TECHNICAL COMMENTARY

NeuRA
Discover. Conquer. Cure.
SCHIZOPHRENIA LIBRARY

Frontal lobe

Introduction

The frontal lobe comprises the anterior portion of the brain and is anatomically defined by four key gyri – the superior, middle, inferior and medial frontal gyri. The prefrontal cortex forms the rostral pole of the frontal lobe and is one of the most highly developed brain regions. The frontal lobe and its regions have widespread connections throughout the brain, particularly the prefrontal cortex. Proposed functions of the prefrontal cortex are involved mainly with executive functions and better cognition, such as working memory, problem solving and planning. The prefrontal cortex has also been implicated as a storage site for declarative memory such as semantic and episodic knowledge. This region has reciprocal connectivity with the amygdala and is in a position to use experience and learning to influence behavioural responses and evaluate situations. The most posterior section of the frontal lobe is the pre-central gyrus, the primary motor cortex, also surrounded by associative and supplementary motor regions.

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 reflect both structural imaging investigations (MRI, DTI), and functional imaging (fMRI, PET, SPECT) as well as metabolic (MRS) investigations of the frontal lobe 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

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

Frontal lobe

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 61 systematic reviews that met our inclusion criteria[3-63].

Structural changes

- High quality evidence found schizophrenia is associated with significant reductions in grey and white matter volume of the frontal lobe.
- Moderate quality evidence found decreased right superior frontal gyrus grey matter in medication-naïve first-episode patients and increased right superior frontal gyrus grey matter in treated first-episode patients.
- Moderate to high quality evidence suggests reduced grey matter in the prefrontal cortex, left orbito-frontal gyrus, left superior frontal gyrus, and bilateral medial, inferior and middle frontal gyri of chronic schizophrenia. People with first-episode schizophrenia also show reduced grey matter in inferior, middle and medial frontal and precentral gyri. A high risk of schizophrenia was particularly associated with reduced grey matter in inferior and superior frontal gyri.
- Moderate quality evidence suggests reduced white matter integrity (fractional anisotropy) in the prefrontal cortex of people with schizophrenia compared to controls. There were also reductions in bilateral inferior fronto-occipital fasciculus tracts.
- Moderate quality evidence suggests people with schizophrenia showed an absence of normal leftward asymmetry in the Sylvian fissure. There was also a higher frequency of abnormal (reversed) asymmetry in the frontal lobe of people with schizophrenia compared to controls.
- High quality evidence suggests significantly greater reductions over time in frontal grey matter and white matter in people with schizophrenia compared to controls.
- Moderate to high quality evidence suggests better overall functioning was associated with larger frontal lobe.
- Moderate to low quality evidence found no overlapping grey matter volume decreases in the frontal lobes of people with schizophrenia or autism.

Functional changes

- Moderate quality evidence suggests increased activation during auditory hallucinations in the inferior and superior frontal gyri, and decreased activation during auditory tasks in the superior frontal gyrus of people with schizophrenia.
- Moderate quality evidence found decreased activation during cognitive control tasks in the right middle/inferior frontal gyrus and bilateral middle frontal gyrus of people with schizophrenia. During timing tasks, there was increased activation in the right inferior frontal gyrus. During executive functioning tasks, people with schizophrenia showed decreased activation in the middle and medial frontal gyri, and decreased activation in the superior and inferior frontal gyri compared to controls.
- Moderate to low quality evidence found decreased activation in the frontal lobe of people with schizophrenia during memory tasks. During episodic encoding, activity is reduced in the right superior frontal gyrus, bilateral inferior frontal gyri, while there is increased activity in the left precentral gyrus. During episodic retrieval, functional activity is reduced in the left inferior frontal gyrus, left middle frontal gyrus, but increased in the left precentral gyrus, right middle frontal gyrus of people with schizophrenia.
- Moderate to low quality evidence found decreased activation during emotion processing tasks in the superior frontal gyrus

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

of people with schizophrenia. There was decreased activation in the inferior frontal gyrus and increased activity in the medial to superior prefrontal gyrus during explicit threat processing of facial stimuli. There was decreased activation in the medial prefrontal cortex and left orbito-frontal cortex during theory of mind tasks. There was decreased activation in the left middle frontal gyrus during reward anticipation tasks. There was decreased activation in the right inferior frontal gyrus during empathy tasks.

- Moderate quality evidence found relatives of people with schizophrenia had decreased resting-state brain activity in the right inferior frontal gyrus compared to controls. The right inferior frontal gyrus showed increased activation during cognitive tasks and decreased activation during emotion tasks. There was also increased activation in the right superior frontal gyrus and decreased activation in the left medial frontal gyrus of relatives during emotion tasks. Moderate to high quality evidence found decreased activity in the right middle frontal gyrus (BA9) and right inferior frontal gyrus (BA44), and increased activity in the right frontopolar (BA10) region of relatives during working memory tasks.
- Moderate to high quality evidence found reduced activation in the left inferior frontal gyrus and bilateral medial frontal gyrus in people at clinical high risk for psychosis during various tasks.
- Moderate to low quality evidence suggests increased activity in the left middle frontal gyrus, left inferior frontal gyrus, left superior frontal gyrus, and medial frontal gyrus following cognitive remediation.
- Moderate to low quality evidence found decreased activation in the right inferior frontal cortex was associated with increased severity of neurological soft signs in people with schizophrenia.
- Moderate quality evidence found decreased phosphomonoester (PME) levels in the prefrontal cortex of people with first-episode psychosis and people with schizophrenia when compared to controls. There were increased phosphodiester (PDE) levels in the prefrontal cortex of first-episode patients. Moderate to low quality evidence found decreased PME and increased PDE levels in the frontal lobe of first-degree relatives of people with schizophrenia.
- Moderate quality evidence suggests N-acetylaspartate (NAA) and creatine (Cr) levels are reduced in frontal grey and white matter, particularly the prefrontal cortex and frontal pole, in both first episode and chronic schizophrenia compared to controls. NAA/Cr ratio was reduced in the prefrontal cortex of people at clinical or familial risk of schizophrenia.
- Moderate to high quality evidence found reduced glutamate (Glu) and increased glutamine (Gln) levels in the frontal cortex of people with schizophrenia compared to controls. There was a medium-sized increase in Glu+Gln in the medial prefrontal cortex of unmedicated people with schizophrenia, and increased Glu/Gln ratio and glutamate+glutamine levels in the frontal lobe of first-degree relatives of people with schizophrenia.
- High quality evidence found a small decrease in myo-inositol levels in the medial prefrontal region in people with schizophrenia. Moderate quality evidence found reduced translocator protein in the frontal cortex of people with schizophrenia.

Structural and functional changes

- Moderate quality evidence found decreased grey matter volume and decreased functional activation in the right medial frontal/anterior cingulate cortex, and decreased grey matter volume and increased functional activation in the left medial frontal/anterior cingulate cortex of

people with first-episode psychosis, with greater severity of abnormality in medicated patients.

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

Achim AM, Lepage M

Episodic memory-related activation in schizophrenia: meta-analysis

British Journal of Psychiatry 2005; 187: 500-509

View review abstract online

Comparison	**Functional activation in people with schizophrenia vs. controls during episodic memory tasks.**
Summary of evidence	**Moderate quality evidence (medium-sized samples, direct, unable to assess precision and consistency) suggests decreases in functional activation during memory encoding tasks in the middle and medial frontal gyri, and reductions during memory retrieval tasks in the medial and inferior frontal cortex.**

Activation during episodic memory tasks

Reduced activation in people with schizophrenia compared to controls for memory encoding tasks, where activation levels met both voxel and simulation threshold;

8 studies, N = 176

Right anterior middle frontal gyrus: Talairach coordinates (24, 54, 2), Activation Likelihood Estimate for Gaussian smoothed foci (FWHM 14mm) (ALE): 0.003886, Voxel probability: 0.000025

Right medial frontal gyrus: Talairach coordinates (20, 44, 20), ALE: 0.003139, Voxel probability: 0.000172

Reduced activation in people with schizophrenia compared to controls for retrieval tasks, where activation levels met both voxel and simulation threshold;

11 studies, N = 298

Left medial frontal gyrus: Talairach coordinates (-4, 54, 4), ALE: 0.005294, Voxel probability: 0.000059

Left inferior frontal gyrus: Talairach coordinates (-42, 26, 16), ALE: 0.006221, Voxel probability: 0.000008

Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Frontal lobe

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	**Functional 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 activation during cognitive control tasks in the right middle/inferior frontal gyrus and bilateral middle frontal gyrus of people with schizophrenia. During timing tasks, there was increased activation in the right inferior frontal gyrus.**
Functional activation	
Cognitive control 29 studies, N = 2,268 *Significant, decreased activation in people with schizophrenia was found in;* Right middle/inferior frontal gyrus (triangular part, BA 45) Bilateral middle frontal gyrus (BA 44, 8) Timing 8 studies, N = 395 *Significant, increased activation in people with schizophrenia was found in;* Right inferior frontal gyrus (orbital part, BA 47)	
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

NeuRA Discover. Conquer. Cure.
SCHIZOPHRENIA LIBRARY

Frontal lobe

Berger GE, Wood SJ, Pantelis C, Velakoulis D, Wellard RM, McGorry PD

Implications of lipid biology for the pathogenesis of schizophrenia

Australian & New Zealand Journal of Psychiatry 2002; 36(3): 355-366

View review abstract online

Comparison	**Comparison of prefrontal cortex phospholipid metabolites (measured by 31P MRS) in people with drug naive first-episode psychosis, newly diagnosed or chronic schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium to large samples, direct, unable to assess precision or consistency) suggests phosphomonoester (PME) levels are reduced in the prefrontal cortex of people with first-episode psychosis and people with schizophrenia. There are also increased phosphodiester (PDE) levels in the prefrontal cortex of first-episode psychosis patients when compared to controls.**
PME levels	
3 of 3 studies (N = 78) reported decreased PME levels in both first episode and newly diagnosed patients. 7 of 11 studies (222/415 patients) reported decreased PME levels in people with chronic schizophrenia.	
PDE levels	
3 of 3 studies (N = 78) reported increased PDE levels in both first episode and newly diagnosed patients. 3 of 10 studies (87/363 patients) reported increased PDE levels in people with chronic schizophrenia. 1 of 10 studies (86/363 patients) reported decreased PDE levels in people with chronic schizophrenia.	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

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

Frontal lobe

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 chronic or first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests people with chronic schizophrenia show grey matter reductions in bilateral insula and inferior frontal, thalamus, and medial frontal/anterior cingulate gyrus compared to controls. People with first-episode schizophrenia show reduced grey matter in superior temporal gyrus/insula and anterior cingulate.**

Grey matter changes

Meta-analysis was performed using Signed Differential Mapping (SDM) analysis on voxel-based morphometry MRI studies of whole brain grey and white matter measures.

N = 4,179, 49 studies

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

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

Bilateral 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, $p = 0.00007$

Subgroup analyses

First-episode patients showed higher grey matter in the bilateral fronto-insular cortex [left (-38, 10, 8), $p < 0.00001$; right (44, 16, 8), $p = 0.0002$], than chronic patients.

Studies with a higher percentage of males showed reduced grey matter in right insula/claustrum [(34. -2, 6), $p = 0.00001$], left inferior frontal/insula [(-40, 4, -8), $p = 0.001$], thalamus [(4, -22, -4) $p = 0.00003$], and left medial frontal [(-4, 32, -16) $p = 0.002$] areas than studies with more females.

