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-cortical 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. 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.
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 criteria³⁶³.

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 gyri 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.
Frontal lobe

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
Frontal lobe

people with first-episode psychosis, with greater severity of abnormality in medicated patients.
Achim AM, Lepage M

Episodic memory-related activation in schizophrenia: meta-analysis

British Journal of Psychiatry 2005; 187: 500-509
View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Functional activation in people with schizophrenia vs. controls during episodic memory tasks.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

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. |
<table>
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<tbody>
<tr>
<td>Precision in results</td>
<td>No confidence intervals are provided.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>
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

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

Implications of lipid biology for the pathogenesis of schizophrenia


View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PME levels</th>
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</thead>
<tbody>
<tr>
<td>3 of 3 studies (N = 78) reported decreased PME levels in both first episode and newly diagnosed patients.</td>
</tr>
<tr>
<td>7 of 11 studies (222/415 patients) reported decreased PME levels in people with chronic schizophrenia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PDE levels</th>
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<tbody>
<tr>
<td>3 of 3 studies (N = 78) reported increased PDE levels in both first episode and newly diagnosed patients.</td>
</tr>
<tr>
<td>3 of 10 studies (87/363 patients) reported increased PDE levels in people with chronic schizophrenia.</td>
</tr>
<tr>
<td>1 of 10 studies (86/363 patients) reported decreased PDE levels in people with chronic schizophrenia.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of heterogeneity is reported.</th>
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<tr>
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<td>No confidence intervals are reported.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Grey matter density in people with chronic or first-episode schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Consistency in results</th>
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<td>Direct</td>
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</table>

**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 \(^1H\)-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 \(-0.26\), \(p < 0.0001\), \(Q = 209.76\), \(I^2 = 66\%\)
  
  - *Significant, medium-sized reductions of NAA in people with first-episode schizophrenia;*
    
    19 studies, \(N = 804\), \(d = -0.45\), 95%CI \(-0.67\) to \(-0.23\), \(p < 0.0001\), \(Q = 60.76\), \(I^2 = 49\%\)
  
  - *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

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Inconsistent</th>
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<tbody>
<tr>
<td>Precision in results</td>
<td>Precise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
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</tbody>
</table>

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](#)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Whole brain volume in people with first-episode schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>High quality evidence (large sample, consistent, precise, direct) finds small reductions in frontal lobe volume in people with first-episode schizophrenia.</td>
</tr>
</tbody>
</table>

**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, I² = 29%

<table>
<thead>
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<tbody>
<tr>
<td>Precision in results</td>
<td>Precise</td>
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</table>

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
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 432mm³, 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 1576mm³, ALE 0.0150

Right inferior frontal gyrus: Talairach coordinates (24, 34, -8), cluster 528mm³, ALE 0.0184

Left middle frontal gyrus: Talairach coordinates (-32, 34, -6), cluster 456mm³, ALE 0.0174

Left inferior frontal gyrus: Talairach coordinates (-48, 6, 22), cluster 416mm³, ALE 0.0142

Left medial frontal gyrus: Talairach coordinates (-8, 46, 8), cluster 288mm³, ALE 0.0120

Right medial frontal gyrus: Talairach coordinates (2, 36, -16), cluster 192mm³, 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 4832mm³, ALE 0.0222

Left medial frontal gyrus: Talairach coordinates (-4, 52, 12), cluster 2976mm³, ALE 0.0196
Frontal lobe

| Left medial frontal gyrus: Talairach coordinates (-6, 34, -14), cluster 2976mm³, ALE 0.0182 |
| Left middle frontal gyrus: Talairach coordinates (-44, 8, 36), cluster 1208mm³, ALE 0.0199 |
| Left inferior frontal gyrus: Talairach coordinates (-50, 6, 30), cluster 1208mm³, ALE 0.0176 |
| Right superior frontal gyrus: Talairach coordinates (30, 54, 10), cluster 416mm³, ALE 0.0147 |
| Right middle frontal gyrus: Talairach coordinates (42, 4, 38), cluster 392mm³, ALE 0.0171 |
| Right inferior frontal gyrus: Talairach coordinates (26, 28, -2), cluster 136mm³, 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 224mm³, 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 400mm³, 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 208mm³, ALE -0.0133

