TECHNICAL COMMENTARY

Functional Magnetic Resonance Imaging

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Introduction

With cognitive, sensory or motor stimulation, specific brain regions are activated, requiring higher energy use and higher levels of blood flow. Functional magnetic resonance imaging (fMRI) measures blood flow to determine activation and deactivation of the specific brain regions associated with particular tasks. fMRI results from people with schizophrenia are compared to results from people without schizophrenia or other comparison groups to help pinpoint the areas of the brain that are affected by the disorder.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000, that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks are high for the intervention or other matter under review. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, if there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found twenty-eight systematic reviews that met our inclusion criteria[3-30].

People with schizophrenia vs. controls:

- During executive functioning and working memory tasks, moderate quality evidence suggests significant decreases in functional activation in the frontal lobe, including the dorsolateral prefrontal cortex, and in neocortical regions, including the parietal and occipital cortices and bilateral claustrum, fusiform gyrus, and cerebellum, and in subcortical regions, including the right putamen, hippocampus and left mediodorsal

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thalamus. Moderate to low quality evidence suggests significant increases in functional activation in the anterior cingulate cortex, temporal lobe, parietal cortex, lingual gyri, insula and the amygdala.

- During executive functioning tasks, moderate quality evidence suggests regions of co-occurring reduced activity in patients with schizophrenia include the middle and medial frontal cortex, as well as the cingulate cortex, mediodorsal thalamus and bilateral claustrum. Regions of co-occurring increased activity in patients with schizophrenia include the anterior cingulate cortex and the inferior parietal lobule.
- During memory encoding tasks, moderate quality evidence suggests significant decreases in functional activation in the medial frontal gyri and the hippocampus. During memory retrieval tasks, decreased activation is seen in the medial and inferior frontal gyri, the cerebellum, hippocampus, and the fusiform gyrus, with increases in the anterior cingulate cortex and the medial temporal gyrus.
- During episodic memory encoding, moderate to low quality evidence suggests reduced activity in the right superior frontal gyrus, bilateral inferior frontal gyri, right inferior parietal gyrus, right lingual gyrus, and right posterior cingulate. There is increased activity in the left precentral gyrus, left middle temporal gyrus, left post-central gyrus, left cingulate and left parahippocampal gyrus. During episodic memory retrieval, there is reduced activity in the left inferior frontal gyrus, left middle frontal gyrus, right cuneus, right cingulate gyrus, bilateral thalamus, and bilateral cerebellum. There is increased activity in the left precentral gyrus, right middle frontal gyrus, right thalamus and right parahippocampal gyrus.
- During emotion processing tasks, moderate and moderate to low quality evidence suggests decreased activation in the amygdala, parahippocampus, superior frontal gyrus and middle occipital gyrus. There is also lower magnitude of activation in the fusiform gyrus, lentiform nucleus, and parahippocampal gyrus. During explicit (effortful) emotion tasks, there is decreased activation in the fusiform gyrus, while during implicit (automatic) emotion tasks, there are decreases in the superior frontal and middle occipital gyri.
- During motor inhibition tasks, moderate to low quality evidence suggests reduced activation of the basal ganglia and inferior frontal cortex, and increased activation of the superior temporal gyrus. These associations were related to increased severity of neurological soft signs.
- During auditory hallucinations, moderate and moderate to low quality evidence suggests increased activation in Broca's area of the temporal lobe, insula, hippocampus, left parietal operculum, left and right postcentral gyrus, and left inferior frontal gyrus, and decreased activation of Broca's area, the left middle temporal gyrus, left premotor cortex, anterior cingulate cortex, and left superior temporal gyrus during external auditory stimulation.
- Following cognitive remediation (40 session over 10 weeks), moderate quality evidence suggests increased activation in the left middle frontal gyrus), left inferior frontal gyrus, left superior frontal gyrus, pre- and postcentral gyrus, bilateral insula, parietal lobe, and medial frontal gyrus.

People with schizophrenia vs. bipolar disorder:

- Moderate quality evidence suggests people with schizophrenia show greater engagement in bilateral posterior associative visual cortices and less engagement in the left thalamus than people with bipolar disorder during facial affect processing.

People with schizophrenia vs. depression:

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- Moderate quality evidence suggests decreased activation at rest in the ventromedial prefrontal cortex, left hippocampus, posterior cingulate cortex, lower precueus and the precuneus, and increased activation in bilateral lingual gyrus of people with schizophrenia compared to controls. In major depression, there was increased activation at rest in the ventromedial prefrontal cortex, left ventral striatum, and left thalamus, and decreased activation in left postcentral gyrus, left fusiform gyrus, and left insula compared to controls.

People with schizophrenia vs. autism spectrum disorders:

- Moderate quality evidence suggests decreased activation in schizophrenia compared to autism spectrum disorders in the anterior cingulate, superior temporal, and left posterior cingulate during facial emotion recognition tasks. During these tasks, there is increased activation in schizophrenia in the cerebellum, left inferior frontal, left parahippocampus, left inferior parietal and right inferior occipital regions. During theory of mind tasks, there is decreased activation in schizophrenia in the right insula, and increased activation in schizophrenia in the right medial frontal, the left frontal paracentral lobule, and in the left posterior cingulate cortex.

People with first-episode psychosis vs. controls:

- Moderate quality evidence suggests there are regions of overlap between structural and functional abnormalities in the insular cortex, superior temporal gyri and medial frontal/anterior cingulate cortex.
- Low quality evidence is unclear as to the direction of the changes in functional activity in the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, anterior frontal cortex, anterior cingulate cortex and the medial temporal gyrus during cognitive tasks.

People at clinical high risk of psychosis vs. controls:

- Moderate to high quality evidence suggests reduced activation in the left inferior frontal gyrus and the left medial frontal gyrus across a range of tasks in people at clinical high risk of psychosis.

First-degree relatives of people with schizophrenia vs. controls:

- Overall, moderate to high quality evidence suggest relatives have increased activation in the right posterior and anterior superior temporal gyrus and decreased activity in the left thalamus and left cerebellum. A combined analysis of structural and functional anomalies demonstrated decreased grey matter with increased activation in the left inferior frontal gyrus and the amygdala, and decreased grey matter with decreased activation in the left thalamus of relatives.
- During cognitive control tasks, there is altered activation in the left middle frontal gyrus, dorsolateral prefrontal cortex, parietal cortex, and the thalamus.
- During working memory tasks, relatives show altered activation in the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, parietal cortex, and the cerebellum.
- During language processing, they show altered activation in the right ventrolateral prefrontal cortex, and the parietal cortex.
- During executive functioning tasks, there is increased activation in the right superior and middle frontal gyri, right thalamus, left inferior parietal cortex, and left precuneus. Decreased activation is found in the right middle, inferior, and left superior frontal gyri, the right precentral gyrus, right lingual gyrus, left thalamus, right parietal cortex, left medial frontal and cingulate gyri, left superior temporal gyrus, and the left cerebellum.
- During emotion tasks, there is increased activation in the left sub-gyral (parietal), right

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superior frontal gyrus, left lentiform nucleus (lateral globus pallidus), left parahippocampal gyrus, left precuneus and the right middle temporal gyrus. Decreased activation is found in the right precentral gyrus, right inferior parietal lobule, left medial frontal gyrus, and right frontal gyrus.

Achim A M, Lepage M

Episodic memory-related activation in schizophrenia: meta-analysis

British Journal of Psychiatry 2005; 187: 500-509

View review abstract online

Comparison	**Whole brain comparison of functional activation in people with schizophrenia vs. controls.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate quality evidence (medium to large sample sizes, direct, unable to assess precision and consistency) suggests decreases in activity in the frontal gyri and the hippocampus during memory encoding tasks. During memory retrieval tasks, decreased activation is seen in the frontal gyri, hippocampus, cerebellum, and the fusiform gyrus, while increases are seen in the anterior medial temporal gyrus.**

Memory encoding tasks

Decreased activity in people with schizophrenia;

8 studies, N = 176

Right anterior middle frontal gyrus: Talairach coordinates 24, 54, 2, ALE 0.003886, Voxel probability 0.000025

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

Right posterior hippocampus: Talairach coordinates 20, -34, 2, ALE 0.003231, Voxel probability 0.000141

Memory retrieval tasks

Decreased activity in people with schizophrenia;

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

Left hippocampus: Talairach coordinates -30, -14, -20, ALE: 0.005559, Voxel probability: 0.000034

Left cerebellum: Talairach coordinates -22, -62, -42, ALE: 0.00675, Voxel probability: 0.000003

Right fusiform gyrus (medial temporo-occipital gyrus): Talairach coordinates 26, -74, -8, ALE: 0.0054,

Voxel probability: 0.000004 *Increased activity in people with schizophrenia;* Right anterior medial temporal gyrus: Talairach coordinates 28, -8, -10, ALE: 0.004105, Voxel probability: 0.000004	
Consistency in results‡	No measure of heterogeneity is provided.
Precision in results§	No confidence intervals are provided.
Directness of results‖	Direct

Anticevic A, Van Snellenburg JX, Cohen RE, Repovs G, Dowd EC, Barch DM

Amygdala recruitment in schizophrenia in response to aversive emotional material: a meta-analysis of neuroimaging studies

Schizophrenia Bulletin 2012; 38(3): 608-21

View review abstract online

Comparison	**Functional activation of the amygdala in people with schizophrenia vs. controls.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate quality evidence (unclear sample size, precise, unable to assess consistency, direct) suggests decreased activation in the amygdala in people with schizophrenia during aversive emotional tasks.**
Aversive emotional task	
35 studies (N not reported) found small decreases in activation of bilateral amygdala, particularly the right side, in people with schizophrenia; Bilateral: d = -0.22, 95%CI -0.37 to -0.08 p = 0.002 Right: d = -0.17, 95%CI -0.37 to -0.03 p = 0.01 Left: d = -0.13, 95%CI -0.31 to 0.04 p = 0.136	
Consistency in results	No measured of heterogeneity is provided.
Precision in results	Precise.

