TECHNICAL COMMENTARY

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Insular

Introduction

The insular cortex is located deep within the lateral (Sylvian) fissure, between the frontal and temporal lobes. The insular has connections with the thalamus, amygdala and cortex (particularly sensory), with suggested functions including the integration of sensory, affective and cognitive components of a painful stimulus to create the sensation of pain; homeostatic regulation; as well as motor control such as speech articulation; it has also been linked with interoceptive (internal) awareness.

Schizophrenia has been associated with altered structure and function of many brain regions. Understanding 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 encompass both structural (MRI) and functional imaging investigations (fMRI, PET) of the insular in 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 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 23 systematic reviews that met our inclusion criteria[3-25].

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

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Structural changes

- Moderate to high quality evidence found reductions in insular grey matter volume in both chronic and first-episode schizophrenia (treated or antipsychotic naïve), as well as in people at high risk (clinical or genetic), compared to controls. These reductions were of greater magnitude in anterior insular compared to posterior insular. The effect also appears larger in females than males.
- Moderate quality evidence found reductions in left insular grey matter volume were associated with increased severity of auditory hallucinations in people with schizophrenia.
- Moderate to low quality evidence found similar grey matter volume reductions in the right insular of people with schizophrenia and in people with autistic spectrum disorders.
- Moderate quality evidence found people at genetic high risk (relatives) showed increased left insular grey matter volume compared to people with chronic schizophrenia, with no differences between relatives and people with first-episode schizophrenia. People at clinical high risk (those with subclinical symptoms) showed increased left insular volume compared to people with first-episode schizophrenia. People at clinical high risk showed increased insular volume when compared to people at genetic high risk.
- People at high-risk (clinical or genetic) who developed a psychotic episode showed decreases in the right insula compared to those who did not develop psychosis.

Functional changes

- Moderate to low quality evidence found increased activation in the insular of people with schizophrenia during auditory hallucinations.
- Moderate quality evidence found increased activation in the right insular during executive function tasks compared to controls.
- Moderate to low quality evidence found decreased activation in the insular cortex during working memory tasks compared to controls.
- Moderate quality evidence found increased activity in the insular in people with schizophrenia compared to controls during emotionally neutral tasks.
- Moderate quality evidence found decreased activation during theory of mind tasks in the right insular of people with schizophrenia compared to people with an autism spectrum disorder.
- Moderate to low quality evidence found increased activity in the bilateral insular after cognitive remediation.

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TECHNICAL COMMENTARY

Insular

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	**Insular grey matter density in people with schizophrenia or first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests people with schizophrenia show grey matter reductions in bilateral insular compared to controls.**

Insular grey matter volume

49 studies, N = 4,179

Areas with reduced grey matter volume in schizophrenia;

Left insular/inferior frontal: Talairach coordinates -42, 8, 6, cluster 1339mm^3, $p < 0.000001$

Right insular/inferior frontal: Talairach coordinates 46, 2, 6, cluster 1047mm^3, $p < 0.000001$

Sub-group analyses

Studies assessing only first-episode schizophrenia were compared to studies assessing schizophrenia and showed more grey matter in people with first-episode schizophrenia in bilateral fronto-insular cortex [left -38, 10, 8, $p < 0.00001$; right 44, 16, 8, $p = 0.0002$].

A higher percentage of males showed reduced grey matter in the right insular/claustrum [34. -2, 6, $p = 0.00001$], and left inferior frontal/insular [-40, 4, -8, $p = 0.001$].

Duration of illness was associated with decreased grey matter in the right fronto-insular cortex 38, -4, 4, $p = 0.0008$.

More severe negative symptoms were associated with smaller grey matter in the left insular -42, 2, 2, $p = 0.00003$.

Note that antipsychotic dose had no significant effect.

Consistency in results‡	No measure of consistency is reported.
Precision in results§	No confidence intervals are provided.

