TECHNICAL COMMENTARY

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Whole brain

Introduction

Investigation of whole brain anomalies considers the collective volume of the entire brain in structural imaging, without considering regionally specific differences in the volume of any individual structures. Alternatively, whole brain imaging can also consider overall grey matter or white matter volume. Whole brain functioning assesses the degree of connectivity across multiple brain regions.

Understanding of any brain alterations in people with schizophrenia may provide insight into changes in brain development associated with the illness onset or progression, however alterations in whole brain volume provide only a non-specific indication of neuropathology.

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 with 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).

Results

We found 17 systematic reviews that met our inclusion criteria[3-19].

Structural changes

- Moderate quality evidence found lower brain weight in people with schizophrenia compared to controls. Moderate to low quality evidence found male patients who

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

died by suicide had significantly heavier brains than males who died of natural causes. Increased male brain weight was associated with younger age of schizophrenia onset.

- Moderate to high quality evidence found people with schizophrenia who were medicated or not medicated showed reductions in intracranial, whole brain grey and white matter, and total brain volume compared to controls. Cortical volume was reduced only in medicated patients. People with first-episode schizophrenia showed reduced intracranial, whole brain, and grey matter volume.
- Moderate quality evidence found people with schizophrenia show a larger ventricle-brain volume ratio than controls. There was increased extracerebral volume and decreased intracranial less intraventricular volume and increased extracerebral plus intraventricular volume.
- Moderate to high quality evidence found greater brain volume and grey matter reductions over time in people with schizophrenia compared to controls.
- Moderate quality evidence found increased whole brain volume in high risk people who transitioned to psychosis compared to high risk people who did not transition to psychosis.
- Moderate to high quality evidence found first-degree relatives of people with schizophrenia have reduced total grey matter volume compared to controls, with no differences in white matter or whole brain volume.
- Moderate to high quality evidence found better overall functioning was associated with larger whole brain volume, with no associations with white matter tracts.
- Moderate to high quality evidence found decreases in whole brain white matter were associated with small increases in negative symptoms and small decreases in positive and general symptoms. Authors state these relationships were not clinically significant and could be explained by increased age which was associated with decreased white matter (positive symptoms tend to be more prominent early on in the disorder, while negative symptoms tend to be more prominent in older age).

Functional changes

- Moderate quality evidence found decreased local organisation and small-worldness (balance of local organisation and global integration) in people with schizophrenia, with no changes in global short communication paths.
- Moderate quality evidence found reduced connectivity within the default network (self-related thought), the affective network (emotion processing), the ventral attention network (processing of salience), the thalamus network (gating information) and the somatosensory network (sensory and auditory perception). There was reduced connectivity between the ventral attention network and the thalamus network, the ventral attention network and the default network, the ventral attention network and the frontoparietal network (external goal-directed regulation), the frontoparietal network and the thalamus network, and the frontoparietal network and the default network. There was increased connectivity between the affective network and the ventral attention network.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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Whole brain

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	**Whole brain volume in first-degree relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample sizes, direct, mostly consistent, precise) suggests relatives have reduced total grey matter volume compared to controls, with no differences in white matter or whole brain volume.**
Whole brain volume	
No differences between groups; 13 studies, N = 1,238, *d* = 0.28 95%CI -0.02 to 0.57, Q = 63.99, *p* < 0.001	
Grey matter volume	
Small effect of decreased 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	
White matter volume	
No differences between groups; 7 studies, N = 529, *d* = 0.40 95%CI -0.04 to 0.83, *p* > 0.05, Q = 33.25, *p* < 0.001	
Consistency in results‡	Inconsistent for total volume and white matter volume, consistent for grey matter volume.
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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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

Dong D, Wang Y, Chang X, Luo C, Yao D

Dysfunction of Large-Scale Brain Networks in Schizophrenia: A Meta-analysis of Resting-State Functional Connectivity

Schizophrenia Bulletin 2018; 44: 168-81

View review abstract online

Comparison	**Functional connectivity during rest in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found reduced connectivity within the default network (self-related thought), the affective network (emotion processing), the ventral attention network (processing of salience), the thalamus network (gating information) and the somatosensory network (sensory and auditory perception). There was reduced connectivity between the ventral attention network and the thalamus network, the ventral attention network and the default network, the ventral attention network and the frontoparietal network (external goal-directed regulation), the frontoparietal network and the thalamus network, and the frontoparietal network and the default network. There was increased connectivity between the affective network and the ventral attention network.**
Functional connectivity	
52 studies, N = 4,412 *Schizophrenia was characterised by;* Reduced connectivity within the default network (self-related thought), the affective network (emotion processing), the ventral attention network (processing of salience), the thalamus network	

(gating information) and the somatosensory network (sensory and auditory perception). Reduced connectivity between the ventral attention network and the thalamus network, the ventral attention network and the default network, the ventral attention network and the frontoparietal network (external goal-directed regulation), the frontoparietal network and the thalamus network, and the frontoparietal network and the default network. Increased connectivity between the affective network and the ventral attention network.	
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