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 less grey matter in bilateral medial frontal gyrus/orbitofrontal cortex [(-2, 32, -16), p = 0.0009] and left insula [(-42, 2, 2), p = 0.00003]. Antipsychotic dose had no significant effect.	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Brugger S, Davis JM, Leucht S, Stone JM

Proton magnetic resonance spectroscopy and illness stage in schizophrenia – a systematic review and meta-analysis

Biological Psychiatry 2011; 69: 495-503

View review abstract online

Comparison	**Comparison of metabolic N-acetyl aspartate (NAA) activity measured by ^{1}H-MRS in people at high risk of schizophrenia (clinical and genetic), first-episode schizophrenia, and chronic schizophrenia patients vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, inconsistent, precise, direct) suggests decreased NAA levels in the frontal lobes of people with first-episode or chronic schizophrenia, and no differences in people at risk.**
NAA	
Frontal lobe *Significant, medium-sized reductions of NAA in people with chronic schizophrenia;* 41 studies, N = 1,679, d = -0.45, 95%CI -0.63 to -0.26, p < 0.0001, Q = 209.76, p < 0.0001, I^2 = 66% *Significant, medium-sized reductions of NAA in people with first-episode schizophrenia;* 19 studies, N = 804, d = -0.45, 95%CI -0.67 to -0.23, p < 0.0001, Q = 60.76, p = 0.001, I^2 = 49% *No differences between people at high-risk of psychosis and controls;* 10 studies, N = 425, d = 0.05, 95%CI -0.33 to 0.43, p = 0.799, Q = 50.71, p < 0.0001, I^2 = 68%	

Frontal lobe

Consistency in results	Inconsistent
Precision in results	Precise
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	**High quality evidence (large sample, consistent, precise, direct) finds small reductions in frontal lobe volume in people with first-episode schizophrenia.**
Brain regions	
Significant, small reductions in first-episode schizophrenia in; Frontal lobe: 22 studies, N = 1,391, g = -0.31, 95%CI -0.44 to -0.19, $p < 0.001$, I^2 = 29%	
Consistency in results	Consistent
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

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Frontal lobe

View review abstract online	
Comparison	**Grey matter changes in people at high risk of schizophrenia or first episode schizophrenia vs. controls. People at high risk of schizophrenia were defined as first- or second-degree relatives of people with schizophrenia, those meeting the Personal Assessment and Crisis Evaluation clinic criteria, or those with a modification of the catechol-O-methyltransferase gene.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests high-risk individuals have grey matter reductions in left inferior frontal gyrus compared to controls. People with first-episode schizophrenia have grey matter reductions in left lateral prefrontal lobe (middle and inferior frontal gyri), and bilateral medial frontal gyrus compared to controls. People with chronic schizophrenia have grey matter reductions in left frontal lobe (inferior, medial, middle), and right frontal lobe (superior, middle, inferior) compared to controls.**

Grey matter changes

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

FWHM 10mm, FDR corrected at p <0.01

Areas of reduced grey matter in high-risk groups vs. controls;

8 studies, N = 1,031

Left inferior frontal gyrus: Talairach coordinates (-48, 26, -2), cluster 432mm^3, ALE 0.0107

Areas of reduced grey matter in first-episode groups vs. controls;

14 studies, N = 1,082

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

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

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

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

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

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

Areas of reduced grey matter in chronic schizophrenia vs. controls;

19 studies, N = 1,664

Left inferior frontal gyrus: Talairach coordinates (-36,16, -4), cluster 4832mm^3, ALE 0.0222

Left medial frontal gyrus: Talairach coordinates (-4, 52, 12), cluster 2976mm^3, ALE 0.0196

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

Left medial frontal gyrus: Talairach coordinates (-6, 34, -14), cluster 2976mm^3, ALE 0.0182 Left middle frontal gyrus: Talairach coordinates (-44, 8, 36), cluster 1208mm^3, ALE 0.0199 Left inferior frontal gyrus: Talairach coordinates (-50, 6, 30), cluster 1208mm^3, ALE 0.0176 Right superior frontal gyrus: Talairach coordinates (30, 54, 10), cluster 416mm^3, ALE 0.0147 Right middle frontal gyrus: Talairach coordinates (42, 4, 38), cluster 392mm^3, ALE 0.0171 Right inferior frontal gyrus: Talairach coordinates (26, 28, -2), cluster 136mm^3, ALE 0.0119 *Subtraction analysis between high-risk individuals and first-episode schizophrenia showed greater grey matter reduction in high risk group;* Left inferior frontal gyrus: Talairach coordinates (-50, 26, -2), cluster 224mm^3, ALE -0.0107 *Subtraction analysis between high-risk individuals and first-episode schizophrenia showed greater grey matter reduction in first-episode group;* Right precentral gyrus: Talairach coordinates (48, -10, -12), cluster 400mm^3, ALE 0.0131 *Subtraction analysis between chronic and first-episode schizophrenia showed greater grey matter reduction in first-episode group;* Left inferior frontal gyrus: Talairach coordinates (-48, 6, 22), cluster 208mm^3, ALE -0.0133 Right inferior frontal gyrus: Talairach coordinates (24, 34, -8), cluster 168mm^3, ALE -0.0146 Left inferior frontal gyrus: Talairach coordinates (-32, 32, -4), cluster 136mm^3, ALE -0.0126 Right precentral gyrus: Talairach coordinates (50, -12, 12), cluster 120mm^3, ALE -0.0121 *Subtraction analysis between chronic and first-episode schizophrenia showed greater grey matter reduction in chronic schizophrenia;* Left medial frontal gyrus: Talairach coordinates (-4, 52, 14), cluster 544mm^3, ALE 0.0156 Left medial frontal gyrus: Talairach coordinates (-6, 34, -14), cluster 392mm^3, ALE 0.0138 Left inferior frontal gyrus: Talairach coordinates (-34, 16, -6), cluster 272mm^3, ALE 0.0138	
Consistency in results	No measure of consistency 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

Frontal lobe

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 no overlapping grey matter volume decreases in the frontal lobes of people with schizophrenia or autism.**
Overlapping brain alterations	
Regions of decreased grey matter volume, reporting the % that is contributed to by schizophrenia and autism studies; Right middle frontal gyrus: Talairach coordinates (43, 33, 21), 100% SZ, 0% ASD Left superior frontal gyrus: Talairach coordinates (-2, 32, 53), 99.9% SZ, 0.1% ASD	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

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

Putative astroglial dysfunction in schizophrenia: A meta-analysis of H-MRS studies of medial prefrontal myo-inositol

Frontiers in Psychiatry 2018; 9 (SEP)

View review abstract online

Comparison	**Medial prefrontal myo-inositol levels measured by ^{1}H-MRS in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) finds a small decrease in myo-inositol levels in the medial prefrontal region in people with schizophrenia.**
Myo-inositol	

Frontal lobe

Medial prefrontal *Significant, small decrease in people with schizophrenia;* 19 studies, N = 1,146, SMD = 0.19, 95%CI 0.05 to 0.32, p = 0.0067, I^2 = 15%, p = 0.09 Studies with more female patients reported greatest reduction in myo-inositol. There were no moderating effects of medication, scanner strength, echo time, repetition time, patient age or duration of illness.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Davidson LL, Heinrichs RW

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

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

View review abstract online

Comparison 1	**Grey matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, mostly inconsistent, precise, direct) suggests grey matter volume is significantly reduced in the frontal lobe in schizophrenia.**
Frontal lobe volume	

Frontal lobe

Left frontal lobe *Small to medium effect size suggests reduced volume in schizophrenia;* N = 2,067, *d* = -0.39, 95%CI -0.55 to -0.23, *p* not reported, SD = 0.47, FSN = 104 Right frontal lobe *Small to medium effect size suggests reduced volume in schizophrenia;* N = 1,951, *d* = -0.41, 95%CI -0.56 to -0.26, *p* not reported, SD = 0.42, FSN = 102 Total frontal lobe *Small to medium effect size suggests reduced volume in schizophrenia;* N = 3,194, *d* = -0.44, 95%CI -0.55 to -0.32, *p* not reported, SD = 0.42, FSN = 170	
Consistency in results	Significant heterogeneity reported in all outcomes except right frontal cortex.
Precision in results	Precise for all outcomes.
Directness of results	Direct
Comparison 2	**Functional activation in people with schizophrenia vs. controls during episodic memory tasks.**
Summary of evidence	**Moderate to high quality evidence (large sample, precise, direct, consistent for individual hemispheres during task) shows a medium to large effect of reduced functional activity in bilateral frontal lobes in people with schizophrenia both during cognitive tasks and at rest.**
Frontal lobe activity during task	
Left frontal lobe *Medium effect size suggests reduced activity in schizophrenia;* N = 390, *d* = -0.54, 95%CI -0.78 to -0.30, SD = 0.38, FSN = 53 Right frontal lobe *Medium effect size suggests reduced activity in schizophrenia;* N = 397, *d* = -0.54, 95%CI -0.90 to -0.18, SD = 0.53, FSN = 48 Total frontal lobe *Large effect size suggests reduced activity in schizophrenia;* N = 879, *d* = -0.81, 95%CI -1.06 to -0.57, SD = 0.52, FSN = 142	

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

Frontal lobe

Frontal lobe activity at rest	
Left frontal lobe *Medium effect size suggests reduced activity in schizophrenia;* N = 617, *d* = -0.48, 95%CI -0.80 to -0.15, SD = 0.74, FSN = 87 Right frontal lobe *Medium effect size suggests reduced activity in schizophrenia;* N = 617, *d* = -0.43, 95%CI -0.74 to -0.12, SD = 0.72, FSN = 76 Total frontal lobe *Medium effect size suggests reduced activity in schizophrenia;* N = 971, *d* = -0.65, 95%CI -0.88 to -0.42, SD = 0.64, FSN = 176	
Consistency in results	Significant heterogeneity reported for all outcomes except left and right frontal lobes during task.
Precision in results	Precise
Directness of results	Direct

Di X Chan RC, Gong QY

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

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

View review abstract online

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

Frontal lobe

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

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

17 studies, N = 712

Pooled analysis identified 4 clusters of reduced white matter volume, encompassing foci in the frontal lobe and internal capsule in people with schizophrenia;

Right frontal white matter: Talairach coordinates (20, 46, 26), Voxel cluster size 544mm^3, ALE 0.010283

Left frontal white matter: Talairach coordinates (-8, 48, -2), Voxel cluster size 336mm^3, ALE 0.010507

Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

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

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

Schizophrenia Research 2019; 209: 22-31

View review abstract online

Comparison	**Grey matter volume in people at clinical high risk of psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, direct, unable to assess precision) found decreased grey matter volume in the right gyrus rectus and bilateral superior frontal gyrus of high-risk individuals.**

Grey matter volume

14 VBM studies, N = 1,331

Decreased grey matter volumes were found in people at high risk in the following areas;

Right gyrus rectus (Z = -2.109)

Right superior frontal gyrus (Z = -2.321) Left superior frontal gyrus (Z = -2.228)	
Consistency in results	Authors report consistent results.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Dong D, Wang Y, Jia X, Li Y, Chang X, Vandekerckhove M, Luo C, Yao D

Abnormal brain activation during threatening face processing in schizophrenia: A meta-analysis of functional neuroimaging studies

Schizophrenia Research 2018; 197: 200-208

View review abstract online

Comparison	**Functional activity during threatening face processing in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests during explicit threat processing of facial stimuli, there was decreased activity in the inferior frontal gyrus and increased activity in the medial prefrontal gyrus to superior prefrontal gyrus in people with schizophrenia, with no differences between patients and controls during implicit threat processing of facial stimuli.**
Functional activity	
19 studies, N = 728 *Decreased activity during explicit threat processing in;* Inferior frontal gyrus: 964 voxels, MNI coordinates 56, 16, 14, $p < 0.001$ *Increased activity during explicit threat processing in;* Medial prefrontal gyrus to superior prefrontal gyrus: 990 voxels, MNI coordinates -8, 58, 12, $p < 0.001$ There were no differences during implicit threat processing.	
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

Egerton A, Modinos G, Ferrera D, McGuire P

Neuroimaging studies of GABA in schizophrenia: a systematic review with meta-analysis

Translational Psychiatry 2017; 7: e1147

View review abstract online

Comparison	**GABA levels measured by ^{1}H-MRS in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds no differences in GABA levels.**

GABA

No significant differences between groups in the medial frontal cortex;

12 studies, N = 904, g = -0.30, 95%CI -0.60 to 0.10, p = 0.10, I^2 = 84%

There were no moderating effects of diagnosis (first-episode psychosis vs. schizophrenia), medications (adjunctive benzodiazepines/anticonvulsants or antipsychotics vs. no antipsychotics), ^{1}H-MRS locations (medial prefrontal vs. all medial frontal), gender, age, illness duration, symptom severity, %grey matter or publication date.

