 0%

Left thalamus: 15 studies, N = 957, *d* = -0.40, 95%CI -0.53 to -0.26, *p* = 0.00001, Q = 8.94, *p* = 0.84, I^2 = 0%

First-episode schizophrenia

Medium effect size showing significantly reduced thalamus;

Right thalamus: 15 studies, N = 384, *d* = -0.45, 95%CI -0.66 to -0.23, *p* = 0.00001, Q = 2.83, *p* = 0.73, I^2 = 0%

Left thalamus: 15 studies, N = 384, *d* = -0.48, 95%CI -0.70 to -0.26, *p* = 0.00001, Q = 2.71, *p* = 0.74, I^2 = 0%

Chronic schizophrenia

Small effect size showing significantly reduced thalamus;

Right thalamus: 15 studies, N = 488, *d* = -0.32, 95%CI -0.50 to -0.14, *p* = 0.0005, Q = 7.92, *p* = 0.24, I^2 = 24%

Left thalamus: 15 studies, N = 488, *d* = -0.33, 95%CI -0.51 to -0.15, *p* = 0.0003, Q = 3.41, *p* = 0.76, I^2 = 0%

Consistency in results‡	Consistent for all outcomes.

Precision in results[§]	Precise for all outcomes.
Directness of results[‖]	Direct

Adriano F, Caltagirone C, Spalletta G

Hippocampal volume reduction in first episode and chronic schizophrenia: a review and meta-analysis

The Neuroscientist 2012; 18(2): 180-200

View review abstract online

Comparison	**Hippocampal volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, mostly inconsistent, precise, direct) suggests reduced hippocampal grey matter volume bilaterally in both first episode and chronic schizophrenia.**

Hippocampus volume

All patients

Medium effect size shows significantly reduced hippocampus;

Right hippocampus: 51 studies, N = 3,799, d = -0.53, 95%CI -0.65 to -0.41, $p < 0.00001$, Q = 140.64, $p < 0.00001$, I^2 = 64%

Left hippocampus: 51 studies, N = 3,799, d = -0.48, 95%CI -0.65 to -0.32, $p < 0.00001$, Q = 287.62, $p < 0.00001$, I^2 = 83%

Subgroup analysis showed similar effects in male-only groups;

Right: N = 1,031, d = -0.63, 95%CI -0.82 to -0.44, $p < 0.00001$, Q not reported, p = 0.003

Left: N = 1,031, d = -0.43, 95%CI -0.80 to -0.07, p = 0.02, Q not reported, $p < 0.00001$

First-episode schizophrenia

Medium effect size shows significantly reduced hippocampus;

Right hippocampus: 13 studies, N = 950, d = -0.56 95%CI -0.72 to -0.40, $p < 0.00001$, Q = 14.36, p = 0.28, I^2 = 16%

Left hippocampus: 13 studies, N = 950, d = -0.60, 95%CI -0.83 to -0.38, $p < 0.00001$, Q = 27.24, p = 0.007, I^2 = 56%

Chronic schizophrenia

Medium effect size shows significantly reduced hippocampus; Right hippocampus: 22 studies, N = 1,635, *d* = -0.65, 95%CI -0.87 to -0.43, *p* < 0.00001, Q = 90.26, *p* < 0.00001, I^2 = 77% Left hippocampus: 22 studies, N = 1,635, *d* = -0.58, 95%CI -0.94 to -0.22, *p* = 0.002, Q = 229.32, *p* < 0.00001, I^2 = 91%	
Consistency in results	Mostly inconsistent.
Precision in results	Precise for all outcomes.
Directness of results	Direct

Antoniades M, Schoeler T, Radua J, Valli I, Allen P, Kempton MJ, McGuire P

Verbal learning and hippocampal dysfunction in schizophrenia: A meta-analysis

Neuroscience and Biobehavioral Reviews 2018; 86: 166-75

View review abstract online

Comparison 1	**Association between verbal learning and hippocampal volume in people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (medium-sized samples, consistent, precise, direct) suggests a small association between increased hippocampal volume and better verbal learning in people with schizophrenia, with no associations in control samples.**
Hippocampal volume	
Total hippocampal volume *Small, significant association between increased volume and better delayed recall;* 3 studies, N = 293, *r* = 0.228, 95%CI 0.047 to 0.394, *p* = 0.0138, I^2 = 14% Left hippocampal volume *Small, significant association between increased volume and better immediate recall;* 5 studies, N = 162, *r* = 0.256, 95%CI 0.089 to 0.409, *p* = 0.0029 *Small, significant association between increased volume and better delayed recall;* 11 studies, N = 431, *r* = 0.131, 95%CI 0.042 to 0.218, *p* = 0.0038	

Right hippocampal volume *Small, significant association between increased volume and better immediate recall;* 5 studies, N = 162, *r* = 0.230, 95%CI 0.094 to 0.358, *p* = 0.001 *Small, significant association between increased volume and better delayed recall;* 8 studies, N = 311, *r* = 0.234, 95%CI 0.135 to 0.329, *p* < 0.0001 There were no significant associations in the analyses of control subjects.	
Consistency in results	Consistent for total hippocampal volume, unable to assess hemispheres (I^2 not reported).
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Association between verbal learning and hippocampal volume in people at genetic risk of schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (small samples, consistent, precise, direct) suggests a small association between increased left hippocampal volume and better immediate recall in people at genetic risk of schizophrenia, with no associations with the right hemisphere or the left hemisphere and delayed recall.**
Hippocampal volume	
Left hippocampal volume *Small, significant association between increased volume and better immediate recall;* 2 studies, N = 89, *r* = -0.356, 95%CI 0.153 to 0.531, *p* = 0.0009, I^2 = 0% *There was no association between volume and delayed recall;* N = 228, *r* = -0.031, 95%CI -0.223 to 0.163, *p* > 0.05, I^2 = 32% Right hippocampal volume *There was no association between volume and immediate recall;* N = 89, *r* = 0.160, 95%CI -0.075 to 0.379, *p* > 0.05, I^2 = 11% *There was no association between volume and delayed recall;* N = 170, *r* = -0.034, 95%CI -0.237 to 0.171, *p* > 0.05, I^2 = 4%	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

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Arnone D, McIntosh AM, Tan GM, Ebmeier KP, Tan GMY

Meta-analysis of magnetic resonance imaging studies of the corpus callosum in schizophrenia

Schizophrenia Research 2008; 101(1-3): 124-32

View review abstract online

Comparison	**Mid-sagittal corpus callosum in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, mostly precise, direct) suggests reductions in the area of the mid-sagittal corpus callosum in people with schizophrenia. This effect was most pronounced in first-episode schizophrenia.**
Corpus callosum volume	
All patients *Small effect size showing significantly reduced callosal area;* 28 studies, N = 1,703, *d* = -0.24, 95%CI -0.4 to -0.07, I^2 = 2% First-episode schizophrenia *Large effect size showing significantly reduced callosal area;* 4 studies, N = 227, *d* = -0.70, 95%CI -1.29 to -0.10, I^2 = 3% Chronic schizophrenia *Small effect size showing significantly reduced callosal area;* 24 studies, N = 1,476, *d* = -0.17, 95%CI -0.33 to -0.001, I^2 = 1%	
Consistency in results	Consistent
Precision in results	Precise for all patients and recurrent patients, imprecise for first-episode patients.
Directness of results	Direct

Baiano M, David A, Versace A, Churchill R, Balestrieri M, Brambilla P

Anterior cingulate volumes in schizophrenia: a systematic review and a meta-analysis of MRI studies

Schizophrenia Research 2007; 93(1-3): 1-12

View review abstract online

Comparison	**Anterior cingulate gyrus volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, some inconsistency, precise, direct) suggests significant reductions in the anterior cingulate gyrus volume of people with schizophrenia.**
Anterior cingulate cortex	
Large effect size shows significant reductions; Total volume: 7 studies, N = 447, *d* = -0.70, 95%CI -1.04 to -0.36, *p* < 0.001, Q = 17.28, *p* = 0.008 Right: 5 studies, N = 304, *d* not reported, Z = 3.27, *p* < 0.001, Q = 1.85, *p* = 0.763 Left: 5 studies, N = 304, *d* not reported, Z = 5.05, *p* < 0.001, Q = 2.28, *p* = 0.685	
Consistency in results	Inconsistent for total volume, consistent within hemispheres.
Precision in results	Precise for total volume, unable to assess within hemispheres.
Directness of results	Direct

Boos HB, Aleman A, Cahn W, Hulshoff Pol H, Kahn RS

Brain volumes in relatives of patients with schizophrenia: a meta-analysis

Archives of General Psychiatry 2007; 64(3): 297-304

View review abstract online

Comparison 1	**Whole brain volume in first degree relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, some inconsistency, precise, direct) suggests first degree relatives of**

	people with schizophrenia have small reductions in total grey matter and hippocampal volume, and small increases in third ventricle volume.
Grey matter volume	
Small decrease in grey matter volume in relatives; 7 studies, N = 534, *d* = 0.18, 95%CI 0.02 to 0.33, *p* < 0.05, Q = 4.68, *p* = 0.70	
Hippocampal volume	
Small decrease in total hippocampal volume in relatives; 9 studies, N = 1,024, *d* = 0.31, 95%CI 0.13 to 0.49, *p* < 0.05, Q = 13.79, *p* = 0.09 *Medium-sized decrease in left hippocampal volume in relatives;* 9 studies, N = 943, *d* = 0.47, 95%CI 0.34 to 0.61, *p* < 0.05, Q = 6.56, *p* = 0.58 *Small decrease in right hippocampal volume in relatives;* 9 studies, N = 943, *d* = 0.23, 95%CI 0.01 to 0.96 *p* < 0.05, Q = 19.43, *p* = 0.01	
Third ventricle volume	
Small increase in third ventricle volume in relatives; 7 studies, N = 832, *d* = 0.21, 95%CI 0.03 to 0.4, *p* < 0.05, Q = 8.31, *p* = 0.22	
Total brain volume	
No significant differences; 13 studies, N = 1,238, *d* = 0.28, 95%CI -0.02 to 0.57, Q = 63.99, *p* < 0.001	
Cerebral spinal fluid volume	
No significant differences; 4 studies, N = 217, *d* = 0.61, 95%CI 0.08 to 1.14, Q = 9.81, *p* = 0.02	
Lateral ventricles	
No significant differences; 7 studies, N = 779, *d* = 0.11, 95%CI -0.05 to 0.27, Q = 5.85, *p* = 0.44	
White matter volume	

No significant differences; 7 studies, N = 529, *d* = 0.40, 95%CI -0.04 to 0.83, Q = 33.25, *p* < 0.001	
Consistency in results	Consistent, apart from total, spinal fluid and white matter volume.
Precision in results	Precise, apart from spinal fluid and right hippocampal volume.
Directness of results	Direct
Comparison 2	**Hippocampal volume in first degree relatives of people with schizophrenia vs. people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests people with schizophrenia have reduced hippocampal volume compared to first degree relatives.**
Hippocampal volume	
Medium-sized decrease in hippocampal volume in people with schizophrenia; 9 studies, N = 846, *d* = 0.43, 95%CI 0.17 to 0.68, Q = 22.28, *p* = 0.004	
Consistency in results	Inconsistent, significant heterogeneity reported.
Precision in results	Precise
Directness of results	Direct

Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ, Yücel M, Velakoulis D, Pantelis C

Neuroanatomical abnormalities in schizophrenia: A multimodal voxelwise meta-analysis and meta-regression analysis

Schizophrenia Research 2011; 127: 46-57

View review abstract online

Comparison	**Whole brain comparison of grey and white matter density in schizophrenia and first episode schizophrenia patients vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess**

	consistency or precision, direct) suggests chronic schizophrenia shows grey matter reductions in bilateral insula and inferior frontal, thalamus, and medial frontal/anterior cingulate gyrus compared to controls. First-episode schizophrenia shows reduced grey matter in superior temporal gyrus/insula and anterior cingulate. White matter reductions were reported in the temporal lobe in both chronic and first-episode schizophrenia, as well as internal capsule in chronic patients.
Grey and white matter changes	
Meta-analysis was performed using Signed Differential Mapping (SDM) analysis on voxel-based morphometry MRI studies of whole brain grey and white matter measures; N = 4,179, 49 studies <u>Grey matter reductions (MRI) in schizophrenia compared to controls</u> Left insula/inferior frontal: Talairach coordinates (-42, 8, 6), cluster 1339mm^3, $p < 0.000001$ Right insula/inferior frontal: Talairach coordinates (46, 2, 6), cluster 1047mm^3, $p < 0.000001$ Bilateral thalamus: Talairach coordinates (-2, -16, 4), cluster 544mm^3, $p < 0.000001$ Bilateral dorsal medial frontal/anterior cingulate: Talairach coordinates (4, 26, 40), cluster 496mm^3, $p = 0.000002$ Left rostral medial frontal/anterior cingulate: Talairach coordinates (-4, 46, -2), cluster 467mm^3, $p = 0.00007$ *Meta-regressions* Studies assessing only first-episode were compared to studies assessing schizophrenia and showed higher GM in FES in bilateral fronto-insula cortex, left (-38, 10, 8), $p < 0.00001$; right (44, 16, 8), $p = 0.0002$ A higher percentage of males showed reduced GM in right insula/claustrum (34. -2, 6), $p = 0.00001$; left inferior frontal/insula (-40, 4, -8), $p = 0.001$; thalamus (4, -22, -4) $p = 0.00003$; left medial frontal (-4, 32, -16) $p = 0.002$ Duration of illness was associated with decreased GM in the right fronto-insula cortex (38, -4, 4), $p = 0.0008$ More severe negative symptoms were associated with smaller GM in bilateral medial frontal gyrus/orbitofrontal cortex (-2, 32, -16), $p = 0.0009$ and left insula (-42, 2, 2), $p = 0.00003$ Note that antipsychotic dose had no significant effect. *Subgroup analysis: Grey matter reductions (MRI) in first-episode schizophrenia compared to controls;* Right posterior insula/superior temporal gyrus: Talairach coordinates (46, -20, 2), cluster 652mm^3, p	

= 0.000005 Right dorsal anterior cingulate: Talairach coordinates (14, 18, 30), cluster 106mm^3, p = 0.0002 N = 1837, 24 studies White matter reductions (MRI) in chronic schizophrenia Bilateral internal capsule (anterior limb, thalamic radiation) Talairach coordinates (12, 0, 10), cluster 409mm^3, p = 0.00004 Right temporal white matter: Talairach coordinates (36, -34, 2), cluster 93mm^3, p = 0.0003 White matter reductions (MRI) in first-episode schizophrenia Right temporal white matter: Talairach coordinates (36, -34, 2), cluster 1029mm^3, p < 0.00001 Left temporal white matter**:** Talairach coordinates (-34, -58, 2), cluster 159mm^3, p = 0.0002

Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Brugger SP, Howes OD

Heterogeneity and Homogeneity of Regional Brain Structure in Schizophrenia: A Meta-analysis

JAMA Psychiatry 2017; 74: 1104-11

View review abstract online

Comparison	**Whole brain volume in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, precise, direct) finds medium-sized reductions in the amygdala and hippocampus, and small reductions in the temporal lobe, anterior cingulate cortex, frontal lobe, and thalamus of people with first-episode schizophrenia. There were also medium-sized increases in lateral and third ventricles. There were no differences in the caudate nucleus or putamen.**
Brain regions	

Significant, small reductions in first-episode schizophrenia in; Temporal lobe: 22 studies, N = 1,458, g = -0.22, 95%CI -0.36 to -0.09, p = 0.001, I^2 = 44% Anterior cingulate cortex: 11 studies, N = 893, g = -0.26, 95%CI -0.43 to -0.10, p = 0.006, I^2 = 48% Frontal lobe: 22 studies, N = 1,391, g = -0.31, 95%CI -0.44 to -0.19, p < 0.001, I^2 = 29% Thalamus: 21 studies, N = 2,125, g = -0.36, 95%CI -0.57 to -0.15, p = 0.001, I^2 = 76% *Significant, medium-sized reductions in first-episode schizophrenia in;* Amygdala: 23 studies, N = 2,315, g = -0.46, 95%CI -0.65 to -0.26, p < 0.001, I^2 = 78% Hippocampus: 36 studies, N = 3,298, g = -0.66, 95%CI -0.84 to -0.47, p < 0.001, I^2 = 74% *Significant, medium-sized increases in first-episode schizophrenia in;* Lateral ventricle: 31 studies, N = 2,798, g = 0.40, 95%CI 0.29 to 0.51, p < 0.001, I^2 = 55% Third ventricle: 13 studies, N = 750, g = 0.43, 95%CI 0.26 to 0.59, p < 0.001, I^2 = 15% *There were no significant differences in;* Caudate nucleus: 22 studies, N = 2,096, g = -0.11, 95%CI -0.28 to 0.05, p = 0.23, I^2 = 79% Putamen: 15 studies, N = 1,809, g = -0.31, 95%CI -0.68 to 0.07, p = 0.11, I^2 = 79%

Consistency in results	Inconsistent, apart from frontal lobe and the third ventricle.
Precision in results	Precise
Directness of results	Direct

Chan RCK, Di X, McAlonan GM, Gong Q

Brain Anatomical Abnormalities in High-Risk Individuals, First-Episode, and Chronic Schizophrenia: An Activation Likelihood Estimation Meta-analysis of Illness Progression

Schizophrenia Bulletin 2011; 37(1) 177-188

View review abstract online

Comparison 1	**Grey matter changes in people at high risk of schizophrenia vs. controls. People at high risk of schizophrenia were defined as first or second-degree relatives of people with schizophrenia, those meeting the Personal Assessment and Crisis Evaluation clinic criteria, or those with a modification of the catechol-O-methyltransferase gene.**

Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests high risk individuals have grey matter reductions in bilateral anterior cingulate gyrus, right insula, left amygdala, left subcallosal gyrus, and left inferior frontal gyrus compared to controls.**
Grey matter changes in high risk individuals	
Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies; FWHM 10mm, FDR corrected at $p < 0.01$ 8 studies, N = 1,031 Right insula: Talairach coordinates (42, -28, 16), cluster 824mm^3, ALE 0.0109 Left amygdala: Talairach coordinates (-28, -8, -12), cluster 800mm^3, ALE 0.0112 Left anterior cingulate: Talairach coordinates (-6, 36, 16), cluster 560mm^3, ALE 0.0114 Right anterior cingulate: Talairach coordinates (4, 30, 20), cluster 560mm^3, ALE 0.0079 Right anterior cingulate: Talairach coordinates (6, 30,26), cluster 560mm^3, ALE 0.0074 Left subcallosal gyrus: Talairach coordinates (-22, 6, -14), cluster 536mm^3, ALE 0.0120 Left inferior frontal gyrus: Talairach coordinates (-48, 26, -2), cluster 432mm^3, ALE 0.0107	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct
Comparison 2	**Grey matter changes in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests people with first-episode schizophrenia have grey matter reductions in the right anterior cingulate gyrus, bilateral insula, left lateral prefrontal lobe (middle and inferior frontal gyri), right medial frontal gyrus, bilateral postcentral gyrus, bilateral superior temporal gyrus, right cerebellum, and right caudate nucleus compared to controls.**
Grey matter changes in first-episode schizophrenia	

Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies;

FWHM 10mm, FDR corrected at $p < 0.01$

14 studies, N = 1,082

Left transverse temporal gyrus: Talairach coordinates (-46, -20, 12), cluster 2616mm^3, ALE 0.0187

Left superior temporal gyrus: Talairach coordinates (-52, -8, 6), cluster 2616mm^3, ALE 0.0162

Left superior temporal gyrus: Talairach coordinates (-58, -28, 12), cluster 2616mm^3, ALE 0.0151

Right precentral gyrus: Talairach coordinates (50, -10, 12), cluster 1576mm^3, ALE 0.0150

Right insula: Talairach coordinates (48, -24, 18), cluster 1576mm^3, ALE 0.0134

Right insula: Talairach coordinates (34, 16, 10), cluster 1392mm^3, ALE 0.0248

Left insula: Talairach coordinates (-34, 20, 6), cluster 1000mm^3, ALE 0.0236

Right cingulate gyrus: Talairach coordinates (6, 16, 38), cluster 1000mm^3, ALE 0.0155

Right cingulate gyrus: Talairach coordinates (8, 26, 32), cluster 1000mm^3, ALE 0.0110

Left superior temporal gyrus: Talairach coordinates (-54, 2, -4), cluster 976mm^3, ALE 0.0159

Left insula: Talairach coordinates (-40, 6, 0), cluster 976mm^3, ALE 0.0105

Right inferior frontal gyrus: Talairach coordinates (24, 34, -8), cluster 528mm^3, ALE 0.0184

Right superior temporal gyrus: Talairach coordinates (52, -8, -8), cluster 504mm^3, ALE 0.0173

Left middle frontal gyrus: Talairach coordinates (-32, 34, -6), cluster 456mm^3, ALE 0.0174