Right inferior frontal gyrus: Talairach coordinates (24, 34, -8), cluster 168mm³, ALE -0.0146

Left inferior frontal gyrus: Talairach coordinates (-32, 32, -4), cluster 136mm³, ALE -0.0126

Right precentral gyrus: Talairach coordinates (50, -12, 12), cluster 120mm³, 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 544mm³, ALE 0.0156

Left medial frontal gyrus: Talairach coordinates (-6, 34, -14), cluster 392mm³, ALE 0.0138

Left inferior frontal gyrus: Talairach coordinates (-34, 16, -6), cluster 272mm³, ALE 0.0138

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


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

#### PLOS One 2010; 5(8): e12233

*View review abstract online*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Regions of overlapping brain alterations in people with schizophrenia and people with autistic spectrum disorders (ASD) vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
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<tr>
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<tr>
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</tbody>
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**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*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Medial prefrontal myo-inositol levels measured by $^1$H-MRS in people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

**Myo-inositol**
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, I² = 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.

<table>
<thead>
<tr>
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</table>

*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](#)

<table>
<thead>
<tr>
<th>Comparison 1</th>
<th>Grey matter volume in people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate to high quality evidence (large sample, mostly inconsistent, precise, direct) suggests grey matter volume is significantly reduced in the frontal lobe in schizophrenia.</td>
</tr>
</tbody>
</table>

Frontal lobe volume
### Frontal lobe

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Significant heterogeneity reported in all outcomes except right frontal cortex.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise for all outcomes.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
<tr>
<td>Comparison 2</td>
<td>Functional activation in people with schizophrenia vs. controls during episodic memory tasks.</td>
</tr>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

#### Frontal lobe activity during task

<table>
<thead>
<tr>
<th>Left frontal lobe</th>
<th>Medium effect size suggests reduced activity in schizophrenia;</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 390, d = -0.54, 95%CI -0.78 to -0.30, SD = 0.38, FSN = 53</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Right frontal lobe</th>
<th>Medium effect size suggests reduced activity in schizophrenia;</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 397, d = -0.54, 95%CI -0.90 to -0.18, SD = 0.53, FSN = 48</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total frontal lobe</th>
<th>Large effect size suggests reduced activity in schizophrenia;</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 879, d = -0.81, 95%CI -1.06 to -0.57, SD = 0.52, FSN = 142</td>
<td></td>
</tr>
</tbody>
</table>
Frontal lobe activity at rest

<table>
<thead>
<tr>
<th></th>
<th>Left frontal lobe</th>
<th>Right frontal lobe</th>
<th>Total frontal lobe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medium effect size suggests reduced activity in schizophrenia;</strong></td>
<td><strong>N = 617, d = -0.48, 95%CI -0.80 to -0.15, SD = 0.74, FSN = 87</strong></td>
<td><strong>N = 617, d = -0.43, 95%CI -0.74 to -0.12, SD = 0.72, FSN = 76</strong></td>
<td><strong>N = 971, d = -0.65, 95%CI -0.88 to -0.42, SD = 0.64, FSN = 176</strong></td>
</tr>
</tbody>
</table>

**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**
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

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of consistency is reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>No confidence intervals are reported.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

**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](#)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Grey matter volume in people at clinical high risk of psychosis vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

**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 \((Z = -2.109)\)
Frontal lobe

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Authors report consistent results.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Unable to assess; no measure of precision is reported.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Functional activity during threatening face processing in people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

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. |
Frontal lobe

| 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**
Frontal lobe

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

View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Grey matter changes in people with first-episode schizophrenia vs. people with chronic schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

### Grey matter changes

27 studies, N = 1,556

*Reductions in first-episode schizophrenia;*

Left inferior frontal gyrus: Talairach coordinates (-28, 30, -6), cluster 736mm³, ALE 0.009, \( p = 0.0004 \)

Right inferior frontal gyrus: Talairach coordinates (26, 10, 18), cluster 360mm³, 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
Frontal lobe

<table>
<thead>
<tr>
<th>Comparison</th>
<th>White matter fractional anisotropy (FA) in people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

**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 $2368\, \text{mm}^3$

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.

