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 higher level cognition, such as working memory, problem solving and planning. The prefrontal cortex has also been implicated as a storage site for declarative memory such as semantic and episodic knowledge. This region has reciprocal connectivity with the amygdala, and is in a position to use experience and learning to influence behavioural responses and evaluate situations. The most posterior section of the frontal lobe is the pre-central gyrus, the primary motor cortex, also surrounded by associative and supplementary motor regions.

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

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia.

Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an
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 thirty-three systematic reviews that met our inclusion criteria³-⁴⁵.

Structural changes: MRI and DTI

- 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 frontal gyrus.

- Moderate quality evidence suggests reduced white matter integrity (fractional anisotropy) in the frontal lobe including the prefrontal cortex of people with schizophrenia compared to controls.

- Moderate to low quality evidence suggest 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 healthy controls.

Functional changes: fMRI, PET, SPECT and MRS

- Moderate quality evidence suggests reduced function in the frontal lobe during memory tasks in schizophrenia; 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. During executive function tasks, people with schizophrenia show reduced activity in the middle and medial frontal gyri, and increased activity in the superior and inferior frontal gyri compared to controls.

- Moderate low quality evidence suggests that functional activity during cognitive control, working memory and emotional face processing tasks shows abnormal activity (mostly increased) in DLPFC of first-degree relatives of people with schizophrenia. Patterns of ventrolateral prefrontal cortex activity were less consistent in relatives, but showed increases during long-term memory and language processing tasks.

- Moderate quality evidence suggests phosphomonoester (PME) levels are decreased in the prefrontal cortex of people with first-episode psychosis and people with schizophrenia. There are increased phosphodiester (PDE) levels in the prefrontal cortex of first-episode psychosis patients when compared to controls. Moderate to low quality evidence suggests reduced PME an increased PDE levels in the frontal lobe of first-degree relatives when compared to controls.

- Moderate quality evidence suggests N-acetylaspartate (NAA) and creatine (Cr) levels are reduced in frontal lobe grey and white matter, particularly the prefrontal cortex and frontal pole, in both first episode and chronic schizophrenia compared to controls. NAA/Cr ratio is reduced in the prefrontal cortex of people at clinical or familial risk of schizophrenia.
Frontal lobe

- Moderate to low quality evidence suggests glutamate/glutamine (Glu/Gln) levels may be increased in the medial prefrontal cortex in the early stages of disorder. Decreases in Glu/Gln were observed in chronic schizophrenia in the DLPFC.
**Abbott C, Bustillo J**

*What have we learned from proton magnetic resonance spectroscopy about schizophrenia? A critical update*

*Current Opinion in Psychiatry 2006; 19(2): 135-9*

**View review abstract online**

| Comparison 1 | N-acetyl aspartate (NAA) and Creatine (Cr) activity (measured by ¹H-MRS) in people with schizophrenia vs. healthy controls (NAA and Cr are reported as a ratio, NAA/Cr). |
| Summary of evidence | Moderate to low quality evidence (small to moderate samples, direct, unable to assess precision or consistency) suggests decreased NAA/Cr levels in chronic schizophrenia in the DLPFC when compared to controls. |

| NAA/Cr |
| 2 studies, N = 115 |
| Three groups: Early schizophrenia (mean < 2 years); chronic schizophrenia (mean > 6 years); and controls. |
| NAA/Cr levels were decreased in the DLPFC in chronic schizophrenia only |

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

| Comparison 2 | Comparison of metabolic Glu and Gln activity (measured by ¹H-MRS) in people with schizophrenia vs. healthy controls |
| Summary of evidence | Moderate to low quality evidence (small to medium-sized samples, direct, unable to assess precision or consistency) suggests Glu/Gln levels may be increased in the early stages of the disorder and decrease as the disorder progresses or as a result of medication. These increases were observed in early schizophrenia in the medial prefrontal cortex. Decreases were observed in chronic schizophrenia in the DLPFC. |

| Glu/Gln |
Frontal lobe

2 studies, N = 102
One study reported decreased Glu/Gln levels in the DLPFC in chronic schizophrenia.
One study reported increased Glu levels in chronic patients with acute exacerbation.

1 study, N = 20
In adolescents with high genetic risk of schizophrenia, both Glu and Gln levels were increased in the medial prefrontal cortex

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

Achim AM, Lepage M

Episodic memory-related activation in schizophrenia: meta-analysis

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

Comparison
Functional activation in people with schizophrenia vs. healthy controls during episodic memory tasks.

Summary of evidence
Moderate quality evidence (large sample sizes, direct, unable to assess precision and consistency) suggests decreases in functional activation during memory encoding tasks in the middle and medial frontal gyri, and reductions during memory retrieval tasks in the medial and inferior frontal cortex.

Activation during episodic memory tasks

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

8 studies, N = 176

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

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

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

11 studies, N = 298

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

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

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


Implications of lipid biology for the pathogenesis of schizophrenia


View review abstract online

Comparison | Comparison of prefrontal cortex phospholipid metabolites (measured by 31P MRS) in people with drug naive first-episode psychosis, newly diagnosed or chronic schizophrenia vs. healthy controls.

Summary of evidence | Moderate quality evidence (medium to large samples, direct, unable to assess precision or consistency) suggests phosphomonoester (PME) levels are reduced in the prefrontal cortex of people with first-episode psychosis and people with schizophrenia. There are also increased phosphodiester (PDE) levels in the prefrontal cortex of first-episode psychosis patients when compared to controls.

PME levels

3 of 3 studies (N = 78) reported decreased PME levels in both first-episode and newly diagnosed patients.

7 of 11 studies (222/415 patients) reported decreased PME levels in people with chronic schizophrenia.

PDE levels
3 of 3 studies (N = 78) reported increased PDE levels in both first-episode and newly diagnosed patients.

3 of 10 studies (87/363 patients) reported increased PDE levels in people with chronic schizophrenia.

1 of 10 studies (86/363 patients) reported decreased PDE levels in people with chronic schizophrenia.

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*Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ, Yücel M, Velakoulis D, Pantelis C*

**Neuroanatomical abnormalities in schizophrenia: A multimodal voxelwise meta-analysis and meta-regression analysis**

*Schizophrenia Research 2011; 127: 46-57*

View review abstract online

**Comparison**

Grey and white matter density in people with chronic or first-episode schizophrenia vs. healthy controls.

