TECHNICAL COMMENTARY

Cingulate gyrus

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Introduction

The cingulate gyrus is part of the medial frontal cortex, located immediately dorsal to the corpus callosum along the sagittal midline. The anterior cingulate gyrus has three key divisions which may be functionally distinct (dorsal, rostral, subcallosal). The dorsal part of the anterior cingulate gyrus has reciprocal connections with the prefrontal and parietal cortices as well as the frontal eye fields, and plays a primary role in balancing top-down and bottom-up processing of external stimuli; that is, monitoring behaviour and incoming stimuli in the context of current goals, and assigning control to other areas in the brain when required. By contrast, the ventral (rostral and subcallosal) parts of the anterior cingulate gyrus are connected with amygdala, nucleus accumbens, hypothalamus, and insula, and are implicated in assessing the salience of sensory information, and regulating emotion and autonomic activity.

Schizophrenia has been associated with alterations in the cingulate gyrus. Understanding of any brain alterations in people with schizophrenia may provide insight into changes in brain development associated with the illness onset or progression. Reviews contained in this technical summary reflect both structural imaging investigations (MRI, DTI), and functional imaging (fMRI, PET) as well as metabolic investigations (MRS) of the cingulate gyrus in people with schizophrenia.

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 prioritised 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

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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).

Results

We found 32 systematic reviews that met our inclusion criteria[3-34].

Structural changes

- Moderate to high quality evidence found reductions in grey and white matter in bilateral regions of the cingulate cortex of people with schizophrenia.
- Specifically, there were grey matter reductions in the anterior and posterior cingulate gyrus of people with schizophrenia and reduced grey matter in the left anterior cingulate/paracingulate gyrus and right dorsal anterior cingulate of first-episode patients. High-risk individuals showed decreases in bilateral median cingulate and the right anterior cingulate gyrus compared to controls and increases in the left anterior cingulate compared to first-episode patients.
- Moderate to low quality evidence found schizophrenia patients with persistent negative symptoms show significant reductions in the left anterior cingulate (BA32).
- Moderate to low quality evidence found overlapping grey matter volume decreases in the right posterior cingulate cortex in both schizophrenia and autism.

Functional changes

- Moderate quality evidence found decreased activity in the posterior cingulate cortex of people with schizophrenia at rest.
- Moderate quality found under-activation in the anterior and middle cingulate cortex of people with schizophrenia compared to controls during attention and inhibition, and over-activation in the anterior cingulate cortex during working memory. During executive functioning, there was increased activity in the left cingulate gyrus and decreased activity in right cingulate gyrus. During cognitive control, there was decreased activity in the bilateral anterior cingulate/paracingulate gyrus. During auditory stimulation, there was decreased activation in the anterior cingulate cortex. During theory of mind tasks, there was decreased activity in the left cingulate gyrus. During reward anticipation tasks there was reduced activation in the right median cingulate/paracingulate gyri.
- Moderate quality evidence finds relatives showed decreased activity in the left cingulate gyrus during executive functioning and working memory tasks compared to controls. There were no differences between relatives and controls during emotion tasks.
- Moderate quality evidence finds decreased activation in the bilateral anterior cingulate and left posterior cingulate in people with schizophrenia compared to those with an autism spectrum disorder during facial emotion recognition tasks. During theory of mind tasks, there is increased activation in the left posterior cingulate cortex in people with schizophrenia.
- Moderate quality evidence suggests decreased N-acetylaspartate and N-

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acetylaspartate/creatine ratio in the anterior cingulate gyrus of people with schizophrenia and their first-degree relatives.

- High quality evidence finds a small decrease in glutathione in the anterior cingulate of people with schizophrenia.

Structural and functional changes

- Moderate to high quality evidence found decreased grey matter volume and decreased functional activity in the left medial posterior cingulate/paracingulate gyrus in drug-free, first-episode patients.
- Moderate quality evidence found decreased grey matter volume and decreased functional activation in the right medial frontal/anterior cingulate and decreased grey matter volume and increased functional activation in the left medial frontal/anterior cingulate in people with first-episode schizophrenia, regardless of medication status.