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of consistency is reported, results appear inconsistent particularly for frontal lobe data.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>No confidence intervals are reported.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

**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. |
# Frontal lobe

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>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.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Grey matter changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis was performed using Activation Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies.</td>
</tr>
<tr>
<td>FWHM 7mm, FDR corrected at ( p &lt; 0.05 )</td>
</tr>
<tr>
<td>42 studies, ( N = 4,189 )</td>
</tr>
<tr>
<td>Regions of decreased grey matter in schizophrenia;</td>
</tr>
<tr>
<td>Left medial frontal gyrus: Talairach coordinates ((-2, 50, 4)), Sum of ranks = 179.6, ( p = 0.00005 )</td>
</tr>
<tr>
<td>Left medial frontal gyrus: Talairach coordinates ((-2, 48, 0)), Sum of ranks = 179.3, ( p = 0.00005 )</td>
</tr>
<tr>
<td>Left deep frontal lobe: Talairach coordinates ((-14, 2, -10)), Sum of ranks = 172.8, ( p = 0.00005 )</td>
</tr>
<tr>
<td>Left deep frontal lobe: Talairach coordinates ((-12, 0, -8)), Sum of ranks = 172.5, ( p = 0.00005 )</td>
</tr>
<tr>
<td>Right medial frontal gyrus: Talairach coordinates ((2, 42, 26)), Sum of ranks = 157.1, ( p = 0.00060 )</td>
</tr>
<tr>
<td>Right medial frontal gyrus: Talairach coordinates ((2, 44, 24)), Sum of ranks = 156.8, ( p = 0.00070 )</td>
</tr>
<tr>
<td>Right medial frontal gyrus: Talairach coordinates ((2, 48, 22)), Sum of ranks = 156.5, ( p = 0.00075 )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of consistency is reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>No confidence intervals are reported.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

*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](#)
## Frontal lobe

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>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.</th>
</tr>
</thead>
</table>

## 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 $1.36 \times 10^{-3}$
- **Left medial orbito-frontal gyrus:** Talairach coordinates (-1.11, 43.03, -21.06), Voxel cluster size 1208mm$^3$, ALE $0.87 \times 10^{-3}$

**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 $-0.76 \times 10^{-3}$
- **Left lateral superior frontal gyrus:** Talairach coordinates (-31.56, 53.64, 19.6), Voxel cluster size 1120mm$^3$, ALE $-0.68 \times 10^{-3}$
- **Right inferior frontal gyrus:** Talairach coordinates (48.39, 2.83, 30.96), Voxel cluster size 1096mm$^3$, ALE $-0.74 \times 10^{-3}$
- **Left lateral orbito-frontal gyrus:** Talairach coordinates (-26.82, 28.11, -4.7), Voxel cluster size 680mm$^3$, ALE $0.74 \times 10^{-3}$
- **Right pre- and post-central gyri:** Talairach coordinates (52.97, -24.28, 43.55), Voxel cluster size
Frontal lobe

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 gyrus: 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 $t = 2.82$, $p = 0.01$

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of consistency is reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>No confidence intervals are reported.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>


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


_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

<table>
<thead>
<tr>
<th>Task Type</th>
<th>Study Count</th>
<th>N</th>
<th>Reduced Activation Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working memory task</td>
<td>1</td>
<td>22</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>18</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>16</td>
<td>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.</td>
</tr>
<tr>
<td>Verbal fluency task</td>
<td>1</td>
<td>20</td>
<td>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.</td>
</tr>
<tr>
<td>Executive control task</td>
<td>1</td>
<td>47</td>
<td>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.</td>
</tr>
<tr>
<td>Context processing task</td>
<td>1</td>
<td>46</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>26</td>
<td>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.</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of heterogeneity is reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>No confidence intervals are reported.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
<tr>
<td>Comparison 2</td>
<td>Functional activity in relatives of people with schizophrenia vs. controls.</td>
</tr>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

### 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
Frontal lobe

| 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**

<table>
<thead>
<tr>
<th>N</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>4 studies, N = 268</td>
</tr>
</tbody>
</table>

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**


[View review abstract online](#)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Functional activation in individuals with schizophrenia vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

**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 472mm³
- Right middle and inferior frontal gyrus: Talairach centre of mass (33, 37, 28), cluster volume 1200mm³
- Left middle frontal gyrus: Talairach centre of mass (-33, 35, 23), cluster volume 1736mm³
- Right inferior frontal gyrus and insula: Talairach centre of mass (38, 16, 5), cluster volume 936mm³

