TECHNICAL COMMENTARY

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Functional Magnetic Resonance Imaging

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 44 systematic reviews that met our inclusion criteria[3-46].

People with schizophrenia vs. controls:

- Moderate quality evidence found decreased local organisation and small-worldness (balance of local organisation and global integration) in people with schizophrenia. There was reduced connectivity within the default network (self-related thought), the affective network (emotion processing), the ventral attention network (processing of salience), the thalamus network (gating information) and the somatosensory network

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au
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(sensory and auditory perception). There was reduced connectivity between the ventral attention network and the thalamus network, the ventral attention network and the default network, the ventral attention network and the frontoparietal network (external goal-directed regulation), the frontoparietal network and the thalamus network, and the frontoparietal network and the default network. There was increased connectivity between the affective network and the ventral attention network.

- 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 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 cognitive control tasks, moderate quality evidence finds decreased activation in the bilateral anterior cingulate/paracingulate gyrus, left inferior parietal gyrus, right middle/inferior frontal gyrus, bilateral middle frontal gyrus, right thalamus, and left cerebellum. There was increased activation in the right middle occipital and bilateral precentral gyri.
- During timing tasks, moderate quality evidence finds decreased activation in the bilateral caudate nuclei, left middle occipital gyrus, right inferior occipital gyrus, bilateral supplementary motor area, and right putamen. There was increased activation during timing tasks in bilateral superior parietal gyri, right inferior frontal gyrus, and right middle temporal gyrus.
- 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, left hippocampus, 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 quality evidence suggests decreased activation in the parahippocampus, superior frontal gyrus, middle occipital gyrus, fusiform gyrus, lentiform nucleus, and thalamus. There were over-activations in left amygdala, left hippocampus, left medial frontal region, left cuneus, and bilateral parietal cortex.

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- During emotionally neutral tasks, there was increased activity in the left and right amygdala and parahippocampus, and the left putamen, hippocampus, and insula in people with schizophrenia compared to controls.
- During explicit threat processing, there was decreased activity in the inferior frontal gyrus, right cerebellum lobule VI, left fusiform gyrus, and thalamus, and increased activity in the medial prefrontal gyrus to superior prefrontal gyrus. During implicit threat processing, there was decreased activity in bilateral amygdala extending into putamen, hippocampus and parahippocampal gyrus, and fusiform gyrus extending into the cerebellum lobule IV/VI. Across tasks, people with schizophrenia showed similar decreased activity in the right amygdala and the left fusiform gyrus.
- During theory of mind tasks, there was decreased activation in the medial prefrontal cortex (frontal medial and paracingulate), right premotor cortex (central opercular, postcentral, precentral), medial occipitoparietal, right lingual gyrus, left orbitofrontal cortex, left lateral occipitotemporal, left cingulate gyrus, and the left middle temporal gyrus. There was increased activation in the left inferior parietal cortex and right inferior parietal cortex. During empathy tasks, there was decreased activation the right inferior frontal gyrus.
- During inhibition tasks, moderate quality evidence found under-activations in the anterior and middle cingulate cortex, and over-activations in parietal and occipital cortex. There was also decreased activation of the basal ganglia and inferior frontal cortex, and increased activation in the superior temporal gyrus.
- During attention tasks, there were under-activations in the anterior and middle cingulate cortex and the basal ganglia, and over-activations in the left supramarginal gyrus.
- During linguistic tasks (mostly semantic reading), there were under-activations in the lateral temporal regions and left putamen, and over-activations in bilateral frontal cortex and left putamen.
- During reward stimuli tasks, moderate quality evidence suggests decreased activation in the right ventral striatum. During reward anticipation tasks, there was reduced activation in the left striatum, the right median cingulate/paracingulate gyri, the left thalamus, the left postcentral gyrus, the left middle frontal gyrus, the cerebellum, and the superior temporal gyrus of people with schizophrenia.
- Moderate quality evidence finds a small association between increased brain activation while performing social cognitive tasks and better functional outcome.
- During auditory hallucinations, 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.
- In people with schizophrenia and formal thought disorder, moderate quality evidence suggests functional alterations (hyperactivation or hypoactivation) in the left superior and middle temporal gyrus.
- Following cognitive remediation (40 session over 10 weeks), moderate to low 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:

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Functional Magnetic Resonance Imaging

- 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:

- Moderate quality evidence suggests decreased activation at rest in the ventromedial prefrontal cortex, left hippocampus, posterior cingulate cortex, lower precuneus 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 decreased grey matter volume and decreased functional activity in the left medial posterior cingulate/paracingulate gyrus, right temporal pole/superior temporal gyrus, left fusiform gyrus, left inferior parietal gyrus, and left caudate nucleus in drug-free patients. There was decreased grey matter volume and increased functional activity in the left superior temporal gyrus, right superior temporal gyrus, left fusiform gyrus, and right lingual gyrus. There was increased grey matter volume and decreased functional activity in the left cerebellum, right gyrus rectus, and right inferior parietal gyrus. There was increased grey matter volume and increased functional activity in the left insula and left cerebellum (lobule IX).
- Moderate to high quality evidence suggests decreased functionality in the right cerebellum (lobule VIII and crus I) and left cerebellum (lobule IX), with no increases in functionality. Functional connectivity strength was reduced in the left fusiform gyrus (BA 30) and left cerebellum (lobule IV/V) and increased functional connectivity strength in the left cerebellum (crus I/II) in medication-naïve people with first-episode schizophrenia.

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.

Relatives of people with schizophrenia vs. controls:

- Overall, moderate to high quality evidence suggest relatives have increased activation in the left optic radiations, left fusiform gyrus, and right posterior and anterior superior temporal gyrus, and decreased activity in the left thalamus, left cerebellum, left precuneus, and right inferior frontal gyrus.
- A combined analysis of structural and functional anomalies demonstrated decreased grey matter with increased

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

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 tasks, there was increased activation in the right inferior frontal gyrus 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 showed poorer accuracy and reaction time compared to controls, with reduced activity in the right middle frontal gyrus (BA9) and right inferior frontal gyrus (BA44), and increased activity in the right frontopolar (BA10), left inferior parietal lobe (BA40), and bilateral thalamus. There was also altered activation in the cerebellum.
- During language processing, relatives 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 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.

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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-sized samples, 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

Alustiza I, Radua J, Pla M, Martin R, Ortuno F

Meta-analysis of functional magnetic resonance imaging studies of timing and cognitive control in schizophrenia and bipolar disorder: Evidence of a primary time deficit

Schizophrenia Research 2017; 188: 21-32

View online review abstract

Comparison	**Brain activation during cognitive control tasks in people with schizophrenia vs. controls.** **Cognitive control is defined as the level of perceived difficulty of the cognitive task and the subsequent mental effort that an individual applies to achieve the cognitive aim.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess consistency or precision) finds decreased activation during cognitive control tasks in the bilateral anterior cingulate/paracingulate gyrus, left inferior parietal gyrus, right middle/inferior frontal gyrus, bilateral middle frontal gyrus, right thalamus, and left cerebellum. There was increased activation during cognitive control tasks in the right middle occipital and bilateral precentral gyri. During timing tasks, there was decreased activation in the bilateral caudate nuclei, left middle occipital gyrus, right inferior occipital gyrus, bilateral supplementary motor area, and right putamen, There was increased activation during timing tasks in bilateral superior parietal gyri, right inferior frontal gyrus, and right middle temporal gyrus.**
Brain activity	

Cognitive control 29 studies, N = 2,268 *Significant, decreased activation in people with schizophrenia was found in;* Bilateral anterior cingulate/paracingulate gyrus (BA 24 and 32) Left inferior parietal gyrus (BA 40) Right middle/inferior frontal gyrus (triangular part, BA 45) Bilateral middle frontal gyrus (BA 44, 8) Right thalamus Left cerebellum *Significant, increased activation in people with schizophrenia was found in;* Right middle occipital (BA 19) Bilateral precentral gyri (BA 6) Timing 8 studies, N = 395 *Significant, decreased activation in people with schizophrenia was found in;* Bilateral caudate nuclei Left middle occipital gyrus (BA 18) Right inferior occipital gyrus (BA 18) Bilateral supplementary motor area (BA 6 and 32) Right putamen *Significant, increased activation in people with schizophrenia was found in;* Bilateral superior parietal gyri (BA 7) Right inferior frontal gyrus (orbital part, BA 47) Right middle temporal gyrus (BA 38)	
Consistency in results	Unable to assess; no measure of consistent is reported.
Precision in results	Unable to assess; no measure of precision is reported (CIs).
Directness of results	Direct

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, direct, unable to assess consistency) 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