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Alustiza I, Radua J, Pla M, Martin R, Ortuno F

Meta-analysis of functional magnetic resonance imaging studies of timing and cognitive control in schizophrenia and bipolar disorder: Evidence of a primary time deficit

Schizophrenia Research 2017; 188: 21-32

View online review abstract

Comparison	**Brain activation during cognitive control tasks in people with schizophrenia vs. controls.** **Cognitive control is defined as the level of perceived difficulty of the cognitive task and the subsequent mental effort that an individual applies to achieve the cognitive aim.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) finds decreased activity during cognitive control tasks in the bilateral anterior cingulate/paracingulate gyrus of people with schizophrenia.**
Functional activity	
29 studies, N = 2,268 *Decreased activity in people with schizophrenia in;* Bilateral anterior cingulate/paracingulate gyrus (BA 24 and 32)	
Consistency in results	Unable to assess; no measure of consistent is reported.
Precision in results	Unable to assess; no measure of precision is reported (CIs).
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 (large sample, inconsistent, precise, direct) finds medium-sized reductions in the total volume of the anterior cingulate gyrus of people with schizophrenia, with similar reductions in each hemisphere.**
Anterior cingulate gyrus volume	
Significant, medium-sized reduction in total volume in patients; 7 studies, N = 447, *d* = -0.70, 95%CI -1.04 to -0.36, *p* < 0.001, Q = 17.28, *p* = 0.008 Subgroup analysis found similar reductions in the right and left anterior cingulate.	
Consistency in results	Inconsistent
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	**Grey matter density in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found grey matter reductions in the medial frontal/anterior cingulate gyrus in people with schizophrenia. First-episode patients showed reduced grey matter in the right dorsal anterior cingulate.**
Anterior cingulate gyrus volume	

49 studies, N = 4,179 *Grey matter reductions in people with schizophrenia were found in;* 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 *Grey matter reductions in first-episode patients were found in;* Right dorsal anterior cingulate: Talairach coordinates (14, 18, 30), cluster 106mm^3, p = 0.0002 24 studies, N = 1,837	
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 a small reduction in the anterior cingulate cortex of people with first-episode schizophrenia.**
Anterior cingulate gyrus volume	
Significant, small reductions in first-episode schizophrenia in; Anterior cingulate cortex: 11 studies, N = 893, g = -0.26, 95%CI -0.43 to -0.10, p = 0.006, I^2 = 48%	
Consistency in results	Inconsistent, apart from frontal lobe and the third ventricle.

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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	**Grey matter changes in people with first-episode schizophrenia and 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 and people with chronic schizophrenia have grey matter reductions in bilateral cingulate gyrus. People with first-episode schizophrenia have reductions in the right cingulate gyrus.**

Cingulate gyrus grey matter volume

At-risk group, grey matter reductions in;

8 studies, N = 1,031

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

First-episode group, grey matter reductions in;

14 studies, N = 1,082

Right cingulate gyrus: Talairach coordinates 6, 18, 38, cluster 448mm^3, ALE 0.0120

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 *Chronic schizophrenia group, grey matter reductions in;* 19 studies, N = 1,664 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	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

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 an autistic spectrum disorder 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.**
Overlapping brain alterations	
Regions of decreased grey matter volume, reporting the % that is contributed to by schizophrenia and autism studies; Right posterior cingulate gyrus: Talairach coordinates 21, -56, 14, 58.9% SZ, 41.1% ASD	
Consistency in results	No measure of consistency is reported.

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

Crossley NA, Mechelli A, Ginestet C, Rubinov M, Bullmore ET, McGuire P

Altered Hub Functioning and Compensatory Activations in the Connectome: A Meta-Analysis of Functional Neuroimaging Studies in Schizophrenia

Schizophrenia Bulletin 2016; 42: 434-42

View review abstract online

Comparison	**Functional activity in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found under-activation in the anterior and middle cingulate cortex during attention and inhibition tasks, and over-activation in the anterior cingulate cortex during working memory tasks. There were no differences with controls during episodic memory, language, theory of mind or emotion tasks.**

Functional activation

314 studies, N = 10,942

Attention tasks

Under-activations in the anterior and middle cingulate cortex.