Directness of results	Direct

Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJS

Default-mode brain dysfunction in mental disorders: A systematic review

Neuroscience and Biobehavioral Reviews 2009; 33(3): 279-296

View review abstract online

Comparison	**Comparison of functional activity and connectivity (measured as the temporal correlation of changes in activity) in default-mode network (DMN) regions, including the precuneus/posterior cingulate cortex, medial prefrontal cortex, and the medial, lateral and inferior parietal cortex in people with schizophrenia vs. controls.**
Summary of evidence	**Low quality evidence (unclear sample size, unable to assess consistency or precision) is unclear of alterations in functional activity in 'default-mode' networks when the brain is at rest, as opposed to conditions in which activation is elicited by a stimulus or task.**
Functional alterations in DMN	
5 studies, N not reported Two studies reported reduced DMN connectivity in people with schizophrenia; one study reported increased DMN connectivity in people with schizophrenia One study reported reduced deactivation of DMN regions following task initiation; one study reported increased deactivation Both outcomes were associated with positive symptomatology	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Cooper D, Barker V, Radua J, Fusar-Poli P, Lawrie SM

Multimodal voxel-based meta-analysis of structural and functional

magnetic resonance imaging studies in those at elevated genetic risk of developing schizophrenia

Psychiatry Research - Neuroimaging 2014; 221(1): 69-77

View review abstract online

Comparison	**Comparison of functional activity in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, direct, unable to assess precision) suggest relatives show increased activation in the right posterior and anterior superior temporal gyrus and decreased activity in the left thalamus and left cerebellum.** **A combined analysis of structural and functional anomalies demonstrated decreased grey matter with increased activation in the left inferior frontal gyrus and the amygdala, and decreased grey matter with decreased activation in the left thalamus of relatives.**

Functional activation or failure of deactivation

13 studies, N = 561

Relatives showed increased activation in;

Right posterior superior temporal gyrus: Talairach coordinates 50 -54 10, $p = 0.00008$

Right anterior superior temporal gyrus: Talairach coordinates 52 6 2, $p = 0.001$

Relatives showed decreased activation in;

Left thalamus: Talairach coordinates -6 -12 16, $p = 0.00008$

Left cerebellum: Talairach coordinates -2 -80 -14, $p = 0.001$

Authors report combined structural and functional anomalies that demonstrated decreased grey matter with increased activation in the left inferior frontal gyrus and the amygdala, and decreased grey matter with decreased activation in the left thalamus of relatives.

Consistency in results	Authors report the results are consistent.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Delvecchio G, Sugranyes G, Frangou S.

Evidence of diagnostic specificity in the neural correlates of facial affect processing in bipolar disorder and schizophrenia: a meta-analysis of functional imaging studies

Psychological Medicine 2013; 43(3): 553-69

View review abstract online

Comparison	**Comparison of functional activation in people with schizophrenia vs. people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to assess precision or consistency) suggests people with schizophrenia show greater engagement in bilateral posterior associative visual cortices and less engagement in the left thalamus than people with bipolar disorder during facial affect processing.**
Facial affect processing	
29 studies, 1018 *People with schizophrenia were less likely to activate the left pulvinar thalamus and more likely to activate the cuneus bilaterally;* Left thalamus pulvinar: Talairach coordinates -5 -26 6, cluster volume 336mm^3 Left occipital cuneus (BA18): Talairach coordinates -6 -92 18, cluster volume 1144mm^3 Right occipital cuneus (BA18): Talairach coordinates 10 -88 20, cluster volume 416mm^3 Differences between the two disorders in amygdala activation were negatively correlated with antipsychotic dose. .Age and sex did not contribute to differences between diagnostic groups.	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

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

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

Neuroscience & Biobehavioral Reviews 2007; 31(4): 465-484 View review abstract online	
Comparison 1	**Whole brain comparison of functional activation in people with first-episode psychosis vs. controls.**
Summary of evidence	**Low quality evidence (one small study per outcome) is unclear as to the direction of the changes in functional activity during cognitive tasks in the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), anterior frontal cortex (AFC), anterior cingulate cortex (ACC) and the medial temporal gyrus.**
Information processing	
1 study, N = 23 Reduced activation in the frontal lobe (*d* = 0.93), parietal lobe (*d* = 1.34), temporal lobe (*d* = 1.37), occipital lobe (*d* = 1.26), and the thalamus (*d* = 1.47) during information processing tasks in medication-naïve patients	
Working memory	
1 study, N = 22 Large effect size suggests reduced activation in the DLPFC (*d* = 1.0) and VLPFC (*d* = 1.09) during working memory tasks in medicated patients 1 study, N = 18 Large effect size suggests reduced activation in the DLPFC (*d* = 1.29), and the middle temporal gyrus (*d* = 1.29) during working memory tasks in medication-naïve patients 1 study, N = 16 Large effect size suggests reduced activation in the DLPFC (*d* = 1.68) during working memory tasks in patients	
Verbal fluency	
1 study, N = 20 Large effect size suggests reduced activation in the DLPFC (*d* = 2.57), right anterior cingulate cortex (*d* = 4.89), VLPFC (*d* = 2.51), and the anterior frontal cortex (*d* = 2.42) during verbal fluency tasks in patients	
Executive control	

1 study, N = 47 Large effect size suggests reduced activation in the DLPFC (*d* = 0.88), and the ACC (*d* = 0.43) during executive control tasks in unmedicated patients	
Context processing	
1 study, N = 46 Large effect size suggests reduced activation in the DLPFC (*d* = 0.76) during context processing tasks in patients Large effect size suggests increased activation in the AFC (*d* = 0.74), and the VLPFC (*d* = 0.74) during context processing tasks in patients 1 study, N = 26 Large effect size suggests reduced activation in the DLPFC (*d* = 1.37) during context processing tasks in patients	
Planning	
1 study, N = 20 Large effect size suggests reduced activation in the DLPFC (*d* = 1.84), the VLPFC (*d* = 1.84) and the AFC (*d* = 1.33) during planning tasks in patients	
Visual attention	
1 study, N = 26 Large effect size suggests reduced activation in the DLPFC (*d* = 0.9), and the VLPFC (*d* = 0.74) during visual tasks in patients	
Consistency in results	No measure of heterogeneity is reported
Precision in results	No confidence intervals are reported
Directness of results	Direct
Comparison 2	**Whole brain comparison of functional activation in people at risk of schizophrenia vs. controls.**
Summary of evidence	**Low quality evidence (one small study per outcome) is unclear as to the direction of the changes in functional activity in the DLPFC, VLPFC, medial frontal gyrus, ACC, striatum, amygdala, thalamus, and cerebellum during cognitive tasks in people at high risk of schizophrenia.**

Verbal initiation
1 study, N = 63 Medium-sized effect suggests reduced activation in the medial frontal gyrus (*d* = 0.5), thalamus (*d* = 0.5), and cerebellum (*d* = 0.5) during visual initiation tasks in non-psychotic relatives of people with schizophrenia
Working memory
1 study with two independent cohorts *Cohort one: N = 41* Medium-sized effect suggests increased activation in the DLPFC (*d* = 0.60), VLPFC (*d* = 0.54), and inferior parietal lobe (*d* = 0.58) during working memory tasks in siblings of people with schizophrenia *Cohort two: N = 40* Small effect size suggests increased activation in the DLPFC (*d* = 0.42), VLPFC (*d* = 0.43), and inferior parietal lobe (*d* = 0.48) during working memory tasks in siblings of people with schizophrenia 1 study, N = 24 Large effect size suggests increased activation in the DLPFC (*d* = 0.79), and ACC (*d* = 0.96) during working memory tasks in non-psychotic relatives of people with schizophrenia 1 study, N = 45 Large effect size suggests increased activation in the DLPFC (*d* = 1.0) during working memory tasks in non-psychotic relatives of people with schizophrenia
Memory guided saccades
1 study, N = 32 Large effect size suggests reduced activation in the striatum (*d* = 1.34) during working memory guided saccades tasks in non-psychotic relatives of people with schizophrenia
Emotional face processing
1 study, N = 39 Medium-sized effect suggests reduced activation in the DLPFC (*d* = 0.51), amygdala (*d* = 1.05) and AFC (*d* = 0.47) during emotional face processing tasks in non-psychotic relatives of people with schizophrenia
Language lateralisation

1 study, N = 24 Large effect size (*d* = 1.31) suggests reduced language lateralisation in monozygotic twins discordant for schizophrenia	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Fusar-Poli, P

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

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

View review abstract online

Comparison	**Whole brain comparison of functional activation in people at clinical high risk for psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample size, direct, consistent, unable to assess precision) suggests reduced activation in the left inferior frontal gyrus and the medial frontal gyrus in people at clinical high risk for psychosis.**
Functional activation	
10 studies, N = 345 Signed Differential Mapping (SDM) analysis of functional activity in people at clinical high risk during any task *A consistent pattern of reduced activation was reported in people at clinical high risk compared to controls in:* Left inferior frontal gyrus: Talairach coordinates -46 16 22, $p < 0.001$ Bilateral medial frontal gyrus: Talairach coordinates -4 26 44, $p < 0.001$ Q = 11.258, $p = 0.54$, $I^2 = 7.286$	
Consistency in results	Consistent
Precision in results	No confidence intervals are reported.