Significantly increased activity in people with schizophrenia compared to controls:

- Left middle frontal gyrus: Talairach centre of mass (-44, 42, -3), cluster volume 560mm³
- Right superior frontal gyrus: Talairach centre of mass (4, 57, 26), cluster volume 264mm³

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No confidence intervals are reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>No measured of heterogeneity is provided.</td>
</tr>
</tbody>
</table>
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 432mm³, 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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Functional activation in relatives of people with schizophrenia vs. controls during an executive functioning task.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary of evidence</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>

### 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 mm³
- Right middle frontal/ precentral gyrus: Talairach coordinates (48/46, 16/24, 32/36), cluster volume 176 mm³

*Decreased activity in relatives of people with schizophrenia compared to controls in;*
- Left medial frontal gyrus: Talairach coordinates (-12, 64, -2), cluster volume 136 mm³
- Right middle frontal gyrus: Talairach coordinates (36, 28, 42), cluster volume 120 mm³
- Right precentral gyrus: Talairach coordinates (50, -4, 22), cluster volume 200 mm³
- Right precentral gyrus: Talairach coordinates (40, -6, 42), cluster volume 200 mm³

### 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 mm³

### 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 mm³
- Right middle frontal/ precentral gyrus: Talairach coordinates (48/46, 16/24, 32/36), cluster volume 176 mm³

*Decreased activity in relatives of people with schizophrenia compared to controls in;*
- Right middle frontal gyrus: Talairach coordinates (36, 28, 42), cluster volume 1008 mm³
- Right inferior frontal gyrus: Talairach coordinates (52/54, 8/8, 18/24), cluster volume 176 mm³
- Right precentral gyrus: Talairach coordinates (40, -6, 42), cluster volume 168 mm³

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of consistency is reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>No confidence intervals are reported.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

*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**
Frontal lobe


View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Whole brain comparison of grey and white matter volume in people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

Frontal lobe

Comparison

Frontal PME and PDE levels measured by ¹H-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


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


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,
Frontal lobe

<table>
<thead>
<tr>
<th>precise, direct) found no association between antipsychotic dose and changes in frontal lobe volume over time.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Longitudinal changes in volume</strong></td>
</tr>
<tr>
<td><em>There were no associations between long-term antipsychotic use and changes in the;</em></td>
</tr>
<tr>
<td>Frontal lobe: 7 studies, N = 500, r = -0.14, 95%CI -0.34 to 0.05, p = 0.15, I² = 71%</td>
</tr>
<tr>
<td><strong>Consistency in results</strong></td>
</tr>
<tr>
<td><strong>Precision in results</strong></td>
</tr>
<tr>
<td><strong>Directness of results</strong></td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th><strong>Comparison</strong></th>
<th>Whole brain functional activation in people with schizophrenia vs. controls: voxel-based comparison.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary of evidence</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>

**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
Frontal lobe

| 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 |

### 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

<table>
<thead>
<tr>
<th>Neurometabolite levels measured by $^1$H-MRS in unmedicated people with schizophrenia vs. controls.</th>
</tr>
</thead>
</table>

### 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, $p = 0.43$, $I^2 = 51\%$, $p = 0.10$
Frontal lobe

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Consistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

There was no significant difference in creatine in the dorsolateral prefrontal cortex.

**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](#)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>White matter fractional anisotropy (FA) in people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (large sample, direct, unable to assess precision and consistency) suggests decreased FA in the frontal lobe of people with schizophrenia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FA</th>
<th>19 studies, N = 640</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe illustrated decreased FA in at least one study between people with schizophrenia and controls.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of consistency is reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>No confidence intervals are reported.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

**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**
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) 408mm³
- Superior frontal gyrus: (26 42 26) 240mm³

Auditory tasks

11 studies, N = 384, showed reduced activation during auditory stimulation tasks in people with schizophrenia;
- Superior frontal gyrus: (24 50 14) 456mm³

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

Comparison | Whole brain comparison of metabolite levels (measured by ¹H-
Frontal lobe 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. |