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

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 and decreased grey matter volume in people with schizophrenia. Moderate to high quality evidence (inconsistent) suggests greater decreases in grey matter volume over time in patients.**
Baseline grey matter volume	
People with schizophrenia showed decreased whole brain volume (WBV) and decreased grey matter volume (GMV); 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 *No significant differences in white matter volume (WMV);* 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	
Changes in grey matter volume over time (4 - 520 weeks)	

People with schizophrenia showed greater decreases in grey matter volume (GMV) over time; 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 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). *There were no significant changes over time in whole brain volume (WBV) or white matter volume (WMV);* 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

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

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 people with schizophrenia who were medicated or not medicated showed reductions in intracranial, whole brain grey and white matter, and total brain volume. Cortical volume was reduced only in medicated 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 × 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 × 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 × 10−9, Q = 96.0, *p* = 0.0037, I^2 = 35% Total white matter: 61 studies, N = 4,170, *d* = -0.17, 95%CI -0.25 to -0.10, *p* = 2.1 × 10−6, Q = 76.1, *p* = 0.078, I^2 = 21% Cortical grey matter: 15 studies, N = 987, *d* = -0.43, 95%CI -0.56 to -0.30, *p* < 1 × 10−9, Q = 13.0, *p* = 0.52, I^2 = 0% *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%

Consistency in results	Mostly inconsistent
Precision in results	Precise
Directness of results	Direct

Harrison PJ, Freemantle N, Geddes JR

Meta-analysis of brain weight in schizophrenia

Schizophrenia Research 2003; 64(1): 25-34

View review abstract online

Comparison	**Post-mortem comparison of brain weight (both fresh and fixed) in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample, imprecise, direct, unable**

	to assess consistency) suggests the brain of a person with schizophrenia weighs significantly less than a healthy brain. **Moderate to low quality evidence (small sample) suggests male patients who died by suicide had significantly heavier brains than those who died of natural causes.** **Moderate quality evidence (large sample) suggests male brain weight was significantly inversely correlated with age of disease onset, suggesting an earlier age at onset in association with heavier brain weight.**
Brain weight	
Total N = 1,334 <u>Differences in weight: females</u> Mean difference = -36.13g (equivalent to 3.7% lower in patients), 95% CI -68.60 to -4.06g <u>Differences in weight: males</u> Mean difference = -19.32g (equivalent to 3% lower in patients), 95%CI -49.94 to 8.31g <u>Differences in weight overall: multivariate analysis</u> Controlled for age, sex, and interactions between series and diagnosis, age and sex Mean difference = -24g (equivalent to 2% lower in patients), 95%CI 1 to 47g, *p* = 0.04 <u>Subgroup analysis of mode of death, with age as a covariate</u> *Male patients who died by suicide had significantly heavier brains than those who died of natural causes;* Suicide: 1,583 ± 137g, N = 10 Natural: 1,376 ± 141g, N = 141 F = 8.48, *p* = 0.004 *A similar trend was observed in female patients (though not significant);* Suicide: 1,343 ± 86g, N = 6 Natural: 1,188 ± 132g, N = 106 F = 3.45, *p* = 0.066 <u>Subgroup analysis of age at disease onset</u> *Brain weight was inversely correlated with age at disease onset (after exclusion of one data group with different onset criterion). Relationship was significant only in males;* Males: Pearson's R = -0.257, *p* = 0.021, N = 80 Females: R = -0.220, *p* = 0.058, N = 75 <u>Subgroup analysis of duration of illness, corrected for age at death</u>	

No significant correlations were reported between brain weight and duration of illness; Males: r = 0.158, p = 0.132 Females: r = 0.110, p = 0.309	
Consistency in results	No measure of consistency is reported.
Precision in results	Imprecise
Directness of results	Direct

Kambeitz J, Kambeitz-Ilankovic L, Cabral C, Dwyer DB, Calhoun VD, Van Den Heuvel MP, Falkai P, Koutsouleris N, Malchow B

Aberrant Functional Whole-Brain Network Architecture in Patients with Schizophrenia: A Meta-analysis

Schizophrenia Bulletin 2016; 42: S13-S21

View review abstract online

Comparison	**Whole-brain analysis of functional connectedness at rest in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests decreased local organisation and small-worldness (balance of local organisation and global integration) in people with schizophrenia, with no changes in global short communication paths.**
Brain network activation	
8 fMRI studies, N = 453 *People with schizophrenia showed medium to large decreases in;* Local organisation: 7 studies, g = -1.33, 95%CI -1.81 to -0.85, p < 0.001, I^2 = 73% Small-worldness (balance of local organisation and global integration): 5 studies, g = -0.65, 95%CI -1.12 to -0.18, p = 0.01, I^2 = 67% The small-worldness analysis included two EEG studies. *There were no differences in;* Global short communication paths: 5 studies, g = 0.63, 95%CI -0.56 to 1.82, p = 0.30, I^2 = 95%	

There were no moderator effects.	
Consistency in results	Inconsistent
Precision in results	Imprecise
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 volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests greater brain volume and grey matter volume reductions over time in people with schizophrenia compared to controls. There were no changes in white matter volume over time.**

Whole brain volume

Progressive changes across longitudinal MRI scans over 1-10 years.