**Summary of evidence**

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

**Grey and white 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.

<table>
<thead>
<tr>
<th>N = 4179, 49 studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left insula/inferior frontal: Talairach coordinates (-42, 8, 6), cluster 1339mm³, p &lt; 0.000001</td>
</tr>
<tr>
<td>Right insula/inferior frontal: Talairach coordinates (46, 2, 6), cluster 1047mm³, p &lt; 0.000001</td>
</tr>
<tr>
<td>Bilateral dorsal medial frontal/anterior cingulate: Talairach coordinates (4, 26, 40), cluster 496mm³,</td>
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</table>
Frontal lobe

\[ p = 0.000002 \]

Left rostral medial frontal/anterior cingulate: Talairach coordinates (-4, 46, -2), cluster 467mm³, \( p = 0.00007 \)

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) \( p = 0.0002 \)] 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.

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*Chan RCK, Di X, McAlonan GM, Gong Q*

**Brain Anatomical Abnormalities in High-Risk Individuals, First-Episode, and Chronic Schizophrenia: An Activation Likelihood Estimation Meta-analysis of Illness Progression**

*Schizophrenia Bulletin* 2011; 37(1) 177-188

[View review abstract online]

| Comparison                          | Grey matter changes in people at high risk of schizophrenia or first episode schizophrenia vs. healthy 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. |
Frontal lobe

Summary of evidence

Moderate quality evidence (large sample size, direct, unable to assess consistency or precision) suggests high-risk individuals have grey matter reductions in left inferior frontal gyrus compared to healthy 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 healthy 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 healthy 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, $N = 1031$

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

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

14 studies, $N = 1082$

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

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

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

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

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

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

19 studies, $N = 1664$

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

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

Left medial frontal gyrus: Talairach coordinates (-6, 34, -14), cluster 2976mm$^3$, ALE 0.0182

Left middle frontal gyrus: Talairach coordinates (-44, 8, 36), cluster 1208mm$^3$, ALE 0.0199

Left inferior frontal gyrus: Talairach coordinates (-50, 6, 30), cluster 1208mm$^3$, ALE 0.0176

Right superior frontal gyrus: Talairach coordinates (30, 54, 10), cluster 416mm$^3$, ALE 0.0147

Right middle frontal gyrus: Talairach coordinates (42, 4, 38), cluster 392mm$^3$, ALE 0.0171
Frontal lobe

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 (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

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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

| Comparison 1 | Grey matter volume in people with schizophrenia vs. healthy controls. |
### Frontal lobe

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>Moderate quality evidence (large sample size, mostly inconsistent, precise, direct) suggests grey matter volume is significantly reduced in the frontal lobe in schizophrenia.</th>
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#### Frontal lobe volume

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| **Left frontal lobe** | Small to medium effect size suggests reduced volume in schizophrenia;  
N = 2067, \( d = -0.39, 95\%CI -0.55 \) to \(-0.23, p \) not reported, SD = 0.47, FSN = 104 |
| **Right frontal lobe** | Small to medium effect size suggests reduced volume in schizophrenia;  
N = 1951, \( d = -0.41, 95\%CI -0.56 \) to \(-0.26, p \) not reported, SD = 0.42, FSN = 102 |
| **Total frontal lobe** | Small to medium effect size suggests reduced volume in schizophrenia;  
N = 3194, \( d = -0.44, 95\%CI -0.55 \) to \(-0.32, p \) not reported, SD = 0.42, FSN = 170 |

#### Consistency in results

Significant heterogeneity reported in all outcomes except right frontal cortex.

#### Precision in results

Precise for all outcomes.

#### Directness of results

Direct

#### Comparison 2

Functional activation in people with schizophrenia vs. healthy controls during episodic memory tasks.

#### Summary of evidence

Moderate to high quality evidence (large sample size, precise, direct, consistent for individual hemispheres during task) shows a medium to large effect of reduced functional activity in bilateral frontal lobes in people with schizophrenia both during cognitive tasks and at rest.

#### Frontal lobe activity during task

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| **Left frontal lobe** | Medium effect size suggests reduced activity in schizophrenia;  
N = 390, \( d = -0.54, 95\%CI -0.78 \) to \(-0.30, SD = 0.38, FSN = 53 |
| **Right frontal lobe** | Medium effect size suggests reduced activity in schizophrenia; |
Frontal lobe

<table>
<thead>
<tr>
<th>N = 397, d = -0.54, 95%CI -0.90 to -0.18, SD = 0.53, FSN = 48</th>
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</thead>
<tbody>
<tr>
<td><strong>Total frontal lobe</strong></td>
</tr>
<tr>
<td><em>Large effect size suggests reduced activity in schizophrenia;</em></td>
</tr>
<tr>
<td>N = 879, d = -0.81, 95%CI -1.06 to -0.57, SD = 0.52, FSN = 142</td>
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**Frontal lobe activity at rest**

<table>
<thead>
<tr>
<th>N = 617, d = -0.48, 95%CI -0.80 to -0.15, SD = 0.74, FSN = 87</th>
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<tbody>
<tr>
<td><strong>Left frontal lobe</strong></td>
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<tr>
<td><em>Medium effect size suggests reduced activity in schizophrenia;</em></td>
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</table>

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

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**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. healthy controls.

### Summary of evidence

Moderate quality evidence (large sample sizes, direct, unable to assess consistency and precision) suggests reduced white...
Frontal lobe

<table>
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<tr>
<th>matter volume in the frontal lobe of people with schizophrenia.</th>
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**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

**Consistency in results**

No measure of consistency is reported.

**Precision in results**

No confidence intervals are reported.

**Directness of results**

Direct

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**Ellison-Wright I, Glahn DC, Laird AR, Thelen, SM, Bullmore E**

*The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis*

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

View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Grey matter changes in people with first-episode schizophrenia vs. people with chronic schizophrenia vs. healthy controls.</th>
</tr>
</thead>
</table>

| Summary of evidence | Moderate quality evidence (large sample size, direct, unable to assess consistency or precision) suggests grey matter reductions in the inferior frontal in first-episode schizophrenia, and in the inferior frontal, medial frontal and the dorsolateral prefrontal in chronic schizophrenia. |

**Grey matter changes**

27 studies, $N = 1556$
Frontal lobe

*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;*
\( N = 1556, 27 \) studies
Significant reduction of volume was seen in the inferior frontal gyrus, \( p < 0.001 \)

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</table>

*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]

**Comparison**
White matter fractional anisotropy (FA) in people with schizophrenia vs. healthy controls.

**Summary of evidence**
Moderate quality evidence (large sample size, direct, unable to fully assess precision and consistency) suggests schizophrenia is associated with significant reductions in white matter integrity in the frontal lobe.