<table>
<thead>
<tr>
<th>NAA/Cr or Cho/Cr</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frontal lobe</strong></td>
<td></td>
</tr>
<tr>
<td>Significant medium-sized reduction in NAA absolute levels;</td>
<td></td>
</tr>
<tr>
<td>11 studies, $d = -0.44$, 95%CI -0.65 to -0.23, $p &lt; 0.001$, $I^2 = 5%$</td>
<td></td>
</tr>
<tr>
<td>Significant, small reduction in NAA/Cr ratio;</td>
<td></td>
</tr>
<tr>
<td>16 studies, $d = -0.22$, 95%CI -0.39 to -0.06, $p &lt; 0.01$, $I^2 = 0%$</td>
<td></td>
</tr>
<tr>
<td>There were no differences in:</td>
<td></td>
</tr>
<tr>
<td>Cr levels: 10 studies, $d = 0.06$, 95%CI -0.16 to 0.28, $p = 0.58$, $I^2 = 11%$</td>
<td></td>
</tr>
<tr>
<td>Cho levels: 10 studies, $d = -0.06$, 95%CI -0.27 to 0.15, $p = 0.57$, $I^2 = 0%$</td>
<td></td>
</tr>
<tr>
<td>Cho/Cr ratio: 13 studies, $d = 0.09$, 95%CI -0.24 to 0.41, $p = 0.61$, $I^2 = 68%$</td>
<td></td>
</tr>
<tr>
<td><strong>DLPFC</strong></td>
<td></td>
</tr>
<tr>
<td>There were no significant differences in:</td>
<td></td>
</tr>
<tr>
<td>NAA levels: 6 studies, $d = -0.46$, 95%CI -1.09 to 0.17, $p = 0.15$, $I^2 = 85%$</td>
<td></td>
</tr>
<tr>
<td>Cr levels: 6 studies, $d = -0.13$, 95%CI -0.10 to 0.36, $p = 0.26$, $I^2 = 0%$</td>
<td></td>
</tr>
<tr>
<td>Cho levels: 6 studies, $d = 0.15$, 95%CI -0.44 to 0.74, $p = 0.62$, $I^2 = 84%$</td>
<td></td>
</tr>
<tr>
<td>NAA/Cr ratio: 3 studies, $d = 0.14$, 95%CI -0.72 to 1.00, $p = 0.75$, $I^2 = 86%$</td>
<td></td>
</tr>
<tr>
<td>Cho/Cr ratio: 2 studies, $d = -0.15$ 95%CI -0.73 to 0.42, $p = 0.60$, $I^2 = 58%$</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Consistent, apart from DLPFC; NAA, Cho, NAA/Cr and Cho/Cr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise, apart from most DLPFC data.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Functional activity during theory of mind tasks in people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

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


View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>White matter integrity, assessed by voxel-based analysis, in people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate to low quality evidence (unclear sample size, direct, unable to assess precision or consistency) suggests reduced FA in the prefrontal cortex.</td>
</tr>
</tbody>
</table>
# Frontal lobe

## FA

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of consistency is reported.</th>
</tr>
</thead>
<tbody>
<tr>
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<td>No confidence intervals are reported.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

**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)

---


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


**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.

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Unable to assess; no measure of consistency is reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Unable to assess; no measure of precision is reported.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>
Frontal lobe

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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Grey matter changes in first episode schizophrenia (treated and medication naïve) vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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-naïve patients.</td>
</tr>
</tbody>
</table>

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;

- Left precentral gyrus: Talairach coordinates (-50, -10, 24), cluster 440mm³, ALE 0.0027
- Left superior frontal gyrus: Talairach coordinates (-8, 66, 10), cluster 320mm³, ALE 0.0021
- Right middle frontal gyrus: Talairach coordinates (22, 38, -14), cluster 760mm³, ALE 0.0036
- Right inferior frontal gyrus: Talairach coordinates (46, 12, 16), cluster 288mm³, ALE 0.0017
- Right inferior frontal gyrus: Talairach coordinates (46, 20, 18), cluster 288mm³, ALE 0.0017

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

- Right precentral gyrus: Talairach coordinates (48, -10, 12), cluster 520mm³, ALE 0.0082
- Right medial frontal gyrus: Talairach coordinates (2, 36, -16), cluster 480mm³, ALE 0.0078
- Left medial frontal gyrus (to anterior cingulate): Talairach coordinates (-6, 48, 8), cluster 928mm³, ALE 0.0078
Frontal lobe