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	**Insular grey matter volume in people with chronic schizophrenia, first-episode schizophrenia and people at high risk of schizophrenia vs. controls. People at high risk of schizophrenia were defined as first or second-degree relatives of people with schizophrenia, those meeting the Personal Assessment and Crisis Evaluation clinic criteria, or those with a modification of the catechol-O-methyltransferase gene.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) suggests people with chronic or first-episode schizophrenia have grey matter reductions in bilateral insular compared to controls. High-risk individuals have grey matter reductions in the right insular.**

Insular grey matter volume

Chronic schizophrenia

19 studies, N = 1,664

Areas showing reductions in schizophrenia vs. controls;

Left insular: Talairach coordinates -46, 8, 0, cluster 4832mm^3, ALE 0.0218

Left insular: Talairach coordinates -40, 0, 8, cluster 4832mm^3, ALE 0.01237

Left insular: Talairach coordinates -38, 0, 14, cluster 4832mm^3, ALE 0.01233

Right insular: Talairach coordinates 40, 10, 4, cluster 2336mm^3, ALE 0.0292

Left insular: Talairach coordinates -40, -22, 14, cluster 328mm^3, ALE 0.0137

First-episode schizophrenia

14 studies, N = 1,082

Areas showing reductions in first-episode schizophrenia vs. controls; Right insular: Talairach: coordinates 48, -24, 18, cluster 1576mm^3, ALE 0.0134 Right insular: Talairach: coordinates 34, 16, 10, cluster 1392mm^3, ALE 0.0248 Left insular: Talairach: coordinates -34, 20, 6, cluster 1000mm^3, ALE 0.0236 Left insular: Talairach: coordinates -40, 6, 0, cluster 976mm^3, ALE 0.0105 <u>High-risk groups</u> 8 studies, N = 1,031 *Areas showing reductions in high-risk groups vs. controls;* Right insular: Talairach coordinates 42, -28, 16, cluster 824mm^3, ALE 0.0109 <u>Subgroup analyses</u> *The first-episode group showed greater grey matter reduction than the chronic group in the;* Left insular: Talairach coordinates -34, 20, 6, cluster 664mm^3, ALE -0.0225 Right insular: Talairach coordinates 34, 16, 12, cluster 512mm^3, ALE -0.0171 *The chronic group showed greater grey matter reduction than the first-episode group in the:* Right insular: Talairach coordinates 42, 10, 2, cluster 984mm^3, ALE 0.0228 *The first-episode group showed greater grey matter reduction than the high-risk group in the;* Left insular: Talairach coordinates -34, 20, 6, cluster 1184mm^3, ALE 0.0232

Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are provided.
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 autistic spectrum disorders (ASD) vs. controls.**

Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess consistency or precision) suggests small overlapping grey matter volume decreases in the right insular.**
Overlapping brain alterations	
Regions of decreased grey matter volume, reporting the % that is contributed to by schizophrenia and autism studies; Left insula/inferior frontal gyrus: Talairach coordinates -38, 22, 0, 99.9% SZ, 0.1% ASD Right insula: Talairach coordinates 32, -17, 15, 77.4% SZ, 22.6% ASD Right insula: Talairach coordinates 39, -20, -4, 76.9% SZ, 23.1% ASD	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Dugre JR, Bitar N, Dumais A, Potvin S

Limbic hyperactivity in response to emotionally neutral stimuli in schizophrenia: A neuroimaging meta-analysis of the hypervigilant mind

American Journal of Psychiatry 2019; 176: 1021-9

View review abstract online

Comparison	**Limbic functional activity during emotionally neutral stimuli in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found increased activity in the insula in people with schizophrenia during emotionally neutral tasks.**
Limbic activity	
23 studies, N = 946 *Schizophrenia was characterised by;* Increased activations in the insula.	

Insular

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

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	**Insular grey matter volume in people with first-episode or chronic schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests insular grey matter reductions in first-episode and chronic schizophrenia.**
Insular grey matter volume	
27 studies, N = 1,556 All patients Significant reduction of volume was found in the bilateral insular, $p < 0.0002$ First- episode schizophrenia Left insular: Talairach coordinates -40, 6, 0, cluster 1552mm^3, ALE 0.01, $p < 0.0002$ Right insular: Talairach coordinates 34, 4, 8, cluster 680mm^3, ALE 0.008, $p = 0.0002$	
Consistency in results	No measure of heterogeneity provided
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Insular

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	**Insular 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 in the insular in people with schizophrenia.**
Insular grey matter volume	
42 studies, N = 4,189 *Regions of decreased grey matter in people with schizophrenia;* Left insular: Talairach coordinates -36, 10, 2, Sum of ranks = 218.3, p = 0.00005 Right insular: Talairach coordinates 40, 8, 2, Sum of ranks = 205.2, p = 0.00005	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are provided.
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	**Insular grey matter volume in people with schizophrenia vs. controls.**