Left inferior frontal gyrus: Talairach coordinates (-48, 6, 22), cluster 416mm^3, ALE 0.0142

Left medial frontal gyrus: Talairach coordinates (-8, 46, 8), cluster 288mm^3, ALE 0.0120

Right caudate: Talairach coordinates (10, 10, 12), cluster 224mm^3, ALE 0.0116

Right post central gyrus: Talairach coordinates (52, -20, 44), cluster 216mm^3, ALE 0.0115

Left post central gyrus: Talairach coordinates (-60, -18, 20), cluster 200mm^3, ALE 0.0117

Right medial frontal gyrus: Talairach coordinates (2, 36, -16), cluster 192mm^3, ALE 0.0125

Right cerebellum: Talairach coordinates (28, -44, -34), cluster 184mm^3, ALE 0.0117

Left uncus: Talairach coordinates (-38, -14, -30), cluster 176mm^3, ALE 0.0124

Between group comparisons: subtraction analysis between high-risk individuals and first-episode schizophrenia;

<u>Greater grey matter reduction in high-risk group</u>

Left inferior frontal gyrus: Talairach coordinates (-50, 26, -2), cluster 224mm^3, ALE -0.0107

Left subcallosal gyrus: Talairach coordinates (-22, 6, -14), cluster 184mm^3, ALE -0.0115

Left amygdala: Talairach coordinates (-30, -8, -12), cluster 128mm^3, ALE -0.0097

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Left anterior cingulate gyrus: Talairach coordinates (-6, -36, 18), cluster 128mm^3, ALE -0.0098 Greater grey matter reduction in first-episode group Left superior temporal gyrus: Talairach coordinates (-52, -8, 6), cluster 1728mm^3, ALE 0.01614 Left transverse temporal gyrus: Talairach coordinates (-46, -20, 12), cluster 1728mm^3, ALE 0.0116 Left insula: Talairach coordinates (-34, 20, 6), cluster 1184mm^3, ALE 0.0232 Right cingulate gyrus: Talairach coordinates (6, 18, 38), cluster 448mm^3, ALE 0.0120 Right precentral gyrus: Talairach coordinates (48, -10, -12), cluster 400mm^3, ALE 0.0131 Left uncus: Talairach coordinates (-18, -2, -22), cluster 368mm^3, ALE 0.0122 Right cerebellum: Talairach coordinates (28, -44, -34), cluster 320mm^3, ALE 0.0116 Left uncus: Talairach coordinates (-38, -14, -30), cluster 272mm^3, ALE 0.0124 Right caudate nucleus: Talairach coordinates (10, 8, 14), cluster 224mm^3, ALE 0.0104 Left thalamus: Talairach coordinates (-2, -14, 4), cluster 192mm^3, ALE 0.0095 Left caudate nucleus: Talairach coordinates (-12, 6, 12), cluster 192mm^3, ALE 0.0099	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct
Comparison 3	**Grey matter changes in chronic schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests chronic schizophrenia have grey matter reductions in bilateral anterior cingulate gyrus, bilateral insula, right superior temporal gyrus, right parahippocampus, bilateral amygdala, left frontal lobe (inferior, medial, middle), right frontal lobe (superior, middle, inferior), thalamus, and left posterior cingulate gyrus compared to controls.**
Grey matter change in chronic schizophrenia	
Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies; FWHM 10mm, FDR corrected at $p < 0.01$ 19 studies, N = 1,664 Left inferior frontal gyrus: Talairach coordinates (-36,16, -4), cluster 4832mm^3, ALE 0.0222 Left insula: Talairach coordinates (-46, 8, 0), cluster 4832mm^3, ALE 0.0218	

Left insula: Talairach coordinates (-40, 0, 8), cluster 4832mm^3, ALE 0.01237
Left insula: Talairach coordinates (-38, 0, 14), cluster 4832mm^3, ALE 0.01233
Left insula: Talairach coordinates (-40, -22, 14), cluster 328mm^3, ALE 0.0137
Right insula: Talairach coordinates (40, 10, 4), cluster 2336mm^3, ALE 0.0292
Left medial frontal gyrus: Talairach coordinates (-4, 52, 12), cluster 2976mm^3, ALE 0.0196
Left medial frontal gyrus: Talairach coordinates (-6, 34, -14), cluster 2976mm^3, ALE 0.0182
Left middle frontal gyrus: Talairach coordinates (-44, 8, 36), cluster 1208mm^3, ALE 0.0199
Left inferior frontal gyrus: Talairach coordinates (-50, 6, 30), cluster 1208mm^3, ALE 0.0176
Right inferior frontal gyrus: Talairach coordinates (26, 28, -2), cluster 136mm^3, ALE 0.0119
Right superior frontal gyrus: Talairach coordinates (30, 54, 10), cluster 416mm^3, ALE 0.0147
Right middle frontal gyrus: Talairach coordinates (42, 4, 38), cluster 392mm^3, ALE 0.0171
Right superior temporal gyrus: Talairach coordinates (54, 4, 0), cluster 2336mm^3, ALE 0.0145
Left anterior cingulate gyrus: Talairach coordinates (0, 38, -4), cluster 2976mm^3, ALE 0.0176
Left anterior cingulate gyrus: Talairach coordinates (-2, 6, -2), cluster 1832mm^3, ALE 0.0316
Left cingulate gyrus: Talairach coordinates (-6, 18, 34), cluster 1744mm^3, ALE 0.0185
Right cingulate gyrus: Talairach coordinates (2, 18, 32), cluster 1744mm^3, ALE 0.0180
Left cingulate gyrus: Talairach coordinates (-2, 8, 40), cluster 1744mm^3, ALE 0.0122
Left thalamus: Talairach coordinates (-2, -18, 6), cluster 1648mm^3, ALE 0.0281
Left amygdala: Talairach coordinates (-16, -6, -12), cluster 840mm^3, ALE 0.0247
Right amygdala: Talairach coordinates (18, -4, -12), cluster 584mm^3, ALE 0.0195
Right post central gyrus: Talairach coordinates (56, -20, 18), cluster 792mm^3, ALE 0.0239
Left uncus: Talairach coordinates (-32, -8, -32), cluster 160mm^3, ALE 0.0137
Right parahippocampal gyrus: Talairach coordinates (12, -36, 0), cluster 160mm^3, ALE 0.0132
Between group comparison: subtraction analysis between chronic and first-episode schizophrenia; <u>Greater grey matter reduction in first-episode group</u>
Left superior temporal gyrus: Talairach coordinates (-52, -8, 6), cluster 944mm^3, ALE -0.0154
Left transverse temporal gyrus: Talairach coordinates (-46, -18, 10), cluster 944mm^3, ALE -0.0154
Left superior temporal gyrus: Talairach coordinates (-58, -28, 12), cluster 448mm^3, ALE -0.0149
Right superior temporal gyrus: Talairach coordinates (52, -8, -8), cluster 408mm^3, ALE -0.0172
Left superior temporal gyrus: Talairach coordinates (-56, 2, -4), cluster 320mm^3, ALE -0.0142
Left insula: Talairach coordinates (-34, 20, 6), cluster 664mm^3, ALE -0.0225
Right insula: Talairach coordinates (34, 16, 12), cluster 512mm^3, ALE -0.0171

Left inferior frontal gyrus: Talairach coordinates (-48, 6, 22), cluster 208mm^3, ALE -0.0133 Right inferior frontal gyrus: Talairach coordinates (24, 34, -8), cluster 168mm^3, ALE -0.0146 Left inferior frontal gyrus: Talairach coordinates (-32, 32, -4), cluster 136mm^3, ALE -0.0126 Right precentral gyrus: Talairach coordinates (50, -12, 12), cluster 120mm^3, ALE -0.0121 Right cingulate gyrus: Talairach coordinates (6, 14, 38), cluster 120mm^3, ALE -0.0119 <u>Greater grey matter reduction in chronic group</u> Left anterior cingulate gyrus: Talairach coordinates (-2, 6, -2), cluster 1896mm^3, ALE 0.0311 Right insula: Talairach coordinates (42, 10, 2), cluster 984mm^3, ALE 0.0228 Left medial frontal gyrus: Talairach coordinates (-4, 52, 14), cluster 544mm^3, ALE 0.0156 Left medial frontal gyrus: Talairach coordinates (-6, 34, -14), cluster 392mm^3, ALE 0.0138 Left inferior frontal gyrus: Talairach coordinates (-34, 16, -6), cluster 272mm^3, ALE 0.0138 Left cerebellum: Talairach coordinates (-2, -70, -4), cluster 168mm^3, ALE 0.0124 Right postcentral gyrus: Talairach coordinates (56, -22, 16), cluster 160mm^3, ALE 0.0151 Right uncus: Talairach coordinates (38, -12, -30), cluster 144mm^3, ALE 0.0127

Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct, apart from subtraction analyses.

Cheung C, Yu K, Fung G, Leung M, Wong C, Li Q, Sham P, Chua S, McAlonan G

Autistic disorders and schizophrenia: related or remote? An anatomical likelihood estimation

PLOS One 2010; 5(8): e12233

View review abstract online

Comparison	**Regions of overlapping brain alterations in people with schizophrenia and people with autistic spectrum disorders (ASD) vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) suggests overlapping grey matter volume decreases in the right posterior cingulate cortex, right parahippocampus and right putamen, and**

	to a lesser extent, in the right insula and left thalamus.
Overlapping brain alterations	
Regions of decreased grey matter volume, reporting the % that is contributed to by schizophrenia and autism studies; Right middle frontal gyrus: Talairach coordinates (43, 33, 21), 100% SZ, 0% ASD Left uncus/amygdala: Talairach coordinates (-16, -2, -21), 100% SZ, 0% ASD Left temporal gyrus: Talairach coordinates (-60, -24, 12), 100% SZ, 0% ASD Left caudate: Talairach coordinates (2, 12, 6), 100% SZ, 0% ASD Left superior frontal gyrus: Talairach coordinates (-2, 32, 53), 99.9% SZ, 0.1% ASD Left insula/inferior frontal gyrus: Talairach coordinates (-38,22,0), 99.9% SZ, 0.1% ASD Right cingulate gyrus: Talairach coordinates (10, 21, 32), 99.8% SZ, 0.2% ASD Left precuneus/cingulate: Talairach coordinates (0, -45, 32), 99.6% SZ, 0.4% ASD Right insula: Talairach coordinates (32, -17, 15), 77.4% SZ, 22.6% ASD Left thalamus: Talairach coordinates (-7, -20, 10), 76.9% SZ, 23.1% ASD Right insula: Talairach coordinates (39, -20, -4), 76.9% SZ, 23.1% ASD Right putamen: Talairach coordinates (28, 0, 6), 61.1% SZ, 38.9% ASD Right posterior cingulate gyrus: Talairach coordinates (21, -56, 14), 58.9% SZ, 41.1% ASD Right parahippocampal gyrus: Talairach coordinates (28, -14, -15), 57.1% SZ, 42.9% ASD Left putamen: Talairach coordinates (-23, 2, 5), 0.2% SZ, 99.8% ASD *Regions of increased grey matter volume, reporting the % that is contributed to by schizophrenia and autism studies;* Left superior temporal gyrus: Talairach coordinates (-34, -50, 6), 92.2% SZ, 7.8% ASD Left putamen: Talairach coordinates (-22, 0, 12), 94.4% SZ, 5.6% ASD	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Cooper D, Barker V, Radua J, Fusar-Poli P, Lawrie SM

Multimodal voxel-based meta-analysis of structural and functional magnetic resonance imaging studies in those at elevated genetic risk of

developing schizophrenia

Psychiatry Research - Neuroimaging 2014; 221(1): 69-77

View review abstract online

Comparison	**Comparison of structural anomalies in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, direct, unable to assess precision) suggest relatives show increased grey matter in the left medial frontal gyrus and decreased grey matter in the left thalamus/putamen, right superior frontal gyrus and left insula.**

Structural anomalies

6 studies, N = 939

Relatives showed increased grey matter in;

Left medial frontal gyrus: Talairach coordinates (-2, -14, 54), $p = 0.00001$

Relatives showed decreased grey matter in;

Left thalamus/putamen: Talairach coordinates (-26, 4, -6), $p = 0.0003$

Right superior frontal gyrus: Talairach coordinates (18, 48, -2), $p = 0.0004$

Left insula: Talairach coordinates (34, -2, 14), $p = 0.0007$

Authors report a combined structural and functional analysis that demonstrated decreased grey matter with increased activation in the left inferior frontal gyrus and amygdala of relatives and decreased grey matter with decreased activation in the left thalamus of relatives.

Consistency in results	Authors report the results are consistent.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Davidson LL, Heinrichs RW

Quantification of frontal and temporal lobe brain-imaging findings in schizophrenia: a meta-analysis

Psychiatry Research 2003; 122(2): 69-87

View review abstract online	
Comparison	**Grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, mostly inconsistent, precise, direct) suggests grey matter volume is significantly reduced in the frontal lobe, temporal lobe, hippocampus and amygdala.**
Frontal lobe volume	
Small to medium-sized reductions in; Left frontal lobe: N = 2,067, *d* = -0.39, 95%CI -0.55 to -0.23, *p* not reported; SD = 0.47, FSN = 104 Right frontal lobe: N = 1,951, *d* = -0.41, 95%CI -0.56 to -0.26, *p* not reported; SD = 0.42, FSN = 102 Total frontal lobe: N = 3,194, *d* = -0.44, 95%CI -0.55 to -0.32, *p* not reported; SD = 0.42, FSN = 170	
Temporal lobe volume	
Small to medium-sized reductions in; Left temporal lobe: N = 2,030, *d* = -0.32, 95%CI -0.46 to -0.19, *p* not reported; SD = 0.37, FSN = 68 Right temporal lobe: N = 1,945, *d* = -0.30, 95%CI -0.42 to -0.17, *p* not reported; SD = 0.34, FSN = 60 Total temporal lobe: N = 2,718, *d* = -0.29, 95%CI -0.40 to -0.18, *p* not reported; SD = 0.34, FSN = 74 Left Superior temporal gyrus: N = 1,152, *d* = -0.55, 95%CI -0.72 to -0.38, *p* not reported; SD = 0.33, FSN = 76 Right Superior temporal gyrus: N = 1,122, *d* = -0.40, 95%CI -0.40 to -0.65, *p* not reported; SD = 0.47, FSN = 48	
Hippocampus/ Amygdala complex volume	
Small to medium-sized reductions in; Left amygdala: N = 970, *d* = -0.39, 95%CI -0.68 to -0.10, *p* not reported SD = 0.53, FSN = 44 Right amygdala: N = 1,109, *d* = -0.38, 95%CI -0.72 to -0.04, *p* not reported SD = 0.67, FSN = 48 Left hippocampus: N = 1,919, *d* = -0.55, 95%CI -0.74 to -0.36, *p* not reported SD = 0.51, FSN = 140 Right hippocampus: N = 1,814, *d* = -0.58, 95%CI -0.74 to -0.41, *p* not reported SD = 0.44, FSN = 144 Left hippocampus/amygdala complex: N = 1302, *d* = -0.41, 95%CI -0.74 to -0.41, *p* not reported SD = 0.44, FSN = 71 Right hippocampus/amygdala complex: N = 1,238, *d* = -0.36, 95%CI -0.54 to -0.18, *p* not reported SD = 0.40, FSN = 57	
Consistency in results	Inconsistent, significant heterogeneity reported in all outcomes except

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	right frontal cortex, and left, right and total temporal cortex.
Precision in results	Precise for all outcomes.
Directness of results	Direct

De Peri L, Crescini A, Deste G, Fusar-Poli P, Sacchette 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: 486-494

View review abstract online

Comparison	**Grey matter volume in people with first-episode schizophrenia or bipolar disorder vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, mostly consistent, precise, direct) suggests significant reductions of intracranial, whole brain, and grey matter volumes and increased lateral ventricle volume in people with first-episode schizophrenia. In people with first-episode bipolar disorder, there were small reductions in whole brain grey matter and total white matter, and no differences in total grey matter or ventricle volume.**

Whole brain volumes

Small reductions in intracranial, whole brain, and grey matter volumes, and increased volumes of left and right lateral ventricles in people with first-episode schizophrenia, with no differences in white matter volume;

Intracranial volume: 17 studies, N = 1,148, g = -0.15, 95%CI -0.27 to -0.04, p = 0.008, Q = 8.33, p = 0.93

Whole brain volume: 21 studies, N = 1,458, g = -0.26, 95%CI -0.40 to -0.12, $p < 0.001$, Q = 34.21, p = 0.02

Grey matter volume: 12 studies, N = 850, g = -0.36, 95%CI -0.50 to -0.23, $p < 0.001$, Q = 13.23, p = 0.27

White matter volume: 6 studies, N = 493, g = -0.14, 95%CI -0.32 to 0.03, p = 0.105, Q = 1.26, p = 0.93

Lateral ventricle volume: 8 studies, N = 627, g = 0.38, 95%CI 0.22 to 0.54, $p < 0.001$, Q = 3.62, p = 0.82

Right lateral ventricle volume: 12 studies, N = 825, *g* = 0.40, 95%CI 0.26 to 0.54, *p* < 0.001, Q = 7.57, *p* = 0.75 Left lateral ventricle volume: 12 studies, N = 825, *g* = 0.49, 95%CI 0.35 to 0.64, *p* < 0.001, Q = 11.09, *p* = 0.37 *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, apart from whole brain volume
Precision in results	Precise
Directness of results	Direct

Di X, Chan RC, Gong QY

White matter reduction in patients with schizophrenia as revealed by voxel-based morphometry: an activation likelihood estimation meta-analysis

Progress in Neuro-Psychopharmacology & Biological Psychiatry 2009; 33(8): 1390-1394

View review abstract online

Comparison	**White matter volume, measured by voxel-based morphometry, in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency and precision) suggests reduced white matter volume in the frontal lobe and internal capsule.**

White matter volume

Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies;

FWHM 10mm, FDR corrected at *p* < 0.01

17 studies, N = 712

Pooled analysis identified 4 clusters of reduced white matter volume, encompassing foci in the frontal lobe and internal capsule
Right frontal white matter: Talairach coordinates (20, 46, 26), voxel cluster size 544mm^3, ALE 0.010283
Left frontal white matter: Talairach coordinates (-8, 48, -2), voxel cluster size 336mm^3, ALE 0.010507
Right internal capsule: Talairach coordinates (16, 4, 8), voxel cluster size 352mm^3, ALE 0.011932
Left internal capsule: Talairach coordinates (-16, 2, 2), voxel cluster size 248mm^3, ALE 0.008271

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	Direct

Ding Y, Ou Y, Pan P, Shan X, Chen J, Liu F, Zhao J, Guo W

Cerebellar structural and functional abnormalities in first episode and drug-naive patients with schizophrenia: A meta-analysis

Psychiatry Research - Neuroimaging 2019; 283: 24-33

View review abstract online

Comparison	**Grey matter volume in medication-naïve people with first-episode schizophrenia vs. controls.** **Note: one study included 28 patients on low-dose risperidone or olanzapine.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, direct, unable to assess precision) suggests reduced grey matter volume in the cerebellar vermic lobule IV/V/VII, left cerebellar lobule IV/V, and left cerebellar Crus I in medication-naïve people with first-episode schizophrenia.**

Cerebellum grey matter volume
11 studies, N = 806
Reduced grey matter was found in;
Cerebellar vermic lobule IV/V: 88 voxels, MNI coordinates (-4, -56, -22), p = 0.000510931
Cerebellar vermic lobule VII: 18 voxels, MNI coordinates (4, -68, -30), p = 0.004108012

Left cerebellar lobule IV/V: 142 voxels, MNI coordinates (-6, -52, -20), *p* = 0.000567675 Left cerebellar Crus I: 393 voxels, MNI coordinates (-40, -54, -36), *p* = 0.001207650 More severe positive and negative symptoms were associated with both decreased and increased cerebellum grey matter. There was no moderating effect of illness duration.	
Consistency in results	Authors report consistent results.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Ding Y, Ou Y, Pan P, Shan X, Chen J, Liu F, Zhao J, Guo W

Brain structural abnormalities as potential markers for detecting individuals with ultra-high risk for psychosis: A systematic review and meta-analysis

Schizophrenia Research 2019; 209: 22-31

View review abstract online

Comparison	**Grey matter volume in people at clinical high risk of psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, direct, unable to assess precision) found increased grey matter volume in bilateral median cingulate, right fusiform gyrus, left superior temporal gyrus, and right thalamus, and decreased grey matter volume in the right gyrus rectus, right superior frontal gyrus, and left superior frontal gyrus of high risk individuals.**
Grey matter volume	
14 VBM studies, N = 1,331 *Increased grey matter volumes were found in people at high risk in the following areas;* Bilateral median cingulate (Z = 1.034) Right fusiform gyrus (Z = 1.051) Left superior temporal gyrus (Z = 1.048)	