**FA**
Meta-analysis was performed using a hybrid of Activation Likelihood Estimate (ALE) analysis and Genome Scan Meta-analysis (GSMA) which combines activation foci from multiple studies, and permits weighting for sample size.

FWHM 7mm, FDR corrected at \( p < 0.05 \)
15 studies, \( N = 790 \)
Frontal lobe FA reduction in people with schizophrenia;
Talairach coordinates (-12, 34, 10), p < 0.0001, Voxel cluster size 2368mm³
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>
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<tbody>
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</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. healthy controls.

Summary of evidence | Moderate quality evidence (large sample sizes, direct, unable to assess consistency or precision) suggests grey matter reductions in bilateral medial frontal gyr and in left deep frontal lobe.

<table>
<thead>
<tr>
<th>Grey matter changes</th>
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Meta-analysis was performed using Activation Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies.
FWHM 7mm, FDR corrected at p < 0.05
42 studies, N = 4189

Regions of decreased grey matter in schizophrenia;
Left medial frontal gyrus: Talairach coordinates (-2, 50, 4), Sum of ranks = 179.6, p = 0.00005
Left medial frontal gyrus: Talairach coordinates (-2, 48, 0), Sum of ranks = 179.3, p = 0.00005
Left deep frontal lobe: Talairach coordinates (-14, 2, -10), Sum of ranks = 172.8, p = 0.00005
Left deep frontal lobe: Talairach coordinates (-12, 0, -8), Sum of ranks = 172.5, p = 0.00005
Frontal lobe

| Right medial frontal gyrus: Talairach coordinates (2, 42, 26), Sum of ranks = 157.1, \( p = 0.00060 \) |
| Right medial frontal gyrus: Talairach coordinates (2, 44, 24), Sum of ranks = 156.8, \( p = 0.00070 \) |
| Right medial frontal gyrus: Talairach coordinates (2, 48, 22), Sum of ranks = 156.5, \( p = 0.00075 \) |

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

**Fornito A, Yucel M, Patt, J, Wood SJ, Pantelis C**

**Mapping grey matter reductions in schizophrenia: An anatomical likelihood estimation analysis of voxel-based morphometry studies**

*Schizophrenia Research 2009; 108(1-3): 104-113*

[View review abstract online](#)

**Comparison**

Grey matter density, volume (GMV) and concentration (GMC, grey matter as a proportion of the whole brain volume) in people with schizophrenia vs. healthy controls.

**Summary of evidence**

Moderate quality evidence (large sample sizes, 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 samples, direct, unable to assess consistency or precision) suggests grey matter volume reductions were reported in the right prefrontal cortex, left orbito-frontal gyrus, left superior frontal gyrus, left medial frontal gyrus, and bilateral inferior and middle frontal gyri.

**Grey matter density**

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

FWHM 12mm, FDR corrected at \( p < 0.05 \)

37 studies, \( N = 3336 \)

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

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Tissue Region</th>
<th>Talairach Coordinates</th>
<th>Voxel Cluster Size</th>
<th>ALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>37 studies, N = 3336</td>
<td>GMC reductions were significantly more frequent than GMV in;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right anterior cingulate gyrus/medial prefrontal gyrus:</td>
<td>(0.04, 53.3, 0.59), Voxel cluster size 5144mm³, ALE 1.36 x 10⁻³</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left medial orbito-frontal gyrus:</td>
<td>(-1.11, 43.03, -21.06), Voxel cluster size 1208mm³, ALE 0.87 x 10⁻³</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GMV reductions were significantly more frequent than GMC in;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left medial superior frontal gyrus:</td>
<td>(-5.6, 31.84, 46.13), Voxel cluster size 1688mm³, ALE -0.76 x 10⁻³</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left lateral superior frontal gyrus:</td>
<td>(-31.56, 53.64, 19.6), Voxel cluster size 1120mm³, ALE -0.68 x 10⁻³</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right inferior frontal gyrus:</td>
<td>(48.39, 2.83, 30.96), Voxel cluster size 1096mm³, ALE -0.74 x 10⁻³</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left lateral orbito-frontal gyrus:</td>
<td>(-26.82, 28.11, -4.7), Voxel cluster size 680mm³, ALE 0.74 x 10⁻³</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right pre and post-central gyri:</td>
<td>(52.97, -24.28, 43.55), Voxel cluster size 408mm³, ALE -0.54 x 10⁻³</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left middle frontal gyrus:</td>
<td>(-42.94, 9.86, 39.04), Voxel cluster size 192mm³, ALE 0.68 x 10⁻³</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right middle/inferior frontal gyri:</td>
<td>(27.67, 58.41, 9.68), Voxel cluster size 192mm³, ALE 0.68 x 10⁻³</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

<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>
</tbody>
</table>
Frontal lobe

**Directness of results**

| Directness of results | Direct |

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

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

*Neuroscience & Biobehavioral Reviews 2007; 31(4): 465-484*

[View review abstract online](#)

**Comparison 1**

| Functional activity in individuals following their first episode of schizophrenia vs. healthy 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**

1 study, N = 23

Reduced activation of frontal lobe ($d = 0.93$) in medication naïve people with schizophrenia compared to controls during information processing tasks.

**Working memory task**

1 study, N = 22

Large effect size suggests reduced activation in the DLPFC ($d = 1.0$) and the VLPFC ($d = 1.09$) of medicated people with schizophrenia compared to controls during working memory tasks.

1 study, N = 18

Large effect size suggests reduced activation in the DLPFC ($d = 1.29$) of medication naïve people with first-episode schizophrenia compared to controls during working memory tasks.