Directness of results	Direct

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

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

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

View review abstract online

Comparison	**Whole brain comparison of functional activation in people with schizophrenia vs. controls.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate to low quality evidence (medium sample size, direct, unable to assess precision or consistency) suggests people with schizophrenia have reduced functional activity in the frontal cortex during working memory tasks and increased functional activity in the cingulate cortex.**

Activation during N-back working memory tasks

Meta-analysis results reported for 60 activation foci

4 studies, N = 134

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

Significantly reduced activity in people with schizophrenia;

Right medial frontal gyrus: Talairach coordinates 7, 44, -13, cluster volume 472mm^3

Right middle and inferior frontal gyrus: Talairach coordinates 33, 37, 28, cluster volume 1200mm^3

Left middle frontal gyrus: Talairach coordinates -33, 35, 23 , cluster volume 1736mm^3

Right inferior frontal gyrus and insula: Talairach coordinates 38, 16, 5, cluster volume 936mm^3

Significantly increased activity in people with schizophrenia;

Left middle frontal gyrus: Talairach coordinates -44, 42, -3, cluster volume 560mm^3

Right superior frontal gyrus: Talairach coordinates 4, 57, 26, cluster volume 264mm^3

Cingulate cortex: Talairach coordinates -2, 14, 35, cluster volume 656mm^3

Consistency in results	No measured of heterogeneity is provided.

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

Goghari MV

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

Psychological Medicine 2001; 41: 1239-1252

View review abstract online

Comparison	**Whole brain comparison of functional activation in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests relatives show increased functional activation during executive functioning in the right superior and middle frontal gyri, right thalamus, left inferior parietal cortex, and the left precuneus. Decreased activation was shown in the right middle, inferior and left superior frontal gyri, right precentral gyrus, right lingual gyrus, left thalamus, right parietal cortex, left medial frontal and cingulate gyri, left superior temporal gyrus, and left cerebellum. During cognitive control tasks, relatives show activation increases in the left middle frontal gyrus. During working memory tasks, relatives show increased activation in the right thalamus, right inferior parietal cortex, right middle frontal gyrus, and the left precuneus, and decreased activation in the right middle and inferior frontal gyri, right precentral gyrus, left thalamus, and the left cingulate 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;

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
Right thalamus: Talairach coordinates 4, -10, 10, cluster volume 344 mm^3
Left inferior parietal gyrus: Talairach coordinates -40/-40, -64/-60, 46/44, cluster volume 192 mm^3
Left precuneus: Talairach coordinates -2, -80, 44, cluster volume 368 mm^3
Decreased activity in relatives of people with schizophrenia;
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
Left thalamus: Talairach coordinates -14/-10/-6, -6/-12/-8, 10/12/12, cluster volume 304 mm^3
Left cingulate gyrus: Talairach coordinates -16, -26, 42, cluster volume 360 mm^3
Right lingual gyrus: Talairach coordinates 10, -78, -2, cluster volume 216 mm^3
Executive functioning task for whole brain studies
Subgroup analysis: only those studies that assessed *whole-brain* voxel-based activation
Increased activity in relatives of people with schizophrenia;
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
Left inferior parietal cortex: Talairach coordinates -40/-40, -64/-60, 46/44, cluster volume 264 mm^3
Left precuneus: Talairach coordinates -2, -80, 44) cluster volume 384 mm^3
Decreased activity in relatives of people with schizophrenia;
Left medial frontal gyrus: Talairach coordinates -12, 64, -2, cluster volume 136 mm^3
Right middle frontal gyrus: Talairach coordinates 36, 28, 42, cluster volume 120 mm^3
Right precentral gyrus: Talairach coordinates 50, -4, 22, cluster volume 200 mm^3
Right precentral gyrus: Talairach coordinates 40, -6, 42, cluster volume 200 mm^3
Left superior temporal gyrus: Talairach coordinates -62/-58, -12/-4, -4/-2, cluster volume 176 mm^3
Left thalamus: Talairach coordinates -10/-14/-6, -12/-6/-8, 12/10/12, cluster volume 368 mm^3
Right parietal cortex: Talairach coordinates 24, -48, 42, cluster volume 144 mm^3
Left cerebellum: Talairach coordinates -8/-14, -42/-40, -32/-38, cluster volume 168 mm^3

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Cognitive control task	
Increased activity in relatives of people with schizophrenia; Left middle/ superior frontal gyrus: Talairach coordinates -28/-26, 48/50, 20/12, cluster volume 168 mm^3	
Working memory task	
Increased activity in relatives of people with schizophrenia; 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 Right thalamus: Talairach coordinates 4, -10, 10, cluster volume 408 mm^3 Left inferior parietal cortex: Talairach coordinates -40/-40, -64/-60, 46/44, cluster volume 264 mm^3 Left precuneus: Talairach coordinates -2, -80, 46, cluster volume 368 mm^3 *Decreased activity in relatives of people with schizophrenia;* Right middle frontal gyrus: Talairach coordinates 38, 36, 34, cluster volume 1008 mm^3 Right inferior frontal gyrus: Talairach coordinates 52/54, 8/8, 18/24, cluster volume 176 mm^3 Right precentral gyrus: Talairach coordinates 40, -6, 42, cluster volume 168 mm^3 Left thalamus: Talairach coordinates -14/-6/-10, -6/-8/-12, 10/12/12, cluster volume 312 mm^3 Left cingulate gyrus: Talairach coordinates -16, -26, 42, cluster volume 200 mm^3	
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

Comparison	**Whole brain functional activation in people with schizophrenia vs. controls: voxel based comparison.** **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 no difference in frontal or non-frontal lobe functional activity during neurocognitive tasks between people with schizophrenia and controls.**
Neurocognitive tasks; working memory, executive function, vigilance tasks combined	
Frontal lobe activity 14 studies, N = 319 *No significant difference observed in frontal lobe activity* Kolmogorov-Smirnov test (KS3) = 0.16, p = 0.94	
Non-frontal lobe 14 studies, N = 319 *No significant difference observed in non-frontal lobe activity* KS3 = 0.14, p = 0.98	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Jardri R, Pouchet A, Pins D, Thomas P

Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis

American Journal of Psychiatry 2011; 168(1): 73-81

View review abstract online

Comparison	**Functional activation in people with schizophrenia during auditory verbal hallucinations.** **Note – this review combines PET and fMRI studies in one meta-**

	analysis.
Summary of evidence	**Moderate to low quality evidence (small sample size, direct, unable to assess precision or consistency) suggests increased activation in the auditory cortex (Broca's area, temporal lobe), insula and hippocampus during auditory hallucinations.**
During hallucinations	
10 studies (128 foci), N = 68, showed increased activation during hallucinations in: Temporal lobe/Broca's area: Talairach coordinates -48 10 7, cluster volume 1312mm^3 , ALE 1.84x10^{-3} Anterior insula: Talairach coordinates -42 0 6, cluster volume 1240mm^3, ALE 1.78x10^{-3} Precentral gyrus: Talairach coordinates -54 0 14, cluster volume 488mm^3, ALE 1.46x10^{-3} Hippocampus/parahippocampus: Talairach coordinates -24 -32 -4, cluster volume 1664mm^3, ALE 1.90x10^{-3} Anterior insula: Talairach coordinates 44 6 -4, cluster volume 964mm^3, ALE 1.66x10^{-3} Frontal operculum: Talairach coordinates 42 12 -10, cluster volume 265mm^3, ALE 1.29x10^{-3} Superior temporal gyrus: Talairach coordinates -54 -44 16, cluster volume 800mm^3, ALE 1.59x10^{-3} Supramarginalis gyrus: Talairach coordinates -52 -20 15, cluster volume 304mm^3, ALE 1.33x10^{-3}	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Kompus K, Westerhausan R, Hugdahl K

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

Neuropsychologia 2011; 49: 3361-9

View review abstract online

Comparison	**Functional activation in people with schizophrenia during auditory verbal hallucinations and during auditory stimulation tasks.** **Note – this review combines PET and fMRI studies in one meta-analysis.**