Inhibition tasks

Under-activations in the anterior and middle cingulate cortex.

Working memory tasks

Over-activations in the anterior cingulate cortex

Episodic memory tasks

No differences were found in the cingulate.

Linguistic tasks (mostly semantic reading)

No differences were found in the cingulate.

Theory of mind tasks

No differences were found in the cingulate.

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Emotion tasks No differences were found in the cingulate.	
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

Das TK, Javadzadeh A, Dey A, Sabesan P, Theberge J, Radua J, Palaniyappan L

Antioxidant defense in schizophrenia and bipolar disorder: A meta-analysis of MRS studies of anterior cingulate glutathione

Progress in Neuro Psychopharmacology and Biological Psychiatry 2018; August

View online review abstract

Comparison	**Glutathione in the anterior cinguate of people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests a small decrease in glutathione in the anterior cingulate of people with schizophrenia.**
Glutathione levels	
A small, significant decrease in glutathione in the anterior cingulate of people with schizophrenia; 13 studies, N = 726, SMD = 0.26, 95%CI 0.07 to 0.44, p = 0.008, I^2 = 29%, p = 0.11 There was a trend-effect finding that studies with longer echo-time of MRS acquisitions were more likely to report reduced glutathione concentrations in patients compared to controls. There were no moderating effects of medication, sex, scanner strength, repetition time, patient age or duration of illness.	
Consistency in results	Consistent
Precision in results	Precise
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 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;* Bilateral median cingulate (Z = 1.034)	
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. controls.**

Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found grey matter reductions in the right anterior cingulate gyrus in people with first-episode schizophrenia.**
Cingulate gyrus grey matter volume	
27 studies, N = 1,556 *First episode group showed reductions in;* Right Anterior cingulate gyrus: Talairach coordinates 8, 16, 38, cluster 464mm^3, ALE 0.007, p = 0.0016	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are 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 vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests grey matter reductions in the left anterior cingulate and the left posterior cingulate.**
Cingulate gyrus grey matter volume	
42 studies, N = 4,189 *Regions of decreased grey matter;* Left anterior cingulate: Talairach coordinates (-2, 44, -4), 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 anterior cingulate: Talairach coordinates (-6, 24, 36), Sum of ranks = 172.5, p = 0.00010	

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

Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are 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 volume 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, and the posterior cingulate gyrus.**
Cingulate gyrus grey matter volume	
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. Also decreased grey matter reported bilaterally in the posterior cingulate, and subgenual cingulate.	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.

Directness of results	Direct
Comparison 2	**Grey matter volume and grey matter concentration (grey matter as a proportion of the whole brain volume) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) suggests grey matter reductions in regions of the anterior cingulate gyrus including subgenual and dorsal areas, and the posterior cingulate.**
Cingulate gyrus grey matter volume and concentration	
37 studies, N = 3,336 *Grey matter reductions in;* Right anterior cingulate gyrus/medial prefrontal cortex: 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: Talairach 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} *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 heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Fusar-Poli P, Perez J, Broome M, Borgwardt S, Placentino A, Caverzasi E, Cortesi M, Veggiotti P, Politi P, Barale F, McGuire P

Neurofunctional correlates of vulnerability to psychosis: A systematic review and meta-analysis