Right thalamus (Z = 1.039) *Decreased grey matter volumes were found in people at high risk in the following areas;* Right gyrus rectus (Z = -2.109) Right superior frontal gyrus (Z = -2.321) Left superior frontal gyrus (Z = -2.228) Authors report no consistent differences in cortical thickness.	
Consistency in results	Authors report consistent results.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E

The anatomy of first episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis

American Journal of Psychiatry 2008; 165(8): 1015-23

View review abstract online

Comparison	**Grey matter changes in people with first-episode schizophrenia vs. chronic schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) finds bilateral caudate head and amygdala grey matter reductions in first-episode schizophrenia, which are absent in chronic schizophrenia. More widespread abnormality was observed in chronic schizophrenia, including decreased medial frontal, dorsolateral prefrontal, hippocampus, and superior temporal cortical grey matter.** **Significant reductions in insula, mediodorsal thalamus, anterior cingulate and inferior frontal gyrus were common to both first episode and chronic schizophrenia.**
Changes reported in first-episode schizophrenia	
Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies of whole brain grey matter reported at baseline; N = 1,556, 27 studies	

Magnetic resonance imaging

First-episode reductions Left caudate head: Talairach coordinates (-12, 6, 12), cluster 528mm^3, ALE 0.01, p = 0.0002 Right caudate head: Talairach coordinates (10, 10, 12), cluster 1392mm^3, ALE 0.012, p < 0.0002 Mediodorsal thalamus: Talairach coordinates (2, -18, 10), cluster 312mm^3, ALE 0.007, p = 0.001 Left insula: Talairach coordinates (-40, 6, 0), cluster 1552mm^3, ALE 0.01, p < 0.0002 Right insula: Talairach coordinates (34, 4, 8), cluster 680mm^3, ALE 0.008, p = 0.0002 Right anterior cingulate gyrus: Talairach coordinates (8, 16, 38), cluster 464mm^3, ALE 0.007, p = 0.0016 Left inferior frontal gyrus: Talairach coordinates (-28, 30, -6), cluster 736mm^3, ALE 0.009, p = 0.0004 Right inferior frontal gyrus: Talairach coordinates (26, 10, 18), cluster 360mm^3, ALE 0.007, p = 0.001 Left uncus/amygdala: Talairach coordinates (-18, -2, -22), cluster 2760mm^3, ALE 0.018, p < 0.0002 Right uncus/amygdala: Talairach coordinates (20, -4, -22), cluster 688mm^3, ALE 0.012, p < 0.0002 Cerebellum: Talairach coordinates (-4, -66, -26), cluster 320mm^3, ALE 0.008, p = 0.0008 First-episode increases Left putamen: Talairach coordinates (-22, 0, 12), cluster 1592mm^3, ALE 0.008, p < 0.0002
Changes reported in chronic schizophrenia
Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies of whole brain grey matter; N = 1,556, 27 studies Significant reduction of volume were seen in the medial frontal gyrus (p <0.0004), the STG (p = 0.0018), the right hippocampus (p = 0.0004) and the dorsolateral prefrontal cortex (p < 0.0002), left middle frontal (p < 0.0002), the left temporal fusiform gyrus (p< 0.0002).
Changes common to first episode and chronic schizophrenia
Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies of whole brain grey matter; N = 1,556, 27 studies Significant reductions in the bilateral insula (p < 0.0002), the mediodorsal thalamus (p < 0.001), the anterior cingulate cortex (p < 0.0016), and the left inferior frontal gyrus (p < 0.001).

Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Ellison-Wright I, Bullmore E

Anatomy of bipolar disorder and schizophrenia: A meta-analysis.

Schizophrenia Research 2010; 117: 1-12

View review abstract online

Comparison	**Grey matter changes in schizophrenia or bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests bilateral reductions in grey matter in the insula and medial frontal gyri, as well as in the left anterior cingulate, left posterior cingulate and mediodorsal thalamic nucleus. There were also increases in the right globus pallidus and left caudate head in people with schizophrenia. In people with bipolar disorder, there were decreases in bilateral insula and perigenual and subgenual anterior cingulate with no regions showing increases in grey matter. Authors report a distinct region of the pregenual cingulate cortex (anterior Brodmann area 24) where grey matter reduction was detected in bipolar disorder studies but not in schizophrenia studies.**

Grey matter changes

Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies, weighted for sample size using sum-rank images;

FWHM 7mm, FDR corrected at $p < 0.05$

Schizophrenia: 42 studies, N = 4,189

Regions of decreased grey matter in schizophrenia;

Left insula: Talairach coordinates (-36, 10, 2), Sum of ranks = 218.3, $p = 0.00005$

Right insula: Talairach coordinates (40, 8, 2), Sum of ranks = 205.2, $p = 0.00005$

Left mediodorsal thalamus: Talairach coordinates (-4, -14, 4), Sum of ranks = 181.3, $p = 0.00005$

Left medial frontal gyrus: Talairach coordinates (-2, 50, 4), Sum of ranks = 179.6, $p = 0.00005$

Left anterior cingulate: Talairach coordinates (-2, 44, -4), Sum of ranks = 179.3, $p = 0.00005$

Left medial frontal gyrus: Talairach coordinates (-2, 48, 0), Sum of ranks = 179.3, $p = 0.00005$

Left anterior cingulate: Talairach coordinates (-2, 46, -2), Sum of ranks = 179.3, *p* =0.00005

Left deep frontal lobe: Talairach coordinates (-14, 2, -10), Sum of ranks = 172.8, *p* = 0.00005

Left deep frontal lobe: Talairach coordinates (-12, 0, -8), Sum of ranks = 172.5, *p* = 0.00005

Left anterior cingulate: Talairach coordinates (-6, 24, 36), Sum of ranks = 172.5, *p* = 0.00010

Right medial frontal gyrus: Talairach coordinates (2, 42, 26), Sum of ranks = 157.1, *p* = 0.00060

Right medial frontal gyrus: Talairach coordinates (2, 44, 24), Sum of ranks = 156.8, *p* = 0.00070

Right medial frontal gyrus: Talairach coordinates (2, 48, 22), Sum of ranks = 156.5, *p* = 0.00075

Left posterior cingulate: Talairach coordinates (-8, -60, 12), Sum of ranks = 158.0, *p* = 0.00050

Regions of increased grey matter in schizophrenia;

Right globus pallidus: Talairach coordinates (16, 0, 4), Sum of ranks = 71.6, *p* = 0.00005

Left caudate head: Talairach coordinates (-6, 8, 4), Sum of ranks = 67.8, *p* = 0.00005

Bipolar disorder: 14 studies, N = 863

Regions of decreased grey matter in bipolar disorder;

Right insula: Talairach coordinates (44, 18, 8), Sum of ranks = 43.5, *p* = 0.00005

Left insula: Talairach coordinates (-32, 16, -10), Sum of ranks = 40.6, *p* = 0.00010

Perigenual anterior cingulate: Talairach coordinates (0, 40, 22), Sum of ranks = 41.2, *p* = 0.00010

Subgenual anterior cingulate: Talairach coordinates (0, 14, -12), Sum of ranks = 37.4, *p* = 0.00140

Authors report a distinct region of the pregenual cingulate cortex (anterior Brodmann area 24) where grey matter reduction was detected in bipolar disorder studies but not schizophrenia studies.

There were no consistent regions of grey matter increase in bipolar disorder.

Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Fornito A, Yucel M, Patti J, Wood SJ, Pantelis C

Mapping grey matter reductions in schizophrenia: An anatomical likelihood estimation analysis of voxel-based morphometry studies

Schizophrenia Research 2009; 108(1-3): 104-113

View review abstract online

Comparison 1	**Grey matter density using voxel-based morphometry analysis in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests bilateral reductions in grey matter volume in the anterior cingulate/medial prefrontal cortex, the insula/operculum, the posterior cingulate, thalamus, medial temporal lobe, and subgenual cingulate; as well as lateralised differences in the left middle and inferior frontal gyri, the left fusiform gyrus, and left inferior parietal gyrus.**
Pooled ALE analysis of all foci: whole brain analysis	
Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies; FWHM 12mm, FDR corrected at $p < 0.05$ 37 studies, N = 3,336 Pooled analysis identified 15 clusters of reduced grey matter, encompassing foci in the frontal, temporal, limbic and subcortical regions. The largest clusters were reported in the bilateral anterior cingulate/medial prefrontal cortex and the bilateral insula/operculum. Also decreased grey matter reported bilaterally in the posterior cingulate, thalamus, medial temporal lobe, and subgenual cingulate. Decreased grey matter was reported in the left middle and inferior frontal gyri, the left fusiform gyrus, and left inferior parietal gyrus.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct
Comparison 2	**Grey matter volume (GMV) and grey matter concentration (GMC, grey matter as a proportion of the whole brain volume) using voxel-based morphometry analysis in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) suggests concentration and volume measures of grey matter provide different accounts of the regions affected in schizophrenia. Volume measured clusters were generally smaller and more spatially dispersed while concentration measured regions remained consistent across all subsets tested, suggesting GMC values may be more robust.**

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	Significant volume reductions were reported in the insula, cingulate gyrus, thalamus, hippocampus, cerebellum, amygdala, frontal and temporal lobes.
Clusters where GMC reductions were significantly more frequent than GMV reductions	
Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies; FWHM 12mm, FDR corrected at $p < 0.05$ 37 studies, N = 3,336 Right insula: Talairach coordinates (39.4, 10.46, 2.06), Voxel cluster size 6952mm^3, ALE 1.81 x 10^{-3} Left insula: Talairach coordinates (-41.02, 14.04, -1.91), Voxel cluster size 6816mm^3, ALE 1.55 x 10^{-3} Right anterior cingulate gyrus/medial prefrontal gyrus: Talairach coordinates (0.04, 53.3, 0.59), Voxel cluster size 5144mm^3, ALE 1.36 x 10^{-3} Left posterior cingulate gyrus: Talairach coordinates (-1.63, -55.9, 24.35), Voxel cluster size 2768mm^3, ALE 0.97 x 10^{-3} Right subgenual cingulate gyrus: alairach coordinates (0.95, 7.2, -0.96), Voxel cluster size 2728mm^3, ALE 1.21 x 10^{-3} Right dorsal anterior cingulate gyrus: Talairach coordinates (4.62, 20.41, 32.78), Voxel cluster size 2144mm^3, ALE 1.13 x 10^{-3} Left thalamus: Talairach coordinates (-0.83, -20.22, 7.67), Voxel cluster size 2048mm^3, ALE 1.44 x 10^{-3} Left amygdala/hippocampus: Talairach coordinates (-18.33, -4.63, -15.34), Voxel cluster size 1592mm^3, ALE 0.98 x 10^{-3} Left medial orbito-frontal gyrus: Talairach coordinates (-1.11, 43.03, -21.06), Voxel cluster size 1208mm^3, ALE 0.87 x 10^{-3} Left cerebellum: Talairach coordinates (-1.35, -70.86, -3.42), Voxel cluster size 336mm^3, ALE 0.73 x 10^{-3} Left occipito-temporal gyrus: Talairach coordinates (-52.58, -62.73, -7.35), Voxel cluster size 296mm^3, ALE 0.72 x 10^{-3} Left hippocampal formation: Talairach coordinates (-30.51, -34.78, -12.2), Voxel cluster size 240mm^3, ALE 0.65 x 10^{-3}	
Clusters where GMV reductions were significantly more frequent than GMC reductions	
Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies; FWHM 12mm, FDR corrected at $p < 0.05$ 37 studies, N = 3,336 Left medial superior frontal gyrus: Talairach coordinates (-5.6, 31.84, 46.13), Voxel cluster size	

1688mm^3, ALE -0.76 x 10^{-3} Left lateral superior frontal gyrus: Talairach coordinates (-31.56, 53.64, 19.6), Voxel cluster size 1120mm^3, ALE -0.68 x 10^{-3} Right inferior frontal gyrus: Talairach coordinates (48.39, 2.83, 30.96), Voxel cluster size 1096mm^3, ALE -0.74 x 10^{-3} Left cerebellum: Talairach coordinates (-19.99, -82.02, -16.2), Voxel cluster size 800mm^3, ALE -0.76 x 10^{-3} Left lateral orbito-frontal gyrus: Talairach coordinates (-26.82, 28.11, -4.7), Voxel cluster size 680mm^3, ALE 0.74 x 10^{-3} Right pre- and post-central gyri: Talairach coordinates (52.97, -24.28, 43.55), Voxel cluster size 408mm^3, ALE -0.54 x 10^{-3} Left middle frontal gyrus: Talairach coordinates (-42.94, 9.86, 39.04), Voxel cluster size 192mm^3, ALE 0.68 x 10^{-3} Right middle/inferior frontal gyri: Talairach coordinates (27.67, 58.41, 9.68), Voxel cluster size 192mm^3, ALE 0.68 x 10^{-3} Left cerebellum: Talairach coordinates (-52.75, -47.02, -22.41), Voxel cluster size 128mm^3, ALE 0.59 x 10^{-3}
GMC vs. GMV: multiple comparisons for reliability
As GMC had fewer foci available for comparison, a random subset was initially selected for comparison with GMV. To increase validity of this comparison, four additional GMC/GMV contrasts were performed with different GMC subsets, and demonstrated high consistency between randomisations. *Both cluster size and ALE statistic were larger for comparisons using concentration measures compared to volume measures;* Cluster size t = 2.54, p = 0.02 ALE statistic t = 2.82, p = 0.01

Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Fusar-Poli P, Borgwardt S, Crescini A, Deste G, Kempton MJ, Lawrie S, McGuire P, Sacchetti E

Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis

Neuroscience and Biobehavioural Reviews 2011; 35: 1175-1185 View review abstract online	
Comparison	**Whole brain comparison of grey matter density in people at high-risk of schizophrenia (both clinical high-risk and genetic high-risk) vs. controls and vs. people with psychosis.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests decreases in the right superior temporal gyrus, left precuneus, left medial frontal gyrus, right middle frontal gyrus, bilateral parahippocampal/hippocampal regions, and bilateral anterior cingulate in people at high-risk compared to controls. Compared to people with psychosis increases were detected in the amygdala bilaterally, medial frontal gyrus, middle temporal gyrus and in the right precuneus.** **People at high clinical risk showed decreases in the bilateral anterior cingulate compared to people at high genetic risk. People at high genetic risk showed decreases in the left parahippocampus, insula and right superior temporal gyrus compared to people at high clinical risk. People at high-risk who developed a psychotic episode showed decreases in the right inferior frontal gyrus, right insula and right superior temporal gyrus compared to those who did not develop psychosis.**
Grey matter volume	
19 studies, N = 1,601 All - clinical and genetic high-risk of psychosis vs. controls Decreases were reported in the right superior temporal gyrus, left precuneus, left medial frontal gyrus, right middle frontal gyrus, bilateral parahippocampal/hippocampal regions, and bilateral anterior cingulate. All - clinical and genetic high-risk of psychosis vs. people with psychosis Increases were reported in the amygdala bilaterally, medial frontal gyrus, middle temporal gyrus, and the right precuneus. Genetic high-risk of psychosis vs. controls Decreases were reported in the left parahippocampal gyrus, and anterior cingulate bilaterally. Clinical high-risk of psychosis vs. controls Decreases were reported in the left hippocampus, insula, right superior temporal gyrus, right inferior frontal gyrus, and medial frontal gyrus. Genetic high-risk of psychosis vs. clinical high-risk of psychosis People at high clinical risk showed decreases in the bilateral anterior cingulate. People at high	

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genetic risk showed decreases in the left parahippocampus, insula and right superior temporal gyrus. People at high-risk who developed a psychotic episode vs. people at high risk who did not develop psychosis People at high-risk who developed a psychotic episode showed decreases in the right inferior frontal gyrus, right insula and right superior temporal gyrus.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Fusar-Poli P, Radua J, McGuire P, Borgwardt S

Neuroanatomical maps of psychosis onset: voxel-wise meta-analysis of antipsychotic-naive VBM studies

Schizophrenia Bulletin 2012; 38(6): 1297-1307

View review abstract online

Comparison	**Whole brain comparison of grey matter density in people at high clinical risk of schizophrenia (according to Attenuated Psychosis Syndrome or Basic Symptoms criteria), and in people in a first episode of schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests significant large reductions in grey matter volume in people with first-episode schizophrenia and in people at clinical high-risk of psychosis compared to controls.** **Moderate quality evidence (unable to assess consistency or precision) suggests specific reductions in the right superior temporal gyrus, left insula and left cerebellum in people with first-episode schizophrenia compared to controls and compared to people at high clinical risk of psychosis. People at clinical high-risk show reductions in the right middle/superior temporal gyrus, right parahippocampal gyrus, left anterior cingulate, and right middle frontal gyrus compared to controls.**
Reduced grey matter volume	

Effect size meta-analysis showed large reductions of grey matter volume;

First-episode: 14 studies, N = 408, g = 0.834, 95%CI 0.549 to 1.119, $p < 0.001$

High risk of psychosis; 14 studies, N = 452, g = 0.687, 95%CI 0.494 to 0.879, $p < 0.001$

Combined: g = 0.733, 95%CI 0.573 to 0.892, $p < 0.001$, Q = 114.258 (p = 0.356), I^2 = 9%

Voxel-based meta-analysis also showed reductions of grey matter volume;

First-episode schizophrenia < controls:

Right superior temporal gyrus: Talairach coordinates (45, 0, -13) Kc = 319mm^3

Left insula: Talairach coordinates (-48, 8, 2) Kc = 28mm^3

Left cerebellum: Talairach coordinates (-4, -52, -26) Kc = 95mm^3

High risk subjects < controls:

Right middle/superior temporal gyrus: Talairach coordinates (50, -30, 10) Kc = 157mm^3

Right parahippocampal gyrus: Talairach coordinates (30, -10, -20) Kc = 63mm^3

Left anterior cingulate: Talairach coordinates (-2, 18, -4) Kc = 75mm^3

Right middle frontal gyrus: Talairach coordinates (42, 32, 30) Kc = 81mm^3

First-episode < high risk subjects:

Right cingulate gyrus: Talairach coordinates (16, 10, 36) Kc = 211mm^3

Left cerebellum: Talairach coordinates (-4, -52, -26) Kc = 225mm^3

Right superior temporal gyrus: Talairach coordinates (48, -16, 6) Kc = 197mm^3

Left insula: Talairach coordinates (-42, 10, 2) Kc = 195mm^3

Consistency in results	Consistent for effect size meta-analysis, unable to assess voxel-based analysis.
Precision in results	Precise for effect size meta-analysis, unable to assess voxel-based analysis.
Directness of results	Direct

Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S

Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies

Neuroscience and Biobehavioural Reviews 2013; 37: 1680-1691

Magnetic resonance imaging

View review abstract online	
Comparison	**Longitudinal brain changes in medicated people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (medium to large samples, consistent, precise, direct) shows decreased whole brain volume, decreased grey matter volume, increased cerebrospinal fluid, and enlarged lateral ventricles.** **Moderate to high quality evidence (inconsistent) suggests greater decreases in grey matter volume and greater increase in lateral ventricles (LV) over time in patients, with accumulative effects of medication accounting for some of the variance in grey matter volume decreases.**
Baseline grey matter volume	
People with schizophrenia showed decreased whole brain volume (WBV), decreased grey matter volume (GMV), increased cerebrospinal fluid (CSF) and enlarged lateral ventricles (LV) compared to controls; WBV: 11 studies, N = 1,010, g = −0.252, 95%CI −0.414 to −0.091, p = 0.002, I^2 = 26.26, p = 0.194 GMV: 8 studies, N = 781, g = −0.192, 95%CI −0.343 to −0.041, p = 0.013, I^2 = 3.70, p =0.821 CSF: 3 studies, N = 158, g = 0.451, 95%CI 0.088 to 0.813, p = 0.045, I^2 = 7.90, p = 0.337 LV: 11 studies, N = 896, g = 0.309, 95%CI 0.144 to 0.467, p < 0.001, I^2 = 17.25, p = 0.279 *No significant differences in white matter volume (WMV), or caudate nucleus (Cd) volume;* WMV: 6 studies, N = 460, g =−0.012, 95%CI −0.294 to 0.269, p = 0.931, I^2 = 42.64, p = 0.121 Cd: 9 studies, N = 363, g = 0.116, 95%CI −0.107 to 0.339, p = 0.308, I^2 = 6.85, p = 0.378	
Changes in grey matter volume over time (4 - 520 weeks)	
People with schizophrenia showed greater decreases in grey matter volume (GMV), and greater increase in lateral ventricles (LV) over time, compared to controls; GMV schizophrenia: 9 studies, g = -0.249, 95%CI -0.399 to -0.093, p = 0.002, controls g = -0.143, 95%CI -0.293 to 0.008, p = 0.094, Q_B = 5.974, p = 0.044 LV schizophrenia: 12 studies, g = 0.207, 95%CI 0.075 to 0.339, p = 0.002, controls g = 0.129, 95%CI -0.025 to 0.283, p = 0.102, Q_B = 9.566, p = 0.029 Moderator analyses revealed GMV decreases in patients were associated with higher cumulative exposure to antipsychotics (β = -0.013, CI 95% -0.033 to -0.001, p = 0.048), but not with psychotic symptoms or duration of illness (both p > 0.05). LV changes were not associated with antipsychotic use or duration of illness (no assessment of symptoms was conducted). *There were no significant changes over time in whole brain volume (WBV), white matter volume*	

(WMV), cerebrospinal fluid (CSF), or caudate nucleus (Cd); WBV schizophrenia: 12 studies, *g* = -0.060, 95%CI -0.183 to 0.063, *p* = 0.339, controls *g* = -0.069, 95%CI -0.208 to 0.070, *p* = 0.333, Q_B = 0.009, *p* = 0.923 WMV schizophrenia: 8 studies, *g* = 0.001, 95%CI -0.184 to 0.184, *p* = 0.998, controls *g* = 0.148, 95%CI -0.032 to 0.328, *p* = 0.108, Q_B = 1.259, *p* = 0.262 CSF schizophrenia: 3 studies, *g* = 0.007, 95%CI -0.339 to 0.352, *p* = 0.970, controls *g* = 0.199, 95%CI -0.256 to 0.654, *p* = 0.391, Q_B = 1.759, *p* = 0.185 Cd schizophrenia: 13 studies, *g* = -0.010, 95%CI -0.183 to 0.164, *p* = 0.913, controls *g* = -0.149, 95%CI -0.357 to 0.059, *p* = 0.160, QB = 0.996 *p* = 0.318	
Consistency in results	Consistent for baseline data, authors report low magnitude but significant heterogeneity in the longitudinal data.
Precision in results	Precise
Directness of results	Direct

Fusar-Poli P, Smieskova R, Serafini G, Politi P, Borgwardt S

Neuroanatomical markers of genetic liability to psychosis and first episode psychosis: A voxelwise meta-analytical comparison.