<table>
<thead>
<tr>
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<tr>
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<td>Direct</td>
</tr>
</tbody>
</table>

Areas where grey matter reductions were larger in magnitude in treatment-naive patients than in treated patients:

Left medial frontal gyrus (to anterior cingulate): Talairach coordinates (-2, 36, -2), cluster 928mm³, ALE 0.0044

Right middle frontal gyrus: Talairach coordinates (44, 36, 18), cluster 304mm³, ALE 0.0059
Right inferior frontal gyrus: Talairach coordinates (24, 34, -8), cluster 832mm³, ALE 0.0115
Left inferior frontal gyrus: Talairach coordinates (-32, 34, -4), cluster 528mm³, ALE 0.0080

Regions where grey matter reductions were larger in magnitude in treated patients than treatment-naive patients:

Left precentral gyrus: Talairach coordinates (-50, -10, 24), cluster 400mm³, ALE 0.0133
Left superior frontal gyrus: Talairach coordinates (-8, 66, 10), cluster 320mm³, ALE 0.0105
Right middle frontal gyrus: Talairach coordinates (22, 38, -14), cluster 568mm³, ALE 0.0172
Right middle frontal gyrus (to inferior frontal): Talairach coordinates (46, 20, 18), cluster 256mm³, ALE 0.0085
Right inferior frontal gyrus (to uncus): Talairach coordinates (22, 14, -14), cluster 296mm³, ALE 0.0076
Right inferior frontal gyrus (to uncus): Talairach coordinates (28, 8, -20), cluster 296mm³, ALE 0.0103

Left medial frontal gyrus (to anterior cingulate): Talairach coordinates (-6, 48, 8), cluster 632mm³, ALE 0.0098
Left inferior frontal gyrus: Talairach coordinates (-32, 34, -4), cluster 488mm³, ALE 0.0151
### Facial emotion processing in schizophrenia: A meta-analysis of functional neuroimaging data

**Li H, Chan R, McAlonan G, Gong QY**

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

**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, 312mm³, 0.051 ALE

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of consistency is reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>No confidence intervals are reported.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

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

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

*Schizophrenia Research* 2018; 192: 9-15

**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,
Frontal lobe

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


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
Frontal lobe

<table>
<thead>
<tr>
<th>Glu, Gln and NAA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medial frontal cortex</strong></td>
</tr>
<tr>
<td>A significant, small reduction in glutamate level in people with schizophrenia;</td>
</tr>
<tr>
<td>9 studies, N = 337, d = -0.391, p = 0.006</td>
</tr>
<tr>
<td>Meta-regression showed a progressive decrease with age in patients compared to controls (p = 0.008).</td>
</tr>
<tr>
<td>A significant, medium-sized increase in glutamine in people with schizophrenia;</td>
</tr>
<tr>
<td>8 studies, N = 275, d = 0.403, p = 0.045</td>
</tr>
<tr>
<td>Meta-regression showed a progressive decrease with age in patients compared to controls (p = 0.0005).</td>
</tr>
<tr>
<td>No significant difference in total glutamate + glutamine levels between patients and controls;</td>
</tr>
<tr>
<td>8 studies, N = 330, d = 0.122, p = 0.393</td>
</tr>
<tr>
<td>No significant difference in glutamate/glutamine ratio levels between patients and controls;</td>
</tr>
<tr>
<td>6 studies, N = 228, d = 0.308, p = 0.062</td>
</tr>
<tr>
<td>Meta-regression showed a progressive decrease with age in patients compared to controls (p = 0.02).</td>
</tr>
<tr>
<td>A significant, small reduction in NAA levels in people with schizophrenia;</td>
</tr>
<tr>
<td>19 studies, N = 779, d = -0.320, p = 0.019</td>
</tr>
<tr>
<td>Meta-regression showed a progressive decrease with age in patients compared to controls (p = 0.04).</td>
</tr>
<tr>
<td>A significant, small reduction in NAA/glutamate ratio in people with schizophrenia;</td>
</tr>
<tr>
<td>7 studies, N = 247, d = -0.357, p = 0.038</td>
</tr>
<tr>
<td>Meta-regression showed a progressive decrease with age in patients compared to controls (p = 0.049).</td>
</tr>
</tbody>
</table>