Bernard JA, Russell CE, Newberry RE, Goen JR, Mittal VA **Patients with schizophrenia show aberrant patterns of basal ganglia activation: Evidence from ALE meta-analysis** **NeuroImage Clinical 2017; 14: 450-63** View review abstract online	
Comparison	**Comparison of basal ganglia functional activity in people with schizophrenia vs. controls.** **Tasks involved motor function, executive function, attention, working memory, emotional processing, language, and reward**

	processing.
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests significantly lower activation in the basal ganglia during various tasks in people with schizophrenia.**
Functional activation	
Patients with schizophrenia had less activation than controls; All tasks: 42 studies, N = 1,290, 41.21% vs. 87.27%, t = -3.098, p = 0.011 Emotion tasks: 7 studies, 0% vs. 100% Executive function: 7 studies, 14.28% vs. 100% Language: 5 studies, 80% vs. 60% Motor: 6 studies, 66.67% vs. 100% Reward: 4 studies, 50% vs. 100% Working memory: 11 studies, 36.36% vs. 63.63%	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Chase HW, Loriemi P, Wensing T, Eickhoff SB, Nickl-Jockschat T

Meta-analytic evidence for altered mesolimbic responses to reward in schizophrenia

Human Brain Mapping 2018; 39: 2917-28

View review abstract online

Comparison	**Comparison of functional activity in response to reward stimuli in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium to large sample, direct, unable to assess consistency or precision) suggests decreased activation in the right ventral striatum in response to reward stimuli in people with schizophrenia compared to controls.**

Functional activation	
The only significant finding was decreased activation in patients in; Right ventral striatum: 7 studies, N = 280, MNI coordinates 10,12, -2	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

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 during various tasks.**
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

Crossley NA, Mechelli A, Ginestet C, Rubinov M, Bullmore ET, McGuire P

Altered Hub Functioning and Compensatory Activations in the Connectome: A Meta-Analysis of Functional Neuroimaging Studies in Schizophrenia

Schizophrenia Bulletin 2016; 42: 434-42

View review abstract online

Comparison	**Comparison of functional activity in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests during working memory tasks, there were under-activations in prefrontal regions, and over-activations in medial temporal and anterior cingulate cortex. During episodic memory tasks, there were under-activations in the left hippocampus, and over-activations in right medial temporal. During attention tasks, there were under-activations in the anterior and middle cingulate cortex and the basal ganglia, and over-activations in the left supramarginal gyrus. During inhibition tasks, there were under-activations in the anterior and middle cingulate cortex, and over-activations in parietal and occipital cortex. During linguistic tasks (mostly semantic reading), there were under-activations in the lateral temporal regions and left putamen, and over-activations in bilateral frontal cortex and left putamen. During theory of mind tasks, there were under-activations in the medial prefrontal, lateral temporal cortical, and right pallidum, and over-activations in frontal regions and the right supramarginal cortex. During emotion tasks, there were under-**

	activations in thalamic and occipito-temporal regions, and over-activations in left amygdala and hippocampus, left medial frontal region, left cuneus, and bilateral parietal cortex.
Functional activation	
314 studies, N = 10,942 Across all tasks, 82% of brain regions showed at least one under-activation. Working memory tasks Under-activations in prefrontal regions; over-activations in medial temporal and anterior cingulate cortex. Episodic memory tasks Under-activations in the left hippocampus; over-activations in right medial temporal. Attention tasks Under-activations in the anterior and middle cingulate cortex and the basal ganglia; over-activations in the left supramarginal gyrus. Inhibition tasks Under-activations in the anterior and middle cingulate cortex; over-activations in parietal and occipital cortex. Linguistic tasks (mostly semantic reading) Under-activations in the lateral temporal regions and left putamen; over-activations in bilateral frontal cortex and left putamen. Theory of mind tasks Under-activations in the medial prefrontal, lateral temporal cortical, and right pallidum; over-activations in frontal regions and the right supramarginal cortex. Emotion tasks Under-activations in thalamic and occipito-temporal regions; over-activations in left amygdala and hippocampus, left medial frontal region, left cuneus, and bilateral parietal cortex.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

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, 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, 1,018 *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

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

Cerebellar structural and functional abnormalities in first episode and drug-naive patients with schizophrenia: A meta-analysis