1 study, N = 16

Large effect size suggests reduced activation of the DLPFC ($d = 1.68$) in people with first-episode schizophrenia compared to controls during working memory tasks.
### Frontal lobe

<table>
<thead>
<tr>
<th>Task</th>
<th>Study Counts</th>
<th>Effect Size</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verbal fluency task</strong></td>
<td>1, N = 20</td>
<td>d = 2.57</td>
<td>Reduced activation of DLPFC and anterior frontal cortex in people with first-episode schizophrenia compared to controls.</td>
</tr>
<tr>
<td><strong>Executive control task</strong></td>
<td>1, N = 47</td>
<td>d = 0.88</td>
<td>Reduced activation of DLPFC in untreated people with first-episode schizophrenia compared to controls.</td>
</tr>
<tr>
<td><strong>Context processing task</strong></td>
<td>1, N = 46</td>
<td>d = 0.76</td>
<td>Reduced activation of DLPFC, and increased activation of AFC and VLPFC in untreated people with first-episode schizophrenia compared to controls.</td>
</tr>
<tr>
<td><strong>Planning task</strong></td>
<td>1, N = 20</td>
<td>d = 1.84</td>
<td>Reduced activation of DLPFC, VLPFC, and AFC in people with first-episode schizophrenia compared to controls.</td>
</tr>
<tr>
<td><strong>Visual attention task</strong></td>
<td>1, N = 26</td>
<td>d = 0.9</td>
<td>Reduced activation of DLPFC, and VLPFC in people with first-episode schizophrenia compared to controls.</td>
</tr>
</tbody>
</table>

**Consistency in results**: No measure of heterogeneity is reported.

**Precision in results**: No confidence intervals are reported.

**Directness of results**: Direct.
### Functional activity in relatives of people with schizophrenia vs. healthy controls.

**Comparison 2**

**Summary of evidence**

Low quality evidence (one small study per outcome) is unclear as to the direction of the changes in functional activity in the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, medial frontal gyrus during verbal initiation, working memory, verbal memory, and emotional face processing tasks in individuals at high risk of developing schizophrenia.

<table>
<thead>
<tr>
<th>Task</th>
<th>Study Count, Participants</th>
<th>Effect Size</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verbal initiation task</strong></td>
<td>1 study, N = 63</td>
<td>Medium $d = 0.5$</td>
<td>Reduced activation of medial frontal gyrus in non-psychotic relatives of people with schizophrenia compared to controls during visual initiation tasks.</td>
</tr>
<tr>
<td><strong>Working memory task</strong></td>
<td>1 study, N = 41</td>
<td>Medium $d = 0.60$, $d = 0.54$, $d = 0.58$</td>
<td>Increased activation of DLPFC, VLPFC, and inferior parietal lobe in siblings of people with schizophrenia compared to controls during working memory tasks.</td>
</tr>
<tr>
<td></td>
<td>1 study, N = 40</td>
<td>Small $d = 0.42$, $d = 0.43$, $d = 0.48$</td>
<td>Increased activation of DLPFC, VLPFC, and inferior parietal lobe in siblings of people with schizophrenia compared to controls during working memory tasks.</td>
</tr>
<tr>
<td></td>
<td>1 study, N = 24</td>
<td>Large $d = 0.79$, $d = 0.96$</td>
<td>Increased activation of DLPFC and anterior cingulate gyrus in non-psychotic relatives of people with schizophrenia compared to controls during working memory tasks.</td>
</tr>
<tr>
<td></td>
<td>1 study, N = 45</td>
<td>Large $d = 1.0$</td>
<td>Increased activation of DLPFC in non-psychotic relatives of people with schizophrenia compared to controls during working memory tasks.</td>
</tr>
<tr>
<td><strong>Verbal memory task</strong></td>
<td>1 study, N = 70</td>
<td>Reduced cerebral perfusion</td>
<td>Reduced cerebral perfusion during a verbal memory task in relatives of people with schizophrenia compared to healthy controls, particularly in the inferior prefrontal cortex.</td>
</tr>
<tr>
<td><strong>Emotional face processing task</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Frontal lobe

<table>
<thead>
<tr>
<th>Study</th>
<th>N = 39</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

#### 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. healthy controls.

#### Summary of evidence
- Moderate to low quality evidence (medium sample sizes, direct, unable to assess precision and inconsistency) suggests reduced Glu/Gln and PME levels and increased PDE levels in the frontal lobe of first-degree relatives when compared to controls.

### Metabolite levels

| Four studies, N = 268, assessed Glu/Gln and reported reduced Glu/Gln in the DLPFC in relatives vs. controls. |
| 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

---

*Glahn DC, Ragland JD, Abramoff A, Barrett J, Laird AR, Bearden CE, Velligan DI*

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

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

[View review abstract online](#)
### Frontal lobe

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Functional activation in individuals with schizophrenia vs. healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary of evidence</strong></td>
<td>Moderate to low quality evidence (medium to large samples, 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 472mm$^3$
    - Right middle and inferior frontal gyrus: Talairach centre of mass (33, 37, 28), cluster volume 1200mm$^3$
    - Left middle frontal gyrus: Talairach centre of mass (-33, 35, 23), cluster volume 1736mm$^3$
    - Right inferior frontal gyrus and insula: Talairach centre of mass (38, 16, 5), cluster volume 936mm$^3$
  - **Significantly increased activity in people with schizophrenia compared to controls**;
    - Left middle frontal gyrus: Talairach centre of mass (-44, 42, -3), cluster volume 560mm$^3$
    - Right superior frontal gyrus: Talairach centre of mass (4, 57, 26), cluster volume 264mm$^3$

<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>
<tr>
<td>Directness of results</td>
<td>Direct</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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Grey matter density in people with schizophrenia vs. healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (large sample sizes, direct, unable to assess consistency or precision) suggests schizophrenia is associated with significant grey matter reductions in the middle frontal gyrus.</td>
</tr>
</tbody>
</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 $p < 0.05$

13 studies, N = 2457

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 $432 \text{mm}^3$, $p < 0.01$, ALE = 0.011

### Consistency in results

No measure of consistency is reported.

### Precision in results

No confidence intervals are reported.

### Directness of results

Direct

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Goghari MV

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

*Psychological Medicine 2001; 41: 1239-1252*

[View review abstract online](#)

### Comparison

<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>Summary of evidence</td>
<td>Moderate quality evidence (unable to assess consistency or precision, direct) suggests relatives of people with schizophrenia show increased functional activation during an executive functioning task in the right superior and middle frontal gyri.</td>
</tr>
</tbody>
</table>
Frontal lobe

Frontal gyri. Decreased activation in relatives compared to controls was shown in the right middle and inferior and left superior frontal gyri, right precentral gyrus, and left medial frontal gyrus. During cognitive control tasks, relatives showed activation increases in the left middle frontal gyrus compared to controls. During working memory tasks, relatives showed increased activation of the right middle frontal gyrus and decreased activation in the right middle and inferior frontal gyri, right precentral gyrus.