Neuroscience & Biobehavioral Reviews 2007; 31(4): 465-484 View review abstract online	
Comparison 1	**Functional activity following a first episode of schizophrenia vs. controls.**
Summary of evidence	**Low quality evidence (one small study per outcome) is unclear as to changes in functional activity in individuals with first-episode schizophrenia.**
Functional activity during verbal fluency paradigm	
1 study, N = 20 Large effect size suggests reduced activation of right anterior cingulate gyrus (*d* = 4.89) in first episode schizophrenia patients compared to controls for verbal fluency tasks.	
Executive control paradigm	
1 study, N = 47 Large effect size suggests reduced activation of anterior cingulate gyrus (*d* = 0.43) in untreated first episode schizophrenia patients compared to controls for executive control tasks.	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct
Comparison 2	**Functional activity in individuals at high-risk of schizophrenia vs. controls.**
Summary of evidence	**Low quality evidence (one small study) is unclear as to changes in functional activity in individuals at high-risk of developing schizophrenia.**
Functional activity during working memory paradigm	
1 study, N = 24 Large effect size suggests increased activation of anterior cingulate gyrus (*d* = 0.96) in non-psychotic relatives of schizophrenia patients compared to controls for working memory tasks.	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.

Directness of results	Direct
Comparison 3	**Metabolic activity in individuals at high genetic risk of schizophrenia vs. controls (NAA and Cr are reported as a ratio, NAA/Cr).**
Summary of evidence	**Moderate quality evidence (medium-sized sample, direct, unable to assess precision and inconsistency) finds reduced NAA/Cr in the anterior cingulate gyrus of individuals at high genetic risk of schizophrenia (first degree relatives).**
Metabolite levels	
4 studies, N = 268 found reduced NAA/Cr in individuals at high-risk of psychosis.	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
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) finds grey matter reductions in the right anterior cingulate gyrus of high-risk individuals compared to controls, and reductions in the left anterior cingulate of first-episode psychosis patients compared to controls. Grey matter decreases in the left anterior cingulate of first-episode psychosis patients was also found when compared to individuals at high-risk.**
Cingulate gyrus grey matter volume	

Grey matter reductions in high-risk participants vs. controls in; N = 870 Right anterior cingulate (BA24/32): Talairach coordinates 2, 30, 12, $p = 0.0001$ *Grey matter reductions in first-episode participants vs. controls in;* N = 408 Left anterior cingulate (BA32): Talairach coordinates -3, 37, 16, $p < 0.0005$ *Grey matter reductions in first-episode participants vs. high-risk participants in;* Left anterior cingulate (BA24): Talairach coordinates -2, 32, 14, $p < 0.0002$	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

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 to high quality evidence (large sample, consistent, direct, unable to assess precision) suggests decreased grey matter volume and decreased functional activity in the left medial posterior cingulate/paracingulate gyrus in drug-free patients.**
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, $p < 0.001$	
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, Ragland JD, Abramoff A, Barrett J, Laird AR, Bearden CE, Velligan DI

Beyond hypofrontality: A quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia

Human Brain Mapping 2005; 25(1): 60-9

View review abstract online

Comparison	**Functional activity in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized sample, direct, unable to assess precision or inconsistency) finds increased functional activity in the cingulate gyrus during working memory tasks in people with schizophrenia.**
Functional activity during N-back working memory tasks	
4 studies, N = 134 *Significantly increased activity in people with schizophrenia in;* Cingulate gyrus: Talairach centre of mass -2, 14, 35, cluster volume 656mm^3	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are 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	**Grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests schizophrenia is associated with grey matter reductions in dorsal, ventral, and subgenual regions of the anterior cingulate.**
Cingulate gyrus grey matter volume	
13 studies, N = 2,457 *Significant reductions in people with schizophrenia in;* 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	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Goghari MV

Executive functioning-related brain abnormalities associated with the genetic liability for schizophrenia: an activation likelihood estimate meta-analysis

Psychological Medicine 2001; 41: 1239-1252

View review abstract online

Comparison	**Whole brain comparison of functional activation in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) finds relatives show decreased activation in the left cingulate gyrus during executive functioning and working memory tasks.**
Executive functioning task	
17 studies, N = 456 *Decreased activity in relatives of people with schizophrenia;* Left cingulate gyrus: Talairach coordinates -16, -26, 42, cluster volume 360 mm^3	
Working memory task	
Decreased activity in relatives of people with schizophrenia; Left cingulate gyrus: Talairach coordinates -16, -26, 42, cluster volume 200 mm^3	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are 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 posterior and anterior cingulate gyrus.**
Reduced grey matter density in schizophrenia	