World Journal of Biological Psychiatry 2014; 15(3): 219-28

View review abstract online

Comparison	**Brain anomalies in relatives of people with schizophrenia or people with first-episode psychosis vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess precision and consistency) suggests that compared to controls, grey matter reductions were observed in the left parahippocampal gyrus and in the right anterior cingulate gyrus in the high risk group, and in the right superior temporal gyrus, the left insula, left cerebellum and left anterior cingulate of first-episode psychosis patients.** **Comparing high-risk groups with first-episode groups, grey matter decreases were observed in the first-episode psychosis group in the left anterior cingulate, in the right precuneus, in the left cerebellum and in the right superior temporal gyrus.**
Grey matter volume	

Grey matter reductions in high-risk participants in; N = 870 Right anterior cingulate (BA24/32): Talairach coordinates (2, 30, 12), $p = 0.0001$ Left parahippocampal gyrus: Talairach coordinates (-28, -4, -12), $p < 0.0002$ *Grey matter reductions in first-episode participants in;* N = 408 Right superior temporal gyrus (BA38): Talairach coordinates (34, -4, -12), $p < 0.0005$ Left insula (BA13): Talairach coordinates (-48, 8, 2), $p < 0.0005$ Left cerebellum: Talairach coordinates (-4, -52, -26), $p < 0.0005$ Left anterior cingulate (BA32): Talairach coordinates (-3, 37, 16), $p < 0.0005$ *Grey matter reductions in first-episode participants vs. high-risk participants in;* Right superior temporal gyrus (BA38): Talairach coordinates (34, 4, -12), $p < 0.0001$ Right precuneus (BA7): Talairach coordinates (10, -50, 38), $p < 0.0002$ Left cerebellum: Talairach coordinates (-4, -52, 26), $p < 0.002$ Left anterior cingulate (BA24): Talairach coordinates (-2, 32, 14), $p < 0.0002$ There were no moderating effects of age, gender, magnet intensity, FMHW, or imaging package. Authors report no evidence of publication bias.

Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Gao X, Zhang W, Yao L, Xiao Y, Liu L, Liu J, Li S, Tao B, Shah C, Gong Q, Sweeney JA, Lui S

Association between structural and functional brain alterations in drug-free patients with schizophrenia: A multimodal meta-analysis

Journal of Psychiatry and Neuroscience 2018; 43: 131-42

View review abstract online

Comparison	**Overlap between regions of functional and structural alteration in drug-free people with first-episode schizophrenia vs.**

	controls. **Note; most patients were drug naïve.**
Summary of evidence	**Moderate quality evidence (large sample, mostly consistent, direct, unable to assess precision) suggests decreased grey matter volume and decreased functional activity in the left medial posterior cingulate/paracingulate gyrus, right temporal pole/superior temporal gyrus, left fusiform gyrus, left inferior parietal gyrus, and left caudate nucleus in drug-free patients. There was decreased grey matter volume and increased functional activity in the left superior temporal gyrus, right superior temporal gyrus, left fusiform gyrus, and right lingual gyrus. There was increased grey matter volume and decreased functional activity in the left cerebellum, right gyrus rectus, and right inferior parietal gyrus. There was increased grey matter volume and increased functional activity in the left insula and left cerebellum (lobule IX).**
Structural and functional alteration	
15 structural MRI studies, N = 971, 16 functional MRI studies, N = 831 *Significant decreased grey matter volume and decreased functional activity in;* Left medial posterior cingulate/paracingulate gyrus: 1,499 voxels, MNI coordinates (-4, -24, 42), $p < 0.001$ Right temporal pole/superior temporal gyrus: 1,446 voxels, MNI coordinates (34, 8, -22), $p < 0.001$ Left fusiform gyrus: 1,075 voxels, MNI coordinates (-34, -54, -22), $p < 0.001$ Left inferior parietal gyrus: 333 voxels, MNI coordinates (-52, -44, 44), $p < 0.001$ Left caudate nucleus: 111 voxels, MNI coordinates (-10, 0, 12), $p < 0.001$ *Significant decreased grey matter volume and increased functional activity in;* Left superior temporal gyrus: 4,575 voxels, MNI coordinates (-56, -32, 20), $p < 0.001$ Right superior temporal gyrus: 1,583 voxels, MNI coordinates (46, -16, -2), $p < 0.001$ Left fusiform gyrus: 307 voxels, MNI coordinates (-36, -68, -12), $p < 0.001$ Right lingual gyrus: 123 voxels, MNI coordinates (18, -70, -12), $p < 0.001$ *Significant increased grey matter volume and decreased functional activity in;* Left cerebellum: 1,170 voxels, MNI coordinates (-6, -28, -18), $p < 0.001$ Right gyrus rectus: 934 voxels, MNI coordinates (2, 60, -18), $p < 0.001$ Right inferior parietal gyrus: 100 voxels, MNI coordinates (42, -56, 46), $p < 0.001$ *Significant increased grey matter volume and increased functional activity in;*	

Left insula: 234 voxels, MNI coordinates (-30, 0, 12), $p < 0.001$ Left cerebellum, lobule IX: 327 voxels, MNI coordinates (-12, -56, -46), $p < 0.001$	
Consistency in results	Authors report most findings were consistent.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Glahn DC, Laird AR, Ellison-Wright I, Thelen SM, Robinson JL, Lancaster JL, Bullmore E, Fox PT

Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis

Biological Psychiatry 2008; 64(9): 774-781

View review abstract online

Comparison	**Whole brain comparison of grey matter density in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) suggests schizophrenia is associated with significant reductions in grey matter in the insula cortex, thalamus, anterior cingulate, frontal cortex, and parahippocampal gyrus. Significant increases in grey matter density were reported in the putamen and caudate head in patients.**

Clusters where schizophrenia patient density reductions were significantly more frequent than healthy control reductions

Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies.

FWHM 12mm, FDR corrected at $p < 0.05$

13 studies, N = 2,457

Left insula cortex: Talairach coordinates (-40, 14, 0), Voxel cluster size 9336mm^3, $p < 0.01$, ALE = 0.026

Right insula cortex: Talairach coordinates (40, 10, 4), Voxel cluster size 6968mm^3, $p < 0.01$, ALE = 0.026

Left parahippocampal gyrus: Talairach coordinates (-18, -2, -16), Voxel cluster size 2504mm^3, $p < 0.01$,

ALE = 0.018 Thalamus: Talairach coordinates (0, -20, 6), Voxel cluster size 2296mm^3, $p < 0.01$, ALE = 0.020 Ventral anterior cingulate: Talairach coordinates (0, 48, 4), Voxel cluster size 1680mm^3, $p < 0.01$, ALE = 0.013 Dorsal anterior cingulate: Talairach coordinates (4, 26, 32), Voxel cluster size 1400mm^3, $p < 0.01$, ALE = 0.013 Subgenual anterior cingulate: Talairach coordinates (0, 6, -12), Voxel cluster size 968mm^3, $p < 0.01$, ALE = 0.012 Left post central gyrus: Talairach coordinates (-62, -16, 18), Voxel cluster size 608mm^3, $p < 0.01$, ALE = 0.012 Left middle frontal gyrus: Talairach coordinates (-46, 10, 36), Voxel cluster size 432mm^3, $p < 0.01$, ALE = 0.011
Clusters where schizophrenia patient density increases were significantly more frequent than control reductions
Meta-analysis was performed using ALE analysis on Voxel-Based Morphometry MRI studies. FWHM 12mm, FDR corrected at $p < 0.05$ 13 studies, N = 2,457 *Regions were much smaller and more discrete;* Left putamen: Talairach coordinates (-38, 0, 16), Voxel cluster size 1248mm^3, $p < 0.01$ Right putamen: Talairach coordinates (28, 6, 2), Voxel cluster size 464mm^3, $p < 0.01$ Right head of caudate nucleus: Talairach coordinates (8, 0, 4), Voxel cluster size 424mm^3, $p < 0.01$
Fractional Similarity Network Analysis subnets co-occurrence
Meta-analysis was performed on Voxel-Based Morphometry MRI studies and combined ALE analysis with Fractional Similarity Network Analysis (FSNA). FWHM 12mm, FDR corrected at $p < 0.05$ 13 studies, N = 2,457 Four subnets were identified: 1. Bilateral insula cortex, left parahippocampal gyrus, left post central gyrus 2. Left middle frontal gyrus, ventral anterior cingulate 3. Thalamus and dorsal anterior cingulate 4. Subgenual cingulate

Consistency in results	No measure of consistency is reported.

Precision in results	No measure of precision is reported.
Directness of results	Direct

Haijma SV, Van Haren N, Cahn W, Koolschijn PCMP, Hulshoff Pol HE, Kahn RS

Brain volumes in schizophrenia: a meta-analysis in over 18000 subjects

Schizophrenia Bulletin 2012; 39(5): 1129-1138

View review abstract online

Comparison	**Whole brain comparison of grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, precise, mostly inconsistent, direct) suggests schizophrenia is associated with significant reductions in the grey matter volume of the whole brain, subregions of the frontal and temporal lobes, subcortical regions (hippocampus, amygdala, thalamus) and similar widespread reductions are seen in antipsychotic-naive patients.**

Reduced grey matter density in schizophrenia

Decreased in medicated patients;

Intracranial volume: 108 studies, N = 7,003, d = -0.17, 95%CI -0.23 to -0.12, $p < 1 \times 10{-}9$, Q = 133.4, p = 0.043, I^2 = 20%

Total brain volume: 119 studies, N = 7,441, d = -0.30, 95%CI -0.36 to -0.25, $p < 1 \times 10{-}9$, Q = 155.4, p = 0.012, I^2 = 24%

Total grey matter: 63 studies, N = 4,326, d = -0.49, 95%CI -0.57 to -0.41, $p < 1 \times 10{-}9$, Q = 96.0, p = 0.0037, I^2 = 35%

Cortical grey matter: 15 studies, N = 987, d = -0.43, 95%CI -0.56 to -0.30, $p < 1 \times 10{-}9$, Q = 13.0, p = 0.52, I^2 = 0%

Total white matter: 61 studies, N = 4,170, d = -0.17, 95%CI -0.25 to -0.10, $p = 2.1 \times 10{-}6$, Q = 76.1, p = 0.078, I^2 = 21%

Frontal lobe GM: 17 studies, N = 1,288, d = -0.49, 95%CI -0.64 to -0.34, $p < 1 \times 10{-}9$, Q = 26.3, p = 0.050, I^2 = 39%

Prefrontal GM: 16 studies, N = 1,263, d = -0.44, 95%CI -0.58 to -0.31, $p < 1 \times 10{-}9$, Q = 17.9, p = 0.27, I^2 = 16%

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Prefrontal WM: 12 studies, N = 965, *d* = -0.29, 95%CI -0.42 to -0.16, *p* = 1.0 × 10−5, Q = 6.4, *p* = 0.85, I^2 = 0%

Anterior cingulate gyrus: 29 studies, N = 1,919, *d* = -0.34, 95%CI -0.46 to -0.22, *p* = 5 × 10−8, Q = 46.3, *p* = 0.016, I^2 = 40%

Posterior cingulate gyrus: 10 studies, N = 635, *d* = -0.32, 95%CI -0.56 to -0.09, *p* = 6.2 × 10−3, Q = 18.5, *p*= 0.030, I^2 = 51%

Superior frontal gyrus: 12 studies, N = 874, *d* = -0.29, 95%CI -0.43 to -0.16, *p* = 2.8 × 10−5, Q = 10.4, *p* = 0.49, I^2 = 0%

Middle frontal gyrus: 11 studies, N = 677, *d* = -0.32, 95%CI -0.48 to -0.17, *p* = 3.2 × 10−5, Q = 6.4, *p* = 0.78, I^2 = 0%

Inferior frontal gyrus: 10 studies, N = 657, *d* = -0.41, 95%CI -0.56 to -0.25, *p* = 2.9 × 10−7, Q = 6.8, *p* = 0.66, I^2 = 0%

Orbitofrontal cortex: 19 studies, N = 1,141, *d* = -0.21, 95%CI -0.37 to -0.05, *p* = 0.010, Q = 29.7, *p* = 0.040, I^2 = 39%

Temporal lobe: 25 studies, N = 1,228, *d* = -0.22, 95%CI -0.34 to -0.09, *p* = 6.9 × 10−4, Q = 27.6, *p* = 0.28, I^2 = 13%

Temporal lobe GM: 19 studies, N = 1,433, *d* = -0.43, 95%CI -0.60 to -0.26, *p* = 6.6 × 10−7, Q = 42.6, *p* = 9.1 × 10−4, I^2 = 58%

Hippocampus: 87 studies, N = 5,141, *d* = -0.52, 95%CI -0.60 to -0.44, *p* < 1 × 10−9, Q = 169.5, *p* < 1 × 10−9, I^2 = 49%

Amygdala: 40 studies, N = 2,205, *d* = -0.31, 95%CI -0.43 to -0.19, *p* = 5.5 × 10−7, Q = 72.1, *p* = 9.9 × 10−4, I^2 = 46%

Parahippocampal gyrus: 20 studies, N = 1,129, *d* = -0.24, 95%CI -0.39 to -0.09, *p* = 2.1 × 10−3, Q = 28.8, *p* = 0.07, I^2 = 34%

Fusiform gyrus GM: 10 studies, N = 690, *d* = -0.52, 95%CI -0.76 to -0.29, *p* = 1.2 × 10−5, Q = 19.0, *p* = 0.0025, I^2 = 53%

Superior temporal gyrus total: 14 studies, N = 800, *d* = -0.27, 95%CI -0.55 to 0.01, *p* = 0.058, Q = 45.7, *p* = 1.6 × 10−5, I^2 = 71%

Superior temporal gyrus GM: 16 studies, N = 1,181, *d* = -0.58, 95%CI -0.75 to -0.41, *p* < 1 × 10−9, Q = 29.5, *p* = 0.014, I^2 = 49%

Planum temporale: 14 studies, N = 849, *d* = -0.42, 95%CI -0.68 to -0.16, *p* = 1.5 × 10−3, Q = 41.2, *p* = 9.0 × 10−5, I^2 = 68%

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Heschl's gyrus: 12 studies, N = 637, *d* = -0.29, 95%CI -0.50 to -0.09, *p* = 4.3 × 10−3, Q = 16.3, *p* = 0.13, I^2 = 32%

Insula: 14 studies, N = 856, *d* = -0.44, 95%CI -0.67 to -0.20, *p* = 2.7 × 10−4, Q = 35.2, *p* = 8.0 × 10−4, I^2 = 63%

Parietal lobe GM: 9 studies, N = 758, *d* = -0.31, 95%CI -0.54 to -0.08, *p* = 7.6 × 10−3, Q = 17.9, *p* = 0.022, I^2 = 55%

Occipital lobe GM: 9 studies, N = 700, *d* = -0.22, 95%CI -0.37 to -0.07, *p* = 4.1 × 10−3, Q = 7.6, *p* = 0.47, I^2 = 0%

Thalamus: 35 studies, N = 2,519, *d* = -0.31, 95%CI -0.40 to -0.22, *p* < 1 × 10−9, Q = 43.3, *p* = 0.13, I^2 = 21%

Nucleus accumbens: 13 studies, N = 904, *d* = -0.29, 95%CI -0.53 to -0.05, *p* = 0.017, Q = 35.1, *p* = 4.5 × 10−4, I^2 = 65.8%

Cerebellum: 20 studies, N = 1,402, *d* = -0.15, 95%CI -0.30 to -0.01, *p* = 0.035, Q = 29.4, *p* = 0.06, I^2 = 35.3%

Increased in medicated patients;

Total CSF: 34 studies, N = 2,326, *d* = 0.36, 95%CI 0.21 to 0.50, *p* = 1.2 × 10−6, Q = 89.9, *p* = 3.6 × 10−7, I^2 = 63%

Lateral ventricles: 46 studies, N = 3,153, *d* = 0.45, 95%CI 0.37 to 0.54, *p* < 1 × 10−9, Q = 60.4, *p* = 0.06, I^2 = 25%

Third ventricle: 25 studies, N = 1,593, *d* = 0.60, 95%CI 0.50 to 0.70, *p* < 1 × 10−9, Q = 18.5, *p* = 0.78, I^2 = 0%

Globus pallidus: 15 studies, N = 1,144, *d* = 0.26, 95%CI 0.02 to 0.50, *p* = 0.034, Q = 53.9, *p* = 1.3 × 10−6, I^2 = 74%

Decreased in antipsychotic-naïve patients;

Intracranial volume: 17 studies, N = 989, *d* = -0.14, 95%CI -0.28 to -0.01, *p* = 0.041, Q = 17.8, *p* = 0.34, I^2 = 10%

Total brain volume: 15 studies, N = 854, *d* = -0.21, 95%CI -0.35 to -0.07, *p* = 3.0 × 10−3, Q = 8.9, *p* = 0.84, I^2 = 0%

Total grey matter: 10 studies, N = 530, *d* = -0.36, 95%CI -0.53 to -0.18, *p* = 6.6 × 10−5, Q = 7.7, *p* = 0.56, I^2 = 0%

Total white matter: 10 studies, N = 530, *d* = -0.18, 95%CI -0.36 to -0.01, *p* = 0.042, Q = 6.8, *p* = 0.66, I^2 = 0%

Hippocampus: 8 studies, N = 445, *d* = -0.43, 95%CI -0.63 to -0.24, *p* = 7.6 × 10−6, Q = 2.4, *p* = 0.93, I^2

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= 0% Thalamus: 8 studies, N = 412, *d* = -0.68, 95%CI -1.08 to -0.28, *p* = 8.3 × 10−4, Q = 21.3, *p* = 3.3 × 10−3, I^2 = 67% Caudate nucleus: 11 studies, N = 721, *d* = -0.38, 95%CI -0.54 to -0.23, *p* = 9.5 × 10−7, Q = 8.3, *p* = 0.60, I^2 = 0% *Increased in antipsychotic-naïve patients;* Total CSF: 7 studies, N = 468, *d* = 0.31, 95%CI 0.07 to 0.55, *p* = 0.011, Q = 8.6, *p* = 0.20, I^2 = 30%	
Consistency in results	Mostly inconsistent
Precision in results	Precise
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 schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, some inconsistency, precise, direct) shows small reductions in all hippocampal subfields in people with schizophrenia.**
Hippocampal subfields	
6 studies, N = 1,789 *Small, significant reductions in all hippocampal subfields in people with schizophrenia;* Left hemisphere Cornu ammonis 1: *d* = -0.304, 95%CI -0.504 to -0.104, *p* = 0.003, Q*p* = *p* < 0.001 Cornu ammonis 2/3: *d* = -0.450, 95%CI -0.624 to -0.275, *p* < 0.00001, Q*p* = 0.253 Cornu ammonis 4 / dentate gyrus: *d* = -0.493, 95%CI -0.708 to -0.279, *p* < 0.00001, Q*p* < 0.000001 Presubiculum: *d* = -0.286, 95%CI -0.405 to -0.167, *p* < 0.00001, Q*p* = 0.300	

Subiculum: *d* = -0.394, 95%CI -0.485 to -0.303, *p* < 0.000001, Q*p* = 0.428 <u>Right hemisphere</u> Cornu ammonis 1: *d* = -0.282, 95%CI -0.391 to -0.173, *p* < 0.000001, Q*p* = 0.279 Cornu ammonis 2/3: *d* = -0.328, 95%CI -0.455 to -0.201, *p* < 0.000001, Q*p* = 0.058 Cornu ammonis 4 / dentate gyrus: *d* = -0.364, 95%CI -0.474 to -0.253, *p* < 0.000001, Q*p* = 0.201 Presubiculum: *d* = -0.349, 95%CI -0.468 to -0.231, *p* < 0.000001, Q*p* = 0.306 Subiculum: *d* = -0.375, 95%CI -0.466 to -0.284, *p* < 0.000001, Q*p* = 0.592	
Consistency in results	Consistent, apart from CA1 and CA4/dentate gyrus.
Precision in results	Precise
Directness of results	Direct
Comparison 2	**Hippocampal changes in people with schizophrenia vs. people with bipolar disorder.**
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 subfields	
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 <u>Right hemisphere</u> 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;* <u>Left hemisphere</u> 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, apart from the presubiculum, subiculum, CA 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 schizophrenia vs. controls or people with bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, inconsistent, some imprecision, direct) suggests a large effect of reduced amygdala volume in people with schizophrenia compared to controls, and a medium-sized effect when compared to people with bipolar disorder.**
Amygdala volume	
A large effect of reduced amygdala volume in people with schizophrenia vs. controls; 20 studies, N not reported, *g* = -0.90, 95%CI -1.62 to -0.18, *p* = 0.014, I^2 = 98% *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% Smaller, but significant effects were found in subgroup analysis of people in the early stages of	

illness.	
Consistency in results	Inconsistent
Precision in results	Imprecise for controlled analysis, precise for bipolar disorder analysis.
Directness of results	Direct

Honea R, Crow TJ, Passingham D, Mackay CE

Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies

American Journal of Psychiatry 2005; 162(12): 2233-2245

View review abstract online

Comparison	**Whole brain comparison of grey matter density using voxel-based morphometry MRI analysis in schizophrenia patients vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests schizophrenia is associated with significant reductions in the grey matter density of the superior and medial temporal lobe, inferior and medial frontal lobe and parahippocampal gyrus.**
Reduced grey matter density in schizophrenia	
15 studies, N = 754, varying FWHM smoothing kernel (range 4-12mm). *Regions showing reduced grey matter density in schizophrenia patients;* Left medial temporal lobe: reduced in 9/15 studies Left superior temporal gyrus: reduced in 8/15 studies Left inferior frontal gyrus: reduced in around 50% of studies Left medial frontal gyrus: reduced in around 50% of studies Right superior temporal gyrus: reduced in around 50% of studies Left parahippocampal gyrus: reduced in around 50% of studies	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.