Summary of evidence	**Moderate quality evidence (medium to large sample sizes, direct, unable to assess precision or consistency) suggests increased activation in the auditory cortex (Broca's area, temporal lobe), insula, and hippocampus during auditory hallucinations, and decreased activation in the auditory cortex during external auditory stimulation in people with schizophrenia.**
During hallucinations (endogenously evoked)	
12 studies, N = 103, showed increased activation during hallucinations in; Insula: Talairach coordinates -44 -2 6, cluster volume 2656mm^3 Hippocampus: Talairach coordinates -24 -32 -4, cluster volume 1064mm^3 Postcentral gyrus: Talairach coordinates -50 -24 40, cluster volume 1016mm^3 Inferior parietal lobule: Talairach coordinates 32 -40 48, cluster volume 960mm^3 Superior temporal gyrus: Talairach coordinates -52 -22 16, cluster volume 952mm^3 Inferior frontal gyrus: Talairach coordinates 40 12 16, cluster volume 408mm^3 Middle temporal gyrus: Talairach coordinates 54 -32 -4, cluster volume 368mm^3 Cerebellum: Talairach coordinates 20 -46 -16, cluster volume 248mm^3 Superior frontal gyrus: Talairach coordinates 26 42 26, cluster volume 240mm^3 Middle temporal gyrus: Talairach coordinates 58 -44 14, cluster volume 200mm^3	
Auditory tasks	
11 studies, N = 384, showed reduced activation during auditory stimulation tasks in people with schizophrenia; Superior temporal gyrus: Talairach coordinates -54 -8 0, cluster volume 1824mm^3 Anterior cingulate cortex: Talairach coordinates -10 0 40, cluster volume 520mm^3 Thalamus: Talairach coordinates 12 -22 18, cluster volume 520mm^3 Superior frontal gyrus: Talairach coordinates 24 50 14, cluster volume 456mm^3 Retrosplenial/hippocampus: Talairach coordinates -12 -38 10, cluster volume 392mm^3	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

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Kühn S, Gallinat J

Quantitative meta-analysis on state and trait aspects of auditory verbal hallucinations in schizophrenia

Schizophrenia Bulletin 2012; 38(4): 779-786

View review abstract online

Comparison	**Functional activation in people with schizophrenia during auditory verbal hallucinations and during auditory stimulation tasks.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate to low quality evidence (small to medium sample sizes, direct, unable to assess precision or consistency) suggests increased activation in the left parietal operculum, left and right postcentral gyrus, and left inferior frontal gyrus during auditory hallucinations, and decreased activation in the left middle temporal gyrus, left premotor cortex, anterior cingulate cortex, and left superior temporal gyrus during external auditory stimulation in people with schizophrenia.**

During hallucinations ("state")

10 studies (123 foci), N = 85, showed increased activation during hallucinations (compared to scans during non-hallucination in the same person) in;

Left parietal operculum: Talairach coordinates -55 -19 16, cluster volume 344mm^3

Left postcentral gyrus: Talairach coordinates -49 -17 41, cluster volume 256mm^3

Right postcentral gyrus: Talairach coordinates 36 -32 50, cluster volume 216mm^3

Left inferior frontal gyrus: Talairach coordinates -48 2 6, cluster volume 208mm^3

Auditory tasks ("trait")

8 studies (43 foci), N = 190, showed decreased activation during auditory stimulation tasks in people with schizophrenia;

Left middle temporal gyrus: Talairach coordinates -56 -30 0, cluster volume 424mm^3

Left premotor cortex: Talairach coordinates -10 3 56, cluster volume 376mm^3

Anterior cingulate cortex: Talairach coordinates -4 26 31, cluster volume 160mm^3

Anterior cingulate cortex: Talairach coordinates -42 2 18, cluster volume 152mm^3

Anterior cingulate cortex: Talairach coordinates -9 4 37, cluster volume 112mm^3 Left superior temporal gyrus: Talairach coordinates -44 -22 0, cluster volume 152mm^3	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Kühn S, Gallinat J

Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis

Schizophrenia Bulletin 2013; 39(2): 358-365

View review abstract online

Comparison	**Resting-state functional activation in people with schizophrenia vs. controls and in people with major depression vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample sizes, direct, unable to assess precision or consistency) suggests decreased activation in the ventromedial prefrontal cortex, left hippocampus, posterior cingulate cortex, lower precueus and the precuneus, and increased activation in bilateral lingual gyrus of people with schizophrenia at rest. In major depression, there is increased activation in the ventromedial prefrontal cortex, left ventral striatum, and left thalamus, and decreased activation in left postcentral gyrus, left fusiform gyrus, and left insula.**
Resting state activity	
The following clusters showed increased activity in people with schizophrenia compared to controls; 11 studies, N = 567 Left lingual gyrus (BA19): Talairach coordinates -11 -57 2, cluster volume 1296mm^3 Right lingual gyrus (BA19): Talairach coordinates 11 -55 2, cluster volume 1200mm^3 *The following clusters showed decreased activity in people with schizophrenia compared to controls;* Precuneus (BA7): Talairach coordinates 3 -44 69, cluster volume 528 Lower precuneus (BA7): Talairach coordinates -6 -70 35, cluster volume 488mm^3 Posterior cingulate (BA23): Talairach coordinates -1 -29 26, cluster volume 384mm^3	

Ventromedial prefrontal cortex (BA32/10/11) Talairach coordinates -10 48 -20, cluster volume 312mm^3
Ventromedial prefrontal cortex (BA24/32): Talairach coordinates -4 40 -9, cluster volume 272mm^3
Left hippocampus: Talairach coordinates -21 -10 -24, cluster volume 264mm^3
Lower precuneus (BA23): Talairach coordinates 10 -42 28, cluster volume 248mm^3
Subgroup analysis of medicated and unmedicated patients showed decreases in resting-state activity in the ventromedial prefrontal cortex only in unmedicated patients.
The following clusters showed increased activity in people with depression compared to controls;
12 studies, N = 514
Left ventral striatum: Talairach coordinates -9 8 -11, cluster volume 488mm^3
vmPFC (BA32/9): Talairach coordinates -9 46 12, cluster volume 249mm^3
Left thalamus: Talairach coordinates -17 -22 10, cluster volume 224mm^3
Subgroup analysis of medicated and unmedicated patients showed increases in resting-state activity in the ventromedial prefrontal cortex only in medicated patients.
The following clusters showed decreased activity in people with depression compared to controls;
Left fusiform gyrus (BA19): Talairach coordinates -33 -78 -18, cluster volume 480mm^3
Left postcentral gyrus (BA40/2/3): Talairach coordinates -42 -22 50, cluster volume 368mm^3
Left insula (BA13): Talairach coordinates -40 6 -20, cluster volume 208mm^3

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

Li H, Chan R, McAlonan G, Gong QY

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

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

View review abstract online

Comparison	**Whole brain comparison of activation in people with schizophrenia vs. controls.**

Summary of evidence	**Moderate to low quality evidence (small to medium samples sizes, direct, unable to assess consistency or precision) suggests that people with schizophrenia show decreased activation during emotion processing tasks in amygdala, parahippocampus, superior frontal gyrus and middle occipital gyrus. People with schizophrenia also showed a lower magnitude of activation in fusiform gyrus, lentiform nucleus, and parahippocampal gyrus. During explicit emotional tasks, people with schizophrenia showed decreased activation in fusiform gyrus, while implicit emotion was association with decreases in superior frontal and middle occipital gyri.**
Facial emotion processing task	
10 studies, N = 133, reported activation foci for control subjects alone; Left fusiform gyrus: Talairach coordinates -38, -66, -13, 21 foci, cluster volume 2048mm^3, 0.100 ALE Left parahippocampal gyrus/amygdala: Talairach coordinates -21, -5, -10, 8 foci, cluster volume 784mm^3, 0.102 ALE Right lentiform nucleus: Talairach coordinates 23, -4, -8, 8 foci, cluster volume 728mm^3, 0.062 ALE Right fusiform gyrus: Talairach coordinates 40, -47, -15, 8 foci, cluster volume 672mm^3, 0.069 ALE Right fusiform gyrus: Talairach coordinates 39, -65, -10, 5 foci, cluster volume 416mm^3, 0.097 ALE Right fusiform gyrus: Talairach coordinates 34, -73, -10, 3 foci, cluster volume 208mm^3, 0.046 ALE *8 studies, N = 95, reported activation for people with schizophrenia;* Left parahippocampal gyrus/amygdala: Talairach coordinates (-21, -8, -14), 5 foci, 480mm^3, 0.068 ALE Right parahippocampal gyrus/amygdala: Talairach coordinates 23, -5, -14, 4 foci, cluster volume 424mm^3, 0.061 ALE Left insula: Talairach coordinates -32, 20, 8, 3 foci, cluster volume 312mm^3, 0.035 ALE Right fusiform gyrus: Talairach coordinates 40, -42, -16, 2 foci, cluster volume 208mm^3, 0.053 ALE *Subtraction meta-analysis suggests these activations were significantly larger in controls than in people with schizophrenia;* Left fusiform gyrus: Talairach coordinates -38, -66, -13, 19 foci, cluster volume 1768mm^3, 0.100 ALE Left parahippocampal gyrus/amygdala: Talairach coordinates-22, -5, -9, 8 foci, cluster volume 464mm^3, 0.091 ALE Right lentiform nucleus: Talairach coordinates 23, -4, -7, 7 foci, cluster volume 424mm^3, 0.062 ALE Right fusiform gyrus: Talairach coordinates 38, -64, -10, 6 foci, cluster volume 408mm^3, 0.097 ALE	