Decreased in medicated patients; 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%	
Consistency in results	Mostly inconsistent
Precision in results	Precise
Directness of results	Direct

Kronbichler L, Tschernegg M, Martin AI, Schurz M, Kronbichler M

Abnormal Brain Activation During Theory of Mind Tasks in Schizophrenia: A Meta-Analysis

Schizophrenia Bulletin 2017; 43: 1240-50

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Comparison	**Functional activity during theory of mind tasks in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) found decreased activation in the left cingulate gyrus of people with schizophrenia during theory of mind tasks.**
Functional activity	
21 studies, N = 623 *Decreased activation in people with schizophrenia in;* Left cingulate gyrus: 34 voxels, MNI coordinates -18, -44, -2	
Consistency in results	Unable to assess; no measure of heterogeneity is reported.
Precision in results	Unable to assess; no confidence intervals are reported.
Directness of results	Direct

Kühn S, Gallinat J

Quantitative meta-analysis on state and trait aspects of auditory verbal hallucinations in schizophrenia

Schizophrenia Bulletin 2012; 38(4): 779-786

View review abstract online

Comparison	**Functional activation during auditory stimulation tasks in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small to medium-size sample, direct, unable to assess precision or consistency) suggests decreased activation in the anterior cingulate cortex of people with schizophrenia during auditory stimulation.**
Auditory stimulation tasks	
8 studies (43 foci), N = 190, showed decreased activation during auditory stimulation tasks in people with schizophrenia in; Anterior cingulate cortex: Talairach coordinates -4, 26, 31, cluster volume 160mm^3 Anterior cingulate cortex: Talairach coordinates -42, 2, 18, cluster volume 152mm^3 Anterior cingulate cortex: Talairach coordinates -9, 4, 37, cluster volume 112mm^3 There were no differences during auditory hallucinations.	
Consistency in results	Unable to assess; no measure of heterogeneity is reported.
Precision in results	Unable to assess; no confidence intervals are reported.
Directness of results	Direct

Kühn S, Gallinat J

Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis

Schizophrenia Bulletin 2013; 39(2): 358-365

View review abstract online

Comparison	**Resting-state functional activation in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests decreased activation in the posterior cingulate cortex of people with schizophrenia.**
Functional activity	
11 studies, N = 567 *The following clusters showed decreased activity in people with schizophrenia compared to controls;* Posterior cingulate (BA23): Talairach coordinates -1, -29, 26, cluster volume 384mm^3	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Leroy A, Amad A, D'Hondt F, Pins D, Jaafari N, Thomas P, Jardri R

Reward anticipation in schizophrenia: A coordinate-based meta-analysis

Schizophrenia Research 2020; Jan: doi.org/10.1016/j.schres.2019.12.041

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Comparison	**Functional activity during reward anticipation in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found reduced activation in the right median cingulate/paracingulate gyri of people with schizophrenia during reward anticipation tasks.**
Functional activation	
11 studies, N = 488 *Schizophrenia was characterised by;* Reduced activation in the right median cingulate/paracingulate gyri.	
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

Leung M, Cheung C, Yu K, Yip B, Sham P, Li Q, Chua S, McAlonan G

Gray Matter in First-Episode Schizophrenia Before and After Antipsychotic Drug Treatment. Anatomical Likelihood Estimation Meta-analyses With Sample Size Weighting

Schizophrenia Bulletin 2011; 37(1): 199-211

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Comparison	**Grey matter changes in first-episode schizophrenia (treated and medication naïve) vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) suggests greater reduction in grey matter in the left posterior cingulate and right anterior cingulate of treatment-naïve first-episode patients compared to treated first-episode patients.**
Cingulate gyrus grey matter volume	

Reductions in treatment naïve first-episode patients;

6 studies, N = 327

Right anterior cingulate gyrus: Talairach coordinates 18, 16, 34, cluster 864mm^3, ALE 0.0050

Right anterior cingulate gyrus: Talairach coordinates 2, -48, 26, cluster 304mm^3, ALE 0.0023