Directness of results	Direct

Huhtaniska S, Jaaskelainen E, Hirvonen N, Remes J, Murray GK, Veijola J, Isohanni M, Miettunen J

Long-term antipsychotic use and brain changes in schizophrenia - a systematic review and meta-analysis

Human Psychopharmacology 2017; 32: doi: 10.1002/hup.2574

View review abstract online

Comparison	**Association between long-term antipsychotic dose and changes in brain regions over time (>2 years) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, some inconsistency, precise, direct) suggests increased antipsychotic dose was associated with decreased parietal and occipital lobe volume, and increased basal ganglia volume over time (>2 years), with no associations with total brain, frontal, temporal, cerebellum, or CSF/ventricle volume.**

Longitudinal changes in volume

Small, significant associations between long-term antipsychotic use and;

Decreased parietal lobe: 4 studies, N = 370, r = -0.14, 95%CI -0.24 to -0.04, p = 0.007, I^2 = 0%

Decreased occipital lobe: 3 studies, N = 168, r = -0.14, 95%CI -0.29 to 0.00, p = 0.052, I^2 = 0%

Increased basal ganglia: 4 studies, N = 225, r = 0.10, 95%CI -0.00 to 0.19, p = 0.044, I^2 = 0%

There were no associations between long-term antipsychotic use and;

Total brain: 3 studies, N = 168, r = -0.15, 95%CI -0.51 to 0.21, p = 0.41, I^2 = 81%

Frontal lobe: 7 studies, N = 500, r = -0.14, 95%CI -0.34 to 0.05, p = 0.15, I^2 = 71%

Temporal lobe: 8 studies, N = 452, r = -0.12, 95%CI -0.33 to 0.09, p = 0.26, I^2 = 72%

Cerebrospinal fluid and ventricles: 5 studies, N = 394, r = 0.13, 95%CI -0.08 to 0.34, p = 0.23, I^2 = 70%

Cerebellum: 3 studies, N = 296, r = 0.01, 95%CI -0.10 to 0.13, p > 0.05, I^2 = 0%

There were no moderating effects of antipsychotic type (first vs. second generation).

Consistency in results	Consistent for parietal, occipital, basal ganglia and cerebellum.
Precision in results	Precise
Directness of results	Direct

Hulshoff Pol HE, Kahn R

What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia

Schizophrenia Bulletin 2008; 34(2): 354-66

View review abstract online

Comparison	**Longitudinal assessments of whole brain volume using MRI analysis in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests people with schizophrenia show reduced volume of frontal lobe, thalamus and caudate over time, and increases in ventricular volume compared to controls. No difference was reported in the hippocampus.**

Longitudinal changes in volume

11 studies, N = 578, FWHM smoothing kernel range not reported.

Regions showing reduced grey matter density over time in schizophrenia patients;

Whole brain: reduced in 2/5

Frontal lobe: reduced in 3/3 studies

Temporal lobe: reduced in 2/4 studies

Thalamus: reduced in 2/2 studies

Caudate: 1/1 study

No difference over time in hippocampus (2/2 studies) or cerebellum (1/1 study).

Regions showing increased grey matter density over time in schizophrenia patients;

Lateral ventricles: 5/6 studies

3rd ventricle: 1/1 study

CSF volume: 1/2 studies	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Kempton MJ, Stahl D, Williams SCR, DeLisi LE

Progressive lateral ventricular enlargement in schizophrenia: A meta-analysis of longitudinal MRI studies

Schizophrenia Research 2010; 120(1): 54-62

View review abstract online

Comparison	**Longitudinal assessments of lateral ventricle volume using MRI analysis in schizophrenia patients vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, precise, direct) suggests people with schizophrenia show an increased rate of enlargement in lateral ventricles over time.**

Longitudinal changes in lateral ventricle volume

People with schizophrenia showed medium-sized increase in the rate of lateral ventricle dilation over time compared to controls;

13 studies, N = 821, g = 0.449, 95%CI 0.192 to 0.707, p = 0.0006, Q = 37.3, p < 0.001, I^2 = 63%

First-episode compared to chronic patients – both showed medium-sized increases over time;

In first-episode patients: 5 studies, g = 0.491, 95%CI -0.113 to 1.095, p = 0.11

In chronic patients: 9 studies, g = 0.407, 95%CI 0.134 to 0.679, p = 0.003

No significant differences between first episode and chronic patients;

g = 0.08, 95%CI -0.542 to 0.711, p = 0.79

No significant association with mean patient interscan interval (13 studies, p = 0.49), mean patient age at baseline scan (13 studies, p = 0.79), percentage of female patients (11 studies, p = 0.27), mean duration of illness at baseline scan (13 studies, p = 0.61), and mean age of onset (13 studies, p = 0.31).

Consistency in results	Inconsistent, significant heterogeneity reported which was not accounted for by subgroup analyses.
Precision in results	Precise for all analyses except first-episode subgroup analysis.
Directness of results	Direct

Konick LC, Friedman L

Meta-analysis of thalamic size in schizophrenia

Biological Psychiatry 2001; 49(1): 28-38

View review abstract online

Comparison	**Thalamic volume in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests schizophrenia patients show significant reductions in thalamic volume.**
Absolute thalamic volume	
Small reduction in thalamic volume; 8 studies, N = 689, *d* = -0.22 95%CI -0.37 to -0.07, *p* = 0.0043, Q = 14.62, *p* = 0.041 *Similar results with one study outlier removed;* 7 studies, N= 657, *d* = -0.18, 95%CI -0.33 to -0.02, *p* = 0.024, Q = 7.96, *p* = 0.24	
Relative thalamic volume (adjusted for brain size)	
Small reduction in thalamic volume; 11 studies N = 622, *d* = -0.32, 95%CI -0.49 to -0.15, *p* < 0.0001, Q = 16.37, *p* = 0.02 *Similar results with one study outlier removed;* 10 studies, N= 590, *d* = -0.25 95%CI -0.43 to -0.07, *p* = 0.003, Q = 8.13, *p* = 0.229	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Kuo SS, Pogue-Geile MF

Variation in fourteen brain structure volumes in schizophrenia: A comprehensive meta-analysis of 246 studies

Neuroscience and Biobehavioral Reviews 2019; 98: 85-94

View review abstract online

Comparison	**Variability in brain volume of people with schizophrenia vs. variability in controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds greater variability in intracranial volume, bilateral lateral ventricle, and third ventricle volume of people with schizophrenia than in these regions in controls. No other brain region showed differences in variability.**
Variability in brain volume	
Increased variability was found in schizophrenia in; Intracranial volume: 125 studies, N = 9,267, variability ratio = 1.028, 95%CI 1.010 to 1.046, p = 0.002, I^2 = 94% Bilateral lateral ventricle: 14 studies, N = 1,376, variability ratio = 1.087, 95%CI 1.030 to 1.146, p = 0.002, I^2 = 96.5% Third ventricle: 17 studies, N = 1,470, variability ratio = 1.141, 95%CI 1.092 to 1.193, $p < 0.001$, I^2 = 94.6	
Consistency in results	Inconsistent.
Precision in results	Appears precise.
Directness of results	Direct

Lahuis B, Kemner C, Van Engeland H

Magnetic resonance imaging studies on autism and childhood-onset schizophrenia in children and adolescents – a review

Acta Neuropsychiatrica 2003; 15(3): 140-147 View review abstract online	
Comparison	**Whole brain volumetry in childhood-onset schizophrenia (COS) vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) suggests child-onset schizophrenia patients exhibit volume reductions in the temporal lobe, thalamus and amygdala, and increased volume in the basal ganglia and ventricles.**
Regions of reduced volume on MRI in COS	
12 studies, N unclear Reduced volume was observed in the cerebrum, particularly the temporal lobe; the thalamus and the amygdala of COS.	
Regions of increased volume on MRI in COS	
12 studies, N unclear Increased volume was observed in the caudate, putamen, globus pallidus, and ventricles of COS.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Li Y, Li WX, Xie DJ, Wang Y, Cheung EFC, Chan RCK

Grey matter reduction in the caudate nucleus in patients with persistent negative symptoms: An ALE meta-analysis

Schizophrenia Research 2018; 192: 9-15 View review abstract online	
Comparison	**Grey matter volume in people with persistent negative symptoms of schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct,**

	unable to assess consistency or precision) suggests schizophrenia patients with persistent negative symptoms show significant reductions in bilateral medial frontal gyrus (Brodmann area [BA] 11/10), the left precentral gyrus (BA44), the left middle frontal gyrus (BA9), the left caudate nucleus (caudate head), the bilateral parahippocampal gyri, the left anterior cingulate (BA32), the thalamus and the insula.
Grey matter volume	
12 studies, N = unclear *There was significantly reduced grey matter volume in;* Left caudate nucleus (caudate head): Talairach coordinates (-4, 6, -2) Left precentral gyrus (BA44): Talairach coordinates (-42, 4, 10) Left middle frontal gyrus (BA9): Talairach coordinates (-50, 16, 30) Left medial frontal gyrus (BA 11): Talairach coordinates (4, 36, -14) Left medial frontal gyrus (BA 11): Talairach coordinates (-2, 36, -14) Left medial frontal gyrus (BA 11): Talairach coordinates (-8, 36, -14) Left medial frontal gyrus (BA 10): Talairach coordinates (8, 50, 10) Left medial frontal gyrus (BA 10): Talairach coordinates (-6, -54, -12) Right medial frontal gyrus (BA 10): Talairach coordinates (22, 52, 14) Left parahippocampal gyrus: Talairach coordinates (-20, -10, -14) Left parahippocampal gyrus (BA30): Talairach coordinates (-16, 38, -4) Right parahippocampal gyrus: Talairach coordinates (18, -4, -16) Left anterior cingulate (BA32): Talairach coordinates (-6, 42, 2) Left thalamus: Talairach coordinates (0, -12, 8) Left insula (BA13): Talairach coordinates (-42, 12, -2) Right insula: Talairach coordinates (40, 14, 0)	
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	Direct

Liu H, Li L, Shen L, Wang X, Hou Y, Zhao Z, Gu L, Mao J

Cavum septum pellucidum and first-episode psychosis: A meta-analysis

PLoS One 2017; 12: e0177715

View review abstract online

Comparison	**Cavum septum pellucidum (CSP) in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (large sample, some inconsistency, imprecise, direct) finds no differences in any or large CSP between people with first-episode schizophrenia and controls.**
Cavum septum pellucidum	
No significant differences in; Any CSP: 10 studies, N = 1,476, OR = 1.41, 95% CI 0.90 to 2.20, p = 0.13, I^2 = 52.7% Large CSP: 10 studies, N = 1,476, OR = 1.10, 95% CI 0.77 to 1.58, p = 0.59, I^2 = 24.1%	
Consistency in results	Inconsistent for any CSP, consistent for large CSP.
Precision in results	Imprecise
Directness of results	Direct

Modinos G, Costafreda SG, van Tol M-J, McGuire PK, Aleman A, Allen P

Neuroanatomy of auditory verbal hallucinations in schizophrenia: a quantitative meta-analysis of voxel-based morphometry studies

Cortex 2013; 49(4): 1046-55

View review abstract online

Comparison	**Association between brain structure and auditory verbal hallucinations in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, consistent, direct, unable to assess precision) suggests the severity of auditory hallucinations is significantly associated with grey matter volume reductions in the left superior temporal gyri, (including the rolandic operculum and Heschl's gyri), and a**

	trend effect for the right superior temporal gyri (including the medial temporal gyrus and Heschl's gyri).
Structural abnormalities associated with hallucinations	
8 studies, N = 322 *Reduced grey matter volume in two clusters were associated with severity of hallucinations;* 1. Left superior temporal gyrus: Talairach coordinates (-52, -18, 2), cluster volume 1680mm^3, p = 0.022, including the left rolandic operculum: Talairach coordinates (-44, -22, 12), and the left Heschl's gyrus: Talairach coordinates (-46, -14, 6). Authors report that 48.6% of the studies report an effect within 10mm of the -52 -18 2 cluster. 2. Right superior temporal gyrus: Talairach coordinates (46, -16, -8) cluster volume 1248mm^3, p = 0.062 (trend), including the right Heschl's gyrus: Talairach coordinates (50, -14, 6), and the right medial temporal gyrus: Talairach coordinates (50, -14, -10). Authors report that 34.2% of the studies report an effect within 10mm of the -52 -18 2 cluster.	
Consistency in results	Authors report the concordance across studies.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Nickl-Jockschat T, Schneider F, Pagel AD, Laird AR, Fox PT, Eickhoff SB

Progressive pathology is functionally linked to the domains of language and emotion: meta-analysis of brain structure changes in schizophrenia patients

European Archives of Psychiatry and Clinical Neurocience 2011; 261: S166-S171

View review abstract online

Comparison	**Whole brain grey matter volume in schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests people with schizophrenia had reduced grey matter volume in the insula, thalamus, amygdala and ventral striatum; and increased grey matter volume in the putamen.**
Grey matter volume	

38 studies, N = 3,651 *Significant reductions were reported in schizophrenia compared to controls;* Left frontal peri-insula region: coordinates (-46, 14, -3) k_E = 457 Bilateral thalamus: coordinates (-4, -20, 9) k_E = 146 Left amygdala: coordinates (-22, -10, -17) k_E = 126 Left ventral striatum: coordinates (-4, 6, -3) k_E = 118 *Significant increases in schizophrenia compared to controls;* Left putamen: coordinates (-26, -2, 13) k_E = 156 *Correlation between increased probability of finding differences between patients and controls and increased mean disease duration of the patients;* Left temporal pole: coordinates (-46, 8, -7) k_E = 34

Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Niu Y, Li Z, Cheng R, Peng B, Liu B, Ma Y

Altered gray matter and brain activity in patients with schizophrenia and their unaffected relatives: A multimodal meta-analysis of voxel-based structural MRI and resting-state fMRI studies

International Journal of Clinical and Experimental Medicine 2017; 10: 1866-78

View review abstract online

Comparison	**Structural alteration in relatives of people with schizophrenia vs. people with schizophrenia and vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) suggests relatives had decreased grey matter in the left putamen and increased grey matter in the left insula and right inferior frontal gyrus compared to people with schizophrenia. Compared to controls, relatives showed decreased grey matter in the left insula, left inferior temporal gyrus and right inferior network.**
Structural alterations	

7 studies, N = 945 *Compared to people with schizophrenia, relatives had increased grey matter in;* Left insula: 700 voxels, MNI coordinates (-40, 12, -8), *p* = 0.00005 Right inferior frontal gyrus: 621 voxels, MNI coordinates (60, 10, 14), *p* = 0.00009 *Compared to people with schizophrenia, relatives had decreased grey matter in;* Left putamen: 358 voxels, MNI coordinates (-26, -2, 8), *p* = 0.00001 9 studies, N = 953 *Compared to controls, relatives had decreased grey matter in;* Left insula: 1,089 voxels, MNI coordinates (-38, -4, -14), *p* = 0.00011 Left inferior temporal gyrus: 53 voxels, MNI coordinates (-58, -46, -22), *p* = 0.00072 Right inferior network: 51 voxels, MNI coordinates (30, -52, -8), *p* = 0.00099	
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	Direct

Nordholm D, Krogh J, Mondelli V, Dazzan P, Pariante C, Nordentoft M

Pituitary gland volume in patients with schizophrenia, subjects at ultra high-risk of developing psychosis and healthy controls: A systematic review and meta-analysis

Psychoneuroendocrinology 2013; 38(11): 2394-404

View review abstract online

Comparison	**Pituitary gland volume in people with schizophrenia, first-episode psychosis, and people at ultra-high risk of psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, some inconsistency, precise, direct) suggests no significant differences in pituitary gland volume, although there is a trend effect of increased pituitary gland volume in high-risk individuals who transitioned to psychosis.**
Grey matter volume	
Non-significant, trend effects of larger pituitary gland volume in both first-episode psychosis and ultra-	

high-risk subjects who had transitioned to psychosis; Transitioned high risk: 2 studies, N = 199, SMD = 0.37, 95%CI 0.00 to 0.75, p = 0.05, I^2 = 0% First-episode psychosis: 4 studies, N = 403, SMD = 0.39, 95%CI -0.05 to 0.84, p = 0.09, I^2 = 77% There was no difference in pituitary volume between patients with schizophrenia combined with first-episode psychosis vs. controls or between ultra-high-risk subjects (with and without transition) and controls.	
Consistency in results	Consistent for high-risk only.
Precision in results	Precise.
Directness of results	Direct

Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM

Are There Progressive Brain Changes in Schizophrenia? A Meta-Analysis of Structural Magnetic Resonance Imaging Studies

Biological Psychiatry 2011; 70(1): 88-96

View review abstract online

Comparison	**Progressive changes in whole brain grey matter volume in schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests greater reductions over time in whole brain volume and grey matter, frontal grey and white matter, parietal white matter, temporal white matter and left caudate volume. There were also significant increases in lateral and third ventricles.**
Grey matter volume	
Progressive changes in grey matter volume reported across longitudinal MRI scans over 1-10 years. 31 studies, N = 1,867 *Significantly greater reductions were reported over time in schizophrenia compared to controls;* Whole brain volume: N = 992, 14 studies, d = -0.404, 95%CI -0.62 to -0.19, p = 0.0002, I^2 = 57% Whole brain GM: N = 928, 12 studies, d = -0.520, 95%CI -0.76 to -0.28, p < 0.0001, I^2 = 62.3% Frontal GM: N = 503, 9 studies, d = -0.340, 95%CI -0.66 to -0.02, p = 0.035, I^2 = 59.8%	