Right fusiform gyrus: Talairach coordinates 40, -50, -15, 5 foci, cluster volume 408mm^3, 0.065 ALE Direct between-group contrasts examined regions of differential activation between people with schizophrenia and controls *13 studies reported reduced activation in people with schizophrenia during an emotion perception task;* Right parahippocampal gyrus/amygdala: Talairach coordinates 26, -8, -12, 4 foci, cluster volume 368mm^3, 0.052 ALE Right superior frontal gyrus: Talairach coordinates 9, 22, 51, 3 foci, cluster volume 288mm^3, 0.051 ALE Left parahippocampal gyrus/amygdala: Talairach coordinates -26, -10, -13, 3 foci, cluster volume 272mm^3, 0.060 ALE Right middle occipital gyrus: Talairach coordinates 48, -72, 4, 2 foci, cluster volume 208mm^3, 0.060 ALE	
Subgroup analysis assessed the studies by task type: explicit emotion and implicit emotion *Subtraction meta-analysis of activation during an explicit emotional task found decreased activation in people with schizophrenia;* Left fusiform gyrus: Talairach coordinates -39, -65, -13, 18 foci, cluster volume 1840mm^3, 0.082 ALE Right fusiform gyrus: Talairach coordinates 40, -52, -14, 5 foci, cluster volume 472mm^3, 0.068 ALE Right fusiform gyrus: Talairach coordinates 38, -64, -10, 5 foci, cluster volume 432mm^3, 0.097 ALE Left amygdala: Talairach coordinates -21, -7, -8, 6 foci, cluster volume 368mm^3, 0.091 ALE Right lentiform nucleus: Talairach coordinates 22, -3, -5, 3 foci, cluster volume 256mm^3, 0.060 ALE *Subtraction meta-analysis of activation during an implicit emotional task suggesting decreased activation in people with schizophrenia;* Right superior frontal gyrus: Talairach coordinates 10, 22, 50, 3 foci, cluster volume 312mm^3, 0.051 ALE Left parahippocampal gyrus/amygdala: Talairach coordinates -26, -10, -14, 3 foci, cluster volume 280mm^3, 0.060 ALE Right left parahippocampal gyrus/amygdala: Talairach coordinates 24, -8, -12, 3 foci, cluster volume 280mm^3, 0.051 ALE Right middle occipital gyrus: Talairach coordinates 48, -72, 4, 2 foci, cluster volume 216mm^3, 0.060 ALE	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.

Directness of results	Direct

Liemburg EJ, Knegtering H, Klein HC, Kortekaas R, Aleman A

Antipsychotic medication and prefrontal cortex activation: a review of neuroimaging findings.

European Neuropsychopharmacology 2012; 22: 387-400

View review abstract online

Comparison	**Functional activation in people with schizophrenia on various antipsychotic medications vs. controls.** **This review includes studies using either fMRI, PET or SPECT.**
Summary of evidence	**Low quality evidence (direct, very small samples, unable to assess precision or consistency) is unclear as to any differences in activation according to medication type.**

Resting state

First generation antipsychotics (high D2 affinity)

One PET study (N = 24) compared patients treated with either sulpiride or chlorpromazine with controls and found no difference in frontal cortex activation.

One SPECT study (N = 25) found no difference in frontal activation between patients treated with haloperidol and controls.

One PET study (N unclear) found no effect of thiothixene over 4-6 weeks of treatment, but found that haloperidol decreased frontal cortex activation after 406 weeks of treatment. A second study (N = 19) also found that haloperidol decreased frontal blood flow after three weeks of treatment. Another PET study (N = 12) showed that withdrawal of haloperidol resulted in increased glucose activity in the frontal cortex. However, one study (N = 11) found that haloperidol increased DLPFC activity but decreased VLPFC activity after 12 weeks of treatment with either haloperidol or 5 weeks of clozapine.

Second generation antipsychotics (high D2 and 5-HT affinity)

One PET study (N = 13) found no effect of risperidone on brain changes after 3 weeks. A SPECT study (N = 24) found no pre-post effect of olanzapine on resting-state prefrontal brain activity.

One study in 24 treatment-resistant patients found no overall effect of clozapine on brain activity, but clozapine-responders showed reductions of activity following treatment. This was supported by three further studies showing reductions of PFC activity after clozapine, but one small cross-over study (N = 10) found increases of activity following several months of clozapine.

Working memory
Second generation antipsychotics One study (N = 10) showed increased activation during working memory in DLPFC when first-generation antipsychotics were substituted with risperidone. Another study (N = 25) showed that switching from first-generation antipsychotics to olanzapine also increased frontal cortex activation. However one study (N = 20) found that olanzapine decreased prefrontal activation. One study (N = 25) found that frontal cortex activation also increased after quetiapine for 12 weeks. One study (N = 11) found no difference in activation when patients were switched from first-generation to aripiprazole for 3-4 weeks.
Learning
One study (N = 22) showed decreased activation during learning in DLPFC following haloperidol, but also found that olanzapine increased activation compared to baseline. However, another study (N = 15) found that haloperidol reduced activity in the PFC after 6 weeks, whereas sertindole increased metabolism.
Emotional processing
Second generation antipsychotics One study (N = 12) found that olanzapine reduced PFC activation during face processing after 4 weeks, but increased it after 8 weeks. Activation also increased in another fMRI study (N = 16) during a monetary reward task following olanzapine. A PET study (N = 12) found that quetiapine over 22 weeks increased PFC activation during emotion processing. This was replicated in a second study (N = 12) after over 5 months of treatment.
Attention/executive function
First generation antipsychotics One SPECT study (N = 24) showed reduced activation during auditory discrimination in DLPFC following fluphenazine. A second PET study (N = 22) also found that fluphenazine lowered glucose metabolism in the superior frontal cortex. Risperidone also decreased activation in the frontal cortex during a letter recognition task (N = 8) after 6 weeks, which was also associated with a decrease in positive symptoms. 8 weeks of clozapine had no effect on SPECT activation during a card sorting task (N = 21) but two studies (N = 21) found reductions following clozapine, and a third study (N = 10) found that substituting clozapine for risperidone extended the hypoactivation during the Stroop task.

Verbal fluency	
Second generation antipsychotics One study (N unclear) showed increased activation during verbal fluency (naming objects in a category) task following 4 weeks of amisulpride. A second study (N = 8) found increased activation during a verbal fluency task following 3 months of quetiapine.	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Lungu O, Barakat M, Laventure S, Debas K, Proulx S, Luck D, Stip E

The incidence and nature of cerebellar findings in schizophrenia: a quantitative review of fMRI literature

Schizophrenia Bulletin 2013; 39(4): 797-806

View review abstract online

Comparison	**Functional activation of the cerebellum in people with schizophrenia vs. controls**
Summary of evidence	**Moderate to low quality evidence (direct, unable to assess precision or consistency) suggests that changes in functional activity in the cerebellum in patients with schizophrenia were most frequently identified during motor, cognitive/executive and emotional tasks.**
Cerebellar activation	
From 234 fMRI studies, 96 (41%) reported at least one focus of activation in the cerebellum in people with schizophrenia compared to controls during task performance; This proportion varied considerably depending on the type of task utilised: Motor tasks: 69.9% of studies identified cerebellum activation. Of these, 50% reported hypoactivation in schizophrenia compared to controls. Cognitive tasks: 43% of studies identified cerebellum activation. Of these, 67% reported hypoactivation in schizophrenia compared to controls. Perceptual tasks: 7.7% of studies identified cerebellum activation. Of these, 100% reported	

hypoactivation in schizophrenia compared to controls. Linguistic/language tasks: 26% of studies identified cerebellum activation. Of these, 100% reported hypoactivation in schizophrenia compared to controls. Emotional tasks: 41% of studies identified cerebellum activation. Of these, 46% reported hypoactivation in schizophrenia compared to controls. Executive tasks: 43% of studies identified cerebellum activation. Of these, 60% reported hypoactivation in schizophrenia compared to controls.	
Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

MacDonald AW, Thermenos HW, Barch DM, Seidman LJ

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

Schizophrenia Bulletin 2009; 35(6): 1142-1162

View review abstract online

Comparison	**Whole brain comparison of functional activation in first-degree relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample sizes, direct, unable to assess precision or consistency) suggests alterations in functional activity during cognitive control tasks (increased *or* decreased) in DLPFC, parietal and thalamus of relatives.** **Moderate to low quality evidence (unclear sample sizes, direct, unable to assess precision or consistency) suggests that functional activity during working memory tasks shows alterations in DLPFC, VLPFC, parietal and cerebellum of relatives** **Moderate to low quality evidence (unclear sample sizes, direct, unable to assess precision or consistency) suggests that during long term memory tasks, only VLPFC of relatives shows functional alteration** **Moderate to low quality evidence (unclear sample sizes, direct, unable to assess precision or consistency) suggests that during**

	language processing tasks the right VLPFC and parietal cortex show functional alterations in relatives
Cognitive control tasks	
7 studies investigated functional activity during cognitive control tasks; 4 studies investigated the anterior cingulate cortex, 3/4 showed no group differences bilaterally. 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. 6 studies investigated the parietal cortex, 3/6 showed increased bilateral activity compared to controls. Activity (hyper- and hypo-) was abnormal in 67% of reports. 6 studies investigated the temporal cortex, 2/6 showed increased activity compared to controls. 6 studies investigated the basal ganglia, 2/6 showed reduced activity compared to controls. 6 studies investigated the cerebellum, 2/6 showed altered activity compared to controls. 6 studies investigated the thalamus, 3/6 showed increased activity compared to controls. Activity (hyper- and hypo-) was abnormal in 86% of reports.	
Working memory tasks	
4 studies (5 independent samples) investigated functional activity during working memory tasks; 4 studies investigated the anterior cingulate cortex, 2/4 showed no group differences bilaterally. 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. 5 studies investigated the parietal cortex, 3/5 showed increased activity compared to controls. Activity (hyper- and hypo-) was abnormal in 67% of reports. 4 studies investigated the temporal cortex, 2/4 showed decreased activity compared to controls. 2 studies investigated the basal ganglia, 1/2 showed increased activity compared to controls. 4 studies investigated the thalamus, 2/4 showed no group differences. 4 studies investigated the cerebellum, 3/4 showed reduced activity compared to controls. Activity (hyper- and hypo-) was abnormal in 60% of reports.	
Long term memory tasks	