Psychiatry Research - Neuroimaging 2019; 283: 24-33

View review abstract online

Comparison	**Cerebellar functionality in medication-naïve people with first-episode schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, direct, unable to assess precision) suggests decreased functionality in the right cerebellum (lobule VIII and crus I) and left cerebellum (lobule IX), with no increases in functionality. Functional connectivity strength was reduced in the left fusiform gyrus (BA 30) and left cerebellum (lobule IV/V) and increased functional connectivity strength in the left cerebellum (crus I/II) in medication-naïve people with first-episode schizophrenia.**
Cerebellar functionality	
Functionality 8 studies, N = 689 *Decreased functional activity was found in;* Right cerebellum, hemispheric lobule VIII: MNI coordinates 22, -62, -58, *p* = 0.000366390 Left cerebellum, hemispheric lobule IX: MNI coordinates -12 -58 -42, *p* = 0.000397384 Right cerebellum, crus I: MNI coordinates 48, -58, -32, *p* = 0.002353311 There were no increases in functional activity. Functional connectivity strength 3 studies, N = 188 *Decreased functional connectivity strength in;* Left cerebellum, hemispheric lobule IV/V: MNI coordinates -22, -34, -24, *p* = 0.000428319 Extending to the left fusiform gyrus, BA 30: MNI coordinates -20 -44 -16, *p* = 0.000185788 *Increased functional connectivity strength in;* Left cerebellum, crus II: MNI coordinates -16 -78 -34, *p* = 0.000015497 Left cerebellum, crus I: MNI coordinates -8 -70 -28, *p* = 0.000061929	
Consistency in results	Authors report consistent results.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

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

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

Schizophrenia Research 2018; 197: 200-208

View review abstract online

Comparison	**Functional activity during threatening face processing in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) suggests across explicit and implicit threat processing, people with schizophrenia showed decreased activity in the right amygdala and the left fusiform gyrus. During explicit threat processing, there was decreased activity in the inferior frontal gyrus, right cerebellum lobule VI, left fusiform gyrus, and thalamus, and increased activity in the medial prefrontal gyrus to superior prefrontal gyrus. During implicit threat processing, there was decreased activity in bilateral amygdala extending into putamen, hippocampus and parahippocampal gyrus, and fusiform gyrus extending into the cerebellum lobule IV/VI.**

Functional activity

19 studies, N = 728

Explicit threat processing

Decreased activity in;

Inferior frontal gyrus: 964 voxels, MNI coordinates 56, 16, 14, $p < 0.001$

Right cerebellum lobule VI: 200 voxels, MNI coordinates 32, -74, -24, $p < 0.001$

Left fusiform gyrus: 276 voxels, MNI coordinates -36, -52, -20, $p < 0.001$

Thalamus extending into right amygdala: 819 voxels, MNI coordinates -4, -6, 2, $p < 0.001$

Increased activity in;

Medial prefrontal gyrus to superior prefrontal gyrus: 990 voxels, MNI coordinates -8, 58, 12, $p < 0.001$

Implicit threat processing

Decreased activity in;

Bilateral amygdala extending into putamen, hippocampus and parahippocampal gyrus: 3,953

voxels, MNI coordinates -30, -6, -8, $p < 0.001$ Fusiform gyrus extending into cerebellum lobule IV/VI: 2,137 voxels, MNI coordinates 26, 4, 88, $p < 0.001$ Across tasks, people with schizophrenia showed decreased activity in the right amygdala and left fusiform gyrus. Meta-regression analyses showed brain abnormalities in schizophrenia were partly modulated by age, gender, medication and severity of symptoms.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Dong D, Wang Y, Chang X, Luo C, Yao D

Dysfunction of Large-Scale Brain Networks in Schizophrenia: A Meta-analysis of Resting-State Functional Connectivity

Schizophrenia Bulletin 2018; 44: 168-81

View review abstract online

Comparison	**Functional connectivity during resting in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found reduced connectivity within the default network (self-related thought), the affective network (emotion processing), the ventral attention network (processing of salience), the thalamus network (gating information) and the somatosensory network (sensory and auditory perception). There was reduced connectivity between the ventral attention network and the thalamus network, the ventral attention network and the default network, the ventral attention network and the frontoparietal network (external goal-directed regulation), the frontoparietal network and the thalamus network, and the frontoparietal network and the default network. There was increased connectivity between the affective network and the ventral attention network.**
Functional connectivity	