### Executive functioning task

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

- **17 studies, N = 456**

  **Increased activity in relatives of people with schizophrenia compared to controls in;**
  - Right middle frontal gyrus: Talairach coordinates (32, 50, 10), cluster volume 376 mm$^3$
  - Right superior frontal gyrus: Talairach coordinates (40, 36, 32), cluster volume 400 mm$^3$
  - Right middle frontal/precentral gyrus: Talairach coordinates (46/46/34, 16/24/12, 16/24/12), cluster volume 792 mm$^3$

  **Decreased activity in relatives of people with schizophrenia compared to controls in;**
  - Right middle frontal gyrus: Talairach coordinates (32, 52, 10), cluster volume 424 mm$^3$
  - Right middle frontal gyrus: Talairach coordinates (38, 36, 34), cluster volume 1008 mm$^3$
  - Right inferior frontal gyrus: Talairach coordinates (52/54, 8/8, 18/24), cluster volume 192 mm$^3$
  - Right precentral gyrus: Talairach coordinates (40, -6, 42), cluster volume 152 mm$^3$
  - Right precentral gyrus: Talairach coordinates (50, -4, 22), cluster volume 144 mm$^3$

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

  **Increased activity in relatives of people with schizophrenia compared to controls in;**
  - Right middle frontal gyrus: Talairach coordinates (32, 50, 10), cluster volume 480 mm$^3$
  - Right middle frontal/ precentral gyrus: Talairach coordinates (48/46, 16/24, 32/36), cluster volume 176 mm$^3$

  **Decreased activity in relatives of people with schizophrenia compared to controls in;**
  - Left medial frontal gyrus: Talairach coordinates (-12, 64, -2), cluster volume 136 mm$^3$
Frontal lobe

<table>
<thead>
<tr>
<th>Cognitive control task</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Increased activity in relatives of people with schizophrenia compared to controls in;</em></td>
</tr>
<tr>
<td>Left middle/ superior frontal gyrus: Talairach coordinates (-28/-26, 48/50, 20/12), cluster volume 168 mm³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Working memory task</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Increased activity in relatives of people with schizophrenia compared to controls in;</em></td>
</tr>
<tr>
<td>Right middle frontal gyrus: Talairach coordinates (32, 50, 10), cluster volume 480 mm³</td>
</tr>
<tr>
<td>Right middle frontal/ precentral gyrus: Talairach coordinates (48/46, 16/24, 32/36), cluster volume 176 mm³</td>
</tr>
<tr>
<td><em>Decreased activity in relatives of people with schizophrenia compared to controls in;</em></td>
</tr>
<tr>
<td>Right middle frontal gyrus: Talairach coordinates (38, 36, 34), cluster volume 1008 mm³</td>
</tr>
<tr>
<td>Right inferior frontal gyrus: Talairach coordinates (52/54, 8/8, 18/24), cluster volume 176 mm³</td>
</tr>
<tr>
<td>Right precentral gyrus: Talairach coordinates (40, -6, 42), cluster volume 168 mm³</td>
</tr>
</tbody>
</table>

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

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

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

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

[View review abstract online](#)
### Summary of evidence

Moderate quality evidence (large sample size, 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 healthy controls.

### Neurocognitive tasks; working memory, executive function, vigilance tasks combined

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frontal lobe activity</strong></td>
<td>14 observational studies, N = 319</td>
</tr>
<tr>
<td></td>
<td><em>No significant difference observed in frontal lobe activity;</em></td>
</tr>
<tr>
<td></td>
<td>Kolmogorov-Smirnov test (KS3) = 0.16, <em>p = 0.94</em></td>
</tr>
<tr>
<td><strong>Non-frontal lobe</strong></td>
<td>14 observational studies, N = 319</td>
</tr>
<tr>
<td></td>
<td><em>No significant difference observed in non-frontal lobe activity;</em></td>
</tr>
<tr>
<td></td>
<td>KS3 = 0.14, <em>p = 0.98</em></td>
</tr>
</tbody>
</table>

### Consistency in results

No measure of heterogeneity is provided.

### Precision in results

No confidence intervals are provided.

### Directness of results

Direct

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**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](#)
### Frontal lobe

**Grey matter density**

<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>

- 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

---

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

**Diffusion tensor imaging in schizophrenia**

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

*View review abstract online*

**Comparison**

- White matter fractional anisotropy (FA) in people with schizophrenia vs. healthy controls.

**Summary of evidence**

- Moderate quality evidence (large sample size, direct, unable to fully assess precision and consistency) suggests decreased FA in the frontal lobe.

**FA**

- 19 studies, N = 640

Frontal lobe illustrated decreased FA in at least one study between people with schizophrenia and controls.

**Consistency in results**

- No measure of consistency is reported.

**Precision in results**

- No confidence intervals are reported.

**Directness of results**

- Direct
Kyriakopoulos M, Bargiotas T, Barker GJ, Frangou S

Diffusion tensor imaging in schizophrenia


View review abstract online

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

**FA**

15 studies, N = unclear

*Regions that illustrated decreased FA in at least one study between people with schizophrenia and controls:*

- Prefrontal cortex (12 studies)
- Internal capsule (4 studies)
- Arcuate fasciculus (5 studies)

**Consistency in results**

No measure of consistency is reported.

**Precision in results**

No confidence intervals are reported.

**Directness of results**

Direct

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

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

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

View review abstract online

| Comparison | Grey matter changes in first episode schizophrenia (treated and medication naïve) vs. healthy controls. |
Summary of evidence

Moderate quality evidence (large sample sizes, indirect, 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.