3 studies investigated functional activity during episodic long term memory tasks; 3 studies investigated the anterior cingulate cortex, 3/3 showed no group differences. 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. 3 studies investigated the parietal cortex, 3/3 showed no group differences. 3 studies investigated the temporal cortex, 3/3 showed no group differences. 3 studies investigated the basal ganglia, 3/3 showed no group differences. 3 studies investigated the thalamus, 3/3 showed no group differences. 3 studies investigated the cerebellum, 2/3 showed no group differences, one showed increased activity compared to controls.
1 study investigated functional activity during procedural long term memory tasks; No group difference was reported for cingulate, VLPFC, temporal cortex and cerebellum. Reduced activity in relatives was shown in DLPFC, parietal, temporal, basal ganglia, and thalamus.
Language processing studies
4 studies investigated functional activity during language processing tasks; 1/4 showed reduced activity in relatives in the anterior cingulate cortex. 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. 3/4 showed increased activity in the right parietal cortex, 1/3 also showed increased activity in the left parietal. 2/4 showed increased activity in the right temporal cortex, 2/4 showed decreased activity in right temporal cortex. 2/4 showed no group differences in left temporal cortex. 4/4 showed no task-related response in the basal ganglia. 3/4 showed no task-related response in the thalamus, 1/4 showed reduced bilateral activity. 3/4 showed no task-related response in the cerebellum, 1/4 showed reduced activity.

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

Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC

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

Archives of General Psychiatry 2009; 66(8): 811-822

View review abstract online

Comparison 1	**Whole brain comparison of functional activation in people with schizophrenia vs. controls: ALE analysis.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to assess precision or consistency) suggests people with schizophrenia show reduced activity in the middle and medial frontal cortex during executive function tasks, as well as in neocortical regions including the inferior parietal and middle occipital gyri and bilateral claustrum, and subcortical regions including the right putamen and left mediodorsal thalamus.** **Moderate quality evidence (large sample size, direct, unable to assess precision or consistency) suggests people with schizophrenia show regions of increased activity during executive function tasks including superior and inferior frontal cortex, inferior parietal cortex, superior temporal and lingual gyri, insula and the amygdala.**

Executive function tasks

41 studies, N = 1217

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

Significantly reduced activity in people with schizophrenia;

Left middle frontal gyrus: Talairach coordinates -38, 30, 30, cluster volume 3096mm^3

Right middle frontal gyrus: Talairach coordinates 32, 24, 42, cluster volume 712mm^3

Right medial frontal gyrus: Talairach coordinates 6, 42, 18, cluster volume 1480mm^3

Right cingulate: Talairach coordinates 2, 18, 34, cluster volume 1704mm^3

Right claustrum: Talairach coordinates 26, 22, 2, cluster volume 1766mm^3

Left middle occipital gyrus: Talairach coordinates -42, -70, 6, cluster volume 416mm^3

Right inferior parietal lobule: Talairach coordinates 36, -58, 42, cluster volume 792mm^3

Left claustrum: Talairach coordinates -28, 24, 0, cluster volume 880mm^3 Right putamen: Talairach coordinates 20, -4, 14, cluster volume 448mm^3 Left mediodorsal thalamus: Talairach coordinates -4, -14, 10, cluster volume 1736mm^3 *Significantly increased activity in people with schizophrenia;* Left superior frontal gyrus: Talairach coordinates -8, -14, 68, cluster volume 440mm^3 Left superior frontal gyrus: Talairach coordinates -2, 52, 24, cluster volume 1320mm^3 Left inferior frontal gyrus: Talairach coordinates -40, 36, 12, cluster volume 656mm^3 Right medial frontal gyrus: Talairach coordinates 8, 44, -12, cluster volume 424mm^3 Left precentral gyrus: Talairach coordinates -54, 4, 30, cluster volume 752mm^3 Left cingulate: Talairach coordinates -2, 10, 40, cluster volume 2208mm^3 Right superior temporal gyrus: Talairach coordinates 38, -36, 6, cluster volume 584mm^3 Left inferior parietal lobule: Talairach coordinates -54, -42, 42, cluster volume 1200mm^3 Right lingual gyrus: Talairach coordinates 14, -74, 6, cluster volume 800mm^3 Right insula: Talairach coordinates 38, 16, 4, cluster volume 1136mm^3 Right amygdala: Talairach coordinates 18, -4, -12, cluster volume 592mm^3	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct
Comparison 2	**Whole brain comparison of functional activation in people with schizophrenia vs. controls: Co-occurring regions of activity change.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate quality evidence (large sample sizes, direct, unable to assess precision or consistency) suggests regions of co-occurring reduced activity in patients with schizophrenia include the middle and medial frontal cortex, as well as the cingulate cortex, mediodorsal thalamus and bilateral claustrum.** **Moderate quality evidence (large sample sizes, direct, unable to assess precision or consistency) suggests regions of co-occurring increased activity in patients with schizophrenia include the anterior cingulate cortex and the inferior parietal lobule.**
Executive function tasks	

41 studies, N = 1217
Fractional similarity network analysis – regions of co-occurring hypoactivation across all tasks where reductions in schizophrenia are larger than in controls;
Left middle frontal gyrus: Talairach coordinates -38, 30, 30, cluster volume 1456mm^3
Right middle frontal gyrus: Talairach coordinates 6, 42, 18, cluster volume 696mm^3
Right anterior cingulate cortex: Talairach coordinates 2, 18, 34, cluster volume 760mm^3
Left mediodorsal thalamus: Talairach coordinates -4, -14, 10, cluster volume 696mm^3
Left claustrum: Talairach coordinates -28, 24, 0, cluster volume 488mm^3
Right claustrum: Talairach coordinates 26, 22, 2, cluster volume 936mm^3
Fractional similarity network analysis – regions of co-occurring hyperactivation across all tasks where increases in schizophrenia are larger than in controls;
Left anterior cingulate cortex: Talairach coordinates -2, 10, 40, cluster volume 1256mm^3
Left inferior parietal lobule: Talairach coordinates -54, -42, 42, cluster volume 584mm^3

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

Ortuno F, Guillen-Grima F, Lopez-Garcia P, Gomez J, Pla J

Functional neural networks of time perception: challenge and opportunity for schizophrenia research.

Schizophrenia Research 2011; 125: 129-35

View review abstract online

Comparison	**Functional activation during time estimation tasks in people with schizophrenia vs. controls.**
Summary of evidence	**Low quality evidence (small sample size, direct, unable to assess precision or consistency) is unclear as to any differences in activation between people with schizophrenia and controls during time perception tasks.**
Time perception tasks	

3 studies, N = 29, explored functional activation during time perception tasks in schizophrenia *Relative to controls, people with schizophrenia showed significantly lower activation in;* Right lentiform nucleus: Talairach coordinates 28 -14 0.89, cluster volume 1408mm^3, ALE 0.007 Right precentral gyrus: Talairach coordinates 48 -6 5.66, cluster volume 1208mm^3, ALE 0.008 Right superior frontal gyrus: Talairach coordinates 16 38 34, cluster volume 560mm^3, ALE 0.006 Right precuneus/parietal: Talairach coordinates 46 -70 34, cluster volume 504mm^3, ALE 0.007 Right thalamus: Talairach coordinates 8 -7 11, cluster volume 488mm^3, ALE 0.006 Left cingulate gyrus: Talairach coordinates -9 24 28, cluster volume 392mm^3, ALE 0.007 Right middle frontal gyrus: Talairach coordinates 36 36 40, cluster volume 224mm^3, ALE 0.006 Right superior frontal gyrus: Talairach coordinates 14 66 8, cluster volume 128mm^3, ALE 0.005

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

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

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

Neuroscience and Biobehavioural Reviews 2012; 36: 2325-2333

View review abstract online

Comparison	**Overlap between regions of functional and structural alteration in people with first-episode psychosis vs. controls**
Summary of evidence	**Moderate quality evidence (large sample sizes, direct, unable to assess precision or consistency) suggests regions of overlap between structural and functional abnormalities in the insular cortex/superior temporal gyri and medial frontal/anterior cingulate cortex in people with first-episode psychosis.**
Regions of overlap	

Analysis of 25 structural MRI studies (N = 2005) and 18 functional MRI studies (N = 765) found regions with both structural and functional alteration in people with first-episode psychosis;

Decreased grey matter volume and decreased functional activation;

Right anterior insula/STG:

Talairach coordinates 42 0 12, cluster volume 439mm^2, $p < 0.0001$

Talairach coordinates 34 24 0, cluster volume 44mm^2, $p = 0.0001$

Left anterior insula/STG

Talairach coordinates -40 12 34, cluster volume 407mm^2, $p < 0.0001$

Right medial frontal/anterior cingulate

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

Decreased grey matter volume and increased functional activation;

Right posterior insula/STG:

Talairach coordinates 34 4 -12, cluster volume 71mm^2 , $p < 0.0001$

Talairach coordinates 38 4 -12, cluster volume 173mm^2, $p < 0.0001$

Talairach coordinates 50 20 10, cluster volume 18mm^2, $p = 0.0001$

Talairach coordinates 56 -16 32, cluster volume 72mm^2, $p = 0.0002$

Left STG/postcentral gyrus

Talairach coordinates -58 -22 14, cluster volume 243mm^2, $p = 0.00005$

Left medial frontal/anterior cingulate

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

Meta-regression analyses showed that antipsychotic medications were associated with greater severity of abnormality, though the differences remained present in antipsychotic-naïve participants.