Right anterior cingulate gyrus: Talairach coordinates 2, -46, 38, cluster 248mm^3, ALE 0.0024

Left posterior cingulate gyrus: Talairach coordinates -20, -62, 14, cluster 304mm^3, ALE 0.0018

Left posterior cingulate gyrus: Talairach coordinates -18, -58, 12, cluster 304mm^3, ALE 0.0017

Reductions in treated first-episode patients;

9 studies, N = 820

Right anterior cingulate gyrus: Talairach coordinates 4, 16, 38, cluster 352mm^3, ALE 0.0046

Right anterior cingulate gyrus: Talairach coordinates 4, 12, 42, cluster 352mm^3, ALE 0.0045

Regions where grey matter reductions were larger in magnitude in treatment-naïve patients than in treated patients;

Right anterior cingulate gyrus: Talairach coordinates 18, 16, 34, cluster 360mm^3, ALE 0.0142

Right anterior cingulate gyrus: Talairach coordinates 2, -46, 38, cluster 176mm^3, ALE 0.0103

Right anterior cingulate gyrus: Talairach coordinates 2, -48, 26, cluster 160mm^3, ALE 0.0097

Left posterior cingulate gyrus: Talairach coordinates -18, 58, 12, cluster 296mm^3, ALE 0.0087

Left posterior cingulate gyrus: Talairach coordinates -20, -62, 14, cluster 296mm^3, ALE 0.0090

Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are 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

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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 the left anterior cingulate (BA32).**
Cingulate gyrus grey matter volume	
12 studies, N = unclear *There was significantly reduced grey matter volume in;* Left anterior cingulate (BA32): Talairach coordinates -6, 42, 2	
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

Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC

Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia

Archives of General Psychiatry 2009. 66(8): 811-822

View review abstract online

Comparison	**Functional activity in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to assess precision or consistency) suggests people with schizophrenia show decreased activity in the right cingulate gyrus, and increased activity in the left cingulate gyrus during executive functioning tasks.**
Activation during executive function tasks	
41 studies, N = 1,217 *Significantly decreased activity in people with schizophrenia in;* Right cingulate: Talairach centre of mass 2, 18, 34, cluster volume 1704mm^3 *Significantly increased activity in people with schizophrenia in;*	

Left cingulate: Talairach centre of mass -2, 10, 40, cluster volume 2208mm^3	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
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

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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 left cingulate gyri in people with first-episode schizophrenia.**
Cingulate gyrus volume	
Voxel-based meta-analysis of regions of reduced grey matter volume in first-episode schizophrenia; 18 studies (185 coordinates) N = 1,176 Left cingulate gyrus: coordinates -8, -4, 38 Left cingulate gyrus: coordinates 0, -42, 38	
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

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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) found decreased grey matter volume and decreased functional activation in the right medial frontal/anterior cingulate, and decreased grey matter volume and increased functional activation in the left medial frontal/anterior cingulate n people with first-episode schizophrenia, regardless of medication status.**
Structural and functional alteration	
25 structural MRI studies (N = 2005) and 18 functional MRI studies (N = 765) *Decreased grey matter volume and decreased functional activation;* Right medial frontal/anterior cingulate: coordinates 4, 22, 30, $p < 0.0001$, 644mm^2 *Decreased grey matter volume and increased functional activation;* 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

Sanches RF, Crippa JA, Hallak JE, Araujo D, Zuardi AW

Proton magnetic resonance spectroscopy of the frontal lobe in

schizophrenics: a critical review of the methodology **Revista do Hospital das Clinicas; Faculdade de Medicina Da Universidade de Sao Paulo 2004; 59(3): 145-152** View review abstract online	
Comparison	**NAA activity in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess precision or consistency) suggests NAA levels are reduced in the cingulate gyrus in people with schizophrenia.**
NAA	
Results consider alterations in cingulate gyrus NAA levels in individuals with schizophrenia; 8/10 studies, N = 301/434 showed decreased NAA in schizophrenia patients	
Consistency in results	No measure of heterogeneity is reported, appears consistent.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Scognamiglio C, Houenou J **A meta-analysis of fMRI studies in healthy relatives of patients with schizophrenia** **Australian and New Zealand Journal of Psychiatry 2014; 48(10): 907-16** View review abstract online	
Comparison	**Functional activation in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) found decreased activation in the right cingulate gyrus of relatives during cognitive but not emotion tasks.**
Cognitive and emotion tasks	