52 studies, N = 4,412 *Schizophrenia was characterised by;* Reduced connectivity within the default network (self-related thought), the affective network (emotion processing), the ventral attention network (processing of salience), the thalamus network (gating information) and the somatosensory network (sensory and auditory perception). Reduced connectivity between the ventral attention network and the thalamus network, the ventral attention network and the default network, the ventral attention network and the frontoparietal network (external goal-directed regulation), the frontoparietal network and the thalamus network, and the frontoparietal network and the default network. Increased connectivity between the affective network and the ventral attention network.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Dugre JR, Bitar N, Dumais A, Potvin S

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

American Journal of Psychiatry 2019; 176: 1021-9

View review abstract online

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

	hippocampus, and insula.
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

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, 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

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

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

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

View review abstract online

Comparison	**Overlap between regions of functional and structural alteration in drug-free people with first-episode schizophrenia vs. controls.** **Note; most patients were drug naïve.**
Summary of evidence	**Moderate quality evidence (large sample, mostly consistent, direct, unable to assess precision) suggests decreased grey matter volume and decreased functional activity in the left medial posterior cingulate/paracingulate gyrus, right temporal pole/superior temporal gyrus, left fusiform gyrus, left inferior parietal gyrus, and left caudate nucleus in drug-free patients. There was decreased grey matter volume and increased functional activity in the left superior temporal gyrus, right superior temporal gyrus, left fusiform gyrus, and right lingual gyrus. There was increased grey matter volume and decreased functional activity in the left cerebellum, right gyrus rectus, and right inferior parietal gyrus. There was increased grey matter volume and increased functional activity in the left insula and left cerebellum (lobule IX).**

Structural and functional alteration
15 structural MRI studies, N = 971, 16 functional MRI studies, N = 831 *Significant decreased grey matter volume and decreased functional activity in;* Left medial posterior cingulate/paracingulate gyrus: 1,499 voxels, MNI coordinates (-4, -24, 42), $p < 0.001$ Right temporal pole/superior temporal gyrus: 1,446 voxels, MNI coordinates (34, 8, -22), $p < 0.001$ Left fusiform gyrus: 1,075 voxels, MNI coordinates (-34, -54, -22), $p < 0.001$

Left inferior parietal gyrus: 333 voxels, MNI coordinates (-52, -44, 44), $p < 0.001$ Left caudate nucleus: 111 voxels, MNI coordinates (-10, 0, 12), $p < 0.001$ *Significant decreased grey matter volume and increased functional activity in;* Left superior temporal gyrus: 4,575 voxels, MNI coordinates (-56, -32, 20), $p < 0.001$ Right superior temporal gyrus: 1,583 voxels, MNI coordinates (46, -16, -2), $p < 0.001$ Left fusiform gyrus: 307 voxels, MNI coordinates (-36, -68, -12), $p < 0.001$ Right lingual gyrus: 123 voxels, MNI coordinates (18, -70, -12), $p < 0.001$ *Significant increased grey matter volume and decreased functional activity in;* Left cerebellum: 1,170 voxels, MNI coordinates (-6, -28, -18), $p < 0.001$ Right gyrus rectus: 934 voxels, MNI coordinates (2, 60, -18), $p < 0.001$ Right inferior parietal gyrus: 100 voxels, MNI coordinates (42, -56, 46), $p < 0.001$ *Significant increased grey matter volume and increased functional activity in;* Left insula: 234 voxels, MNI coordinates (-30, 0, 12), $p < 0.001$ Left cerebellum, lobule IX: 327 voxels, MNI coordinates (-12, -56, -46), $p < 0.001$		
Consistency in results	Authors report most findings were consistent.	
Precision in results	Unable to assess; no measure of precision is reported.	
Directness of results	Direct	

Glahn DC, Ragland JD, Abramoff A, Barrett J, Laird AR, Bearden CE, Velligan DI **Beyond hypofrontality: A quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia** **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 (small sample, 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 sample, direct, unable to assess consistency or precision) 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
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.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, direct, unable to assess precision or consistency) suggests no difference in frontal or non-frontal lobe functional activity during neurocognitive tasks between people with schizophrenia and controls.**
Neurocognitive tasks; working memory, executive function, vigilance tasks combined	
Frontal lobe activity 14 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, 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

Kambeitz J, Kambeitz-Ilankovic L, Cabral C, Dwyer DB, Calhoun VD, Van Den Heuvel MP, Falkai P, Koutsouleris N, Malchow B

Aberrant Functional Whole-Brain Network Architecture in Patients with Schizophrenia: A Meta-analysis