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

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

Prefrontal activation deficits during episodic memory in schizophrenia

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

View review abstract online	
Comparison	**Whole brain comparison of functional activation during episodic memory tasks in people with schizophrenia vs. controls.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess precision or consistency) suggests functional activity during episodic encoding is reduced in the right superior frontal gyrus, bilateral inferior frontal gyri, right inferior parietal gyrus, right lingual gyrus, and right posterior cingulate of people with schizophrenia.** **Moderate to low quality evidence (unclear sample size, direct, unable to assess precision or consistency) suggests functional activity during episodic encoding is increased in the left precentral gyrus, left middle temporal gyrus, left post-central gyrus, left cingulate and left parahippocampal gyrus of people with schizophrenia.** **Moderate to low quality evidence (unclear sample size, direct, unable to assess precision or consistency) suggests functional activity during episodic retrieval is reduced in the left inferior frontal gyrus, left middle frontal gyrus, right cuneus, right cingulate gyrus, bilateral thalamus, bilateral cerebellum of people with schizophrenia.** **Moderate to low quality evidence (unclear sample size, direct, unable to assess, precision or consistency) suggests functional activity during episodic retrieval is increased in the left precentral gyrus, right middle frontal gyrus, right thalamus and right parahippocampal gyrus of people with schizophrenia.**
Episodic encoding	

Seven studies contributing 40 foci
Significantly reduced activity in people with schizophrenia;
Right superior frontal gyrus: Talairach coordinates 22, 48, 14, cluster volume 4608mm^3
Right superior frontal gyrus: Talairach coordinates 6, 36, 48 cluster volume 1104mm^3
Right inferior frontal gyrus: Talairach coordinates 40, 30, 12, cluster volume 2760mm^3,
Left inferior frontal gyrus: Talairach coordinates -36, 26, 12, cluster volume 1424mm^3
Right inferior parietal gyrus: Talairach coordinates 50, -48, 36, cluster volume 1056mm^3
Right lingual gyrus: Talairach coordinates 18, -86, 0, cluster volume 1192mm^3
Right posterior cingulate gyrus: Talairach coordinates 4, -36, 32, cluster volume 896mm^3
Four studies contributing 20 foci
Significantly greater activity in people with schizophrenia;
Left precentral gyrus: Talairach coordinates -46, -8, 40, cluster volume 2704mm^3
Left middle temporal gyrus: Talairach coordinates -44, -42, -8, cluster volume 352mm^3
Left post-central gyrus: Talairach coordinates -44, -28, 36, cluster volume 344mm^3
Left cingulate gyrus: Talairach coordinates -2, 6, 38, cluster volume 1368mm^3
Left parahippocampal gyrus: Talairach coordinates -28, -50, -4, cluster volume 304mm^3
Episodic retrieval
Ten studies contributing 76 foci
Significantly reduced activity in people with schizophrenia;
Left inferior frontal gyrus: Talairach coordinates -40, 22, 20, cluster volume 3048mm^3
Left precentral gyrus: Talairach coordinates -36, -2, 28, cluster volume 1064mm^3
Left middle frontal gyrus: Talairach coordinates -38, 32, 38, cluster volume 888mm^3
Right anterior cingulate gyrus: Talairach coordinates 4, 26, -6, cluster volume 888mm^3
Left middle temporal gyrus: Talairach coordinates -56, -42, 0, cluster volume 560mm^3
Right cuneus: Talairach coordinates 16, -86, 10, cluster volume 2568mm^3
Left thalamus: Talairach coordinates -4, -8, 18, cluster volume 1496mm^3
Right thalamus: Talairach coordinates 8, -24, 10, cluster volume 1448mm^3
Right posterior cingulate gyrus: Talairach coordinates 10, -52, 20, cluster volume 520mm^3
Left cerebellum: Talairach coordinates -24, -62, -42, cluster volume 1488mm^3
Right cerebellum: Talairach coordinates 30, -80, -34, cluster volume 624mm^3
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 pre-central, left middle temporal and right posterior cingulate foci were not activated Six studies contributing 26 foci *Significantly greater activity in people with schizophrenia;* Left precentral gyrus: Talairach coordinates -28, -26, 66, cluster volume 1296mm^3 Right medial frontal gyrus: Talairach coordinates 12, 44, 10, cluster volume 1168mm^3 Right middle frontal gyrus: Talairach coordinates 34, 36, -16, cluster volume 600mm^3 Right middle temporal: Talairach coordinates 60, -58, 0 cluster volume 336mm^3 Right thalamus: Talairach coordinates 26, -30, 6, cluster volume 792mm^3 Right parahippocampal gyrus: Talairach coordinates 20, -36, -4, cluster volume not reported *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 and the right middle temporal gyrus were not activated	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct

Ramsay IS, Macdonald AW

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

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

View review abstract online

Comparison	**Functional activation changes in response to cognitive remediation vs. various control conditions in people with schizophrenia. Training duration was an average of 10 weeks**

	comprising 40 sessions.
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess precision or consistency) suggests increased activity in the left middle frontal gyrus), left inferior frontal gyrus, left superior frontal gyrus, pre- and postcentral gyrus, bilateral insula, parietal lobe, and medial frontal gyrus after cognitive remediation.**
Cognitive remediation	
9 studies, N = 128 *The following clusters showed increases in activation after cognitive remediation compared to control conditions;;* Left middle frontal gyrus, left precentral gyrus: Talairach coordinates -40 -8 40, 624mm^3 Left inferior frontal gyrus, left insular cortex, left precentral gyrus: Talairach coordinates -44 6 24, cluster volume 496mm^3 Right superior parietal lobe: Talairach coordinates 32 -66 50, cluster volume 448mm^3 Right postcentral gyrus: Talairach coordinates 38 -24 42, cluster volume 440mm^3 Thalamus, lentiform nucleus, caudate: Talairach coordinates -10 -2 0, cluster volume 312mm^3 Right insular cortex: Talairach coordinates 38 16 4, cluster volume 264mm^3 Left superior frontal gyrus, left middle frontal gyrus: Talairach coordinates -28 52 6, cluster volume 264mm^3 Left medial frontal gyrus: Talairach coordinates -6 -8 68, cluster volume 248mm^3	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Scognamiglio C, Houenou J.

A meta-analysis of fMRI studies in healthy relatives of patients with schizophrenia

Australian and New Zealand Journal of Psychiatry 2014; 48(10): 907-16

View review abstract online

Comparison	**Functional activation in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample sizes, direct, unable to assess consistency or precision) suggests a general pattern of over-activation in right-sided frontal, parietal and temporal regions, and under-activation in the cingulate gyrus of relatives. Results were similar across cognitive and emotion tasks, although relatives additionally over-activated in the left parahippocampal gyrus during emotion tasks.**
Cognitive and emotion tasks	
Cognitive and emotion tasks combined 21 studies, N = 1245 *The following areas showed increased activation in relatives compared to controls;* Right middle temporal gyrus (BA37): Talairach coordinates 46 −60 2, $p < 0.0001$ Right inferior frontal gyrus (BA44): Talairach coordinates 52 10 20, $p < 0.001$ Right superior parietal lobule (BA7): Talairach coordinates 18 −68 56, $p < 0.01$ *The following areas showed increased activation in controls compared to relatives;* Left cingulate gyrus (BA24): Talairach coordinates −2 −2 38, $p < 0.001$ The jackknife analysis indicated consistency in results. Cognitive tasks 17 studies *The following areas showed increased activation in relatives compared to controls;* Right inferior frontal gyrus (BA45): Talairach coordinates 54 12 20, $p < 0.001$ Right parietal precuneus (BA7): Talairach coordinates 14 −66 52, $p < 0.001$ Right middle temporal gyrus (BA37): Talairach coordinates 46 −60 2, $p < 0.001$ Right caudate (right transverse temporal gyrus, BA41): Talairach coordinates 32 −36 4, $p < 0.01$ Right superior temporal gyrus (BA39): Talairach coordinates 56 −58 18, $p < 0.01$ Left precentral gyrus (BA6): Talairach coordinates −32 −18 64, $p < 0.01$ Right inferior parietal lobule (BA40): Talairach coordinates 54 −32 34, $p < 0.01$ *The following areas showed increased activation in controls compared to relatives;* Right cingulate gyrus (BA31): Talairach coordinates 8 −8 44, $p < 0.01$ Emotion tasks:	