31 studies, N = 1,867

Significantly greater reductions were reported over time in schizophrenia in;

Whole brain volume: 14 studies, N = 992, d = -0.404, 95%CI -0.62 to -0.19, p = 0.0002, I^2 = 57%

Whole brain grey matter: 12 studies, N = 928, d = -0.520, 95%CI -0.76 to -0.28, p < 0.0001, I^2 = 62.3%

There were no differences in;

Whole brain white matter: 11 studies, N = 846, d = -0.129, 95%CI -0.41 to 0.15, p = 0.366, I^2 = 70.6%

Consistency in results	Inconsistent
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 a larger ventricle-brain volume ratio than controls. Older research with fewer authors is 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

Smieskova R, Fusar-Poli P, Allen P, Bendfeldt K, Stieglitz RD, Drewe J, Radue E

W, McGuire PK, Riecher-Rossler A, Borgwardt SJ

Neuroimaging predictors of transition to pscyhosis – 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 of psychosis who transition to psychosis (HR-T), compared to high risk individuals who do not transition (HR-NT) 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 people who transition to psychosis compared to high risk people who do not transition to psychosis.**
Grey matter volume	
Meta-analysis of whole brain volume, comprising whole brain, total intracranial and total grey matter volume estimates. *Small effect of larger global volumes in HR-T than HR-NT;* 7 studies, N = unclear, *d* = 0.36, 95%CI 0.27 to 0.46, *p* not reported	
Consistency in results	No measure of consistency is reported.
Precision in results	Precise
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 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 decreased whole brain volume in people with first-episode schizophrenia.**
Whole brain volume	
Significant reduction in average brain volume in first-episode schizophrenia; N = 1,174, 21 studies The average schizophrenia patient's brain volume was 2.7% smaller than controls.	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
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

Schizophrenia Research 2006; 82(1): 75-88

View review abstract online

Comparison	**Whole brain volume in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample, precise, consistent, direct) suggests reduced whole brain volume in first-episode schizophrenia, with no differences in intracranial volume.**
Whole brain volume	
Small effect size suggests reduced brain volume in first-episode schizophrenia; 11 studies, N = 762, d = 0.242, 95%CI 0.091 to 0.393, p = 0.002, Q = 10.4, p = 0.4	
Intracranial volume	

No significant difference between groups; 4 studies, N = 270, *d* = 0.067, 95%CI -0.179 to 0.313, *p* = 0.592, Q = 2.85, *p* = 0.41	
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 volume change over time in longitudinal studies of schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, precise, inconsistent, direct) suggests medium to large reductions in whole brain volume 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 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	
Consistency in results	Inconsistent
Precision in results	Precise
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

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 sample, inconsistent, precise, direct) suggests better overall functioning was associated with larger whole brain volume, with no associations with 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, $p < 0.05$ *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, $p < 0.001$	
Consistency in results	Inconsistent
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

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Whole brain

View review abstract online	
Comparison	**Whole brain volume, intracranial volume, extracerebral volume, and intraventricular volume changes over time in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests decreased brain and intracranial volume, and increased extracerebral volume in people with schizophrenia. There were also decreases in intracranial minus intraventricular volume, and increases in extracerebral plus intraventricular volume.**
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, $t = -2.64$, $p < 0.02$. 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, $t = -4.11$, $p < 0.001$.	
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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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Comparison	**Whole brain volume 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.**
Whole brain volume	
Small reduction in 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%)	
Consistency in results	Consistent
Precision in results	Precise for whole brain, imprecise for ventricles.
Directness of results	Direct

Yang X, Cao D, Liang X, Zhao J

Schizophrenia symptomatic associations with diffusion tensor imaging measured fractional anisotropy of brain: a meta-analysis

Neuroradiology 2017; 59: 699-708

View review abstract online

Comparison	**Association between whole brain white matter integrity and symptoms in people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) found decreased whole brain white matter was associated with small increases in negative symptoms and small decreases in positive and general symptoms. Authors state these relationships were not clinically significant and could be explained by increased age which was associated with decreased white matter (positive symptoms tend to be more prominent early on in the disorder, while negative symptoms tend to be more**

Whole brain

	prominent in older age).
White matter	
33 studies, N = 1,121 *Small, significant effects of associations between increases in whole brain white matter and decreases in negative symptoms and increases in positive and general symptoms;* Negative symptoms: r = -0.29, 95%CI -0.23 to -0.35, p < 0.00001, I^2 = 48% Positive symptoms: r = 0.16, 95%CI 0.04 to 0.27, p = 0.007, I^2 = 75% General symptoms: r = 0.26, 95%CI 0.15 to 0.35, p = 0.004, I^2 = 77% There was a significant moderating effect of age; decreased age was associated with increased white matter.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

ALE = activation likelihood estimate, CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences, df = degrees of freedom, fMRI = functional magnetic resonance imaging, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), 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, vs. = versus

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[20].

† 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[20].

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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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

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

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[22].

‖ 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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