Schizophrenia Bulletin 2016; 42: S13-S21

View review abstract online

Comparison	**Whole-brain analysis of functional connectedness at rest in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests decreased local organisation and small-worldness (balance of local organisation and global integration) in people with schizophrenia, with no changes in global short communication paths.**
Brain network activation	
8 fMRI studies, N = 453 *People with schizophrenia showed medium to large decreases in;* Local organisation: 7 studies, g = -1.33, 95%CI -1.81 to -0.85, p < 0.001, I^2 = 73% Small-worldness (balance of local organisation and global integration): 5 studies, g = -0.65, 95%CI -1.12 to -0.18, p = 0.01, I^2 = 67% The small-worldness analysis included two EEG studies. *There were no differences in;* Global short communication paths: 5 studies, g = 0.63, 95%CI -0.56 to 1.82, p = 0.30, I^2 = 95%	

There were no moderator effects.	
Consistency in results	Inconsistent
Precision in results	Imprecise
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 to low quality evidence (small sample, 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

Kronbichler L, Tschernegg M, Martin AI, Schurz M, Kronbichler M

Abnormal Brain Activation During Theory of Mind Tasks in Schizophrenia: A Meta-Analysis

Schizophrenia Bulletin 2017; 43: 1240-50

View review abstract online

Comparison	**Functional activity during theory of mind tasks in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests decreased activation in the medial prefrontal cortex (frontal medial and paracingulate), right premotor cortex (central opercular, postcentral, precentral), medial occipitoparietal, right lingual gyrus, left orbito-frontal cortex, left lateral occipitotemporal, and left cingulate gyrus. There was increased activation in the left inferior parietal cortex and right inferior parietal cortex.**

Functional activity	
21 studies, N = 623 *Decreased activation in;* Medial prefrontal cortex (frontal medial and paracingulate): 1,573 voxels, MNI coordinates -2, 52, 18 Right premotor cortex (central opercular, postcentral, precentral): 1,101 voxels, MNI coordinates 54, -14, 18 Medial occipitoparietal: 128 voxels, MNI coordinates -4, -76, 14 Right lingual gyrus: 99 voxels, MNI coordinates 12, -58, 2 Left orbito-frontal cortex: 30 voxels, MNI coordinates -30, 22, -24 Left lateral occipitotemporal: 27 voxels, MNI coordinates -48, -72, 22 Left cingulate gyrus: 34 voxels, MNI coordinates -18, -44, -2 *Increased activation in;* Left inferior parietal cortex: 486 voxels, MNI coordinates -42, -48, 38 Right inferior parietal cortex: 405 voxels, MNI coordinates 58, -40, 40	
Consistency in results	Unable to assess; no measure of heterogeneity is reported.
Precision in results	Unable to assess; no confidence intervals are reported.
Directness of results	Direct

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 samples, 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	Unable to assess; no measure of heterogeneity is reported.
Precision in results	Unable to assess; 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, direct, unable to assess precision or consistency) suggests decreased activation in the ventromedial prefrontal cortex, left hippocampus, posterior cingulate cortex, lower precuneus 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

Leroy A, Amad A, D'Hondt F, Pins D, Jaafari N, Thomas P, Jardri R

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

Schizophrenia Research 2020; Jan: doi.org/10.1016/j.schres.2019.12.041

View review abstract online

Comparison	**Functional activity during reward anticipation in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found reduced activation in the left striatum, the right median cingulate/paracingulate gyri, the left thalamus, the left postcentral gyrus, the left middle frontal gyrus, the cerebellum, and the superior temporal gyrus.**
Functional activation	
11 studies, N = 488 *Schizophrenia was characterised by;* Reduced activation in the left striatum, the right median cingulate/paracingulate gyri, the left thalamus, the left postcentral gyrus, the left middle frontal gyrus, the cerebellum, and the superior temporal gyrus. This functional signature was linked to the severity of psychotic symptoms and persisted after controlling for the dose of antipsychotic medications.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.