Consistency in results	Inconsistent
Precision in results	Precise
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

NeuRA Discover. Conquer. Cure.
SCHIZOPHRENIA LIBRARY

Frontal lobe

American Journal of Psychiatry 2008; 165(8): 1015-23 View review abstract online	
Comparison	**Grey matter changes in people with first-episode schizophrenia vs. people with chronic schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests grey matter reductions in the inferior frontal in first-episode schizophrenia, and in the inferior frontal, medial frontal and the dorsolateral prefrontal in chronic schizophrenia.**
Grey matter changes	
27 studies, N = 1,556 *Reductions in first-episode schizophrenia;* Left inferior frontal gyrus: Talairach coordinates (-28, 30, -6), cluster 736mm^3, ALE 0.009, p = 0.0004 Right inferior frontal gyrus: Talairach coordinates (26, 10, 18), cluster 360mm^3, ALE 0.007, p = 0.001 *Reductions in chronic schizophrenia;* Significant reduction of volume was seen in the medial frontal gyrus (p <0.0004), the STG (p = 0.0018), the dorsolateral prefrontal cortex (p < 0.0002), and the left middle frontal (p < 0.0002). *Changes common to first episode and chronic schizophrenia;* N = 1,556, 27 studies Significant reduction of volume was seen in the inferior frontal gyrus, p < 0.001	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Ellison-Wright I, Bullmore E

Meta-analysis of diffusion tensor imaging studies in schizophrenia

Schizophrenia Research 2009; 108(1-3): 3-10

View review abstract online

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

Frontal lobe

Comparison	**White matter fractional anisotropy (FA) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision and consistency) suggests schizophrenia is associated with significant reductions in white matter integrity in the frontal lobe.**
FA	
Meta-analysis was performed using a hybrid of Activation Likelihood Estimate (ALE) analysis and Genome Scan Meta-analysis (GSMA) which combines activation foci from multiple studies and permits weighting for sample size. FWHM 7mm, FDR corrected at $p < 0.05$ 15 studies, N = 790 *Frontal lobe FA reduction in people with schizophrenia;* Talairach coordinates (-12, 34, 10), $p < 0.0001$, Voxel cluster size 2368mm^3 7/15 studies reported one or more coordinate that lay within 20mm of this maximal focus of decreased FA. White matter tracts traversing this region include inter-hemispheric fibres (genu of corpus callosum) cingulum bundle, left anterior thalamic radiation, left corticobulbar tract, left inferior fronto-occipital fasciculus.	
Consistency in results	No measure of consistency is reported, results appear inconsistent particularly for frontal lobe data.
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. controls.**

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

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Frontal lobe

Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests grey matter reductions in bilateral medial frontal gyri and in left deep frontal lobe.**
Grey matter changes	
Meta-analysis was performed using Activation Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies. FWHM 7mm, FDR corrected at $p < 0.05$ 42 studies, N = 4,189 *Regions of decreased grey matter in schizophrenia;* Left medial frontal gyrus: Talairach coordinates (-2, 50, 4), Sum of ranks = 179.6, $p = 0.00005$ Left medial frontal gyrus: Talairach coordinates (-2, 48, 0), Sum of ranks = 179.3, $p = 0.00005$ Left deep frontal lobe: Talairach coordinates (-14, 2, -10), Sum of ranks = 172.8, $p = 0.00005$ Left deep frontal lobe: Talairach coordinates (-12, 0, -8), Sum of ranks = 172.5, $p = 0.00005$ Right medial frontal gyrus: Talairach coordinates (2, 42, 26), Sum of ranks = 157.1, $p = 0.00060$ Right medial frontal gyrus: Talairach coordinates (2, 44, 24), Sum of ranks = 156.8, $p = 0.00070$ Right medial frontal gyrus: Talairach coordinates (2, 48, 22), Sum of ranks = 156.5, $p = 0.00075$	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Fornito A, Yucel M, Patt, 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	**Grey matter density, volume (GMV) and concentration (GMC, grey matter as a proportion of the whole brain volume) in people with schizophrenia vs. controls.**

Frontal lobe

Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests grey matter density reductions in the anterior cingulate/medial prefrontal cortex, and left middle and inferior frontal gyri in people with schizophrenia** **Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests grey matter volume reductions were reported in the right prefrontal cortex, left orbito-frontal gyrus, left superior frontal gyrus, left medial frontal gyrus, and bilateral inferior and middle frontal gyri**
Grey matter density	
Meta-analysis was performed using Activation Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies. FWHM 12mm, FDR corrected at $p < 0.05$ 37 studies, N = 3,336 Pooled analysis identified 15 clusters of reduced grey matter, encompassing foci in the frontal, temporal, limbic and subcortical regions. The largest clusters of reduced volume were reported in the bilateral anterior cingulate/medial prefrontal cortex. Decreased grey matter was also reported in the left middle and inferior frontal gyri.	
GMC and GMV	
37 studies, N = 3,336 *GMC reductions were significantly more frequent than GMV in;* Right anterior cingulate gyrus/medial prefrontal gyrus: Talairach coordinates (0.04, 53.3, 0.59), Voxel cluster size 5144mm^3, ALE 1.36 x 10^{-3} Left medial orbito-frontal gyrus: Talairach coordinates (-1.11, 43.03, -21.06), Voxel cluster size 1208mm^3, ALE 0.87 x 10^{-3} *GMV reductions were significantly more frequent than GMC in;* Left medial superior frontal gyrus: Talairach coordinates (-5.6, 31.84, 46.13), Voxel cluster size 1688mm^3, ALE -0.76 x 10^{-3} Left lateral superior frontal gyrus: Talairach coordinates (-31.56, 53.64, 19.6), Voxel cluster size 1120mm^3, ALE -0.68 x 10^{-3} Right inferior frontal gyrus: Talairach coordinates (48.39, 2.83, 30.96), Voxel cluster size 1096mm^3, ALE -0.74 x 10^{-3} Left lateral orbito-frontal gyrus: Talairach coordinates (-26.82, 28.11, -4.7), Voxel cluster size 680mm^3, ALE 0.74 x 10^{-3} Right pre- and post-central gyri: Talairach coordinates (52.97, -24.28, 43.55), Voxel cluster size	

408mm^3, ALE -0.54 x 10^{-3} Left middle frontal gyrus: Talairach coordinates (-42.94, 9.86, 39.04), Voxel cluster size 192mm^3, ALE 0.68 x 10^{-3} Right middle/inferior frontal gyri: Talairach coordinates (27.67, 58.41, 9.68), Voxel cluster size 192mm^3, ALE 0.68 x 10^{-3} As GMC had fewer foci available for comparison, a random subset was initially selected for comparison with GMV. To increase validity of this comparison, four additional GMC/GMV contrasts were performed with different GMC subsets, and demonstrated high consistency between randomisations. Both cluster size and ALE statistic were larger for comparisons using concentration measures compared to volume measures. Cluster size t = 2.54, *p* = 0.02 ALE statistic t = 2.82, p = 0.01	
Consistency in results	No measure of consistency is reported.
Precision in results	No 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 in individuals following their first episode of schizophrenia vs. controls.**
Summary of evidence	**Low quality evidence (one small study per outcome) is unclear as to the direction of the changes in functional activity in first-episode schizophrenia in the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and anterior frontal cortex during information processing, working memory, verbal fluency, executive control, context processing, planning and visual attention tasks.**
Information processing task	

Frontal lobe

1 study, N = 23 Reduced activation of frontal lobe (*d* = 0.93) in medication naïve people with schizophrenia compared to controls during information processing tasks.
Working memory task
1 study, N = 22 Large effect size suggests reduced activation in the DLPFC (*d* = 1.0) and the VLPFC (*d* = 1.09) of medicated people with schizophrenia compared to controls during working memory tasks. 1 study, N = 18 Large effect size suggests reduced activation in the DLPFC (*d* = 1.29) of medication naïve people with first-episode schizophrenia compared to controls during working memory tasks. 1 study, N = 16 Large effect size suggests reduced activation of the DLPFC (*d* = 1.68) in people with first-episode schizophrenia compared to controls during working memory tasks.
Verbal fluency task
1 study, N = 20 Large effect size suggests reduced activation of the DLPFC (*d* = 2.57), VLPFC (*d* = 2.51) and anterior frontal cortex (*d* = 2.42) in people with first-episode schizophrenia compared to controls during verbal fluency tasks.
Executive control task
1 study, N = 47 Large effect size suggests reduced activation of the DLPFC (*d* = 0.88) in untreated people with first-episode schizophrenia compared to controls during executive control tasks.
Context processing task
1 study, N = 46 Large effect size suggests reduced activation of the DLPFC (*d* = 0.76) in untreated people with first-episode schizophrenia compared to controls during context processing tasks Large effect size suggests increased activation of the AFC (*d* = 0.74) and the VLPFC (*d* = 0.74) in untreated people with first-episode schizophrenia compared to controls during context processing tasks 1 study, N = 26 Large effect size suggests reduced activation of the DLPFC (*d* = 1.37) in untreated people with first-episode schizophrenia compared to controls during context processing tasks

Frontal lobe

Planning task	
1 study, N = 20 Large effect size suggests reduced activation of the DLPFC (*d* = 1.84), VLPFC (*d* = 1.84) and AFC (*d* = 1.33) in people with first-episode schizophrenia compared to controls during planning tasks	
Visual attention task	
1 study, N = 26 Large effect size suggests reduced activation of the DLPFC (*d* = 0.9) and the VLPFC (*d* = 0.74) in people with first-episode schizophrenia compared to controls during visual attention 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 relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Low quality evidence (one small study per outcome) is unclear as to the direction of the changes in functional activity in the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, medial frontal gyrus during verbal initiation, working memory, verbal memory, and emotional face processing tasks in individuals at high risk of developing schizophrenia.**
Verbal initiation task	
1 study, N = 63 Medium effect size suggests reduced activation of medial frontal gyrus (*d* = 0.5) in non-psychotic relatives of people with schizophrenia compared to controls during visual initiation tasks.	
Working memory task	

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

1 study, N = 41 Medium effect size suggests increased activation of the DLPFC (*d* = 0.60), VLPFC (*d* = 0.54) and inferior parietal lobe (*d* = 0.58) in siblings of people with schizophrenia compared to controls during working memory tasks. 1 study, N = 40 Small effect size suggests increased activation of the DLPFC (*d* = 0.42), and VLPFC (*d* = 0.43) and inferior parietal lobe (*d* = 0.48) in siblings of people with schizophrenia compared to controls during working memory tasks. 1 study, N = 24 Large effect size suggests increased activation of the DLPFC (*d* = 0.79) and anterior cingulate gyrus (*d* = 0.96) in non-psychotic relatives of people with schizophrenia compared to controls during working memory tasks. 1 study, N = 45 Large effect size suggests increased activation of the DLPFC (*d* = 1.0) in non-psychotic relatives of people with schizophrenia compared to controls during working memory tasks.	
Verbal memory task	
1 study, N = 70 Reduced cerebral perfusion during a verbal memory task in relatives of people with schizophrenia compared to controls, particularly in the inferior prefrontal cortex.	
Emotional face processing task	
1 study, N = 39 Medium effect size suggests reduced activation of the DLPFC (*d* = 0.51), and AFC (*d* = 0.47) in non-psychotic relatives of people with schizophrenia compared to controls during emotional face processing tasks.	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals reported
Directness of results	Direct
Comparison 3	**Metabolite levels (measured by ^{1}H-MRS) in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small samples, direct, unable to assess precision or consistency) suggests increased Glu/Gln ratio, reduced PME, and increased PDE in the frontal lobe of first-degree relatives of people with schizophrenia.**

Frontal lobe

Metabolite levels	
4 studies, N = 268 One study, N = 42, assessed Glu/Gln and reported increased Glu/Gln ratio in the DLPFC in relatives. Three studies, N = 116, assessed PME and PDE and reported reduced PME levels and reduced phospholipid synthesis in the frontal lobe of relatives who later developed schizophrenia. Increased PDE levels were found in relatives; disrupted membrane metabolism; increased phospholipid breakdown.	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Fusar-Poli, P

Voxel-wise meta-analysis of fMRI studies in patients at clinical high risk for psychosis

Journal of Psychiatry Neuroscience 2012; 37(2): 106-12

View review abstract online

Comparison	**Functional activation in people at clinical high risk for psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, direct, consistent, unable to assess precision) suggests reduced activation in the left inferior frontal gyrus and bilateral medial frontal gyrus in people at clinical high risk for psychosis.**
Functional activation	
10 studies, N = 345 *A consistent pattern of reduced activation was reported in people at clinical high risk in:* Left inferior frontal gyrus: Talairach coordinates -46, 16, 22, $p < 0.001$ Bilateral medial frontal gyrus: Talairach coordinates -4, 26, 44, $p < 0.001$ $Q = 11.258$, $p = 0.54$, $I^2 = 7.286$	

Frontal lobe

Consistency in results	Consistent
Precision in results	No confidence intervals are 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 activation in individuals with schizophrenia vs. controls**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized sample, direct, unable to assess precision or inconsistency) suggests people with schizophrenia have reduced functional activity in the frontal cortex during working memory tasks.**