**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 |


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

[View review abstract online](http://example.com)

| 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 |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary of evidence</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Executive function tasks</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALE analysis – FWHM 12mm, False Discovery Rate (FDR) corrected model</strong></td>
<td></td>
</tr>
<tr>
<td>Significantly reduced activity in people with schizophrenia compared to controls;</td>
<td></td>
</tr>
<tr>
<td>Left middle frontal gyrus: Talairach centre of mass (-38, 30, 30), cluster volume 3096mm³</td>
<td></td>
</tr>
<tr>
<td>Right middle frontal gyrus: Talairach centre of mass (32, 24, 42), cluster volume 712mm³</td>
<td></td>
</tr>
<tr>
<td>Right medial frontal gyrus: Talairach centre of mass (6, 42, 18), cluster volume 1480mm³</td>
<td></td>
</tr>
<tr>
<td>Significantly increased activity in people with schizophrenia compared to controls;</td>
<td></td>
</tr>
<tr>
<td>Left superior frontal gyrus: Talairach centre of mass (-8, -14, 68), cluster volume 440mm³</td>
<td></td>
</tr>
<tr>
<td>Left superior frontal gyrus: Talairach centre of mass (-2, 52, 24), cluster volume 1320mm³</td>
<td></td>
</tr>
<tr>
<td>Left inferior frontal gyrus: Talairach centre of mass (-40, 36, 12), cluster volume 656mm³</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of heterogeneity is provided.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>No confidence intervals are reported.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

*Mondino M, Brunelin J, Saoud M*

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

View review abstract online

Comparison
Comparison of NAA/Cr ratio (measured by 1H-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
I² is not reported. Forest plot appears inconsistent, most likely due to differences in age.

Precision in results
Precise

Directness of results
Direct

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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Functional alteration during rest in relatives of people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

**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, \( p = 0.00023 \)

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Unable to assess; no measure of consistency is reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Unable to assess; no measure of precision is reported.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

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


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

*View review abstract online*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Progressive changes in grey matter volume in schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

**Grey matter volume**

Progressive changes in grey matter volume reported across longitudinal MRI scans over 1-10 years.

31 studies, \( N = 1,867 \)
Frontal lobe

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, $p = 0.0001$, $I^2 = 0%$

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Consistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Translocator protein (measured by PET) in people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (small sample, consistent, imprecise, direct) finds reduced translocator protein in the frontal cortex of people with schizophrenia.</td>
</tr>
</tbody>
</table>

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).

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Authors report results were consistent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Appears imprecise.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Overlap between regions of functional and structural alteration in people with first-episode psychosis vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

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 644mm², \( p < 0.0001 \)

- Decreased grey matter volume and increased functional activation;
  
  Left medial frontal/anterior cingulate
  
  Talairach coordinates -14, 40, 10, cluster volume 117mm², \( p = 0.0001 \)

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
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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Functional activation during episodic memory tasks in individuals with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

### 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 $(-44, -28, 36)$
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 \(3048\, \text{mm}^3\), Talairach centre of mass \((-40, 22, 20)\)
- Left precentral gyrus: cluster volume \(1064\, \text{mm}^3\), Talairach centre of mass \((-36, -2, 28)\)
- Left middle frontal gyrus: cluster volume \(888\, \text{mm}^3\), 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 \(1296\, \text{mm}^3\), Talairach centre of mass \((-28, -26, 66)\)
- Right medial frontal gyrus: cluster volume \(1168\, \text{mm}^3\), Talairach centre of mass \((12, 44, 10)\)
- Right middle frontal gyrus: cluster volume \(600\, \text{mm}^3\), 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.