Insular

Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests bilateral reductions in grey matter volume in the insular/operculum.**
Insular 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 of reduced volume were reported in the bilateral insular/operculum. *Clusters where grey matter reductions, as a proportion of the whole brain volume, were significantly more frequent than grey matter volume reductions;* Right insular: Talairach coordinates 39.4, 10.46, 2.06, Voxel cluster size 6952mm^3, ALE 1.81 x 10^{-3} Left insular: Talairach coordinates -41.02, 14.04, -1.91, Voxel cluster size 6816mm^3, ALE 1.55 x 10^{-3}	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

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

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

Neuroscience and Biobehavioural Reviews 2011; 35: 1175-1185

View review abstract online

Comparison	**Insular grey matter density in people at high-risk of schizophrenia (both clinical high-risk and genetic high-risk) vs. controls and vs. people with psychosis.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests people at high genetic risk showed decreases in the insula compared to people at high clinical risk. People at high-risk who developed a psychotic episode showed decreases in the right insula compared to those who did not develop psychosis.**

Insular grey matter volume	
19 studies, N = 1,601 Genetic high-risk of psychosis vs. clinical high-risk of psychosis People at high genetic risk showed decreases in the insular. People at high-risk who developed a psychotic episode vs. people at high risk who did not develop psychosis People at high-risk who developed a psychotic episode showed decreases in the right insular.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

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

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

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

View review abstract online

Comparison	**Insular grey matter density in people at high clinical risk of schizophrenia (according to Attenuated Psychosis Syndrome or Basic Symptoms criteria), and in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests reductions in the left insular of people with first-episode schizophrenia compared to controls and compared to people at high clinical risk of psychosis.**
Insular grey matter volume	
28 studies, N = 860 *Reductions of grey matter volume in people with first-episode schizophrenia vs. controls;* Left insula: Talairach coordinates -48, 8, 2 Kc = 28mm^3 *Reductions of grey matter volume in people with first-episode schizophrenia vs. people at high*	

clinical risk; Left insula: Talairach coordinates -42, 10, 2 Kc = 195mm^3	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

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

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

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

View review abstract online

Comparison	**Brain anomalies in relatives of people with schizophrenia or people with first-episode psychosis vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess precision and consistency) suggests reduced grey matter in the left insula of first-episode psychosis patients than controls. There were no differences in insular grey matter between people with first-episode schizophrenia and relatives.**
Grey matter volume	
Grey matter reductions in first-episode participants in; N = 870 Left insula (BA13): Talairach coordinates -48, 8, 2, $p < 0.0005$ *There were no differences in insular grey matter between people with first-episode schizophrenia and relatives;* N = 1,278	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

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

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

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

View review abstract online

Comparison	**Overlap between regions of functional and structural alteration in drug-free people with first-episode schizophrenia vs. controls.** **Note; most patients were drug naïve.**
Summary of evidence	**Moderate quality evidence (large sample, mostly consistent, direct, unable to assess precision) suggests increased or decreased grey matter volume and increased functional activity in the left insular.**
Structural and functional alteration	
15 structural MRI studies, N = 971, 16 functional MRI studies, N = 831 *Significant increased grey matter volume and increased functional activity in;* Left insular: 234 voxels, MNI coordinates -30, 0, 12, $p < 0.001$ Note that some regions of the bilateral insular also showed decreased grey matter and increased functional activity.	
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

Insular

Human Brain Mapping 2005; 25(1): 60-9 View review abstract online	
Comparison	**Functional activation in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small samples, direct, unable to assess precision or inconsistency) suggests people with schizophrenia have reduced functional activity in the insular cortex during working memory tasks.**
Activation during N-back working memory tasks	
4 studies, N = 134 *Significantly reduced activity in people with schizophrenia compared to controls in;* Right inferior frontal gyrus and insular: Talairach centre of mass 38, 16, 5, cluster volume 936mm^3	
Consistency in results	No measured of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

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

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

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

View review abstract online

Comparison	**Insular 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 significant reductions in grey matter in the insular cortex.**
Insular grey matter volume	

13 studies, N = 2,457 *Areas of reduced grey matter in schizophrenia;* Left insular cortex: Talairach coordinates -40, 14, 0, Voxel cluster size 9336mm^3, $p < 0.01$, ALE = *0.026* Right insular cortex: Talairach coordinates 40, 10, 4, Voxel cluster size 6968mm^3, $p < 0.01$, ALE = 0.026	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Kompus K, Westerhausan R, Hugdahl K