N-back working memory tasks

ALE analysis – FWHM 10mm, False Discovery Rate (FDR) corrected model

4 studies, N = 134

Significantly reduced activity in people with schizophrenia compared to controls;

Right medial frontal gyrus: Talairach centre of mass (7, 44, -13), cluster volume 472mm^3

Right middle and inferior frontal gyrus: Talairach centre of mass (33, 37, 28), cluster volume 1200mm^3

Left middle frontal gyrus: Talairach centre of mass (-33, 35, 23), cluster volume 1736mm^3

Right inferior frontal gyrus and insula: Talairach centre of mass (38, 16, 5), cluster volume 936mm^3

Significantly increased activity in people with schizophrenia compared to controls

Left middle frontal gyrus: Talairach centre of mass (-44, 42, -3), cluster volume 560mm^3

Right superior frontal gyrus: Talairach centre of mass (4, 57, 26), cluster volume 264mm^3

Consistency in results	No confidence intervals are reported.
Precision in results	No measured of heterogeneity is 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 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 density 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 grey matter reductions in the middle frontal gyrus.**

Grey matter density

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

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

13 studies, N = 2,457

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

Left middle frontal gyrus: Talairach coordinates (-46, 10, 36), Voxel cluster size 432mm^3, $p < 0.01$, ALE = 0.011

Consistency in results	No measure of consistency 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	**Functional activation in relatives of people with schizophrenia vs. controls during an executive functioning task.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests relatives of people with schizophrenia show increased functional activation during an executive functioning task in the right superior and middle frontal gyri. Decreased activation in relatives compared to controls was shown in the right middle and inferior and left superior frontal gyri, right precentral gyrus, and left medial frontal gyrus. During cognitive control tasks, relatives showed activation increases in the left middle frontal gyrus compared to controls. During working memory tasks, relatives showed increased activation of the right middle frontal gyrus and decreased activation in the right middle and inferior frontal gyri, right precentral gyrus.**

Executive functioning task

All VBM studies, including those assessing voxel-based activation in *apriori* regions of interest, were included in this analysis.

17 studies, N = 456

Increased activity in relatives of people with schizophrenia compared to controls in;

Right middle frontal gyrus: Talairach coordinates (32, 50, 10), cluster volume 376 mm^3

Right superior frontal gyrus: Talairach coordinates (40, 36, 32), cluster volume 400 mm^3

Right middle frontal/precentral gyrus: Talairach coordinates (46/46/34, 16/24/12, 16/24/12), cluster volume 792 mm^3

Decreased activity in relatives of people with schizophrenia compared to controls in;

Right middle frontal gyrus: Talairach coordinates (32, 52, 10), cluster volume 424 mm^3

Right middle frontal gyrus: Talairach coordinates (38, 36, 34), cluster volume 1008 mm^3

Right inferior frontal gyrus: Talairach coordinates (52/54, 8/8, 18/24), cluster volume 192 mm^3

Right precentral gyrus: Talairach coordinates (40, -6, 42), cluster volume 152 mm^3

Right precentral gyrus: Talairach coordinates (50, -4, 22), cluster volume 144 mm^3

Subgroup analysis: only those studies that assessed *whole-brain* voxel-based activation

Frontal lobe

Increased activity in relatives of people with schizophrenia compared to controls in; Right middle frontal gyrus: Talairach coordinates (32, 50, 10), cluster volume 480 mm^3 Right middle frontal/ precentral gyrus: Talairach coordinates (48/46, 16/24, 32/36), cluster volume 176 mm^3 *Decreased activity in relatives of people with schizophrenia compared to controls in;* Left medial frontal gyrus: Talairach coordinates (-12, 64, -2), cluster volume 136 mm^3 Right middle frontal gyrus: Talairach coordinates (36, 28, 42), cluster volume 120 mm^3 Right precentral gyrus: Talairach coordinates (50, -4, 22), cluster volume 200 mm^3 Right precentral gyrus: Talairach coordinates (40, -6, 42), cluster volume 200 mm^3	
Cognitive control task	
Increased activity in relatives of people with schizophrenia compared to controls in; Left middle/ superior frontal gyrus: Talairach coordinates (-28/-26, 48/50, 20/12), cluster volume 168 mm^3	
Working memory task	
Increased activity in relatives of people with schizophrenia compared to controls in; Right middle frontal gyrus: Talairach coordinates (32, 50, 10), cluster volume 480 mm^3 Right middle frontal/ precentral gyrus: Talairach coordinates (48/46, 16/24, 32/36), cluster volume 176 mm^3 *Decreased activity in relatives of people with schizophrenia compared to controls in;* Right middle frontal gyrus: Talairach coordinates (38, 36, 34), cluster volume 1008 mm^3 Right inferior frontal gyrus: Talairach coordinates (52/54, 8/8, 18/24), cluster volume 176 mm^3 Right precentral gyrus: Talairach coordinates (40, -6, 42), cluster volume 168 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

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Frontal lobe

Schizophrenia Bulletin 2012; 39(5): 1129-1138 View review abstract online	
Comparison	**Whole brain comparison of grey and white matter volume in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large samples, precise, mostly inconsistent, direct) suggests schizophrenia is associated with significant reductions in grey and white matter volume of the frontal lobe.**
Grey and white matter density	
Decreased in medicated patients; Frontal lobe grey matter: 17 studies, N = 1,288, *d* = -0.49, 95%CI -0.64 to -0.34, $p < 1 \times 10{-}9$, Q = 26.3, *p* = 0.050, I^2 = 39% Prefrontal grey matter: 16 studies, N = 1,263, *d* = -0.44, 95%CI -0.58 to -0.31, $p < 1 \times 10{-}9$, Q = 17.9, *p* = 0.27, I^2 = 16% Prefrontal white matter: 12 studies, N = 965, *d* = -0.29, 95%CI -0.42 to -0.16, $p = 1.0 \times 10{-}5$, Q = 6.4, *p* = 0.85, I^2 = 0% Inferior frontal gyrus: 10 studies, N = 657, *d* = -0.41, 95%CI -0.56 to -0.25, $p = 2.9 \times 10{-}7$, Q = 6.8, *p* = 0.66, I^2 = 0% Orbitofrontal cortex: 19 studies, N = 1,141, *d* = -0.21, 95%CI -0.37 to -0.05, *p* = 0.010, Q = 29.7, *p* = 0.040, I^2 = 39%	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Haszto CS, Stanley JA, Iyengar S, Prasad KM

Regionally Distinct Alterations in Membrane Phospholipid Metabolism in Schizophrenia: A Meta-analysis of Phosphorus Magnetic Resonance Spectroscopy Studies

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 2019; 5: 264–80

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

Frontal lobe

View review abstract online	
Comparison	**Frontal PME and PDE levels measured by ^{1}H-MRS in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, some imprecision, direct, some publication bias) finds a medium-sized decrease in PME in the frontal lobe people with schizophrenia. There were no differences in frontal PDE levels.**
PME and PDE	
A significant, medium-sized effect of lower PME levels in the frontal regions of people with schizophrenia; 10 studies, N = 744, *g* = -0.54, 95%CI -1.05 to -0.03, *p* = 0.0038, I^2 = 92% Authors report possible publication bias. *There were no differences in PDE levels;* 17 studies, N = 792, *g* = 0.23, 95%CI -0.06 to 0.53, *p* = 0.12, I^2 = 79% Authors report possible publication bias.	
Consistency in results	Inconsistent
Precision in results	Precise, apart from PME.
Directness of results	Direct

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

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

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

View review abstract online

Comparison	**Association between long-term antipsychotic dose and changes in brain regions over time (>2 years) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent,**

	precise, direct) found no association between antipsychotic dose and changes in frontal lobe volume over time.
Longitudinal changes in volume	
There were no associations between long-term antipsychotic use and changes in the; Frontal lobe: 7 studies, N = 500, r = -0.14, 95%CI -0.34 to 0.05, p = 0.15, I^2 = 71%	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Hill K, Mann L, Laws KR, Stephenson CM, Nimmo-Smith I, McKenna PJ, Stephenson CME

Hypofrontality in schizophrenia: a meta-analysis of functional imaging studies

Acta Psychiatrica Scandinavica 2004; 110(4): 243-56

View review abstract online

Comparison	**Whole brain functional activation in people with schizophrenia vs. controls: voxel-based comparison.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests no difference in frontal or non-frontal lobe functional activity during neurocognitive tasks between people with schizophrenia and controls.**
Neurocognitive tasks; working memory, executive function, vigilance tasks combined	
Frontal lobe activity 14 observational studies, N = 319 *No significant difference observed in frontal lobe activity;* Kolmogorov-Smirnov test (KS3) = 0.16, p = 0.94	
Non-frontal lobe 14 observational studies, N = 319	

No significant difference observed in non-frontal lobe activity; KS3 = 0.14, *p* = 0.98	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Honea R, Crow TJ, Passingham D, Mackay CE

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

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

View review abstract online

Comparison	**Grey matter density 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 the grey matter density of the inferior and medial frontal lobe.**
Grey matter density	
15 studies, N = 754, varying FWHM smoothing kernel (range 4-12mm) *Regions showing reduced grey matter density in people with schizophrenia;* Left inferior frontal gyrus: reduced in around 50% of studies Left medial frontal gyrus: reduced in around 50% of studies	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Iwata Y, Nakajima S, Plitman E, Mihashi Y, Caravaggio F, Chung JK, Kim J, Gerretsen P, Mimura M, Remington G, Graff-Guerrero A

Neurometabolite levels in antipsychotic-naive/free patients with schizophrenia: A systematic review and meta-analysis of ^{1}H-MRS studies

Progress in Neuro-Psychopharmacology & Biological Psychiatry 2018; 86: 340-52

View review abstract online

Comparison	**Neurometabolite levels measured by ^{1}H-MRS in unmedicated people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (small to medium-sized samples, consistent, precise, direct) finds unmedicated people with schizophrenia have a medium-sized decrease in N-acetylaspartate (NAA) in frontal white matter (using <3T MRI scanners only), and a medium-sized increase in glutamate+glutamine (Glx) in the medial prefrontal cortex. There were no differences in glutamate or creatine.**

NAA

Significant, medium-sized decrease in NAA in frontal white matter in unmedicated people with schizophrenia;

Studies using <3T MRI scanners: 3 studies, N = 167, SMD = -0.63, 95%CI -0.95 to -0.31, p = 0.0001, I^2 = 0%, p = 0.79

There were no significant differences in NAA in the medial prefrontal cortex or dorsolateral prefrontal cortex.

Glx

A significant, medium-sized increase in Glx in the medial prefrontal cortex of unmedicated people with schizophrenia;

3 studies, N = 99, SMD = 0.47, 95%CI 0.06 to 0.88, p = 0.03, I^2 = 0%, p = 0.60

There were no significant differences in Glx levels the dorsolateral prefrontal cortex or medial temporal lobe.