Grey matter density

Meta-analysis was performed using Anatomical Likelihood Estimate (ALE) analysis on Voxel-Based Morphometry MRI studies. FWHM 8mm, FDR corrected at $p < 0.05$

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

- 6 studies, N = 327
  - Left precentral gyrus: Talairach coordinates (-50, -10, 24), cluster 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;

- 9 studies, N = 820
  - 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 0.0057
  - 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

Areas where grey matter reductions were larger in magnitude in treatment-naïve patients than in treated patients;
Frontal lobe

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 middle frontal gyrus (to inferior frontal): Talairach coordinates (46, 12, 16), 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

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

Right precentral gyrus: Talairach coordinates (48, -10, 12), cluster 432mm³, ALE 0.0143
Left medial frontal gyrus (to anterior cingulate): Talairach coordinates (-6, 48, 8), cluster 632mm³, ALE 0.0098
Left medial frontal gyrus (to anterior cingulate): Talairach coordinates (-2, 36, -2), cluster 360mm³, ALE 0.0077
Right medial frontal gyrus: Talairach coordinates (2, 36, -16), cluster 384mm³, ALE 0.0135
Right middle frontal gyrus: Talairach coordinates (44, 36, 18), cluster 280mm³, ALE 0.0112
Right inferior frontal gyrus: Talairach coordinates (24, 34, -6), cluster 512mm³, ALE 0.0185
Left inferior frontal gyrus: Talairach coordinates (-32, 34, -4), cluster 488mm³, ALE 0.0151

<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>

MacDonald AW, Thermenos HW, Barch DM, Seidman L

Imaging genetic liability to schizophrenia: systematic review of fMRI studies of patients' nonpsychotic relatives


View review abstract online

March 2017
### Frontal lobe

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Functional activation in first-degree relatives of people with schizophrenia vs. healthy controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary of evidence</strong></td>
<td>Moderate to low quality evidence (large sample size, direct, unable to assess precision or consistency) suggests functional activity during cognitive control and working memory tasks shows abnormal activity (mostly increased) in the DLPFC of relatives. Patterns of VLPFC activity were less consistent, but showed increases during long-term memory tasks. Moderate to low quality evidence (large sample size, direct, unable to assess precision or consistency) suggests during language processing tasks, the right VLPFC shows functional alterations in relatives.</td>
</tr>
</tbody>
</table>

### Cognitive control tasks

7 studies investigated functional activity during cognitive control tasks, \( N = 308; \)

- 7 studies investigated DLPFC, 4/7 showed increased bilateral activity compared to controls. Activity (hyper- and hypo-) was abnormal in 82% of reports.
- 7 studies investigated VLPFC, 2/7 showed no group differences, two showed abnormal activity.

### Working memory tasks

4 studies (5 independent samples) investigated functional activity during working memory tasks, \( N = 239; \)

- 5 studies investigated DLPFC, 4/5 showed increased activity compared to controls. Activity (hyper- and hypo-) was abnormal in 67% of reports.
- 4 studies investigated VLPFC, 2/4 showed increased activity compared to controls. Activity (hyper- and hypo-) was abnormal in 67% of reports.

### Long-term memory tasks

3 studies investigated functional activity during episodic long-term memory tasks, \( N = 195; \)

- 3 studies investigated DLPFC, 2/3 showed no group differences, one showed increased activity in the right hemisphere.
- 3 studies investigated VLPFC, 2/3 showed increased activity compared to controls.

1 study investigated functional activity during procedural long-term memory tasks, \( N = 27; \)

- No group difference was reported for VLPFC.
- Reduced activity in relatives was shown in DLPFC.
Frontal lobe

<table>
<thead>
<tr>
<th>Language processing studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 studies investigated functional activity during language processing tasks, N = 164; 1/4 showed no group differences in DLPFC, and 1/4 showed reduced activity in the right hemisphere (2/4 showed no task-related response). 2/4 showed increased VLPFC activity compared to controls in the right hemisphere only.</td>
</tr>
</tbody>
</table>

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


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


View review abstract online

Comparison 1

Whole brain comparison of functional activation in individuals with schizophrenia vs. healthy controls: ALE analysis

Note – this review combines PET and fMRI studies in one meta-analysis

Summary of evidence

Moderate quality evidence (large sample size, 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

Moderate quality evidence (observational, large sample) suggests people with schizophrenia also show regions of increased activity in the superior and inferior frontal gyri during executive function tasks

Executive function tasks
41 studies, N = 1217

**ALE analysis – FWHM 12mm, False Discovery Rate (FDR) corrected model**

*Significantly reduced activity in people with schizophrenia compared to controls;*

- Left middle frontal gyrus: Talairach centre of mass (-38, 30, 30), cluster volume 3096mm$^3$
- Right middle frontal gyrus: Talairach centre of mass (32, 24, 42), cluster volume 712mm$^3$
- Right medial frontal gyrus: Talairach centre of mass (6, 42, 18), cluster volume 1480mm$^3$

*Significantly increased activity in people with schizophrenia compared to controls;*

- Left superior frontal gyrus: Talairach centre of mass (-8, -14, 68), cluster volume 440mm$^3$
- Left superior frontal gyrus: Talairach centre of mass (-2, 52, 24), cluster volume 1320mm$^3$
- Left inferior frontal gyrus: Talairach centre of mass (-40, 36, 12), cluster volume 656mm$^3$

<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*

*Frontiers in Psychiatry* 2013; 4: 99
*View review abstract online*

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Comparison of NAA/Cr ratio (measured by 'H-MRS) in the prefrontal cortex of people at risk of schizophrenia vs. age and sex matched controls. Clinical high-risk subjects were people who developed a brief psychotic episode (&lt;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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (large sample, direct, inconsistent, precise) suggests NAA/Cr ratio is reduced in the prefrontal cortex of people at clinical or familial risk of schizophrenia.</td>
</tr>
</tbody>
</table>
### NAA/Cr

NAA/Cr was significantly lower in the high-risk group;

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>( I^2 ) is not reported. Forest plot appears inconsistent, most likely due to differences in age.</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>

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]).

---

### Moncrieff J, Leo J

**A systematic review of the effects of antipsychotic drugs on brain volume**

*Psychological Medicine 2010; 40: 1409-1422*

[View review abstract online](#)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Brain volume in chronic medicated schizophrenia, first-episode schizophrenia, drug-naïve schizophrenia, and healthy controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Low quality evidence (sample sizes unclear, indirect, unable to assess consistency or precision) is unclear as the effect of antipsychotic medications on brain structure.</td>
</tr>
</tbody>
</table>

#### Brain volume changes over time

26 longitudinal studies compared people with either first-episode schizophrenia or psychosis (\( N = 767 \)) or chronic schizophrenia (\( N = 360 \)) to healthy controls;

16 of 26 studies found that patients in general showed a greater overall reduction in whole-brain, cortical, or grey matter volume, and a greater increase in CSF or ventricular volume compared to controls. Three studies found the frontal lobe grey matter to be most consistently affected, however 4 additional studies found diffuse changes throughout the brain. Changes of the temporal lobe were inconsistent, three of five studies found reductions and two studies found no difference.