Directness of results	Direct

Li S, Hu N, Zhang W, Tao B, Dai J, Gong Y, Tan Y, Cai D, Lui S

Dysconnectivity of multiple brain networks in schizophrenia: A meta-analysis of resting-state functional connectivity

Frontiers in Psychiatry 2019; 10: 482

[View review abstract online]

Comparison	**Functional connectivity during resting in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found reduced connectivity between the seed regions and the areas in the auditory network (left insula), core network (right superior temporal cortex), default mode network (right medial prefrontal cortex, and left precuneus and anterior cingulate cortices), self-referential network (right superior temporal cortex), and somatomotor network (right precentral gyrus) in schizophrenia patients.**
Functional connectivity	
70 studies, N = 5,155 *Schizophrenia was characterised by;* Reduced connectivity between the seed regions and the areas in the auditory network (left insula), core network (right superior temporal cortex), default mode network (right medial prefrontal cortex, and left precuneus and anterior cingulate cortices), self-referential network (right superior temporal cortex), and somatomotor network (right precentral gyrus) in schizophrenia patients.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

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-sized sample, 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

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 (unclear sample size, direct, unable to assess precision or consistency) suggests 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. Functional activity during working memory tasks shows alterations in DLPFC, VLPFC, parietal and cerebellum of relatives. During long term memory tasks, only VLPFC of relatives shows functional alteration. 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

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

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.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests 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 = 1,217 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.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests 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.**
Executive function tasks	
41 studies, N = 1,217 *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	

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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

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

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

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

View review abstract online

Comparison	**Functional alteration in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, direct, unable to assess consistency or precision) suggests relatives had decreased resting-state brain activity in the left precuneus and the right inferior frontal gyrus, and increased brain activity in the left optic radiations and left fusiform gyrus.**

Functional alterations
3 studies, N = 214 *Compared to controls, relatives had decreased brain activity in;* Left precuneus: 2,176 voxels, MNI coordinates -4, -54, 42, p = 0.00019 Right inferior frontal gyrus: 947 voxels, MNI coordinates 42, 34, 26, p = 0.00023 *Compared to controls, relatives had increased brain activity in;* Left optic radiations: 513 voxels, MNI coordinates -18, -96, 0, p = 0.00003

Left fusiform gyrus: 274 voxels, MNI coordinates -24, -38, -16, *p* = 0.00002	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

O'Neill A, Mechelli A, Bhattacharyya S

Dysconnectivity of large-scale functional networks in early psychosis: A meta-analysis

Schizophrenia Bulletin 2019; 45: 579-90

View review abstract online

Comparison	**Functional connectivity during resting in people with first-episode psychosis vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess consistency or precision) found the default mode network seeds primarily displayed within-network hypoconnectivity (largest clusters including the middle orbital gyrus, and ventral anterior cingulate gyrus). The salience network seeds displayed hypoconnectivity with regions in the default mode network and central executive networks (largest clusters located in the bilateral middle temporal gyri).**
Functional connectivity	
70 studies, N = 5,155 *First-episode psychosis was characterised by;* The default mode network seeds primarily displayed within-network hypoconnectivity (largest clusters including the middle orbital gyrus, and ventral anterior cingulate gyrus). The salience network seeds displayed hypoconnectivity with regions in the default mode network and central executive networks (largest clusters located in the bilateral middle temporal gyri). Negative symptoms were positively correlated with all default mode network functional connectivity abnormalities. Antipsychotic treated patients displayed greater hypoconnectivity than antipsychotic-naïve patients	

between both the default mode network / salience network seeds and prefrontal regions.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

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

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

Neuroscience and Biobehavioural Reviews 2012; 36: 2325-2333

View review abstract online

Comparison	**Overlap between regions of functional and structural alteration in people with first-episode psychosis vs. controls**
Summary of evidence	**Moderate quality evidence (large sample, direct, unable to assess precision or consistency) suggests 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, with greater severity of abnormality in medicated patients.**
Regions of overlap	
Analysis of 25 structural MRI studies (N = 2,005) and 18 functional MRI studies (N = 765) found regions with both structural and functional alteration in people with first-episode psychosis; *Decreased grey matter volume and decreased functional activation;* Right 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.**

	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. **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.** **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 postcentral 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	

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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 in people with schizophrenia vs. various control conditions. Training duration was an average of 10 weeks comprising 40 sessions.**
Summary of evidence	**Moderate to low quality evidence (small sample, direct, unable to assess precision or consistency) suggests increased activity in the left middle frontal gyrus, left inferior frontal gyrus, left superior frontal gyrus, pre- and postcentral gyrus, bilateral insula, parietal lobe, and medial frontal gyrus after cognitive remediation.**
Changes in activation	
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