There was no significant difference in glutamate levels in the medial prefrontal cortex;

3 studies, N =136, SMD = -0.02, 95%CI -0.36 to 0.39, p = 0.89, I^2 = 0%, p = 0.52

Creatine

There was no significant difference in creatine levels in the medial prefrontal cortex;

3 studies, N = 344, SMD = 0.16, 95%CI -0.24 to 0.57, p = 0.43, I^2 = 51%, p = 0.10

There was no significant difference in creatine in the dorsolateral prefrontal cortex.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Kanaan RA, Kim JS, Kaufmann WE, Pearlson GD, Barker GJ, McGuire PK

Diffusion tensor imaging in schizophrenia

Biological Psychiatry 2005; 58(12): 921-929

View review abstract online

Comparison	**White matter fractional anisotropy (FA) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision and consistency) suggests decreased FA in the frontal lobe of people with schizophrenia.**
FA	
19 studies, N = 640 Frontal lobe illustrated decreased FA in at least one study between people with schizophrenia and controls.	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
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

Frontal lobe

Neuropsychologia 2011; 49: 3361-9 View review abstract online	
Comparison	**Functional activation in people with schizophrenia during auditory verbal hallucinations and during auditory stimulation tasks.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, direct, unable to assess precision or consistency) suggests increased activation during auditory hallucinations in the inferior and superior frontal gyri, and decreased activation during auditory tasks in the superior frontal gyrus of people with schizophrenia.**
During hallucinations (endogenously evoked)	
12 studies, N = 103, showed increased activation during hallucinations in; Inferior frontal gyrus: (40 12 16) 408mm^3 Superior frontal gyrus: (26 42 26) 240mm^3	
Auditory tasks	
11 studies, N = 384, showed reduced activation during auditory stimulation tasks in people with schizophrenia; Superior frontal gyrus: (24 50 14) 456mm^3	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Kraguljac NV, Reid M, White D, Jones R, den Hollander J, Lowman D, Lahti AC

Neurometabolites in schizophrenia and bipolar disorder – a systematic review and meta-analysis

Psychiatry Research: Neuroimaging 2012. 203: 111-25

View review abstract online

Comparison	**Whole brain comparison of metabolite levels (measured by ^{1}H-**

	MRS) in people with schizophrenia vs. healthy controls.
Summary of evidence	**Moderate to high quality evidence (unclear sample sizes, consistent, precise, direct) suggests reduced NAA and NAA/Cr levels in the frontal lobe, but not in the DLPFC, of people with schizophrenia. There were no differences in Cr, Cho, or Cho/Cr levels.**
NAA/Cr or Cho/Cr	
Frontal lobe *Significant medium-sized reduction in NAA absolute levels;* 11 studies, d = -0.44, 95%CI -0.65 to -0.23, $p < 0.001$, I^2 = 5% *Significant, small reduction in NAA/Cr ratio;* 16 studies, d = -0.22, 95%CI -0.39 to -0.06, $p < 0.01$, I^2 = 0% *There were no differences in;* Cr levels: 10 studies, d = 0.06, 95%CI -0.16 to 0.28, p = 0.58, I^2 = 11% Cho levels: 10 studies, d = -0.06, 95%CI -0.27 to 0.15, p = 0.57, I^2 = 0% Cho/Cr ratio: 13 studies, d = 0.09, 95%CI -0.24 to 0.41, p = 0.61, I^2 = 68% DLPFC *There were no significant differences in:* NAA levels: 6 studies, d = -0.46, 95%CI -1.09 to 0.17, p = 0.15, I^2 = 85% Cr levels: 6 studies, d = -0.13, 95%CI -0.10 to 0.36, p = 0.26, I^2 = 0% Cho levels: 6 studies, d = 0.15, 95%CI -0.44 to 0.74, p = 0.62, I^2 = 84% NAA/Cr ratio: 3 studies, d = 0.14, 95%CI -0.72 to 1.00, p = 0.75, I^2 = 86% Cho/Cr ratio: 2 studies, d = -0.15 95%CI -0.73 to 0.42, p = 0.60, I^2 = 58%	
Consistency in results	Consistent, apart from DLPFC; NAA, Cho, NAA/Cr and Cho/Cr.
Precision in results	Precise, apart from most DLPFC data.
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

View review abstract online

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) suggests decreased activation in the medial prefrontal cortex (frontal medial and paracingulate) and left orbito-frontal cortex of people with schizophrenia during theory of mind tasks.**
Functional activity	
21 studies, N = 623 *Decreased activation in;* Medial prefrontal cortex (frontal medial and paracingulate): 1,573 voxels, MNI coordinates -2, 52, 18 Left orbito-frontal cortex: 30 voxels, MNI coordinates -30, 22, -24	
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

Kyriakopoulos M, Bargiotas T, Barker GJ, Frangou S

Diffusion tensor imaging in schizophrenia

European Psychiatry: the Journal of the Association of European Psychiatrists 2008; 23(4): 255-273

View review abstract online

Comparison	**White matter integrity, assessed by voxel-based analysis, in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess precision or consistency) suggests reduced FA in the prefrontal cortex.**

Frontal lobe

FA	
15 studies, N = unclear *Regions that illustrated decreased FA in at least one study between people with schizophrenia and controls:* Prefrontal cortex (12 studies); Internal capsule (4 studies); Arcuate fasciculus (5 studies)	
Consistency in results	No measure of consistency 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

View review abstract online

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 left middle frontal gyrus of people with schizophrenia during reward anticipation.**
Functional activation	
11 studies, N = 488 *Schizophrenia was characterised by;* Reduced activation in the left middle frontal gyrus.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	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

View review abstract online

Comparison	**Grey matter changes in first episode schizophrenia (treated and medication naïve) vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests greater reduction in treatment naïve first-episode schizophrenia in the precentral, superior frontal gyrus, middle and right inferior frontal gyri compared to treated first episode patients. Greater reductions in treated first-episode patients were observed in bilateral medial and inferior, and left middle frontal gyri, and right precentral gyrus compared to treatment-naive patients.**

Grey matter density

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

FWHM 8mm, FDR corrected at p <0.05

Areas of reduced activity in treatment naïve first-episode patients vs. controls;

6 studies, N = 327

Left precentral gyrus: Talairach coordinates (-50, -10, 24), cluster 440mm^3, ALE 0.0027

Left superior frontal gyrus: Talairach coordinates (-8, 66, 10), cluster 320mm^3, ALE 0.0021

Right middle frontal gyrus: Talairach coordinates (22, 38, -14), cluster 760mm^3, ALE 0.0036

Right inferior frontal gyrus Talairach coordinates (46, 12, 16), cluster 288mm^3, ALE 0.0017

Right inferior frontal gyrus: Talairach coordinates (46, 20, 18), cluster 288mm^3, ALE 0.0017

Areas of reduced density in treated first-episode patients vs. controls;

9 studies, N = 820

Right precentral gyrus: Talairach coordinates (48, -10, 12), cluster 520mm^3, ALE 0.0082

Right medial frontal gyrus: Talairach coordinates (2, 36, -16), cluster 480mm^3, ALE 0.0078

Left medial frontal gyrus (to anterior cingulate): Talairach coordinates (-6, 48, 8), cluster 928mm^3, ALE

0.0057 Left medial frontal gyrus (to anterior cingulate): Talairach coordinates (-2, 36, -2), cluster 928mm^3, ALE 0.0044 Right middle frontal gyrus: Talairach coordinates (44, 36, 18), cluster 304mm^3, ALE 0.0059 Right inferior frontal gyrus: Talairach coordinates (24, 34, -8), cluster 832mm^3, ALE 0.0115 Left inferior frontal gyrus: Talairach coordinates (-32, 34, -4), cluster 528mm^3, ALE 0.0080 *Areas where grey matter reductions were larger in magnitude in treatment-naïve patients than in treated patients;* Left precentral gyrus: Talairach coordinates (-50, -10, 24), cluster 400mm^3, ALE 0.0133 Left superior frontal gyrus: Talairach coordinates (-8, 66, 10), cluster 320mm^3, ALE 0.0105 Right middle frontal gyrus: Talairach coordinates (22, 38, -14), cluster 568mm^3, ALE 0.0172 Right middle frontal gyrus (to inferior frontal): Talairach coordinates (46, 20, 18), cluster 256mm^3, ALE 0.0085 Right middle frontal gyrus (to inferior frontal): Talairach coordinates (46, 12, 16), cluster 256mm^3, ALE 0.0087 Right inferior frontal gyrus (to uncus): Talairach coordinates (22, 14, -14), cluster 296mm^3, ALE 0.0076 Right inferior frontal gyrus (to uncus): Talairach coordinates (28, 8, -20), cluster 296mm^3, ALE 0.0103 *Regions where grey matter reductions were larger in magnitude in treated patients than treatment-naïve patients;* Right precentral gyrus: Talairach coordinates (48, -10, 12), cluster 432mm^3, ALE 0.0143 Left medial frontal gyrus (to anterior cingulate): Talairach coordinates (-6, 48, 8), cluster 632mm^3, ALE 0.0098 Left medial frontal gyrus (to anterior cingulate): Talairach coordinates (-2, 36, -2), cluster 360mm^3, ALE 0.0077 Right medial frontal gyrus: Talairach coordinates (2, 36, -16), cluster 384mm^3, ALE 0.0135 Right middle frontal gyrus: Talairach coordinates (44, 36, 18), cluster 280mm^3, ALE 0.0112 Right inferior frontal gyrus: Talairach coordinates (24, 34, -6), cluster 512mm^3, ALE 0.0185 Left inferior frontal gyrus: Talairach coordinates (-32, 34, -4), cluster 488mm^3, ALE 0.0151	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Frontal lobe

Li H, Chan R, McAlonan G, Gong QY

Facial emotion processing in schizophrenia: A meta-analysis of functional neuroimaging data

Schizophrenia Bulletin 2010; 36(5): 1029-1039

View review abstract online

Comparison	**Functional activation during facial emotion processing in 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 during emotion processing tasks in the superior frontal gyrus of people with schizophrenia.**
Facial emotion processing task	
13 studies, N = unclear *Decreased activation during an implicit emotional task in people with schizophrenia;* Right superior frontal gyrus: Talairach coordinates (10, 22, 50), 3 foci, 312mm^3, 0.051 ALE	
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	**Grey matter volume in people with persistent negative symptoms of schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct,**

	unable to assess consistency or precision) suggests schizophrenia patients with persistent negative symptoms show significant reductions in bilateral medial frontal gyrus (Brodmann area [BA] 9/11/10), with most reductions apparent in the left hemisphere.
Grey matter volume	
12 studies, N = unclear *There was significantly reduced grey matter volume in;* Left medial frontal gyrus (BA 9): Talairach coordinates (-50, 16, 30) Left medial frontal gyrus (BA 11): Talairach coordinates (4, 36, -14) Left medial frontal gyrus (BA 11): Talairach coordinates (-2, 36, -14) Left medial frontal gyrus (BA 11): Talairach coordinates (-8, 36, -14) Left medial frontal gyrus (BA 10): Talairach coordinates (8, 50, 10) Left medial frontal gyrus (BA 10): Talairach coordinates (-6, -54, -12) Right medial frontal gyrus (BA 10): Talairach coordinates (22, 52, 14)	
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

Marsman A, van den Heuvel MP, Klomp DWJ, Kahn RS, Luijten PR, Hulshoff Pol HE

Glutamate in schizophrenia: a focused review and meta-analysis of ^{1}H-MRS studies

Schizophrenia Bulletin 2013; 39(1): 120-9

View review abstract online

Comparison	**Glutamate, glutamine and N-acetylaspartate in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, direct, unable to assess precision or consistency) suggests reduced Glu and increased Gln levels in the frontal cortex of people with schizophrenia, with greater reductions associated**

	with age.
Glu, Gln and NAA	
Medial frontal cortex *A significant, small reduction in glutamate level in people with schizophrenia;* 9 studies, N = 337, *d* = -0.391, *p* = 0.006 Meta-regression showed a progressive decrease with age in patients compared to controls (*p* = 0.008). *A significant, medium-sized increase in glutamine in people with schizophrenia;* 8 studies, N = 275, *d* = 0.403, *p* = 0.045 Meta-regression showed a progressive decrease with age in patients compared to controls (*p* = 0.0005). *No significant difference in total glutamate + glutamine levels between patients and controls;* 8 studies, N = 330, *d* = 0.122, *p* = 0.393 *No significant difference in glutamate/glutamine ratio levels between patients and controls;* 6 studies, N = 228, *d* = 0.308, *p* = 0.062 Meta-regression showed a progressive decrease with age in patients compared to controls (*p* = 0.02). *A significant, small reduction in NAA levels in people with schizophrenia;* 19 studies, N = 779, *d* = -0.320, *p* = 0.019 Meta-regression showed a progressive decrease with age in patients compared to controls (*p* = 0.04). *A significant, small reduction in NAA/glutamate ratio in people with schizophrenia;* 7 studies, N = 247, *d* = -0.357, *p* = 0.038 Meta-regression showed a progressive decrease with age in patients compared to controls (*p* = 0.049).	
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, M.J., Laird, A.R., Thelen S., Carter, C.S., Glahn, D.C.