Three studies examined the longitudinal effect of antipsychotics in treated patients;

One large RCT (\( N = 161 \)) found a significantly greater decline in total grey matter volume after 1
year in patients randomised to first generation haloperidol, compared to those on second generation olanzapine. However, within individual brain regions, namely the frontal, occipital, and parietal lobes, both groups showed significant grey matter volume reduction after 1 year ($p < 0.05$).

Another study ($N = 96$) found less grey matter loss in patients with higher doses of second generation olanzapine (non-significant trend, $p = 0.07$).

However, one smaller study ($N$ unclear) found no difference in grey matter volume between patients treated with first generation haloperidol or second generation olanzapine, or risperidone and controls.

Five studies have indicated no difference in volume changes between patients taking first generation and second generation antipsychotics.

Fourteen studies examined correlative linear relationships between antipsychotics and brain volume;

Nine of 14 studies showed no association.

One study showed an association between volume reduction and lifetime dose of medication ($r = 0.5$, $p = 0.009$).

One study found an association between treatment duration and ventricular size, but not cortical or hippocampal volume (no statistics).

Two studies found an association between current medication dose and volume reduction in frontal lobe ($r = 0.75$, $p < 0.001$), one of which was restricted to first-episode patients.

One study compared childhood-onset schizophrenia to children with transient psychosis and behavioural problems, and reported that schizophrenia showed greater loss of grey matter over time, although the comparison group showed greater overall volume deficits.

Five studies examined longitudinal effects in drug-naïve patients ($N = 120$);

Two of five studies reported reduction of grey matter after commencement of a drug treatment in patients compared to controls, however three of five studies did not report any global volume changes.

21 studies compared cross-sectional brain volume in drug-naïve patients ($N = 657$) and controls;

The majority of studies ($N$ not reported) did not report any differences in whole brain or total grey matter volume compared to controls. Three of these were in chronically unmedicated patients and reported no difference in global volumes.

5 of 21 studies reported volumetric differences between patients and controls, including grey matter volume, ventricular volume and cerebellar volume.

Three studies in people at high risk of schizophrenia also reported no difference in global grey matter, whole brain or ventricular volumes, including within the subset that transition to psychosis.
### Frontal lobe

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of consistency is reported, results appear inconsistent.</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>

**Navari S, Dazzan P**  
*Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings.*

*Psychological Medicine 2009; 39(11): 1763-1777*  
[View review abstract online](#)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Brain volumetry in medicated, drug free and drug naïve people with schizophrenia and healthy controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Low quality evidence (sample sizes unclear, direct, unable to assess consistency or precision) is unclear as the effect of antipsychotic medications on brain structure.</td>
</tr>
</tbody>
</table>

**Brain volume in drug-free and drug-naïve schizophrenia**
**Frontal lobe**

<table>
<thead>
<tr>
<th>Comparison of grey matter volume in drug-free or drug-naïve patients compared to treated patients and controls;</th>
<th>1 study, N unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both patient groups showed reduced cortical grey matter, particularly in DLPFC, compared to controls.</td>
<td></td>
</tr>
</tbody>
</table>

**Whole brain comparison of grey matter volume in patients medicated for less than 12 weeks prior to the treatment period being investigated, compared to drug-naïve patients and controls;**

<table>
<thead>
<tr>
<th>2 studies, N unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients medicated with first generation antipsychotics showed reduced cortical grey matter, including volume of frontal, and reduced cortical thickness of frontal cortex.</td>
</tr>
</tbody>
</table>

**Longitudinal whole brain comparison of grey matter volume in drug-free or drug-naïve patients, compared to treated patients and controls;**

<table>
<thead>
<tr>
<th>2 studies, N unclear, varying follow up (range 4 weeks – 2 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two studies showed both no change in prefrontal volume and reductions in prefrontal volume in drug naïve patients over a treatment course.</td>
</tr>
</tbody>
</table>

**Longitudinal whole brain comparison of grey matter volume in patients medicated for less than 12 weeks prior to the treatment period being investigated, compared to drug naïve patients and controls;**

<table>
<thead>
<tr>
<th>5 studies, N unclear, varying follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three studies found no longitudinal changes in cortical and prefrontal cortex volumes in patients previously medicated in the short term.</td>
</tr>
<tr>
<td>Two further studies reported reductions in total cortical and frontal cortex volume at follow up, one study reported an association to typical antipsychotics.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consistency in results</th>
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<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**

Frontal lobe

**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. healthy controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary of evidence</strong></td>
<td>High quality evidence (large sample sizes, consistent, precise, direct) suggests significantly greater reductions over time in frontal grey and white matter in people with schizophrenia compared to healthy 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 = 1867

*Significantly greater reductions were reported over time in schizophrenia compared to controls;*

- Frontal GM: N = 503, 9 studies, $d = -0.340$, 95%CI -0.66 to -0.02, $p = 0.035$, $I^2 = 59.8\%$
- Frontal WM: N = 323, 5 studies, $d = -0.512$, 95%CI -0.76 to -0.26, $p = 0.0001$, $I^2 = 0\%$

**Consistency in results** Consistent

**Precision in results** Precise

**Directness of results** Direct

---

*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. healthy controls.</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 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.</td>
</tr>
</tbody>
</table>
Moderate to low quality evidence (large sample, direct, unable to assess precision or consistency) suggests functional activity during episodic retrieval is reduced in the left inferior frontal gyrus and left middle frontal gyrus, and increased in the left precentral gyrus and right middle frontal gyrus of people with schizophrenia compared to controls.

### Episodic encoding task

<table>
<thead>
<tr>
<th>Area</th>
<th>Volume</th>
<th>Talairach Centre of Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right superior frontal gyrus</td>
<td>4608mm³</td>
<td>(22, 48, 14)</td>
</tr>
<tr>
<td>Right superior frontal gyrus</td>
<td>1104mm³</td>
<td>(6, 36, 48)</td>
</tr>
<tr>
<td>Right inferior frontal gyrus</td>
<td>2760mm³</td>
<td>(40, 30, 12)</td>
</tr>
<tr>
<td>Left inferior frontal gyrus</td>
<td>1424mm³</td>
<td>(-36, 26, 12)</td>
</tr>
</tbody>
</table>

### Episodic retrieval task

<table>
<thead>
<tr>
<th>Area</th>
<th>Volume</th>
<th>Talairach Centre of Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left inferior frontal gyrus</td>
<td>3048mm³</td>
<td>(-40, 22, 20)</td>
</tr>
<tr>
<td>Left precentral gyrus</td>
<td>1064mm³</td>
<td>(-36, -2, 28)</td>
</tr>
<tr>
<td>Left middle frontal gyrus</td>
<td>888mm³</td>
<td>(-38, 32, 38)</td>
</tr>
</tbody>
</table>
Subgroup analysis

Seven of ten studies (63 foci) controlled for group performance differences.