4 studies *The following areas showed increased activation in relatives compared to controls;* Left sub-gyral (parietal, BA40): Talairach coordinates −22 −48 56, $p < 0.01$ Right superior frontal gyrus (BA9): Talairach coordinates 12 46 26, $p < 0.01$ Left lentiform nucleus (lateral globus pallidus): Talairach coordinates −24 -12 −6, $p < 0.01$ Left parahippocampal gyrus (BA28): Talairach coordinates: −20 −14 −20, $p < 0.01$ Left precuneus (BA7): Talairach coordinates −6 −46 48, $p < 0.01$ Right middle temporal gyrus (BA39): Talairach coordinates 50 −66 10, $p < 0.01$ *The following areas showed increased activation in controls compared to relatives;* Right precentral gyrus (BA6): Talairach coordinates 54 −6 32, $p < 0.01$ Right inferior parietal lobule (BA40): Talairach coordinates 40 −50 56, $p < 0.01$ Left medial frontal gyrus (BA6): Talairach coordinates−2 −20 62, $p < 0.01$ Right inferior frontal gyrus (BA47): Talairach coordinates 52 28 −12, $p < 0.01$

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

Sugranyes G, Kyriakopoulos M, Corrigall R, Taylor E, Frangou S

Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition

PLoS ONE 2011; 6(10): e25322

View review abstract online

Comparison	**Functional activation during social cognition processing in schizophrenia vs. autism spectrum disorders.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess precision or consistency) suggests decreased activation in schizophrenia compared to autism spectrum disorders in the anterior cingulate, superior temporal, and left posterior**

	cingulate during facial emotion recognition tasks. During these tasks, there is increased activation in schizophrenia in the cerebellum, left inferior frontal, left parahippocampus, left inferior parietal and right inferior occipital regions. **During theory of mind tasks, there is decreased activation in schizophrenia in the right insula, and increased activation in schizophrenia in the right medial frontal, the left frontal paracentral lobule, and in the left posterior cingulate cortex.**
Facial emotion recognition	
17 studies, N = 511 <u>Facial emotion processing</u> *The following clusters showed decreased activation in schizophrenia vs. autism spectrum disorders;* Left anterior cingulate: Talairach coordinates 0 26 20, cluster volume 392mm^3 Right anterior cingulate: Talairach coordinates 10 34 20, cluster volume 376mm^3 Left posterior cingulate: Talairach coordinates -20 -62 4, cluster volume 320mm^3 Left superior temporal: Talairach coordinates -56 -24 6, cluster volume 1824mm^3 Right superior temporal: Talairach coordinates 40 -48 14, cluster volume 432mm^3 *The following clusters showed increased activation in schizophrenia vs. autism spectrum disorders;* Left inferior frontal: Talairach coordinates -36 28 2, cluster volume 392mm^3 Left parahippocampus: Talairach coordinates -22 -22 -10, cluster volume 392mm^3 Left inferior parietal: Talairach coordinates -50 -44 -40, cluster volume 360mm^3 Right inferior occipital: Talairach coordinates 32 -84 -4, cluster volume 304mm^3 Left cerebellum culmen: Talairach coordinates -30 -46 -20, cluster volume 352mm^3 Right cerebellum culmen: Talairach coordinates 32 -44 -18, cluster volume 304mm^3 Left cerebellum declive: Talairach coordinates -30 -76 -20, cluster volume, 384mm^3 Right cerebellum declive: Talairach coordinates 26 68 -14, cluster volume 376mm^3	
Theory of mind	
16 studies, N = 463 *The following cluster showed decreased activation in schizophrenia vs. autism spectrum disorders;* Right insula: Talairach coordinates 32 -2 12, cluster volume 200mm^3 *The following clusters showed increased activation in schizophrenia vs. autism spectrum disorders;* Right medial frontal: Talairach coordinates 8 60 4, cluster volume 168mm^3	

Left frontal paracentral lobule: Talairach coordinates 0 -36 52, cluster volume 656mm^3 Left posterior cingulate: Talairach coordinates 0 -16 24, cluster volume 624mm^3 Left posterior cingulate: Talairach coordinates -6 -30 34, cluster volume 200mm^3	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

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. 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.**
Working memory tasks	
No significant differences between groups; Combined hemispheric DLPFC activation: 30 studies, N = 808, *d* = 0.20, 95%CI -0.05 to 0.44, *p* = 0.13 Left hemisphere DLPFC activation: 28 studies, N = 776, *d* = 0.23, 95%CI -0.05 to 0.51, *p* = 0.11 Right hemisphere DLPFC activation: 28 studies, N = 776, *d* = 0.15, 95%CI -0.13 to 0.42, p = 0.34 Subgroup analyses restricted to studies reporting performance data for the same sample on two or more loads of the same working memory task yielded similar results. Moderator analyses revealed that reaction time was a significant moderator of between-group differences. Accuracy was not a significant moderator.	

Consistency in results	No measure of heterogeneity is reported.
Precision in results	Precise for all outcomes except right hemisphere DLPFC activation in the restricted analysis.
Directness of results	Direct

Whalley HC, Papmeyer M, Sprooten E, Lawrie Sm, Sussmann JE, McIntosh AM

Review of functional magnetic resonance imaging studies comparing bipolar disorder and schizophrenia

Bipolar Disorder 2012; 14: 411-431

View review abstract online

Comparison	**Functional activation in people with schizophrenia vs. people with bipolar disorder.**
Summary of evidence	**Low quality evidence (unclear sample sizes, direct, unable to assess precision or consistency) is unable to determine the differences in functional activation between people with schizophrenia and people with bipolar disorder.**
Emotion, reward and memory tasks	
Three of four studies reported over-activation of subcortical medial temporal lobe (hippocampus, amygdala), striatum and mid cingulate cortex in bipolar disorder compared to schizophrenia. One study reported increased activation in people with schizophrenia in the anterior cingulate cortex. One study reported over-activation of the DLPFC in bipolar disorder compared to schizophrenia during an emotion task, and another study reported over-activation of DLPFC in schizophrenia compared to bipolar disorder during a memory task.	
Executive function and language tasks	
One study showed over-activation of the insula in schizophrenia compared to bipolar disorder. Five additional studies reported over-activation of prefrontal cortex (medial and lateral) in schizophrenia compared to bipolar disorder. One study also found increased activation in bipolar disorder compared to schizophrenia in the parietal cortex, cerebellum and fusiform gyrus.	
Consistency in results	No measure of heterogeneity is provided, appears inconsistent.

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

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

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

Schizophrenia Bulletin 2013; doi:10.1093/schbul/sbt063

View review abstract online

Comparison	**Localised brain regions associated with neurological soft signs in people with schizophrenia**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess precision or consistency) suggests that people with schizophrenia showed reduced activation in the basal ganglia and inferior frontal cortex, and increased activation in the superior temporal gyrus, that were associated with increased severity of neurological soft signs.**

Neurological soft signs and motor inhibition tasks

15 studies (N not reported) assessed correlates of neurological soft sign severity while performing motor inhibition tasks (go/no-go) in people with schizophrenia compared to controls.

Patients (9 studies)

NSS severity correlated with activation in:

Left insula: Talairach coordinates -32 22 -2

Right superior temporal gyrus: Talairach coordinates 50 -54 18

Left middle temporal gyrus: Talairach coordinates -40 -60 26

Right lentiform nucleus: Talairach coordinates 18 0 4

Right insula: Talairach coordinates 36 16 6

Right precuneus: Talairach coordinates 24 -70 42

Controls alone (9 studies)

NSS severity correlated with activation in:

Right inferior frontal gyrus: Talairach coordinates 40 28 0 Right middle temporal gyrus: Talairach coordinates 44 -58 22 Left fusiform gyrus: Talairach coordinates -38-64 8 Right lingual gyrus: Talairach coordinates 8 -94 2 Left parahippocampal gyrus: Talairach coordinates -26 -8 -12 Left middle frontal gyrus: Talairach coordinates -40 12 44 *Areas with reduced activation in patients vs. controls and with NSS severity correlating;* Left lentiform nucleus (putamen) : Talairach coordinates -24 10 -4 Right lentiform nucleus (putamen) : Talairach coordinates 20 4 -4 Left lentiform nucleus (globus pallidus) : Talairach coordinates -22 -6 12 Right inferior frontal gyrus: Talairach coordinates 40 22 4 Left brainstem: Talairach coordinates -2 -30 -10 *Areas with increased activation in patients vs. controls and with NSS severity correlating;* Left superior temporal gyrus: Talairach coordinates -46 0 -10	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Explanation of acronyms

AFC = anterior frontal cortex, ALE = Activation Likelihood Estimate for Gaussian smoothed foci, β = slope , BD = bipolar disorder, CI = Confidence Interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardized mean differences (see below for interpretation of effect sizes), DLPFC = dorsolateral prefrontal cortex, FDR = False Discovery Rate correction for multiple comparisons, FWHM = full width at half maximum, applied as a smoothing kernel, fMRI = Functional Magnetic Resonance Imaging, KS3 = Kolmogorov-Smirnov test for homogeneity of distributions, MNI = Montreal Neurological Institute system for stereotactic space, N = number of participants, NSS = neurological soft signs, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PET = Positron Emission Tomography, Q = Q statistic (chi-square) for the test of heterogeneity in results across studies, r, r^2 = correlation coefficients, VLPFC = ventrolateral prefrontal cortex

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Functional Magnetic Resonance Imaging

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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 which 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[31].

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† Different effect measures are reported by different reviews.

ALE analysis (Activation Likelihood Estimate) refers to a voxel-based meta-analytic technique for functional imaging in which each activation point (focus) is spatially smoothed into Gaussian distribution space, and summed to create a statistical map estimating the likelihood of activation of each voxel, as determined by the entire set of included studies. 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. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect[31].

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[32]. lnOR 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 (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to

possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

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

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

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

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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