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

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Frontal lobe

Archives of General Psychiatry, 2009. 66(8): p. 811-822 View review abstract online	
Comparison 1	**Whole brain comparison of functional activation in individuals with schizophrenia vs. controls: ALE analysis** **Note – this review combines PET and fMRI studies in one meta-analysis**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests patients with schizophrenia show reduced activity in the middle and medial frontal gyri during executive function tasks. People with schizophrenia also show regions of increased activity in the superior and inferior frontal gyri during executive function tasks.**
Executive function tasks	
41 studies, N = 1,217 ALE analysis – FWHM 12mm, False Discovery Rate (FDR) corrected model *Significantly reduced activity in people with schizophrenia compared to controls;* Left middle frontal gyrus: Talairach centre of mass (-38, 30, 30), cluster volume 3096mm^3 Right middle frontal gyrus: Talairach centre of mass (32, 24, 42), cluster volume 712mm^3 Right medial frontal gyrus: Talairach centre of mass (6, 42, 18), cluster volume 1480mm^3 *Significantly increased activity in people with schizophrenia compared to controls;* Left superior frontal gyrus: Talairach centre of mass (-8, -14, 68), cluster volume 440mm^3 Left superior frontal gyrus: Talairach centre of mass (-2, 52, 24), cluster volume 1320mm^3 Left inferior frontal gyrus: Talairach centre of mass (-40, 36, 12), cluster volume 656mm^3	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Mondino M, Brunelin J, Saoud M

N-acetyl-aspartate level is decreased in the prefrontal cortex in subjects at-risk for schizophrenia

Frontal lobe

Frontiers in Psychiatry 2013; 4: 99 View review abstract online	
Comparison	**Comparison of NAA/Cr ratio (measured by ^{1}H-MRS) in the prefrontal cortex of people at risk of schizophrenia vs. age and sex matched controls.** **Clinical high-risk subjects were people who developed a brief psychotic episode (<7 days) resolved without any intervention or people who exhibited schizotypal traits, i.e., subthreshold non-clinical psychotic symptoms. Genetic high-risk subjects were first or second-degree relatives of patients with schizophrenia, frequently unaffected siblings of patients.**
Summary of evidence	**Moderate to high quality evidence (large sample, direct, inconsistent, precise) suggests NAA/Cr ratio is reduced in the prefrontal cortex of people at clinical or familial high risk of schizophrenia.**
NAA/Cr	
NAA/Cr was significantly lower in the high-risk group; 9 studies, N = 442, *d* = -0.42, 95%CI -0.61 to -0.23, *p* < 0.0001 In the subgroup analysis of age, the effect size was larger in studies with younger samples than in studies with older samples (<40 years, *d* = -0.82, >40 years *d* = 0.11 [NS]).	
Consistency in results	I^2 is not reported. Forest plot appears inconsistent, most likely due to differences in age.
Precision in results	Precise
Directness of results	Direct

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

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

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

View review abstract online

Frontal lobe

Comparison	**Functional alteration during rest in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, direct, unable to assess consistency or precision) suggests relatives had decreased resting-state brain activity in the right inferior frontal gyrus compared to controls.**
Functional alterations	
3 studies, N = 214 *Compared to controls, relatives had decreased brain activity in;* Right inferior frontal gyrus: 947 voxels, MNI coordinates 42, 34, 26, p = 0.00023	
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

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 grey matter volume in schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests significantly greater reductions over time in frontal grey and white matter in people with schizophrenia compared to controls.**
Grey matter volume	
Progressive changes in grey matter volume reported across longitudinal MRI scans over 1-10 years. 31 studies, N = 1,867	

Significantly greater reductions were reported over time in schizophrenia compared to controls; Frontal GM: N = 503, 9 studies, *d* = -0.340, 95%CI -0.66 to -0.02, *p* = 0.035, I^2 = 59.8% Frontal WM: N = 323, 5 studies, *d* = -0.512, 95%CI -0.76 to -0.26, *p* = 0.0001, I^2 = 0%

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

Plaven-Sigray P, Matheson GJ, Collste K, Ashok AH, Coughlin JM, Howes OD, Mizrahi R, Pomper MG, Rusjan P, Veronese M, Wang Y, Cervenka S

Positron Emission Tomography Studies of the Glial Cell Marker Translocator Protein in Patients With Psychosis: A Meta-analysis Using Individual Participant Data

Biological Psychiatry 2018; 84: 433-42

View review abstract online

Comparison	**Translocator protein (measured by PET) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (small sample, consistent, imprecise, direct) finds reduced translocator protein in the frontal cortex of people with schizophrenia.**

Translocator protein
A significant decrease in translocator protein in people with schizophrenia; 5 studies, N = 152 Frontal cortex: total distribution volume = -0.48, 95%CredInt -0.88 to -0.08, *p* < 0.05 There were no moderating effects of medication (drug free vs. medicated).

Consistency in results	Authors report results were consistent.
Precision in results	Appears imprecise.
Directness of results	Direct

Frontal lobe

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

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

Neuroscience and Biobehavioural Reviews 2012; 36: 2325-2333

View review abstract online

Comparison	**Overlap between regions of functional and structural alteration in people with first-episode psychosis vs. controls**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests decreased grey matter volume and decreased functional activation in the right medial frontal/anterior cingulate cortex, and decreased grey matter volume and increased functional activation in the left medial frontal/anterior cingulate cortex of people with first-episode psychosis, with greater severity of abnormality in medicated patients.**

Regions of overlap

Analysis of 25 structural MRI studies (N = 2,005) and 18 functional MRI studies (N = 765) found regions with both structural and functional alteration in people with first-episode psychosis;

Decreased grey matter volume and decreased functional activation;

Right medial frontal/anterior cingulate

Talairach coordinates 4, 22, 30, cluster volume 644mm^2, $p < 0.0001$

Decreased grey matter volume and increased functional activation;

Left medial frontal/anterior cingulate

Talairach coordinates -14, 40, 10, cluster volume 117mm^2, $p = 0.0001$

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 heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

NeuRA Discover. Conquer. Cure. SCHIZOPHRENIA LIBRARY

Frontal lobe

Ragland JD, Laird AR, Ranganath C, Blumenfeld RS, Gonzales SM, Glahn DC

Prefrontal activation deficits during episodic memory in schizophrenia

American Journal of Psychiatry 2009; 166(8): 863-874

View review abstract online

Comparison	**Functional activation during episodic memory tasks in individuals with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess precision or consistency) suggests functional activity during episodic encoding is reduced in the right superior frontal gyrus and bilateral inferior frontal gyri and increased in the left precentral gyrus of people with schizophrenia compared to controls. Functional activity during episodic retrieval is reduced in the left inferior frontal gyrus and left middle frontal gyrus and increased in the left precentral gyrus and right middle frontal gyrus of people with schizophrenia compared to controls.**

Episodic encoding task

Seven studies contributing 40 foci investigated functional activity during episodic encoding tasks.

ALE analysis – FWHM 12mm, False Discovery Rate (FDR) corrected model $p < 0.05$

Significantly greater activity in controls compared to people with schizophrenia;

Right superior frontal gyrus: cluster volume 4608mm^3, Talairach centre of mass (22, 48, 14)

Right superior frontal gyrus: cluster volume 1104mm^3, Talairach centre of mass (6, 36, 48)

Right inferior frontal gyrus: cluster volume 2760mm^3, Talairach centre of mass (40, 30, 12)

Left inferior frontal gyrus: cluster volume 1424mm^3, Talairach centre of mass (-36, 26, 12)

Four studies contributing 20 foci investigated functional activity during episodic encoding tasks.

ALE analysis – FWHM 12mm, False Discovery Rate (FDR) corrected model $p < 0.05$

Significantly increased activity in people with schizophrenia compared to controls;

Left precentral gyrus: cluster volume 2704mm^3, Talairach centre of mass (-46, -8, 40)

Left post-central gyrus: cluster volume 344mm^3, Talairach centre of mass (-44, -28, 36)

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

Frontal lobe

Episodic retrieval task	
Ten studies contributing 76 foci investigated functional activity during episodic retrieval tasks. ALE analysis – FWHM 12mm, False Discovery Rate (FDR) corrected model $p < 0.05$ *Significantly greater activity in controls compared to people with schizophrenia;* Left inferior frontal gyrus: cluster volume 3048mm^3, Talairach centre of mass (-40, 22, 20) Left precentral gyrus: cluster volume 1064mm^3, Talairach centre of mass (-36, -2, 28) Left middle frontal gyrus: cluster volume 888mm^3, Talairach centre of mass (-38, 32, 38) Subgroup analysis Seven of ten studies (63 foci) controlled for group performance differences. ALE analysis excluding those studies which did not control for performance differences, all foci showed similar activation patterns except the left precentral was not activated. Six studies contributing 26 foci investigated functional activity during episodic retrieval tasks. ALE analysis – FWHM 12mm, False Discovery Rate (FDR) corrected model $p < 0.05$ *Significantly greater activity in people with schizophrenia compared to controls;* Left precentral gyrus: cluster volume 1296mm^3, Talairach centre of mass (-28, -26, 66) Right medial frontal gyrus: cluster volume 1168mm^3, Talairach centre of mass (12, 44, 10) Right middle frontal gyrus: cluster volume 600mm^3, Talairach centre of mass (34, 36, -16) Subgroup analysis Four of six studies (21 foci) controlled for group performance differences. ALE analysis excluding those studies which did not control for performance differences, all foci showed similar activation patterns except the right medial frontal gyrus was not activated.	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
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

Frontal lobe

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 left middle frontal gyrus, left inferior frontal gyrus, left superior frontal gyrus, and medial frontal gyrus following cognitive remediation.**
Changes in activation	
9 studies, N = 128 *The following clusters showed increases in activation after cognitive remediation;* Left middle frontal gyrus, left precentral gyrus: Talairach coordinates -40, -8, 40, 624mm^3 Left inferior frontal gyrus, left insular cortex, left precentral gyrus: Talairach coordinates -44, 6, 24, cluster volume 496mm^3 Left superior frontal gyrus, left middle frontal gyrus: Talairach coordinates -28, 52, 6, cluster volume 264mm^3 Left medial frontal gyrus: Talairach coordinates -6, -8, 68, cluster volume 248mm^3	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Saarinen AIL, Huhtaniska S, Pudas J, Bjornholm L, Jukuri T, Tohka J, Grano N, Barnett JH, Kiviniemi V, Veijola J, Hintsanen M, Lieslehto J

Structural and functional alterations in the brain gray matter among first-degree relatives of schizophrenia patients: A multimodal meta-analysis of fMRI and VBM studies

Schizophrenia Research 2020; Jan: doi.org/10.1016/j.schres.2019.12.023

View review abstract online

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

Frontal lobe

Comparison	**Functional activation in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, direct, unable to assess precision) suggests increased activation in the right inferior frontal gyrus during cognitive tasks.**
Cognitive tasks	
Relatives showed increased activation in the right inferior frontal gyrus; MNI co-ordinates 46, 12, 32, p = 0.000001967, 616 voxels, I^2 = 0%	
Consistency in results	Consistent
Precision in results	No confidence intervals are provided.
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 and Cr activity (measured by ^{1}H-MRS) in the frontal lobes of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests NAA levels are reduced in the frontal lobe, particularly the DLPFC and frontal pole in people with schizophrenia compared to controls.**
NAA	

Frontal lobe

Frontal lobe 18/26 studies (N = 781/1,127) show decreased NAA in people with schizophrenia. 8/26 studies (N = 346/1,127) show no significant difference in NAA levels. DLPFC 8/12 studies (N = 346/586) show decreased NAA in people with schizophrenia. Frontal pole 6/9 studies (N = 252/388) show decreased NAA in people with schizophrenia.