Frontal WM: N = 323, *5* studies, *d* = -0.512, 95%CI -0.76 to -0.26, *p* = 0.0001, I^2 = 0% Parietal WM: N = 227, 4 studies, *d* = -0.533, 95%CI -0.84 to -0.23, *p* = 0.001, I^2 = 4.0% Temporal WM: N = 259, 6 studies, *d* = -0.485, 95%CI -0.76 to -0.21, *p* = 0.001, I^2 = 0% Left caudate N = 253, 3 studies, *d* = -0.336, 95%CI -0.60 to -0.07, *p* = 0.013, I^2 = 0% *Significantly greater increases were reported over time in schizophrenia compared to controls;* Lateral ventricles: N = 719, 10 studies, *d* = 0.530, 95%CI 0.28 to 0.78, *p* < 0.0001, I^2 = 51.7% Third ventricle: N = 466, 6 studies, *d* = 0.180, 95%CI -0.01 to 0.37, *p* = 0.059, I^2 = 0% *No differences between groups for;* Whole brain WM: N = 846, 11 studies, *d* = -0.129, 95%CI -0.41 to 0.15, *p* = 0.366, I^2 = 70.6% Cerebellum: N = 476, 6 studies, *d* = -0.029, 95%CI -0.17 to 0.22, *p* = 0.773, I^2 = 5.2% Parietal GM: N = 364, 7 studies, *d* = -0.161, 95%CI -0.50 to 0.18, *p* = 0.352, I^2 = 52.6% Temporal GM: N = 439, 10 studies, *d* = -0.204, 95%CI -0.58 to 0.17, *p* = 0.289, I^2 = 68% Occipital GM: N = 282, 6 studies, *d* = -0.174, 95%CI -0.67 to 0.32, *p* = 0.491, I^2 = 69.9% Occipital WM: N = 227, 4 studies, *d* = -0.327, 95%CI -0.74 to 0.08, *p* = 0.117, I^2 = 45.9% Right hippocampal/amygdala complex (HAC): N = 153, 5 studies, *d* = -0.060, 95%CI -0.38 to 0.26, *p* = 0.716, I^2 = 0% Left hippocampal/amygdala complex (HAC): N = 153, 5 studies, *d* = 0.107, 95%CI -0.22 to 0.43, *p* = 0.518, I^2 = 0% Right amygdala: N = 235, 5 studies, *d* = -0.138, 95%CI -0.43 to 0.16, *p* = 0.362, I^2 = 12.5% Right caudate: N = 253, 3 studies, *d* = -0.132, 95%CI -0.49 to 0.23, *p* = 0.470, I^2 = 41.6% Left hippocampus: N = 524, 8 studies, *d* = 0.089, 95%CI -0.16 to 0.34, *p* = 0.490, I^2 = 42.9% Right hippocampus: N = 524, 8 studies, *d* = 0.145, 95%CI -0.15 to 0.44, *p* = 0.337, I^2 = 57.2% Left amygdala: N = 235, 5 studies, *d* = 0.019, 95%CI -0.24 to 0.28, *p* = 0.887, I^2 = 0%	
Consistency in results	Inconsistent for all except cerebellum, third ventricle, frontal, parietal and temporal WM, bilateral HAC, left amygdala and caudate.
Precision in results	Precise
Directness of results	Direct

Olabi B, Ellison-Wright I, Bullmore E, Lawrie SM

Structural brain changes in first episode schizophrenia compared with

fronto-temporal lobar degeneration: a meta-analysis

BMC Psychiatry 2012; 12: 104

View review abstract online

Comparison	**Brain volume in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests grey matter volume reductions in the caudate, amygdala, inferior and middle frontal and postcentral gyri, thalamus, temporal gyri, and medial frontal and cingulate gyri in people with first-episode schizophrenia.**

Brain volume in FES

Voxel-based meta-analysis of regions of reduced grey matter volume in first-episode schizophrenia;

18 studies (185 coordinates) N = 1,176

Right caudate: coordinates (2, 14, 0)

Right caudate: coordinates (10, 10, 12)

Left uncus: coordinates (-18, -2, -22)

Left amygdala: coordinates (-12, 0, -14)

Right superior temporal gyrus: coordinates (48, -24, 10)

Right superior temporal gyrus: coordinates (48, -26, 16)

Left insula: coordinates (-36, 20, 6)

Left transverse temporal gyrus: coordinates (-46, -18, 10)

Right middle temporal gyrus: coordinates (54, -26, -2)

Left superior temporal gyrus: coordinates (-58, -26, 12)

Left superior temporal gyrus: coordinates (-56, 2, -4)

Right insula: coordinates (36, 8, 10)

Right postcentral gyrus: coordinates (54, -20, 44)

Left middle frontal gyrus: coordinates (-30, 50, 4)

Right inferior frontal gyrus: coordinates (-22, 28, -6)

Left postcentral gyrus: coordinates (-60, -18, 20)

Right amygdala: coordinates (20, -4, -22)

Left superior temporal gyrus: coordinates (-32, 14, -22)

Left inferior temporal gyrus: coordinates (-46, -14, -18) Left cingulate gyrus: coordinates (-8, -4, 38) Right insula/claustrum: coordinates (34, -14, 12) Right medial frontal gyrus: coordinates (14, 34, 36) Left cingulate gyrus: coordinates (0, -42, 38) Right medial frontal gyrus: coordinates (6, 6, 48) Authors report overlapping grey matter deficits in the bilateral caudate head, left insula and bilateral uncus in patients with first-episode schizophrenia and in patients with fronto-temporal lobar degeneration.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Palaniyappan L, Balain V, Radua J, Liddle PF

Structural correlates of auditory hallucinations in schizophrenia: a meta-analysis

Schizophrenia Research 2012; 137: 169-173

View review abstract online

Comparison	**Voxel-based meta-analysis of whole brain studies grey matter density correlated with auditory hallucinations in schizophrenia patients.**
Summary of evidence	**Moderate to low quality evidence (medium-sized sample, direct, unable to assess consistency or precision) suggests reductions in grey matter volume in the insula cortex and superior temporal gyrus were associated with increased severity of auditory hallucinations in patients with schizophrenia.**
Grey matter density	
Voxel-based meta-analysis of 7 studies (N = 350) identified regions of grey matter in schizophrenia that showed *negative* correlation with the severity of auditory hallucinations. Left insula cluster: Talairach coordinates (-42, -4, 2), uncorrected p = 0.000001, 717 voxels	

Right superior temporal gyrus cluster: Talairach coordinates (58, -6, 10), uncorrected p = 0.0008, 318 voxels	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Radua J, Borgwardt S, Crecini A, Mataix-Cols D, Meyer-Lindenberg A, McGuire PK, Fusar-Poli P

Multimodal meta-analysis of structural and functional brain changes in first episode psychosis and the effects of antipsychotic medications

Neuroscience and Biobehavioural Reviews 2012; 36: 2325-2333

View review abstract online

Comparison	**Overlap between regions of functional and structural alteration in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests there are regions of overlap between structural and functional abnormalities in the insula cortex/superior temporal gyri and the medial frontal/anterior cingulate cortex in people with first-episode schizophrenia, regardless of medication status.**

Structural and functional alteration

Analysis of 25 structural MRI studies (N = 2005) and 18 functional MRI studies (N = 765) found regions with both structural and functional alteration in first-episode schizophrenia compared to controls.

Decreased grey matter volume and decreased functional activation;

Right anterior insula/STG: Coordinates (42, 0, 12), $p < 0.0001$, 439mm^2, Coordinates (34, 24, 0), $p = 0.0001$, 44mm^2

Left anterior insula/STG: Coordinates (-40, 12, 34), $p < 0.0001$, 407mm^2

Right medial frontal/anterior cingulate: Coordinates (4, 22, 30), $p < 0.0001$, 644mm^2

Decreased grey matter volume and increased functional activation;

Right posterior insula/STG: Coordinates (34, 4, -12), $p < 0.0001$, 71mm^2, Coordinates (38, 4, -12), p

< 0.0001, 173mm^2, Coordinates (50, 20, 10), p = 0.0001, 18mm^2, Coordinates (56, -16, 32), p = 0.0002, 72mm^2 Left STG/postcentral gyrus: Coordinates (-58, -22, 14), p = 0.00005, 243mm^2 Left medial frontal/anterior cingulate: Coordinates (-14, 40, 10), p = 0.0001, 117mm^2 Meta-regression analyses showed that antipsychotic medications were associated with greater severity of abnormality, though the differences remained present in antipsychotic-naïve participants.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Saunders TS, Mondelli V, Cullen AE

Pituitary volume in individuals at elevated risk for psychosis: A systematic review and meta-analysis

Schizophrenia Research 2019; 213: 23-31

View review abstract online

Comparison	**Pituitary volume in people at high risk for psychosis (clinical or genetic) vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests people at high risk for psychosis show greater pituitary volume than controls, particularly high-risk individuals who transition to psychosis.**
Pituitary volume	
A small effect of larger pituitary volume in people at high risk for psychosis; 10 studies, N = 913, g = 0.16, 95%CI 0.01 to 0.32, p = 0.04, I2 = 28% *There was also a reduction in whole brain volume;* g = -0.17, 95%CI -0.30 to -0.03, p = 0.020 Subgroup analyses for CHR and FHx groups showed no significant differences relative to controls. Subgroup analysis of high-risk individuals who transitioned to psychosis showed the largest pituitary volume increases compared to controls (g = 0.55). Larger effect sizes were associated with more high-risk individuals receiving antipsychotic	

medication.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Sayo A, Jennings RG, Van Horn JD

Study factors influencing ventricular enlargement in schizophrenia: a 20 year follow-up meta-analysis

NeuroImage 2012; 59: 154-167

View review abstract online

Comparison	**Factors influencing the ventricle-brain ratio in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests people with schizophrenia show enlarged ventricles compared to controls, and older research with fewer authors are more likely to report significant results.**
Ventricular-brain ratio	
72 studies, N = 3,463 Ventricle-brain ratio (VBR), ventricular area/volume divided by total brain area/volume can be used as a measure of brain atrophy. People with schizophrenia showed a significantly larger VBR compared to normal controls, t = 9.67, $p < 0.0001$, suggesting significantly enlarged ventricles in the schizophrenia group. Significant moderating effects were reported for control VBR (potential sampling bias) ($p = 0.0035$), number of authors and year of publication ($p = 0.0031$), such that older papers tended to have fewer authors and were more likely to report significant results. Diagnostic criteria also showed moderating influences ($p < 0.0001$) such that acute patients showed lower VBR than those with chronic illness.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.

Directness of results	Direct

Shah C, Zhang W, Xiao Y, Yao L, Zhao Y, Gao X, Liu L, Liu J, Li S, Tao B, Yan Z, Fu Y, Gong Q, Lui S

Common pattern of gray-matter abnormalities in drug-naive and medicated first-episode schizophrenia: a multimodal meta-analysis

Psychological Medicine 2017; 47: 401-13

View review abstract online

Comparison	**Grey matter changes in first-episode schizophrenia (treated and medication naïve) vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests common decreases in grey matter in the left superior temporal gyrus, right anterior cingulate/paracingulate gyri, right insula, right gyrus rectus, and left hippocampus. There were common increases in grey matter in the left paracentral lobule. Grey matter in the left supramarginal gyrus and left middle temporal gyrus were increased in antipsychotic-naive patients, but decreased in treated patients, while left median cingulate/paracingulate gyri and right hippocampus grey matter was decreased in antipsychotic-naive patients but increased in treated patients.**

Grey matter decreased in both medicated and medication naïve first-episode patients

24 studies, N = 1,358

Left superior temporal gyrus: MNI coordinates (-44, -8, -8)

Right anterior cingulate/paracingulate gyri, BA 10: MNI coordinates (4, 44, 8)

Right insula, BA 48: MNI coordinates (38, -4, 10)

Right gyrus rectus, BA 11: MNI coordinates (6, -50, -28)

Left hippocampus, BA 20: MNI coordinates (-26, -16, -22)

Grey matter increased in both medicated and medication naïve first-episode patients

24 studies, N = 1,358

Left paracentral lobule, BA 6: MNI coordinates (-12, -14, 66)

Grey matter decreased in medicated but increased in medication naïve first-episode patients	
24 studies, N = 1,358 Left supramarginal gyrus, BA 48: MNI coordinates (-58, -26, 28) Left middle temporal gyrus, BA 21: MNI coordinates (-52, -46, 6)	
Grey matter increased in medicated but decreased in medication naïve first-episode patients	
24 studies, N = 1,358 Left median cingulate/paracingulate gyri, BA 23: MNI coordinates (-2, -48, 34) Right hippocampus, BA 20: MNI coordinates (34, -28, -6)	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Shepherd AM, Matheson S, Laurens KR, Carr VJ, Green MJ

Systematic meta-analysis of insula volume in schizophrenia

Biological Psychiatry 2012; 72(9): 775-784

View review abstract online

Comparison	**Cross sectional studies of insula cortex grey matter volume in schizophrenia patients vs. controls**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests medium-sized reductions of insula volume in schizophrenia, of greater magnitude in anterior insula compared to posterior insula, with no difference between first episode and chronic patients. The effect also appears larger in females.**
Insula volume	
Medium-sized reductions in bilateral insula in people with schizophrenia; 17 effect sizes, N = 945, g = -0.446, 95%CI -0.639 to -0.252, $p < 0.001$, $I^2 = 76\%$, $p < 0.001$ *Medium-sized effects were reported in both right and left insula;*	

Left: N = 844, *g* = -0.453, 95%CI -0.670 to -0.236, *p* < 0.001, I^2 = 61% Right: N = 844, *g* = -0.442, 95%CI -0.652 to -0.231, *p* < 0.001, I^2 = 58% *A medium-sized reduction in anterior and a small reduction in posterior insula;* Anterior insula: N = 605, *g* = -0.643, 95%CI -0.886 to -0.399, *p* < 0.001, I^2 = 52% Posterior insula: N = 453, *g* = -0.321, 95%CI -0.609 to -0.034, *p* = 0.028, I^2 = 55% *Medium-sized effects were reported in both first episode and chronic schizophrenia;* First-episode: N = 439, *g* = -0.455, 95%CI -0.797 to -0.114, *p* < 0.01, I^2 = 83% Chronic: N = 543, *g* = -0.438, 95%CI -0.678 to -0.198, *p* < 0.001, I^2 = 70% *Only females with schizophrenia showed a significant reduction;* Males: N = 298, *g* = -0.275, 95%CI -0.624 to 0.073, *p* = 0.122, I^2 = 74% Females: N = 189, *g* = -0.529, 95%CI -0.875 to -0.182, *p* < 0.01, I^2 = 57% Meta-regression identified no moderating effects of whole brain volume, patients' age, medication dose, or illness duration.

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Smieskova R, Fusar-Poli P, Allen P, Bendfeldt K, Stieglitz RD, Drewe J, Radue EW, McGuire PK, Riecher-Rossler A, Borgwardt SJ

Neuroimaging predictors of transition to psychosis – A systematic review and meta-analysis

Neuroscience and Biobehavioural Reviews 2010; 34: 1207-1222

View review abstract online

Comparison	**Grey matter volume changes in people at high risk who transition to psychosis (HR-T) vs. high risk individuals who do not transition (HR-NT) and vs. controls.**
Summary of evidence	**Moderate quality evidence (unclear sample size, precise, direct, unable to assess consistency) suggests whole brain volume is increased in high risk patients who transition to psychosis compared to high risk patients who do not transition to psychosis and compared to first-episode psychosis patients.**

	Moderate to low quality evidence (unable to assess consistency or precision) suggests grey matter is reduced in the insula, cingulate cortex (ACC and PCC), superior temporal gyrus, PFC, and cerebellum in HR-T compared to HR-NT.
Grey matter volume	
Meta-analysis conducted only for whole brain volume, comprising whole brain, total intracranial and total grey matter volume estimates. 7 studies, N = unclear *Small effect of larger global volumes in HR-T compared to HR-NT and first-episode patients;* *d* = 0.36, 95%CI 0.27 to 0.46, *p* not reported HR-T patients also showed relative reductions in insula (3 studies), anterior cingulate (3 studies), posterior cingulate (2 studies), superior temporal cortex (3 studies), prefrontal cortex (3 studies), cerebellum (3 studies) compared to HR-NT. Compared to controls, HR-T showed reductions in cingulate cortex and insula (2 studies). Compared to first-episode, HR-T showed increased superior and medial temporal (2 studies).	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Sommer I, Aleman A, Ramsey N, Bouma A

Handedness, language lateralisation and anatomical asymmetry in schizophrenia: meta-analysis

British Journal of Psychiatry 2001; 178: 344-351

View review abstract online

Comparison	**Differences in anatomical asymmetry in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, mostly inconsistent, imprecise, direct) suggests people with schizophrenia showed an absence of normal leftward asymmetry in the planum temporale and Sylvian fissure, and an excess rightward asymmetry in the STG**

	(particularly posterior). There was also a higher frequency of abnormal (reversed) asymmetry in the frontal and occipital lobes in people with schizophrenia compared to controls.
Anatomical asymmetry	
Significantly higher frequency of absent or reversed frontal lobe asymmetry in people with schizophrenia compared to controls; 3 studies, N = 383, weighted difference rate = 0.24, 95%CI 0.15 to 0.34, $p = 0.05$, Q = 8.4, $p = 0.05$ *Significantly higher frequency of absent or reversed occipital lobe asymmetry in people with schizophrenia compared to controls;* 5 studies, N = 579, weighted difference rate = 0.22, 95%CI 0.12 to 0.28, $p = 0.01$, Q = 87.55, $p = 0.003$ <u>Planum temporale</u> *Significant left asymmetry in controls but not in people with schizophrenia;* Controls: 11 studies, N = 187, $d = 0.7$, 95%CI 0.49 to 0.91, $p < 0.01$ Q = 4.3, $p = 0.89$ Schizophrenia: 11 studies, N = 191, $d = 0.18$, 95%CI -0.33 to 0.69, $p = 0.24$ Q = 48.7, $p < 0.01$ *Significantly less asymmetry of the planum temporale in people with schizophrenia compared to controls;* 11 studies, N = 368, $d = -0.51$, 95%CI -1.04 to 0.02, $p = 0.03$, Q = 54.5, $p = 0.0005$ <u>Sylvian Fissure</u> *Significant left asymmetry in both controls and people with schizophrenia;* Controls: 3 studies, N = 100, $d = 0.87$, 95%CI 0.43 to 1.32, $p < 0.01$, Q = 9.85, $p = 0.04$ Schizophrenia: 3 studies, N = 97, $d = 0.31$, 95%CI -1.04 to 0.2, $p < 0.01$, Q = 4.72, $p = 0.32$ *Significantly less asymmetry of the Sylvian fissure in people with schizophrenia compared to controls;* 3 studies, N = 185, $d = -0.62$, 95%CI -1.04 to 0.2, $p < 0.01$, Q = 11.1, $p = 0.03$ <u>Temporal horn of the lateral ventricle</u> *Significant right asymmetry in both controls and people with schizophrenia;* Controls: 12 studies, N = 303, $d = -0.25$, 95%CI -0.41 to -0.09, $p < 0.01$, Q = 9.32, $p = 0.59$ Schizophrenia: 12 studies, N = 324, $d = -0.42$, 95%CI -0.88 to -0.04, $p = 0.04$, Q = 92.5, $p < 0.01$ *No significant difference in degree of asymmetry of the temporal horn between people with schizophrenia and controls;* 12 studies, N = 629, $d = -0.11$, 95%CI -0.61 to 0.4, $p = 0.34$, Q = 106.83, $p < 0.01$	

Superior temporal gyrus (STG) *Significant right asymmetry reported in schizophrenia only (trend level in controls);* Controls: 17 studies, N = 399, *d* = -0.47, 95%CI -1.1 to 0.14, *p* = 0.07, Q = 140.23, *p* < 0.01 Schizophrenia: 17 studies, N = 469, *d* = -0.73, 95%CI -1.2 to -0.25, *p* < 0.01, Q = 151.7, *p* < 0.01 *No significant difference in degree of asymmetry of STG between people with schizophrenia and controls;* 17 studies, N = 1,020, *d* = 0.21, 95%CI -0.08 to 0.51, *p* = 0.08, Q = 93.3, *p* < 0.01 Posterior segment of the superior temporal gyrus *Significant right asymmetry reported in schizophrenia only (trend level in controls);* Controls: 5 studies, N = 130, *d* = -0.2, 95%CI -0.44 to 0.05, *p* = 0.06, Q = 1.5, *p* = 0.9 Schizophrenia: 5 studies, N = 108, *d* = -0.9, 95%CI-0.17 to -0.62, *p* < 0.01, Q = 4.85, *p* = 0.43 *Significantly greater right asymmetry of posterior STG in people with schizophrenia compared to controls;* 5 studies, N = 238, *d* = 0.7, 95%CI 0.4 to 1, *p* < 0.01, Q = 5.42, *p* = 0.37

Consistency in results	Inconsistent for all measures except posterior STG
Precision in results	Imprecise
Directness of results	Direct

Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA

Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies

British Journal of Psychiatry 2006; 188(6): 510-8

View review abstract online

Comparison	**Whole brain volumetry in first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) suggests the average brain and hippocampal volume is significantly decreased and the ventricular volume is significantly increased in people with first-episode schizophrenia.**
Whole brain volumetry	

Significant reduction in average brain volume in first-episode schizophrenia compared to controls; N = 1,174, 21 studies The average schizophrenia patient's brain volume was 2.7% smaller than controls.
Hippocampal volumetry
Significant reduction in average hippocampal volume in first-episode schizophrenia compared to controls; N = 587, 11 studies The average schizophrenia patient's left hippocampus volume was 8.2% smaller than controls. The average schizophrenia patient's right hippocampus volume was 8.3% smaller than controls.
Ventricular volumetry
Significant increase in average ventricular volume in first-episode schizophrenia compared to controls; N = 587, 9 studies The average schizophrenia patient's left lateral ventricle volume was 33.7% larger than controls. The average schizophrenia patient's right lateral ventricle volume was 24.7% larger than controls. The average schizophrenia patient's third ventricle volume was 25.3% larger than controls.

Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Sun J, Maller JJ, Guo L, Fitzgerald PB

Superior temporal gyrus volume change in schizophrenia: A review on Region of Interest volumetric studies

Brain Research Reviews 2009; 61(1): 14-32

View review abstract online

Comparison	**Superior temporal gyrus volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess**

	consistency or precision) suggests a volume deficit in the superior temporal gyrus in schizophrenia patients. Further association is seen with aspects of the clinical syndrome, suggesting the STG may be involved in the production of symptoms such as auditory hallucinations. This involvement may also be lateralised, as the left STG was more strongly correlated than the right STG.
Region-of-interest volumetric analysis of the superior temporal gyrus (STG) and its subregions	
5 of 46 studies reported follow up ranging from 1 to 10 years. All other studies reported at baseline. 46 studies, N = 2,771 35/46 (N = 1,682/2,771) studies report significant volume differences in the superior temporal gyrus. 12/35 (N = 1,117/1,682) studies show unilateral (left) reduction of STG volume. 13/35 (N = 565/1,682) show a bilateral reduction of STG volume.	
Correlation with clinical syndrome	
Psychotic syndrome and auditory hallucination were negatively correlated with the left anterior STG volume (4 studies, N = 171). Thought disorder negatively correlated with many different subregions including left posterior STG (3 studies, N = 125); right STG (1 study, N = 80); anterior STG (1 study, N = 18).	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Taylor H, Ricciardi A, Dazzan P

A review of caudate nucleus volume in first-episode psychosis

Clinical Neuropsychiatry 2007; 4(5-6): 191-198

View review abstract online

Comparison	**Cross sectional comparison of caudate nucleus volume in antipsychotic naive first-episode psychosis patients vs. controls.**
Summary of evidence	**Moderate to low quality evidence (medium-sized sample, direct,**

	unable to assess precision or consistency) suggests bilateral caudate nucleus is significantly reduced in drug naive first-episode psychosis patients compared to controls.
Bilateral caudate nucleus volume	
7 studies, N = 212 4 of 7 studies reported consistently reduced volume in bilateral caudate nucleus in patients. 3 of 7 studies reported no significant difference in caudate nucleus volume, although 2 of the 3 had methodological limitations.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct
Comparison 2	**Cross sectional comparison of medicated first-episode psychosis patients (maximum 12-week treatment with first- or second-generation antipsychotics) vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests no significant difference in bilateral caudate volume in medicated first-episode psychosis patients compared to controls.**
Bilateral caudate nucleus volume	
4 studies, N = 428 4 of 4 studies reported no significant difference in bilateral caudate nucleus volume	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct
Comparison 3	**Longitudinal comparison of medicated first-episode psychosis patients compared to controls, measured at several varying time points.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests no significant difference in bilateral caudate volume over time in medicated first-episode**

	psychosis patients compared to controls.
Bilateral caudate nucleus volume	
6 studies, N = 548 6 of 6 studies reported no significant difference in overall bilateral caudate nucleus volume	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Torres US, Portela-Oliveira E, Borgwardt S, Busatto GF

Structural brain changes associated with antipsychotic treatment in schizophrenia as revealed by voxel-based morphometric MRI: an activation likelihood estimation meta-analysis

BMC Psychiatry 2013; 13: 342

View review abstract online

Comparison	**Brain changes with antipsychotic treatment in people with schizophrenia vs. mixed controls (healthy controls, drug-free patients, or pre-post medication in patients).**
Summary of evidence	**Moderate to low quality evidence (large sample size, indirect, unable to assess consistency or precision) suggests four areas of relative volumetric decrease in the left lateral temporal cortex, left inferior frontal gyrus, superior frontal gyrus extending to the left middle frontal gyrus, and right rectal gyrus, and three areas of relative volumetric increase in the left dorsal anterior cingulate cortex, left ventral anterior cingulate cortex and right putamen.**
Brain changes with medication use	
10 studies, N = 548 *The following clusters showed consistent structural decreases in patients on antipsychotics compared to controls;* Left lateral temporal cortex (BA20): Talairach coordinate -48 -16 -20, cluster volume 408mm^3	

Left inferior frontal gyrus (BA44): Talairach coordinate -48, 6, 22, cluster volume 192mm^3 Superior frontal gyrus/left middle frontal gyrus (BA6): Talairach coordinate -22, 12, 48, cluster volume 120mm^3 Right rectal gyrus (BA11): Talairach coordinate 4, 38, -24, cluster volume 104mm^3 *The following clusters showed consistent structural increases in patients on antipsychotics compared to controls;* Left dorsal anterior cingulate cortex (BA 24): Talairach coordinate -2, 24, 6, cluster volume 416mm^3 Left ventral anterior cingulate cortex (BA 24): Talairach coordinate -4, 2, 26, cluster volume 152mm^3 Right putamen: Talairach coordinate 24, -4, 4, cluster volume 264mm^3

Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Indirect; mixed control group.

Trzesniak C, Oliveira IR, Kempton MJ, Galvao-de Almeid A, Chagas MHN, Ferrari MCF, Filho AS, Zuardi AW, Prado DA, Busatto GF, McGuire PK, Hallak JEC, Crippa JAS

Are cavum septum pellucidum abnormalities more common in schizophrenia spectrum disorders? A systematic review and meta-analysis

Sczhiophrenia Research 2011; 125: 1-12

View review abstract online

Comparison	**Prevalence of cavum septum pellucidum (CSP) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, imprecise, direct) suggests schizophrenia spectrum disorders may be associated with increased frequency of large cavum septum pellucidum compared to controls.**
Cavum septum pellucidum of any size	

Septum pellucidum are two thin membranes lying along the medial wall of the lateral ventricles. These membranes usually fuse during early development, but non-fused membranes form a cavity, known as cavum septum pellucidum (CSP).

Small effect size suggests no significant difference in prevalence of CSP of any size in schizophrenia, suggesting small CSP may be attributable to normal variation;

15 studies, N = 1,920, OR = 1.19, 95%CI 0.82 to 1.71, $p = 0.37$, Q = 32.3, $p < 0.01$, $I^2 = 56.7\%$

Authors report no evidence of publication bias ($p = 0.30$).

Furthermore, meta-regression identified year of publication as a moderator of CSP prevalence (of any size), with studies prior to 2000 showing higher prevalence compared to controls, while studies post-2000 show no difference to controls (slope = -0.082, $p = 0.005$).

Large size cavum septum pellucidum

Medium effect size suggests a significantly higher frequency of large CSP in schizophrenia;

15 studies, N = 1,920, OR = 1.59, 95%CI 1.07 to 2.38, $p = 0.02$, Q = 13.7, $p = 0.48$, $I^2 = 0\%$

Authors also report significant publication bias relating to this comparison, $p < 0.01$.

Consistency in results	Consistent for large CSP only.
Precision in results	Imprecise
Directness of results	Direct

Trzesniak C, Kempton MJ, Busatto GF, Oliveira IR, Galvao-de Almeida A, Kambeitz J, Ferrari MCF, Filho AS, Chagas MHN, Zuardi AW, Hallak JEC, McGuire PK, Crippa JAS

Adhesio interthalamica alterations in schizophrenia spectrum disorders: a systematic review and meta-analysis

Progress in Neuro-psychopharmacology and Biological Psychiatry 2011; 35: 877-886

View review abstract online

Comparison	**Prevalence of absent adhesio interthalamica (AI) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, imprecise, direct) suggests schizophrenia may be associated with increased frequency of an absent adhesio interthalamica**

	compared to controls.
Prevalence of non-AI	
Adhesio interthalamica is a small midline structure that joins the two thalami in the centre of the brain. This structure usually develops during early gestation (weeks 13-14) and while the functional implications of absent AI are unclear, they suggest a developmental interruption. *Small effect size suggests significantly increased prevalence of absent AI in people with schizophrenia;* 11 studies, N = 1,540, OR = 1.98, 95%CI 1.33 to 2.94, p = 0.0008, Q = 14.0, p = 0.17, I^2 = 28.6% Authors report no evidence of publication bias (p = 0.94). Furthermore, meta-regression showed no significant moderating effect of mean patient age (p = 0.39), or duration of illness (p = 0.93). <u>Subgroup analyses for males and females</u> *Increased non-AI prevalence in females with schizophrenia;* 8 studies, N = 476, OR = 2.66, 95%CI 1.41 to 4.99, p = 0.002 *Increased non-AI prevalence in males with schizophrenia;* 9 studies, N = 790, OR = 1.72, 95%CI 1.03 to 2.88, p = 0.040 <u>Subgroup analysis for AI length</u> *When present, people with schizophrenia showed significantly shorter AI;* g = 0.979, 95%CI 0.719 to 1.239, p < 0.001, Q = 3.54, p = 0.17, I^2 = 43.5% Authors report no evidence of publication bias (p = 0.40). Furthermore, meta-regression showed no significant moderating effect of mean patient age (p = 0.73).	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Vita A, De Peri L, Silenzi C, Dieci M

Brain morphology in first-episode schizophrenia: A meta-analysis of quantitative magnetic resonance imaging studies

Magnetic resonance imaging

Schizophrenia Research 2006; 82(1): 75-88 View review abstract online	
Comparison	**Whole brain volumetry in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large samples, precise, consistent, direct) suggests there are small reductions in the volumetry of the whole brain and medium-sized reductions in the hippocampus of first-episode schizophrenia patients. Evidence also suggests there are medium-sized increases in ventricular volume (right and left lateral ventricles, and third ventricle).**
Total and regional brain volumes	
Significant volume reductions were reported in: Whole brain volume: 11 studies, N = 762, *d* = 0.242, 95%CI 0.091 to 0.393, *p* = 0.002, Q = 10.4, *p* = 0.4 Right hippocampus: 6 studies, N = 455, *d* = 0.473, 95%CI 0.268 to 0.677, *p* = 0.000, Q = 3.63, *p* = 0.6 Left hippocampus: 6 studies, N = 455, *d* = 0.659, 95%CI 0.452 to 0.866, *p* = 0.000, Q = 9.57, *p* = 0.08 *Significant volume increases were found in:* Right lateral ventricle: 8 studies, N = 447, *d* = -0.467 95%CI -0.659 to -0.275, *p* = 0.000, Q = 1.33, *p* = 0.98 Left lateral ventricle: 8 studies, N = 447, *d* = -0.608, 95%CI -0.802 to -0.414, *p* = 0.000, Q = 4.25, *p* = 0.74 Third ventricle: 6 studies, N = 366, *d* = -0.591, 95%CI -0.804 to -0.377, *p* = 0.000, Q = 3.63, *p* = 0.6 *No significant differences were found for:* Intracranial volume: 4 studies, N = 270, *d* = 0.067, 95%CI -0.179 to 0.313, *p* = 0.592, Q = 2.85, *p* = 0.41 Right temporal lobe: 4 studies, N = 222, *d* = 0.068, 95%CI -0.20 to 0.336, *p* = 0.617, Q = 2.99, *p* = 0.39 Left temporal lobe: 4 studies, N = 222, *d* = 0.154, 95%CI -0.114 to 0.423, *p* = 0.258, Q = 1.78, *p* = 0.61 Right amygdala: 4 studies, N = 203, *d* = 0.088, 95%CI -0.193 to 0.369, *p* = 0.537, Q = 2.51, *p* = 0.47 Left amygdala: 4 studies, N = 203, *d* = 0.195, 95%CI -0.086 to 0.476, *p* = 0.173, Q = 1.49, *p* = 0.68	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Vita A, De Peri L, Sacchetti E

Progressive loss of cortical grey matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies

Translational Psychiatry 2012; 2: e190

View review abstract online

Comparison	**Whole brain and regional volume change over time in longitudinal studies of schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (small to large samples, mostly precise, inconsistent, direct) suggests medium to large reductions over time in whole brain volume, superior temporal gyrus, heschl's gyrus and planum temporal in people schizophrenia. People with first-episode schizophrenia also showed significant reductions of frontal, temporal and parietal lobes over time.**

Total and regional brain volumes: group differences

Medium to large reductions in volume over time in schizophrenia in;

Total GMV: 13 studies, N = 1,084, g = -0.50, 95%CI -0.80 to -0.20, p = 0.001, I^2 = 78%, p < 0.001

Left STG: 6 studies, N = 179, g = -0.80, 95%CI -1.55 to -0.04, p = 0.03, I^2 = 83%, p < 0.001

Left anterior STG: 5 studies, N = 177, g = -0.71, 95%CI -1.23 to -0.20, p = 0.006, I^2 = 63%, p = 0.02

Right posterior STG: 5 studies, N = 177, g = -0.62, 95%CI -0.92 to -0.32, p < 0.001, I^2 = 39%, p > 0.05

Left posterior STG: 5 studies, N = 177, g = -1.14, 95%CI -1.67 to -0.62, p < 0.001, I^2 = 62%, p = 0.03

Left Heschl's gyrus: 4 studies, N = 125, g = -1.05, 95%CI -1.68 to -0.43, p = 0.001, I^2 = 63%, p = 0.04

Left planum temporale: 3 studies, N = 101, g = -1.18, 95%CI -2.13 to -0.23, p = 0.01, I^2 = 79%, p = 0.008

No differences between groups over time in;

Frontal GMV: 7 studies, N = 666, g = -0.18, 95%CI -0.48 to 0.12, p = 0.24, I^2 = 65%, p = 0.009

Temporal GMV: 7 studies, N = 666, g = -0.24, 95%CI -0.57 to 0.08, p = 0.14, I^2 = 70%, p = 0.003

Parietal GMV: 6 studies, N = 623, g = -0.06, 95%CI -0.43 to 0.30, p = 0.71, I^2 = 74%, p = 0.002

Occipital GMV: 6 studies, N = 590, g = 0.14, 95%CI -0.26 to 0.55, p = 0.48, I^2 = 76%, p = 0.001

Right STG: 6 studies, N = 179, *g* = -0.35, 95%CI -1.13 to 0.42, *p* = 0.37, I^2 = 84 *p* < 0.001
Right anterior STG: 5 studies, N = 177, *g* = -0.32, 95%CI -0.82 to 0.18, *p* = 0.21, I^2 = 65%, *p* = 0.02
Right Heschl's gyrus: 4 studies, N = 125, *g* = -0.13, 95%CI -0.48 to 0.21, *p* = 0.44, I^2 = 0%, *p* > 0.05
Right Planum temporale: 3 studies, N = 101, *g* = -0.37, 95%CI -0.76 to 0.02, *p* = 0.06, I^2 = 0%, *p* > 0.05
Subgroup analysis in first-episode schizophrenia
Medium to large reductions in volume over time in;
Total GMV: 7 studies, N = 678, *g* = -0.58, 95%CI -0.90 to -0.26, *p* < 0.001, I^2 = 66%, *p* = 0.006
Frontal GMV: 4 studies, N = 533, *g* = -0.39, 95%CI -0.57 to 0.22, *p* < 0.001, I^2 = 0%, *p* > 0.05
Temporal GMV: 4 studies, N = 533, *g* = -0.37, 95%CI -0.71 to -0.04, *p* = 0.028, I^2 = 63%, *p* = 0.04
Parietal GMV: 3 studies, N = 490, *g* = -0.30, 95%CI -0.48 to -0.12, *p* = 0.001, I^2 = 0%, *p* > 0.05
Left Heschl's gyrus: 3 studies, N = 97, *g* = -1.33, 95%CI -1.77 to -0.90, *p* < 0.001, I^2 = 63%, *p* = 0.04
No differences between groups over time in;
Occipital GMV: 3 studies, N = 490, *g* = 0.13, 95%CI -0.31 to 0.05, *p* = 0.15, I^2 = 0%, *p* > 0.05
Right Heschl's gyrus: 3 studies, N = 97, *g* = -0.14, 95%CI -0.53 to 0.25, *p* = 0.48, I^2 = 15%, *p* > 0.05

Consistency in results	Mostly inconsistent. Consistent for right posterior STG, heschls gyrus and planum temporale, plus first-episode subgroup: frontal, parietal, occipital and Heschl's gyrus GMV.
Precision in results	Mostly precise. Imprecise for left and right STG, anterior STG, left posterior STG, left heschl's gyrus and planum temporale.
Directness of results	Direct

Vitolo E, Tatu MK, Pignolo C, Cauda F, Costa T, Ando A, Zennaro A

White matter and schizophrenia: A meta-analysis of voxel-based morphometry and diffusion tensor imaging studies

Psychiatry Research: Neuroimaging 2017; 270: 8-21

View review abstract online

Comparison	**White matter integrity in people with schizophrenia vs. controls.** **The meta-analysis combined MRI and DTI studies.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) found white matter reductions in**

	the anterior commissure, corpus callosum, fornix, internal capsule, bilateral anterior segment of the arcuate fasciculus, left long segment of the arcuate fasciculus, bilateral arcuate fasciculus, bilateral cingulum, bilateral cortico-ponto-cerebellum tract, bilateral cortico spinal tract, bilateral inferior fronto-occipital fasciculus, bilateral inferior longitudinal fasciculus, bilateral inferior cerebellar penduculus, bilateral optic radiation, bilateral posterior segment of the arcuate fasciculus, bilateral superior longitudinal fasciculus 1, 2 and 3, bilateral superior cerebellar penduculus and bilateral uncinate fasciculus.
FA	
34 studies, N = 2,231 *There were white matter reductions in;* Anterior commissure: 16,636 voxels, MNI coordinates (-25, 8, -25), p = 0.000904 Corpus callosum: 114,544 voxels, MNI coordinates (17, 35, 35), p = 0.000655 Fornix: 26,318 voxels, MNI coordinates (-29, 10, -27), p = 0.000924 Internal capsule: 63,671 voxels, MNI coordinates (-19, -1, 17), p = 0.000525 Left anterior segment of arcuate fasciculus: 5,391 voxels, MNI coordinates (-51, -7, 15), p = 0.000036 Right anterior segment of arcuate fasciculus: 8,780 voxels, MNI coordinates (50, -10, 29), p = 0.000378 Left long segment of arcuate fasciculus: 7,639 voxels, MNI coordinates (-34, -40, -1), p = 0.000218 Left arcuate fasciculus: 24,480 voxels, MNI coordinates (-34, -40, -1), p = 0.000112 Right arcuate fasciculus: 23,307 voxels, MNI coordinates (44, -38, -1), p = 0.000258 Left cingulum: 42,476 voxels, MNI coordinates (-19, -43, 39), p = 0.000566 Right cingulum: 38,840 voxels, MNI coordinates (18, 35, 32), p = 0.001913 Left cortico-ponto-cerebellum tract: 2,176 voxels, MNI coordinates (16, -37, -32), p = 0.000226 Right cortico-ponto-cerebellum tract: 766 voxels, MNI coordinates (25, -17, 5), p = 0.000206 Left cortico spinal tract: 29,175 voxels, MNI coordinates (-19, -1, 17), p = 0.000409 Right cortico spinal tract: 23,730 voxels, MNI coordinates (29, -19, 5), p = 0.000592 Left inferior fronto-occipital fasciculus: 22,154 voxels, MNI coordinates (-31, -22, -7), p = 0.000725 Right inferior fronto-occipital fasciculus: 23,185 voxels, MNI coordinates (41, -31, -7), p = 0.001700 Left inferior longitudinal fasciculus: 20,131 voxels, MNI coordinates (-34, -40, -1), p = 0.000900 Right inferior longitudinal fasciculus: 16,338 voxels, MNI coordinates (41, -31, -7), p = 0.002284 Left inferior cerebellar penduculus: 5,648 voxels, MNI coordinates (-7, -33, -22), p = 0.000235	

Right inferior cerebellar penduculus: 5,302 voxels, MNI coordinates (14, -38, -31), *p* = 0.000502 Left optic radiation: 7,923 voxels, MNI coordinates (-34, -40, -1), *p* = 0.000797 Right optic radiation: 5,982 voxels, MNI coordinates (29, -19, 5), *p* = 0.002349 Left posterior segment of arcuate fasciculus: 11,088 voxels, MNI coordinates (-34, -40, -1), *p* = 0.000313 Right posterior segment of arcuate fasciculus: 12,107 voxels, MNI coordinates (41, -34, -4), *p* = 0.001262 Left superior longitudinal fasciculus1: 109,025 voxels, MNI coordinates (-19, -43, 39), *p* = 0.000169 Right superior longitudinal fasciculus1: 98,037 voxels, MNI coordinates (20, 35, 35), *p* = 0.001150 Left superior longitudinal fasciculus2: 112,229 voxels, MNI coordinates (-20, -4, 53), *p* = 0.000059 Right superior longitudinal fasciculus2: 117,581 voxels, MNI coordinates (20, 35, 35), *p* = 0.000437 Left superior longitudinal fasciculus3: 72,219 voxels, MNI coordinates (-49, -37, 14), *p* = 0.000115 Right superior longitudinal fasciculus3: 119,900 voxels, MNI coordinates (23, 27, 31), *p* = 0.000078 Left superior cerebellar penduculus: 8,012 voxels, MNI coordinates (-7, -31, -22), *p* = 0.000772 Right superior cerebellar penduculus: 8,113 voxels, MNI coordinates (13, -24, -7), *p* = 0.000741 Left uncinate fasciculus: 12,282 voxels, MNI coordinates (-25, 9, -21), *p* = 0.000883 Right uncinate fasciculus: 13,022 voxels, MNI coordinates (16, 27, 2), *p* = 0.000888 Older patients showed reduced white matter in the right splenium of corpus callosum and the right cortico spinal tract. Younger patients showed white matter reductions of the left cortico spinal tract, the right cingulum bundle, the right superior temporal gyrus, and the left superior longitudinal fasciculus3. Longer duration of illness was associated with white matter reductions in the bilateral uncinate fasciculus, the left inferior longitudinal fasciculus, the right inferior fronto-occipital fasciculus and the right posterior cingulum bundle. Shorter duration of illness was associated with white matter reductions in the right anterior cingulum bundle, the right median cingulate gyrus, and the left superior longitudinal fasciculus3. A higher percentage of male patients showed reduced white matter traits in the right superior longitudinal fasciculus2, the left inferior temporal gyrus, the bilateral superior longitudinal fasciculus3, the right superior temporal gyrus, the right posterior segment of arcuate fasciculus, and the left body of corpus callosum. Female patients showed reduced white matter traits in the right genu of corpus callosum, the right inferior fronto-occipital fasciculus, the right superior longitudinal fasciculus3, the left superior cerebellar penduculus, the left optic radiation, and the left long segment of the arcuate fasciculus.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.