The "paradoxical" engagement of primary auditory cortex in patients with auditory verbal hallucinations: a meta-analysis of functional neuroimaging studies

Neuropsychologia 2011; 49: 3361-9

View review abstract online

Comparison	**Functional activation in people with schizophrenia during auditory verbal hallucinations.**
Summary of evidence	**Moderate to low quality evidence (small sample, direct, unable to assess precision or consistency) suggests increased activation in the insular during auditory hallucinations in people with schizophrenia.**
During hallucinations	
12 studies, N = 103, showed increased activation during hallucinations in; Insular: Talairach coordinates -44, -2, 6 cluster volume 2656mm^3	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Insular

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

Grey 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

View review abstract online

Comparison	**Insular grey matter volume in people with first-episode schizophrenia (treated and medication naïve) vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests grey matter reductions in both treated and medication-naïve first-episode schizophrenia patients compared to controls.**

Insular grey matter volume

6 studies, N = 327

Areas of reduced grey matter in medication-naïve schizophrenia;

Right insular: Talairach coordinates 40, 0, 4, cluster 288mm^3, ALE 0.0023

Left insular: Talairach coordinates -36, 4, 0, cluster 504mm^3, ALE 0.0026

9 studies, N = 820

Areas of reduced grey matter in treated schizophrenia;

Right insular: Talairach coordinates 34, 16, 12, cluster 856mm^3, ALE 0.0108

Right insular: Talairach coordinates 50, -22, 18, cluster 456mm^3, ALE 0.0056

Left insular: Talairach coordinates -32, 20, 6, cluster 808mm^3, ALE 0.0083

Left insular: Talairach coordinates -48, -22, 14, cluster 504mm^3, ALE 0.0066

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

Right insular: Talairach coordinates 40, 0, 4, cluster 160mm^3, ALE 0.0097

Left insular: Talairach coordinates -38, 6, 0, cluster 408mm^3, ALE 0.0114

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

Right insular: Talairach coordinates 34, 16, 12, cluster 776mm^3, ALE 0.0187

Right insular: Talairach coordinates 40, 12, 4, cluster 776mm^3, ALE 0.0075

Right insular: Talairach coordinates 50, -20, 18, cluster 280mm^3, ALE 0.0098 Left insular: Talairach coordinates -34, 22, 4, cluster 664mm^3, ALE 0.0145 Left insular: Talairach coordinates -48, -22, 14, cluster 296mm^3, ALE 0.0111	
Consistency in results	No measure of consistency 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

View review abstract online

Comparison	**Insular 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 patients with persistent negative symptoms showed reductions in bilateral insular.**
Insular grey matter volume	
12 studies, N = unclear *There was significantly reduced grey matter volume in;* Left insula (BA13): Talairach coordinates -42, 12, -2 Right insula: Talairach coordinates 40, 14, 0	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Insular

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 activation 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 also show regions of increased activity in the right insular during executive function tasks,**
Functional activity	
41 studies, N = 1,217 *Significantly increased activity in people with schizophrenia compared to controls;* Right insular Talairach centre of mass 38, 16, 4, cluster volume 1136mm^3	
Consistency in results	No measure of consistency is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

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

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

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

View review abstract online

Comparison	**Insular grey matter volume in relatives of people with schizophrenia vs. people with schizophrenia and vs. controls.**

Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) suggests relatives had increased grey matter in the left insular compared to people with schizophrenia. Compared to controls, relatives showed decreased grey matter in the left insular.**
Insular grey matter volume	
7 studies, N = 945 *Compared to people with schizophrenia, relatives had increased grey matter in;* Left insula: 700 voxels, MNI coordinates -40, 12, -8, p = 0.00005 9 studies, N = 953 *Compared to controls, relatives had decreased grey matter in;* Left insula: 1,089 voxels, MNI coordinates -38, -4, -14, p = 0.00011	
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

Palaniyappan L, Balain V, Radua J, Liddle PF

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

Schizophrenia Research 2012; 137: 169-173

View review abstract online

Comparison	**Correlations between insular grey matter density and auditory hallucinations in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests reductions in the grey matter volume of the left insular cortex was associated with increased severity of auditory hallucinations.**
Insular grey matter volume	
7 studies, N = 350	