Consistency in results	No measure of heterogeneity is reported.
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 quality evidence (large sample, direct, unable to assess consistency or precision) found increased activation in relatives in the right inferior frontal gyrus during cognitive tasks. During emotion tasks, there was increased activation in the right superior frontal gyrus and decreased activation in the left medial frontal gyrus and right inferior frontal gyrus of relatives.**

Cognitive and emotion tasks
Cognitive and emotion tasks combined 21 studies, N = 1,245 *The following areas showed increased activation in relatives compared to controls;* Right inferior frontal gyrus (BA44): Talairach coordinates 52, 10, 20, $p < 0.001$

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

Cognitive tasks 17 studies *The following areas showed increased activation in relatives compared to controls;* Right inferior frontal gyrus (BA45): Talairach coordinates 54, 12, 20, $p < 0.001$ Emotion tasks: 4 studies *The following areas showed increased activation in relatives compared to controls;* Right superior frontal gyrus (BA9): Talairach coordinates 12, 46, 26, $p < 0.01$ *The following areas showed increased activation in controls compared to relatives;* Left medial frontal gyrus (BA6): Talairach coordinates -2, -20, 62, $p < 0.01$ Right inferior frontal gyrus (BA47): Talairach coordinates 52, 28, -12, $p < 0.01$

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

View review abstract online

Comparison	**Grey matter changes in first-episode schizophrenia (treated and medication naïve) vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests decreased right superior frontal gyrus grey matter in medication-naïve patients and increased right superior frontal gyrus grey matter in treated patients compared to controls.**
Grey matter changes in medication naïve first-episode patients	

13 studies, N = 522 *Grey matter decreases were found in patients in;* Right superior frontal gyrus: 454 voxels, MNI coordinates (2, 46, -2), *p* = 0.001367629	
Grey matter changes in treated first-episode patients	
11 studies, N = 836 *Grey matter increases were found in patients in;* Right superior frontal gyrus: 277 voxels, MNI coordinates (20, -10, 66), *p* = 0.00067091	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Sommer I Aleman A, Ramsey N, Bouma A

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

British Journal of Psychiatry 2001; 178: 344-351

View review abstract online

Comparison	**Differences in anatomical asymmetry in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium to large samples, inconsistent, precise, direct) suggest people with schizophrenia show an absence of normal leftward asymmetry in the Sylvian fissure. There was also a higher frequency of abnormal (reversed) asymmetry in the frontal lobe in people with schizophrenia compared to controls.**
Anatomical asymmetry	

Frontal lobe

Significantly higher frequency of absent or reversed frontal lobe asymmetry in people with schizophrenia compared to controls;

3 studies, N = 383, weighted difference rate = 0.24, 95%CI 0.15 to 0.34, $p = 0.05$, Q = 8.4, $p = 0.05$

Significantly less asymmetry of the Sylvian fissure in people with schizophrenia compared to controls;

3 studies, N = 185, $d = -0.62$, 95%CI -1.04 to 0.20, $p < 0.01$, Q = 11.1, $p = 0.03$

Consistency in results	Inconsistent
Precision in results	Precise
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

View review abstract online

Comparison	**NAA activity (measured by ^{1}H-MRS) in grey and white matter in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (unclear sample size, precise, direct, inconsistent) suggests people with schizophrenia have NAA reductions in both grey and white matter in the frontal lobe when compared to controls.**

NAA

All patients grey matter

25 studies consider NAA, N unclear

Patient average 94.2% of control levels

16 studies consider NAA, N = 848

Patient NAA < Control NAA; $p < 0.0001$

Patient average frontal cortex 93.6% of control levels, SD = 11.3

Least squares (LS) mean difference NAA level in patients = 4.12U, 95%CI 4.03 to 4.21 LS mean difference NAA level in controls = 4.31U, 95%CI 4.23 to 4.39 LS ratio = 95.6% <u>All patients white matter</u> 18 studies consider NAA, N unclear Patient average 94.8% of control levels 24 studies consider NAA, N = 518 Patient NAA < Control NAA, $p < 0.0001$ Patient average frontal cortex 93.5% of control levels, SD = 6.2 Least squares (LS) mean difference NAA in patients = 5.98U, 95%CI 5.79 to 6.16 LS mean difference NAA level in controls = 6.48U, 95%CI 6.30 to 6.66 LS ratio = 92.3% <u>First-episode psychosis</u> 4 studies consider NAA, N = 146 Patient average 82.3% of control levels, SD = 17.8 <u>Chronic patients</u> 8 studies consider NAA, N = 333 Chronic patient average 90.1% of control levels, SD = 5.4

Consistency in results	Significant heterogeneity reported, $p < 0.0001$.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Van Snellenberg JX, Torres IJ, Thornton AE

Functional neuroimaging of working memory in schizophrenia: task performance as a moderating variable

Neuropsychology 2006; 20(5): 497-510

View review abstract online

Comparison	**DLPFC activation during working memory tasks in people with schizophrenia vs. controls.**

	Note – this review combines PET and fMRI studies in one meta-analysis.
Summary of evidence	**Moderate to high quality evidence (large samples, precise, direct, unable to assess consistency) suggests no significant reduction in the functional activation of DLPFC during working memory tasks in people with schizophrenia compared to controls.**
Working memory tasks	
No significant differences between groups; Combined hemispheric DLPFC activation: 30 studies, N = 808, *d* = 0.20, 95%CI -0.05 to 0.44, *p* = 0.13 Left hemisphere DLPFC activation: 28 studies, N = 776, *d* = 0.23, 95%CI -0.05 to 0.51, *p* = 0.11 Right hemisphere DLPFC activation: 28 studies, N = 776, *d* = 0.15, 95%CI -0.13 to 0.42, *p* = 0.34 Subgroup analyses restricted to studies reporting performance data for the same sample on two or more loads of the same working memory task yielded similar results. Moderator analyses revealed that reaction time was a significant moderator of between-group differences. Accuracy was not a significant moderator.	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	Precise for all outcomes except right hemisphere DLPFC activation in the restricted analysis.
Directness of results	Direct

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

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

Psychiatry Research: Neuroimaging 2017; 270: 8-21

View review abstract online

Comparison	**White matter integrity in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found white matter reductions in bilateral inferior fronto-occipital fasciculus.**

FA	
34 studies, N = 2,231 *There were white matter reductions in;* Left inferior fronto-occipital fasciculus: 22,154 voxels, *p* = 0.000725, MNI = -31, -22, -7 Right inferior fronto-occipital fasciculus: 23,185 voxels, *p* = 0.001700, MNI = 41, -31, -7	
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

Vucurovic K, Caillies S, Kaladjian A

Neural correlates of theory of mind and empathy in schizophrenia: An activation likelihood estimation meta-analysis

Journal of Psychiatric Research 2020; 120: 163-74

View review abstract online

Comparison	**Functional activation during empathy processing in schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess precision or consistency) suggests decreased activation in schizophrenia in a 664mm3 volume cluster of the right inferior frontal gyrus during empathy tasks.**
Emotion processing	
13 studies, N = 482 *The following cluster showed decreased activation in schizophrenia in;* A 664mm3 volume cluster of the right inferior frontal gyrus (Talairach x=47.8, y=25.6, z=9.6; ALE=0.02; BA45).	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.

Directness of results	Direct

Wenneberg C, Glenthoj BY, Hjorthoj C, Buchardt Zingenberg FJ, Glenthoj LB, Rostrup E, Broberg BV, Nordentoft M

Cerebral glutamate and GABA levels in high-risk of psychosis states: A focused review and meta-analysis of ^{1}H-MRS studies

Schizophrenia Research Jan: doi: 10.1016/j.schres.2019.10.050

View review abstract online

Comparison	**Cerebral glutamate and GABA levels measured by ^{1}H-MRS in people at high risk of psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (small to medium-sized samples, consistent, precise, direct) finds a medium-sized increase in glutamate+glutamine in the frontal lobe of people at genetic high risk.**

GABA, Glx

A medium-sized, significant effect showed higher glutamate + glutamine levels in the frontal lobe of people at genetic high risk;

4 studies, N = 140, SMD = -0.55, 95%CI -0.89 to -0.21, p = 0.001, I^2 = 0%

There were no significant differences in the analysis that combined clinical and genetic high-risk individuals.

No significant differences were found in GABA levels.

Consistency in results	Consistent
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

NeuRA Discover. Conquer. Cure. SCHIZOPHRENIA LIBRARY

Frontal lobe

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 samples, inconsistent, precise, direct) suggests better overall functioning was associated with larger frontal lobe.**
Brain volume and functional outcome	
37 studies, N = 1,187 *Better functioning was associated with larger volumes in;* Frontal lobe: 12 studies, r = 0.35, 95%CI 0.22 to 0.47, $p < 0.0001$, Q = 106.01, $p < 0.001$	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

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

Meta-analysis of regional brain volumes in schizophrenia

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

View review abstract online

Comparison	**Frontal lobe volume in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests no differences in frontal lobe volume between people with schizophrenia and controls.**

Frontal lobe

Frontal lobe volume	
Left frontal volume: 13 studies, N = 762, *d* = -0.34, no CIs reported, *p* = 0.08 (average volume 95% of control volume, 95%CI 92 to 98%) Right frontal volume: 13 studies, N = 762, *d* = -0.36, no CIs reported, *p* = 0.64 (average volume 95% of control volume, 95%CI 93 to 97%)	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Zhang R, Picchioni M, Allen P, Toulopoulou T

Working memory in unaffected relatives of patients with schizophrenia: A meta-analysis of functional magnetic resonance imaging studies

Schizophrenia Bulletin 2016; 42: 1068-77

View review abstract online

Comparison	**Functional activity during working memory tasks in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, unable to assess consistency, precise, direct) suggests decreased activity in the right middle frontal gyrus (BA9) and right inferior frontal gyrus (BA44), and increased activity in the right frontopolar (BA10) region of relatives during working memory tasks.**
Functional activity	
15 studies, N = 547 *Decreased activity in relatives in;* Right middle frontal gyrus (BA9): Talairach coordinates 34, 36, 34 Right inferior frontal gyrus (BA44): Talairach coordinates 52, 10, 18 *Increased activity in relatives in;* Right frontopolar (BA10): Talairach coordinates 32, 50, 10	

Frontal lobe

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Precise
Directness of results	Direct

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

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

Schizophrenia Bulletin 2013; doi:10.1093/schbul/sbt063

View review abstract online

Comparison	**Localised brain regions associated with neurological soft signs in people with schizophrenia**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess precision or consistency) suggests people with schizophrenia showed reduced activation in the right inferior frontal cortex that was associated with increased severity of neurological soft signs.**
Neurological soft signs and motor inhibition tasks	
15 studies (N not reported) *Areas with reduced activation in patients vs. controls and with NSS severity correlating;* Right inferior frontal gyrus: Talairach coordinates 40, 22, 4	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Explanation of acronyms

AFC = anterior frontal cortex, ALE = activation likelihood analysis, Cho = choline, CI = confidence

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

interval, Cr = creatine, CredInt = credible interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences, DLPFC = dorsolateral prefrontal cortex, FA = fractional anisotropy, FDR = false discovery rate correction for multiple comparisons, fMRI = functional magnetic resonance imaging, FSN = fail-safe N, FWHM = full-width at half maximum smoothing kernel, Gln = glutamine, Glu = glutamate, Glx = glutamate+glutamine, GMC = grey matter concentration, GMV = grey matter volume, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), KS = Kolgorov smirnov, MNI = Montreal Neurological Institute, MRS = magnetic resonance spectroscopy, N = number of participants, NAA = N-acetyl aspartate, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PET = positron emission tomography, PDE = phosphodiesters, PME = phosphomonoesters, *r* = correlation coefficient, SD = standard deviation, SPECT = single-photon emission computed tomography, Q = Q statistic (chi-square) for the test of heterogeneity, VLPFC = ventrolateral prefrontal cortex, vs. = versus

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Frontal lobe

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[64].

† 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[64].

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[65]. 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[66].

‖ 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.

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

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Mondino M, Brunelin J, Saoud M (2013): N-acetyl-aspartate level is decreased in the prefrontal cortex in subjects at-risk for schizophrenia. *Frontiers in Psychiatry* 4.
4. Achim AM, Lepage M (2005): Episodic memory-related activation in schizophrenia: meta-analysis. *British Journal of Psychiatry* 187: 500-9.
5. Berger GE, Wood SJ, Pantelis C, Velakoulis D, Wellard RM, McGorry PD (2002): Implications of lipid biology for the pathogenesis of schizophrenia. *Australian & New Zealand Journal of Psychiatry* 36: 355-66.
6. Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E (2008): The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. *American Journal of Psychiatry* 165: 1015-23.
7. Ellison-Wright I, Bullmore E (2009): Meta-analysis of diffusion tensor imaging studies in schizophrenia. *Schizophrenia Research* 108: 3-10.
8. Fornito A, Yucel M, Patti J, Wood SJ, Pantelis C (2009): Mapping grey matter reductions in schizophrenia: An anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophrenia Research* 108: 104-13.
9. Fusar-Poli P, Perez J, Broome M, Borgwardt S, Placentino A, Caverzasi E*, et al.* (2007): Neurofunctional correlates of vulnerability to psychosis: a systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews* 31: 465-84.
10. Glahn DC, Ragland JD, Abramoff A, Barrett J, Laird AR, Bearden CE*, et al.* (2005): Beyond hypofrontality: a quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Human Brain Mapping* 25: 60-9.
11. Glahn DC, Laird AR, Ellison-Wright I, Thelen SM, Robinson JL, Lancaster JL*, et al.* (2008): Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. *Biological Psychiatry* 64: 774-81.
12. Hill K, Mann L, Laws KR, Stephenson CM, Nimmo-Smith I, McKenna PJ*, et al.* (2004): Hypofrontality in schizophrenia: a meta-analysis of functional imaging studies. *Acta Psychiatrica Scandinavica* 110: 243-56.
13. Honea R, Crow TJ, Passingham D, Mackay CE (2005): Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *American Journal of Psychiatry* 162: 2233-45.
14. Kanaan RA, Kim JS, Kaufmann WE, Pearlson GD, Barker GJ, McGuire PK (2005): Diffusion tensor imaging in schizophrenia. *Biological Psychiatry* 58: 921-9.
15. Kyriakopoulos M, Bargiotas T, Barker GJ, Frangou S (2008): Diffusion tensor imaging in schizophrenia. *European Psychiatry: the Journal of the Association of European Psychiatrists* 23: 255-73.
16. Minzenberg MJ, Laird AR, S. T, Carter CS, Glahn DC (2009): Meta-analysis of 41 Functional Neuroimaging Studies of Executive Function in Schizophrenia. *Archives of General Psychiatry* 66: 811-22.
17. Sanches RF, Crippa JA, Hallak JE, Araujo D, Zuardi AW (2004): 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* 59: 145-52.
18. Steen RG, Hamer RM, Lieberman JA (2005): Measurement of brain metabolites by 1H magnetic resonance spectroscopy in patients with schizophrenia: a systematic review and meta-analysis. *Neuropsychopharmacology* 30: 1949-62.