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Directness of results	Direct

Wang LX, Li P, He H, Guo F, Tian P, Li C, Cui LB, Xi YB, Yin H

The Prevalence of Cavum Septum Pellucidum in Mental Disorders Revealed by MRI: A Meta-Analysis

The Journal of Neuropsychiatry and Clinical Neurosciences: appineuropsych18030060

View review abstract online

Comparison	**Prevalence of a cavum septum pellucidum in people with schizophrenia vs. controls.** **The septum pellucidum is a brain midline structure comprising two translucent parallel membranes, which fuse in an anterior to posterior direction in the first 3–6 months of life. Failure of the fusion leads to the occurrence of cavum septum pellucidum.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, inconsistent, imprecise, direct) suggests no differences in rates of cavum septum pellucidum in people with schizophrenia compared to controls.**
Cavum septum pellucidum	
No significant differences between groups; 10 studies, unclear sample size, OR = 1.29, 95%CI 0.88 to1.89, p = 0.20, I^2 = 50.60%, p = 0.03	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Wojtalik JA, Smith MJ, Keshavan MS, Eack SM

A Systematic and Meta-analytic Review of Neural Correlates of Functional Outcome in Schizophrenia

Magnetic resonance imaging

Schizophrenia Bulletin 2017; 43: 1329-47 View review abstract online	
Comparison	**Association between functional outcomes and grey matter volume in people with schizophrenia.** **Functional outcomes include global functioning, social functioning, resource needs, quality of life, socioeconomic status, independent living, employment, and role functioning.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests better overall functioning was associated with larger volumes in whole brain, frontal lobe, parietal lobe, occipital lobe, cerebellum, and limbic regions. Better functioning was also associated with smaller ventricle volumes. There were no associations with the temporal lobe or white matter tracts.**
Brain volume and functional outcome	
37 studies, N = 1,187 *Better functioning was associated with larger volumes in;* Whole brain: 8 studies, r = 0.25, 95%CI 0.13 to 0.37, $p < 0.0001$, Q = 37.07, $p < 0.05$ Frontal lobe: 12 studies, r = 0.35, 95%CI 0.22 to 0.47, $p < 0.0001$, Q = 106.01, $p < 0.001$ Limbic regions: 15 studies, r = 0.38, 95%CI 0.25 to 0.51, $p < 0.0001$, Q = 166.54, $p < 0.001$ Parietal lobe: 5 studies, r = 0.29, 95%CI 0.01 to 0.57, $p = 0.039$, Q = 67.29, $p < 0.001$ Occipital lobe: 6 studies, r = 0.30, 95%CI 0.10 to 0.50, $p = 0.004$, Q = 40.80, $p < 0.001$ Cerebellum: 4 studies, r = 0.17, 95%CI 0.09 to 0.26, $p < 0.0001$, Q = 10.96, $p > 0.05$ *Better functioning was associated with smaller volumes in;* Ventricles: 10 studies, r = -0.31, 95%CI -0.41 to -0.21, $p < 0.0001$, Q = 45.09, $p < 0.05$ *There were no associations with;* White matter tracts: 4 studies, r = 0.32, 95%CI -0.12 to 0.75, $p = 0.150$, Q = 112.87, $p < 0.001$ Temporal lobe: 8 studies, r = 0.19, 95%CI -0.10 to 0.48, $p = 0.191$, Q = 54.51, $p < 0.001$	
Consistency in results	Inconsistent, apart from the cerebellum.
Precision in results	Precise
Directness of results	Direct

Woods BT, Ward KE, Johnson EH

Meta-analysis of the time course of brain volume reduction in schizophrenia: implications for pathogenesis and early treatment

Schizophrenia Research 2005; 73: 221- 228

View review abstract online

Comparison	**Quantitative volumetric whole brain MRI measuring brain volume, intracranial volume, extracerebral volume, and intraventricular volume. Volume changes over time are assessed on cross-sectional measurements using derivations of sums of these measurements.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) suggests brain volume is significantly decreased in people with schizophrenia, and volume loss in schizophrenia occurs to a quantitatively similar degree before and after BV_{max} (suggesting no clear progression of brain volume loss over time).**

Whole brain volume

20 studies, N = 2,031, examined brain volume (BV) and intracranial volume (ICV) in the context of the inferred maximal brain volume over time (BV_{max}).

17 of these studies, N = 1,831, also examined extracerebral volume (ECV) and intraventricular volume (IVV).

Significant reduction in the mean BV in people with schizophrenia compared to controls. Mean volume difference was 34mL, $t = -4.94$, $p < 0.0001$.

Significant reduction in mean ICV in people with schizophrenia compared to controls. Mean volume difference was 20.1mL, $t = -2.64$, $p < 0.02$.

Subset analysis

Significant increase in mean ECV in people with schizophrenia compared to controls. Mean volume difference 14.1mL, $t = -3.6$, $p < 0.001$.

Significant decrease in ICV – IVV in people with schizophrenia compared to controls (representing changes in volume occurring earlier in life, prior to BV_{max}). Mean difference 20.2mL, $t = -2.56$, $p < 0.05$.

Significant increase in ECV + IVV in people with schizophrenia compared to controls (representing changes in volume occurring later in life, after BV_{max}). Mean difference 17.1mL, $t = -4.11$, $p < 0.001$.

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Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET

Meta-analysis of regional brain volumes in schizophrenia

American Journal of Psychiatry 2000; 157(1): 16-25

View review abstract online

Comparison 1	**Whole brain volumetry in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (medium to large samples, consistent, precise, direct) finds small reductions in whole brain, grey and white matter volume in people with schizophrenia. Moderate to high quality evidence (imprecise) finds increases in lateral, third, and fourth ventricles.**

Whole brain volume

Small reduction of total brain volume in schizophrenia;

Whole brain volume: 31 studies, N = 1,867, schizophrenia volume was 98% of control volume (95%CI 97% to 99%)

Whole brain grey matter: 6 studies, N = 349, schizophrenia volume was 96% of control volume (95%CI 97% to 99%)

Whole brain white matter: 6 studies, N = 349, schizophrenia volume was 98% of control volume (95%CI 95% to 100%)

Ventricular volume

Total ventricles: 30 studies, N = 1,896, schizophrenia volume was 126% of control volume (95%CI 120% to 132%)

Left lateral ventricle: 18 studies, N = 1,053, schizophrenia volume was 130% of control volume (95%CI 120% to 141%)

Right lateral ventricle: 18 studies, N = 1,053, schizophrenia volume was 120% of control volume (95%CI 113% to 128%)

Left frontal horn: 3 studies, N = 129, schizophrenia volume was 113% of control volume (95%CI 97% to

132%) Right frontal horn: 3 studies, N = 129, schizophrenia volume was 117% of control volume (95%CI 105% to 132%) Left body ventricle: 3 studies, N = 129, schizophrenia volume was 147% of control volume (95%CI 124% to 174%) Right body ventricle: 3 studies, N = 129, schizophrenia volume was 148% of control volume (95%CI 126% to 174%) Left occipital horn: 3 studies, N = 129, schizophrenia volume was 129% of control volume (95%CI 113% to 147%) Right occipital horn: 3 studies, N = 129, schizophrenia volume was 128% of control volume (95%CI 110% to 149%) Left temporal horn: 13 studies, N = 791, schizophrenia volume was 134% of control volume (95%CI 118% to 153%) Right temporal horn: 13 studies, N = 791, schizophrenia volume was 119% of control volume (95%CI 109% to 131%) Third ventricle: 22 studies, N = 1,143, schizophrenia volume was 126% of control volume (95%CI 119% to 134%) Fourth ventricle: 5 studies, N = 253, schizophrenia volume was 107% of control volume (95%CI 96% to 119%)	
Consistency in results	Consistent
Precision in results	Precise for whole brain, imprecise for ventricles.
Directness of results	Direct
Comparison 2	**Hemispheric volumetry in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) finds small reductions in hemispheric volume in people with schizophrenia.**
Hemispheric volume	
Left hemisphere: 15 studies, N = 897, schizophrenia volume was 97% of control volume (95%CI 96% to 99%) Right hemisphere: 15 studies, N = 897, schizophrenia volume was 97% of control volume (95%CI 96% to 99%)	
Consistency in results	Consistent

Precision in results	Precise
Directness of results	Direct
Comparison 3	**Lobar volumetry in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) finds small reductions in frontal lobe and superior temporal gyrus volume in people with schizophrenia.**
Regional volume	
<u>Frontal lobe</u> Left frontal volume: 13 studies, N = 762, schizophrenia volume was 95% of control volume (95%CI 92% to 98%) Right frontal volume: 13 studies, N = 762, schizophrenia volume was 95% of control volume (95%CI 93% to 97%) <u>Temporal lobe</u> Left temporal volume: 25 studies, N = 1362, schizophrenia volume was 98% of control volume (95%CI 96% to 99%) Right temporal volume: 25 studies, N = 1362, schizophrenia volume was 97% of control volume (95%CI 96% to 98%) Left superior temporal gyrus: 10 studies, N = 585, schizophrenia volume was 97% of control volume (95%CI 95% to 100%) Right superior temporal gyrus: 10 studies, N = 585, schizophrenia volume was 97% of control volume (95%CI 95% to 100%) Left anterior superior temporal gyrus: 8 studies, N = 377, schizophrenia volume was 93% of control volume (95%CI 88% to 99%) Right anterior superior temporal gyrus: 7 studies, N = 347, schizophrenia volume was 95% of control volume (95%CI 91% to 98%) Left posterior superior temporal gyrus: 5 studies, N = 222, schizophrenia volume was 93% of control volume (95%CI 87% to 99%) Right posterior superior temporal gyrus: 4 studies, N = 192, schizophrenia volume was 103% of control volume (95%CI 98% to 108%)	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Comparison 4	**Hippocampal-amygdala volumetry in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample size, consistent, precise, direct) suggests small reductions in hippocampus and parahippocampal volume in people with schizophrenia.**
Hippocampus-amygdala volume	
Left amygdala: 7 studies, N = 283, schizophrenia volume was 91% of control volume (95%CI 87% to 94%) Right amygdala: 7 studies, N = 283, schizophrenia volume was 91% of control volume (95%CI 87% to 95%) Left hippocampus-amygdala: 15 studies, N =731, schizophrenia volume was 95% of control volume (95%CI 92% to 99%) Right hippocampus-amygdala: 15 studies, N = 731, schizophrenia volume was 94% of control volume (95%CI 92% to 97%) Left hippocampus: 24 studies, N = 1298, schizophrenia volume was 93% of control volume (95%CI 90% to 97%) Right hippocampus: 24 studies, N = 1298, schizophrenia volume was 94% of control volume (95%CI 91% to 96%) Left parahippocampus: 8 studies, N = 353, schizophrenia volume was 89% of control volume (95%CI 83% to 95%) Right parahippocampus: 8 studies, N = 353, schizophrenia volume was 92% of control volume (95%CI 86% to 98%)	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct
Comparison 5	**Basal ganglia and thalamic volumetry in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample size, consistent, precise, direct) suggests increased caudate, putamen, and right globus pallidus volume, and decreased thalamus volume in people with schizophrenia.**
Basal ganglia volume	
Left caudate: 10 studies, N = 565, schizophrenia volume was 101% of control volume (95%CI 97% to	

106%) Right caudate: 10 studies, N = 565, schizophrenia volume was 99% of control volume (95%CI 95% to 103%) Left putamen: 7 studies, N = 255, schizophrenia volume was 104% of control volume (95%CI 99% to 110%) Right putamen: 7 studies, N = 255, schizophrenia volume was 104% of control volume (95%CI 97% to 110%) Left globus pallidus: 2 studies, N = 84, schizophrenia volume was 118% of control volume (95%CI 110% to 126%) Right globus pallidus: 2 studies, N = 84, schizophrenia volume was 121% of control volume (95%CI 109% to 135%)	
Thalamic volume	
Left thalamus: 3 studies, N = 210, schizophrenia volume was 96% of control volume (95%CI 90% to 101%) Right thalamus: 3 studies, N = 210, schizophrenia volume was 96% of control volume (95%CI 92% to 102%)	
Consistency in results	All outcomes are consistent.
Precision in results	Precise, apart from globus pallidus.
Directness of results	Direct

Xiao Y, Zhang W, Lui S, Yao L, Gong Q

Similar and different gray matter deficits in schizophrenia patients and their unaffected biological relatives

Frontiers in Psychiatry 2013; 4: 150

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Comparison	**Regions of overlapping brain alterations in people with schizophrenia and relatives vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) suggests grey matter volume reductions in the left basal ganglia/claustrum in both patients and relatives.**

Grey matter volume	
No overlapping regions for increased grey matter volume in patients or relatives vs. controls; <u>Regions of increased grey matter volume in patients vs. controls</u> Right basal ganglia: Talairach coordinates (20, 2, 4), $p < 0.001$ Left basal ganglia: Talairach coordinates (-22, -2, 8), $p < 0.001$ Right parahippocampus: Talairach coordinates (38, -26, -16), $p < 0.001$ Left precentral gyrus: Talairach coordinates (-38, -8, 46), $p < 0.001$ Left inferior temporal gyrus: Talairach coordinates (-46, -12, -30), $p < 0.001$ Right cerebellum: Talairach coordinates (22, -54, -34), $p < 0.01$ <u>Regions of decreased grey matter volume in patients vs. controls</u> Right cuneus: Talairach coordinates (22, -98, -2), $p < 0.001$ Right superior frontal gyrus: Talairach coordinates (28, 60, 4), $p < 0.001$ Right insula: Talairach coordinates (42, 2, 12), $p < 0.01$ Left basal ganglia/claustrum: Talairach coordinates (-30, 16, 2), $p < 0.01$ <u>Regions of increased grey matter volume in relatives vs. controls</u> Right hippocampus: Talairach coordinates (24, -20, -20), $p < 0.0001$ Right fusiform gyrus: Talairach coordinates (44, -30, -20), $p < 0.0001$ Right precentral gyrus: Talairach coordinates (56, 2, 28), $p < 0.0001$ Right cuneus: Talairach coordinates (10, -60, 32), $p < 0.001$ <u>Regions of decreased grey matter volume in relatives vs. controls</u> Left basal ganglia/claustrum: Talairach coordinates (-34, -4, -6), $p < 0.0001$ Right parahippocampus: Talairach coordinates (26, -48, -4), $p < 0.0001$ Left fusiform gyrus: Talairach coordinates (-52, -42, -22), $p < 0.001$ Bilateral medial frontal: Talairach coordinates (2, 58, 2), $p < 0.001$ Right inferior temporal gyrus: Talairach coordinates (42, -64, -16), $p < 0.01$ Left parahippocampus: Talairach coordinates (-26, -54, -6), $p < 0.01$	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Zakzanis KK, Poulin P, Hansen KT, Jolic D

Searching the schizophrenic brain for temporal lobe deficits: a systematic review and meta-analysis

Psychological Medicine 2000; 30(3): 491-504

View review abstract online

Comparison 1	**Temporal lobe volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium-sized samples, direct, unable to assess consistency or precision) suggests a temporal lobe volume deficit in schizophrenia, particularly in the left hemisphere.**
Bilateral whole temporal lobe volume	
Small to medium-sized reduction in bilateral temporal lobe volume in schizophrenia; 9 studies, N unclear, *d* = 0.39, SD = 0.45	
Laterality of temporal lobe volume	
Left temporal lobe *Large reduction in left temporal lobe volume in schizophrenia;* 15 studies, N = 317, *d* = 0.88, SD = 1.4 Right temporal lobe *Medium-sized reduction in right temporal lobe volume in schizophrenia;* 15 studies, N = 317, *d* = 0.51, SD = 0.37 *Left temporal lobe showed significantly lower volume than right temporal lobe;* F = 3.11, $p < 0.05$	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Zhao Q, Li Z, Huang J, Yan C, Dazzan P, Pantelis C, Cheung EFC, Lui SSY, Chan RCK

Neurological soft signs are not "soft" in brain structure and functional networks: evidence from meta-analysis

Schizophrenia Bulletin 2013, doi:10.1093/schbul/sbt063

View review abstract online

Comparison	**Localised brain regions associated with neurological soft signs in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests people with schizophrenia showed reduced grey matter volume of the precentral and inferior frontal gyri, left postcentral and inferior parietal lobe and thalamus, and reduced white matter volume of middle temporal and cerebellum that were associated with increased severity of neurological soft signs.**
Neurological soft signs	
Patients < controls (6 studies) *NSS severity correlated with grey matter volume in:* Left precentral gyrus: Talairach coordinates (-56, -6, 40) Left precentral gyrus: Talairach coordinates (-46, -8, 50) Right precentral gyrus: Talairach coordinates (56, -4, 40) Left inferior frontal gyrus: Talairach coordinates (-54, 20, 20) Left postcentral gyrus: Talairach coordinates (-48, -26, 52) Left inferior parietal lobe: Talairach coordinates (-50, -40, 44) Thalamus: Talairach coordinates (2, -12, 14) *NSS severity correlated with white matter volume in:* Right middle temporal gyrus: Talairach coordinates (44, -68, 22) Cerebellar culmen: Talairach coordinates (0, -56, -16) Left inferior frontal gyrus: Talairach coordinates (-36, 34, -6)	
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	Direct

Explanation of acronyms

ALE = anatomical likelihood estimate, CI = confidence interval, COS = child-onset schizophrenia, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences, F = ratio of between sample variance and within sample variance, FDR = false discovery rate correction for multiple comparisons, FSN = fail safe number, FWHM = full width at half maximum, applied as a smoothing kernel, GMC = grey matter concentration, GMV = grey matter volume, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MNI = Montreal Neurological Institute, MRI = magnetic resonance imaging, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic (chi-square) for the test of heterogeneity in results across studies, *r* = correlation coefficient, SD = standard deviation, SMD = standardised mean difference, STG = superior temporal gyrus, τ^2 = tau squared, vs. = versus, Fisher's z = normalised scores.

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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[70].

† Different effect measures are reported by different reviews. ALE analysis (Anatomical Likelihood Estimate) refers to a voxel-based meta-analytic technique for structural imaging in which each point of statistically significant structural difference is spatially smoothed into Gaussian distribution space, and summed to create a statistical map estimating the likelihood of difference in each voxel, as determined by the entire set of included studies. Incorporated with the Genome Scan Meta-analysis (GSMA), the meta-analysis of coordinates from multiple studies can be weighted for sample size to create a random effect analysis. The ALE statistic (if reported) represents the probability of a group difference occurring at each voxel included in the analysis.

Fractional similarity network analysis refers to a network analysis technique in which secondary networks are identified within the larger framework of activity, creating a matrix for regional co-activity.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomized 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), which 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 effect[70].

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, a 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. A 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[71]. 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.

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Magnetic resonance imaging

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

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).

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) which 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, this criteria should be relaxed[72].

‖ 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, which allows indirectcomparisons 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 so is 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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