17 studies Cognitive tasks *The following areas showed decreased activation in relatives than controls;* Right cingulate gyrus (BA31): Talairach coordinates 8, -8, 44, $p < 0.01$ Emotion tasks No differences were found in the cingulate.	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are provided.
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

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Comparison	**Grey matter changes in first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found grey matter decreases in the left anterior cingulate/paracingulate gyrus in first-episode patients.**
Cingulate gyrus grey matter volume	
11 studies, N = 836 *Grey matter decreases were found in patients in;* Left anterior cingulate/paracingulate gyrus: 1,947 voxels, MNI coordinates -2, 36, 16, p ~0	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.

Directness of results	Direct

Steen RG, Hamer RM, Lieberman JA

Measurement of brain metabolites by ^{1}H magnetic resonance spectroscopy in patients with schizophrenia: a systematic review and meta-analysis

Neuropsychopharmacology 2005; 30(11): 1949-1962

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Comparison	**NAA activity in people with schizophrenia vs. controls**
Summary of evidence	**Moderate to low quality evidence (sample size unclear, direct inconsistent, unable to assess precision) suggests that NAA may be decreased in the anterior cingulate gyrus, but not in the posterior cingulate.**
NAA	
Anterior cingulate gyrus: 12 studies, N unclear, patient average 95.9% of control levels Posterior cingulate gyrus: 5 studies, N unclear, patient average 100.0% of control levels	
Consistency in results	Significant heterogeneity reported, $p < 0.0001$.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Sugranyes G, Kyriakopoulos M, Corrigall R, Taylor E, Frangou S

Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition

PLoS ONE 2011; 6(10): e25322

View review abstract online

Comparison	**Functional activation during social cognition processing in schizophrenia vs. autism spectrum disorders.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess precision or consistency) finds decreased activation in the bilateral anterior cingulate and left posterior cingulate in people with schizophrenia compared to those with an autism spectrum disorder during facial emotion recognition tasks. During theory of mind tasks, there is increased activation in the left posterior cingulate cortex in people with schizophrenia.**
Facial emotion recognition	
17 studies, N = 511 *The following clusters showed decreased activation in schizophrenia vs. autism spectrum disorders;* Left anterior cingulate: Talairach coordinates 0, 26, 20, cluster volume 392mm^3 Right anterior cingulate: Talairach coordinates 10, 34, 20, cluster volume 376mm^3 Left posterior cingulate: Talairach coordinates -20, -62, 4, cluster volume 320mm^3	
Theory of mind	
16 studies, N = 463 *The following clusters showed increased activation in schizophrenia vs. autism spectrum disorders;* Left posterior cingulate: Talairach coordinates 0, -16, 24, cluster volume 624mm^3 Left posterior cingulate: Talairach coordinates -6, -30, 34, cluster volume 200mm^3	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
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

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Cingulate gyrus

Comparison	**White matter integrity in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) found white matter reductions in bilateral cingulate in people with schizophrenia.**
White matter	
34 studies, N = 2,231 *There were white matter reductions in;* 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 Longer duration of illness was associated with white matter reductions in the right posterior cingulum bundle. Shorter duration of illness was associated with white matter reductions in the right anterior cingulum bundle.	
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 = activation likelihood estimate for Gaussian smoothed foci, CI = confidence interval, Cr = creatine amino acid, d = Cohen's d and g = Hedges' g = standardised mean differences, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MNI = Montreal Neurological Institute system for stereotactic space, N = number of participants, NAA = N-acetylaspartate amino acid, 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, SMD = standardised mean difference, vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCTs 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[35].

† 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 randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) 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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[35].

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[36]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, *r*) indicate the strength of association or relationship 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[37].

‖ 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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