<table>
<thead>
<tr>
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<tr>
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</table>

*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*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

#### 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, 624mm³
- Left inferior frontal gyrus, left insular cortex, left precentral gyrus: Talairach coordinates -44, 6, 24, cluster volume 496mm³
- Left superior frontal gyrus, left middle frontal gyrus: Talairach coordinates -28, 52, 6, cluster volume 264mm³
- Left medial frontal gyrus: Talairach coordinates -6, -8, 68, cluster volume 248mm³

#### Consistency in results
No measure of heterogeneity is provided.

#### Precision in results
No confidence intervals are provided.

#### Directness of results
Direct

---


**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*
## Frontal lobe

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Functional activation in relatives of people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

### Cognitive tasks

*Relatives showed increased activation in the right inferior frontal gyrus; MNI co-ordinates 46, 12, 32, $p = 0.000001967$, 616 voxels, $I^2 = 0\%$*

<table>
<thead>
<tr>
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<tbody>
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<tr>
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</tr>
</tbody>
</table>

### 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](#)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>NAA and Cr activity (measured by $^1$H-MRS) in the frontal lobes of people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

| NAA                                           |                                                     |
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](#)

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**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, \( p < 0.001 \)
Frontal lobe

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

<table>
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</table>


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

Psychological Medicine 2017; 47: 401-13

View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Grey matter changes in first-episode schizophrenia (treated and medication naïve) vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

Grey matter changes in medication naïve first-episode patients
Frontal lobe

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

<table>
<thead>
<tr>
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</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

**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](#)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Differences in anatomical asymmetry in people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Inconsistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

**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*


[View review abstract online](#)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>NAA activity (measured by $^1$H-MRS) in grey and white matter in people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

### 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%

All patients white matter
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%

First-episode psychosis
4 studies consider NAA, N = 146
Patient average 82.3% of control levels, SD = 17.8

Chronic patients
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.
Frontal lobe

<table>
<thead>
<tr>
<th>FA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>34 studies, N = 2,231</td>
<td></td>
</tr>
<tr>
<td><em>There were white matter reductions in;</em></td>
<td></td>
</tr>
<tr>
<td>Left inferior fronto-occipital fasciculus: 22,154 voxels, <em>p</em> = 0.000725, MNI = -31, -22, -7</td>
<td></td>
</tr>
<tr>
<td>Right inferior fronto-occipital fasciculus: 23,185 voxels, <em>p</em> = 0.001700, MNI = 41, -31, -7</td>
<td></td>
</tr>
<tr>
<td>Consistency in results</td>
<td>Unable to assess; no measure of consistency is reported.</td>
</tr>
<tr>
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</tr>
<tr>
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</tbody>
</table>

**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*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Functional activation during empathy processing in schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

**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. |
Frontal lobe

<table>
<thead>
<tr>
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</table>

**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**


*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**
## Outcome in Schizophrenia

**Schizophrenia Bulletin 2017; 43: 1329-47**

*View review abstract online*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests better overall functioning was associated with larger frontal lobe.</td>
</tr>
<tr>
<td><strong>Brain volume and functional outcome</strong></td>
<td></td>
</tr>
<tr>
<td>37 studies, N = 1,187</td>
<td></td>
</tr>
<tr>
<td><em>Better functioning was associated with larger volumes in;</em></td>
<td></td>
</tr>
<tr>
<td>Frontal lobe: 12 studies, $r = 0.35$, 95%CI 0.22 to 0.47, $p &lt; 0.0001$, $Q = 106.01$, $p &lt; 0.001$</td>
<td></td>
</tr>
</tbody>
</table>

### Consistency in results
- Inconsistent

### Precision in results
- Precise

### Directness of results
- Direct

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

**Meta-analysis of regional brain volumes in schizophrenia**


*View review abstract online*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Frontal lobe volume in people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>High quality evidence (large sample, consistent, precise, direct) suggests no differences in frontal lobe volume between people with schizophrenia and controls.</td>
</tr>
</tbody>
</table>
Frontal lobe

### Frontal lobe volume

<table>
<thead>
<tr>
<th></th>
<th>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%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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%)</td>
</tr>
</tbody>
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</table>

### Zhang R, Picchioni M, Allen P, Touloupolou 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](#)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Functional activity during working memory tasks in relatives of people with schizophrenia vs. controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>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.</td>
</tr>
</tbody>
</table>

### 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

<table>
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<tr>
<th>Consistency in results</th>
<th>Unable to assess; no measure of consistency is reported.</th>
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</table>

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

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
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, I² = 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
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\(^64\).

\(^6\) 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
Frontal lobe

to 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 unforeseen 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 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. I² 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. I² can be calculated from Q (chi-square) for the test of heterogeneity with the following formula:

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

§ 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.

‖ 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 indirect comparisons 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.
References

Frontal lobe

Frontal lobe


Frontal lobe