ALE analysis excluding those studies which did not control for performance differences, all foci showed similar activation patterns except the left precentral was not activated.

Six studies contributing 26 foci investigated functional activity during episodic retrieval tasks. ALE analysis – FWHM 12mm, False Discovery Rate (FDR) corrected model $p < 0.05$

*Significantly greater activity in people with schizophrenia compared to controls;*

Left precentral gyrus: cluster volume 1296mm$^3$, Talairach centre of mass (-28, -26, 66)

Right medial frontal gyrus: cluster volume 1168mm$^3$, Talairach centre of mass (12, 44, 10)

Right middle frontal gyrus: cluster volume 600mm$^3$, Talairach centre of mass (34, 36, -16)

Subgroup analysis

Four of six studies (21 foci) controlled for group performance differences. ALE analysis excluding those studies which did not control for performance differences, all foci showed similar activation patterns except the right medial frontal gyrus was not activated.

<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>
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</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</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. healthy controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (large samples, direct, unable to fully assess precision or consistency) suggests NAA levels are</td>
</tr>
</tbody>
</table>
Frontal lobe

<table>
<thead>
<tr>
<th>NAA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced in the frontal lobe, particularly the DLPFC and frontal pole in people with schizophrenia compared to healthy controls.</td>
<td></td>
</tr>
</tbody>
</table>

**Frontal lobe**

18/26 studies (N = 781/1127) show decreased NAA in people with schizophrenia.

8/26 studies (N = 346/1127) 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.

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


**The Effects of Antipsychotics on the Brain: What Have We Learnt from Structural Imaging of Schizophrenia? - A Systematic Review**


View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Grey matter volume changes in treated and untreated people with schizophrenia compared to healthy 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) is largely unclear as to the role of medication in mediating structural alterations in people with schizophrenia.</td>
</tr>
</tbody>
</table>

Grey matter volume changes
Frontal lobe

3 studies, N unclear

1 study reported first-episode psychosis patients treated with typical antipsychotics showed increased inferior frontal gyrus volume.

2 studies used VBM methodology to assess structural changes following administration of antipsychotics. First-episode patients treated with risperidone in the short term showed reduced frontal lobe volume compared to controls. In early-onset patients, second generation antipsychotics were associated with reduced frontal lobe volume compared to healthy controls.

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

Comparison

Differences in anatomical asymmetry in people with schizophrenia vs. controls.

Summary of evidence

Moderate to low quality evidence (inconsistent, imprecise, direct) suggest people with schizophrenia show an absence of normal leftward asymmetry in the Sylvian fissure. There was also a higher frequency of abnormal (reversed) asymmetry in the frontal lobe in people with schizophrenia compared to controls.

Anatomical asymmetry

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 0.2, p < 0.01, Q = 11.1, p = 0.03
Frontal lobe

Consistency in results | Inconsistent
---|---
Precision in results | Imprecise
Directness of results | Direct

**Steen RG, Hamer RM, Lieberman JA**

**Measurement of brain metabolites by \(^1\)H magnetic resonance spectroscopy in patients with schizophrenia: a systematic review and meta-analysis**


[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. healthy 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
Frontal lobe

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Significant heterogeneity reported, $p &lt; 0.0001$.</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>

**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**

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

Note – this review combines PET and fMRI studies in one meta-analysis.

**Summary of evidence**

Moderate to high quality evidence (large sample sizes, 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.
Frontal lobe

### Working memory tasks

*No significant differences between groups;*

<table>
<thead>
<tr>
<th>DLPFC Activation</th>
<th>Observational Studies</th>
<th>N</th>
<th>Effect Size (d)</th>
<th>95% Confidence Interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined hemispheric</td>
<td>30</td>
<td>808</td>
<td>0.20</td>
<td>-0.05 to 0.44</td>
<td>0.13</td>
</tr>
<tr>
<td>Left hemisphere DLPFC</td>
<td>28</td>
<td>776</td>
<td>0.23</td>
<td>-0.05 to 0.51</td>
<td>0.11</td>
</tr>
<tr>
<td>Right hemisphere DLPFC</td>
<td>28</td>
<td>776</td>
<td>0.15</td>
<td>-0.13 to 0.42</td>
<td>0.34</td>
</tr>
</tbody>
</table>

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 comparisons and measures of functional activity.

---

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

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


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

Frontal lobe volume
Frontal lobe

Left frontal volume: 13 studies, N = 762  $d = -0.34$, no CIs reported; $p = 0.08$ (average volume 95% of control volume, 95%CI 92 to 98%)

Right frontal volume: 13 studies, N = 762  $d = -0.36$, no CIs reported; $p = 0.64$ (average volume 95% of control volume, 95%CI 93 to 97%)

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Consistent – no significant heterogeneity is reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise – CI range does not exceed 10% in either direction.</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

**Explanation of acronyms**

AFC = anterior frontal cortex, ALE = activation likelihood analysis, CI = Confidence Interval, Cr = creatine, $d =$ Cohen’s $d$ and $g =$ Hedges’ $g =$ standardized mean differences (see below for interpretation of effect size), 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, Gin = glutamine, Glu = glutamate, GMC = grey matter concentration, GMV = grey matter volume, $I^2 =$ the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), KS = Kolgorov smirnov, MNI = Montreal Neurological Institute, MRS = magnetic resonance spectroscopy, N = number of participants, NAA = N-acetyl aspartate, $p =$ statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PET = positron emission tomography, PDE = phosphodiesters, PME = phosphomonoesters, 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
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.

† 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.

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. InOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios...
measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (e.g., 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 being in units of standard deviations to allow comparison across different scales. Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. 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;

\[ I^2 = \left( \frac{Q - d^1}{Q} \right) \times 100\% \]

§ 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 relaxed38.

‖ 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.
Frontal lobe

References

Frontal lobe


Frontal lobe