Reductions in grey matter correlated with the severity of auditory hallucination in; Left insular cluster: Talairach coordinates -42, -4, 2, uncorrected *p* = 0.000001, 717 voxels	
Consistency in results	No measure of consistency is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Ramsay IS, Macdonald AW

Brain Correlates of Cognitive Remediation in Schizophrenia: Activation Likelihood Analysis Shows Preliminary Evidence of Neural Target Engagement

Schizophrenia Bulletin 2015; 41(6): 1276-84

View review abstract online

Comparison	**Functional activation changes in response to cognitive remediation in people with schizophrenia vs. various control conditions. Training duration was an average of 10 weeks comprising 40 sessions.**
Summary of evidence	**Moderate to low quality evidence (small sample, direct, unable to assess precision or consistency) suggests increased activity in the bilateral insular after cognitive remediation.**
Changes in activation	
9 studies, N = 128 *The following clusters showed increases in activation after cognitive remediation;* Left insular cortex: Talairach coordinates -44, 6, 24, cluster volume 496mm^3 Right insular cortex: Talairach coordinates 38, 16, 4, cluster volume 264mm^3	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Insular

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

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

Psychological Medicine 2017; 47: 401-13

View review abstract online

Comparison	**Insular grey matter changes in first-episode schizophrenia (treated and medication naïve) vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests decreased right insular grey matter of first-episode patients.**
Insular grey matter volume	
24 studies, N = 1,358 *Reductions were found in;* Right insula, BA 48: MNI coordinates 38, -4, 10	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

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

Systematic meta-analysis of insular volume in schizophrenia

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

View review abstract online

Comparison	**Insular grey matter volume in people with schizophrenia vs. controls**
Summary of evidence	**Moderate to high quality evidence (large samples, precise, inconsistent, direct) suggests medium-sized reductions of**

	insular volume in schizophrenia, of greater magnitude in anterior insular compared to posterior insular, with no difference between first-episode and chronic patients. The effect also appears larger in females.
Insular grey matter volume	
Medium-sized reductions in bilateral insular in people with schizophrenia; N = 945, *g* = -0.446, 95%CI -0.639 to -0.252, *p* < 0.001, Q = 66.64, *p* < 0.001, I^2 = 76% *Medium effects were reported in both right and left insular;* Left: N = 844, *g* = -0.453, 95%CI -0.670 to -0.236, *p* < 0.001, I^2 = 61% Right: N = 844, *g* = -0.442, 95%CI -0.652 to -0.231, *p* < 0.001, I^2 = 58% *A medium-sized reduction was reported in anterior and a small reduction in posterior insular in people with schizophrenia;* Anterior insular: N = 605, *g* = -0.643, 95%CI -0.886 to -0.399, *p* < 0.001, I^2 = 52% Posterior insular: N = 453, *g* = -0.321, 95%CI -0.609 to -0.034, *p* = 0.028, I^2 = 55% *Medium-sized effects were reported in both first episode and chronic schizophrenia;* First-episode: N = 439, *g* = -0.455, 95%CI -0.797 to -0.114, *p* < 0.01, I^2 = 83% Chronic: N = 543, *g* = -0.438, 95%CI -0.678 to -0.198, *p* < 0.001, I^2 = 70% *Only females with schizophrenia showed a significant reduction compared to controls;* Males: N = 298, *g* = -0.275, 95%CI -0.624 to 0.073, *p* = 0.122, I^2 = 74% Females: N = 189, *g* = -0.529, 95%CI -0.875 to -0.182, *p* < 0.01, I^2 = 57% Meta-regression identified no predictive value of whole brain volume, patients' age, medication dose, or illness duration.	
Consistency in results	Inconsistent
Precision in results	Precise
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

Insular

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 sample, direct, unable to assess precision or consistency) suggests decreased activation during theory of mind tasks in the right insular of people with schizophrenia compared to people with an autism spectrum disorder.**
Theory of mind	
16 studies, N = 463 *The following cluster showed decreased activation in schizophrenia vs. autism spectrum disorders;* Right insular: Talairach coordinates 32, -2, 12, 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

Explanation of acronyms

ALE = activation likelihood estimate, CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect size), I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, MNI = Montreal Neurological Institute, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic (chi-square) for the test of heterogeneity, vs. = versus

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

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Insular

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[26].

† 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[26].

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[27]. 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[28].

‖ 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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