19. Van Snellenberg JX, Torres IJ, Thornton AE (2006): Functional neuroimaging of working memory in schizophrenia: task performance as a moderating variable. *Neuropsychology* 20: 497-510.
20. Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET (2000): Meta-analysis of regional brain volumes in schizophrenia. *American Journal of Psychiatry* 157: 16-25.
21. Davidson LL, Heinrichs RW (2003): Quantification of frontal and temporal lobe brain-imaging findings in schizophrenia: a meta-analysis. *Psychiatry Research* 122: 69-87.
22. Ragland JD, Laird AR, Ranganath C, Blumenfeld RS, Gonzales SM, Glahn DC (2009): Prefrontal activation deficits during episodic memory in schizophrenia. *American Journal of Psychiatry* 166: 863-74.
23. Ellison-Wright I, Bullmore E (2010): Anatomy of bipolar disorder and schizophrenia: A meta-analysis. *Schizophrenia Research* 117: 1-12.
24. Chan RCK, Di X, McAlonan GM, Gong Q-y (2009): Brain Anatomical Abnormalities in High-Risk Individuals, First-Episode, and Chronic Schizophrenia: An Activation Likelihood Estimation Meta-analysis of Illness Progression. *Schizophrenia Bulletin*.
25. Leung M, Cheung C, Yu K, Yip B, Sham P, Li Q*, et al.* (2009): Gray Matter in First-Episode Schizophrenia Before and After Antipsychotic Drug Treatment. Anatomical Likelihood Estimation Meta-analyses With Sample Size Weighting. *Schizophrenia Bulletin*.
26. Di X, Chan RC, Gong QY (2009): White matter reduction in patients with schizophrenia as revealed by voxel-based morphometry: an activation likelihood estimation meta-analysis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 33: 1390-4.
27. Sommer I, Ramsey N, Kahn R, Aleman A, Bouma A (2001): Handedness, language lateralisation and anatomical asymmetry in schizophrenia: meta-analysis.[see comment]. *British Journal of Psychiatry* 178: 344-51.
28. Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ*, et al.* (2011): Neuroanatomical abnormalities in schizophrenia: A multimodal voxelwise meta-analysis and meta-regression analysis. *Schizophrenia Research* 127: 46-57.
29. Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM (2011): Are There Progressive Brain Changes in Schizophrenia? A Meta-Analysis of Structural Magnetic Resonance Imaging Studies. *Biological Psychiatry*.
30. Goghari VM (2011): Executive functioning-related brain abnormalities associated with the genetic liability for schizophrenia: an activation likelihood estimation meta-analysis. *Psychological Medicine* 41: 1239-52.
31. Das TK, Dey A, Sabesan P, Javadzadeh A, Theberge J, Radua J*, et al.* (2018): Putative astroglial dysfunction in schizophrenia: A meta-analysis of H-MRS studies of medial prefrontal myo-inositol. *Frontiers in Psychiatry* 9 (SEP) (no pagination).
32. Iwata Y, Nakajima S, Plitman E, Mihashi Y, Caravaggio F, Chung JK*, et al.* (2018): Neurometabolite levels in antipsychotic-naive/free patients with schizophrenia: A systematic review and meta-analysis of 1H-MRS studies. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 86: 340-52.
33. Egerton A, Modinos G, Ferrera D, McGuire P (2017): Neuroimaging studies of GABA in schizophrenia: a systematic review with meta-analysis. *Translational Psychiatry* 7: e1147.
34. Plaven-Sigray P, Matheson GJ, Collste K, Ashok AH, Coughlin JM, Howes OD*, et al.* (2018): Positron Emission Tomography Studies of the Glial Cell Marker Translocator Protein in Patients With Psychosis: A Meta-analysis Using Individual Participant Data. *Biological Psychiatry* 84: 433-42.
35. Brugger S, Davis JM, Leucht S, Stone JM (2011): Proton magnetic resonance spectroscopy and illness stage in schizophreniaa systematic review and meta-analysis. *Biological Psychiatry* 69: 495-503.
36. Kraguljac NV, Reid M, White D, Jones R, den Hollander J, Lowman D*, et al.* (2012): Neurometabolites in schizophrenia and bipolar disorder - a systematic review and meta-analysis. *Psychiatry Research* 203: 111-25.

37. Marsman A, Van Den Heuvel MP, Klomp DWJ, Kahn RS, Luijten PR, Hulshoff Pol HE (2013): Glutamate in schizophrenia: A focused review and meta-analysis of 1H-MRS studies. *Schizophrenia Bulletin* 39: 120-9.
38. Kompus K, Westerhausen R, Hugdahl K (2011): The "paradoxical" engagement of the primary auditory cortex in patients with auditory verbal hallucinations: a meta-analysis of functional neuroimaging studies. *Neuropsychologia* 49: 3361-9.
39. Li H, Chan R, McAlonan G, Gong Q (2010): Facial emotion processing in schizophrenia: A meta-analysis of functional neuroimaging data. *Schizophrenia Bulletin* 36: 1029-39.
40. Alustiza I, Radua J, Pla M, Martin R, Ortuno F (2017): 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* 56: 179-89.
41. Dong D, Wang Y, Jia X, Li Y, Chang X, Vandekerckhove M*, et al.* (2018): Abnormal brain activation during threatening face processing in schizophrenia: A meta-analysis of functional neuroimaging studies. *Schizophrenia Research* 197: 200-8.
42. Fusar-Poli P (2012): Voxel-wise meta-analysis of fMRI studies in patients at clinical high risk for psychosis. *Journal of Psychiatry & Neuroscience* 37: 106-12.
43. Kronbichler L, Tschernegg M, Martin AI, Schurz M, Kronbichler M (2017): Abnormal Brain Activation During Theory of Mind Tasks in Schizophrenia: A Meta-Analysis. *Schizophrenia Bulletin* 43: 1240-50.
44. Niu Y, Li Z, Cheng R, Peng B, Liu B, Ma Y (2017): Altered gray matter and brain activity in patients with schizophrenia and their unaffected relatives: A multimodal meta-analysis of voxel-based structural MRI and resting-state fMRI studies. *International Journal of Clinical and Experimental Medicine* 10: 1866-78.
45. Radua J, Borgwardt S, Crescini A, Mataix-Cols D, Meyer-Lindenberg A, McGuire PK*, et al.* (2012): Multimodal meta-analysis of structural and functional brain changes in first episode psychosis and the effects of antipsychotic medication. *Neuroscience and Biobehavioral Reviews* 36: 2325-33.
46. Ramsay IS, Macdonald AW (2015): Brain Correlates of Cognitive Remediation in Schizophrenia: Activation Likelihood Analysis Shows Preliminary Evidence of Neural Target Engagement. *Schizophrenia Bulletin* 41: 1276-84.
47. Scognamiglio C, Houenou J (2014): A meta-analysis of fMRI studies in healthy relatives of patients with schizophrenia. *Australian and New Zealand Journal of Psychiatry* 48: 907-16.
48. Zhang R, Picchioni M, Allen P, Toulopoulou T (2016): Working memory in unaffected relatives of patients with schizophrenia: A meta-analysis of functional magnetic resonance imaging studies. *Schizophrenia Bulletin* 42: 1068-77.
49. Zhao Q, Li Z, Huang J, Yan C, Dazzan P, Pantelis C*, et al.* (2013): Neurological Soft Signs Are Not "Soft" in Brain Structure and Functional Networks: Evidence From ALE Meta-analysis. *Schizophrenia Bulletin*: doi:10.1093/schbul/sbt063.
50. Vitolo E, Tatu MK, Pignolo C, Cauda F, Costa T, Ando A*, et al.* (2017): White matter and schizophrenia: A meta-analysis of voxel-based morphometry and diffusion tensor imaging studies. *Psychiatry Research: Neuroimaging* 270: 8-21.
51. Brugger SP, Howes OD (2017): Heterogeneity and Homogeneity of Regional Brain Structure in Schizophrenia: A Meta-analysis. *JAMA Psychiatry* 74: 1104-11.
52. Cheung C, Yu K, Fung G, Leung M, Wong C, Li Q*, et al.* (2010): Autistic Disorders and Schizophrenia: Related or Remote? An Anatomical Likelihood Estimation. *PLoS ONE* 5: e12233.
53. Haijma SV, Van Haren N, Cahn W, Koolschijn PCMP, Hulshoff Pol HE, Kahn RS (2012): Brain Volumes in Schizophrenia: A Meta-Analysis in Over 18 000 Subjects. *Schizophrenia Bulletin* 39: 1129-38.
54. Huhtaniska S, Jaaskelainen E, Hirvonen N, Remes J, Murray GK, Veijola J*, et al.* (2017): Long-term antipsychotic use and brain changes in schizophrenia - a systematic review and meta-analysis. *Human Psychopharmacology* 32: doi: 10.1002/hup.2574.

55. Li Y, Li WX, Xie DJ, Wang Y, Cheung EFC, Chan RCK (2018): Grey matter reduction in the caudate nucleus in patients with persistent negative symptoms: An ALE meta-analysis. *Schizophrenia Research* 192: 9-15.
56. Shah C, Zhang W, Xiao Y, Yao L, Zhao Y, Gao X*, et al.* (2017): Common pattern of gray-matter abnormalities in drug-naive and medicated first-episode schizophrenia: a multimodal meta-analysis. *Psychological Medicine* 47: 401-13.
57. Wojtalik JA, Smith MJ, Keshavan MS, Eack SM (2017): A Systematic and Meta-analytic Review of Neural Correlates of Functional Outcome in Schizophrenia. *Schizophrenia Bulletin* 43: 1329-47.
58. Haszto CS, Stanley JA, Iyengar S, Prasad KM (2019): Regionally Distinct Alterations in Membrane Phospholipid Metabolism in Schizophrenia: A Meta-analysis of Phosphorus Magnetic Resonance Spectroscopy Studies. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 5: 264–80.
59. Wenneberg C, Glenthoj BY, Hjorthoj C, Buchardt Zingenberg FJ, Glenthoj LB, Rostrup E*, et al.* (2020): Cerebral glutamate and GABA levels in high-risk of psychosis states: A focused review and meta-analysis of 1H-MRS studies. *Schizophrenia Research* Jan: doi: 10.1016/j.schres.2019.10.050.
60. Ding Y, Ou Y, Pan P, Shan X, Chen J, Liu F*, et al.* (2019): Brain structural abnormalities as potential markers for detecting individuals with ultra-high risk for psychosis: A systematic review and meta-analysis. *Schizophrenia Research* 209: 22-31.
61. Leroy A, Amad A, D'Hondt F, Pins D, Jaafari N, Thomas P*, et al.* (2020): Reward anticipation in schizophrenia: A coordinate-based meta-analysis. *Schizophrenia Research* Jan: doi.org/10.1016/j.schres.2019.12.041.
62. Saarinen AIL, Huhtaniska S, Pudas J, Bjornholm L, Jukuri T, Tohka J*, et al.* (2020): Structural and functional alterations in the brain gray matter among first-degree relatives of schizophrenia patients: A multimodal meta-analysis of fMRI and VBM studies. *Schizophrenia Research* Jan: doi.org/10.1016/j.schres.2019.12.023.
63. Vucurovic K, Caillies S, Kaladjian A (2020): Neural correlates of theory of mind and empathy in schizophrenia: An activation likelihood estimation meta-analysis. *Journal of Psychiatric Research* 120: 163-74.
64. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
65. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
66. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*