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

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

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

View review abstract online

Comparison	**Functional activation in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, direct, unable to assess precision) suggests increased activation in the right inferior frontal gyrus during cognitive tasks.**
Cognitive tasks	
Relatives showed increased activation in the right inferior frontal gyrus; MNI co-ordinates 46, 12, 32, p = 0.000001967, 616 voxels, I^2 = 0%	
Consistency in results	Consistent
Precision in results	No confidence intervals are provided.
Directness of results	Direct

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.**

<table>
<tr><td></td><td>controls.</td></tr>
<tr><td>Summary of evidence</td><td>Moderate quality evidence (large sample, 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.</td></tr>
<tr><td colspan="2" align="center">Cognitive and emotion tasks</td></tr>
<tr><td colspan="2" align="center"><u>Cognitive and emotion tasks combined</u>
21 studies, N = 1,245
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.
<u>Cognitive tasks</u>
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
<u>Emotion tasks:</u>
4 studies
The following areas showed increased activation in relatives compared to controls;</td></tr>
</table>

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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 *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.

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

Vucurovic K, Caillies S, Kaladjian A

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

Journal of Psychiatric Research 2020; 120: 163-74

[View review abstract online]

Comparison	**Functional activation during theory of mind and empathy processing in schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, direct, unable to assess precision or consistency) suggests decreased activation in schizophrenia in a 1408mm3 volume cluster of the left middle temporal gyrus during theory of mind tasks, and decreased activation in schizophrenia in a 664mm3 volume cluster of the right inferior frontal gyrus during empathy tasks.**
Theory of mind	
17 studies, N = 560 *The following clusters showed decreased activation in schizophrenia in;* A 1408mm3 volume cluster of the left middle temporal gyrus (Talairach: x=−47.4, y=−69.7, z=13.2; ALE=0.02; BA39).	
Emotion processing	
13 studies, N = 482 *The following cluster showed decreased activation in schizophrenia in;* A 664mm3 volume cluster of the right inferior frontal gyrus (Talairach x=47.8, y=25.6, z=9.6; ALE=0.02; BA45).	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Wensing T, Cieslik EC, Muller VI, Hoffstaedter F, Eickhoff SB, Nickl-Jockschat T

Neural correlates of formal thought disorder: An activation likelihood estimation meta-analysis

Human Brain Mapping 2017; 38: 4946-65

View review abstract online

Comparison	**Functional activation in people with schizophrenia and formal thought disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (medium to large samples, direct, unable to assess precision or consistency) suggests functional alterations (hyperactivation or hypoactivation) in the left superior and middle temporal gyrus.**
Functional activation	
17 studies, N = 282 *The following regions showed hyperactivation or hypoactivation;* Left superior temporal gyrus: 114 voxels, MNI coordinates -54, -32, 9 Left middle temporal gyrus: 72 voxels, MNI coordinates -46, -54, 3	
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

Wojtalik JA, Smith MJ, Keshavan MS, Eack SM

A Systematic and Meta-analytic Review of Neural Correlates of Functional Outcome in Schizophrenia

Schizophrenia Bulletin 2017; 43: 1329-47

View review abstract online

Comparison	**Association between functional outcomes and brain activity in**

	people with schizophrenia. **Functional outcomes include global functioning, social functioning, resource needs, quality of life, socioeconomic status, independent living, employment, and role functioning.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, inconsistent, precise, direct) finds a small association between increased brain activation while performing social cognitive tasks and better functional outcome.**
Brain activity and functional outcome	
Small association between increased brain activation while performing social cognitive tasks and better functional outcome; 10 studies, N = 211, r = 0.25, 95%CI 0.00 to 0.49, p = 0.046, Qp < 0.0001	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Zhang R, Picchioni M, Allen P, Toulopoulou T

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

Schizophrenia Bulletin 2016; 42: 1068-77

View review abstract online

Comparison	**Functional activity during working memory tasks in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, some inconsistency, precise, direct) suggests poorer accuracy and reaction time in working memory tasks in relatives of people with schizophrenia compared to controls. Regions showing reduced activity were the right middle frontal gyrus (BA9) and right inferior frontal gyrus (BA44). Regions showing increased activity were right frontopolar (BA10), left inferior parietal lobe (BA40) and bilateral thalamus.**

Functional activity	
15 studies, N = 547 *Significant, small to medium-sized effects of poorer accuracy and reaction time in relatives;* Accuracy: $d = 0.32$, 95%CI 0.15 to 0.50, $p < 0.01$, Q$p > 0.05$ Reaction time: $d = -0.28$, 95%CI -0.48 to -0.09, $p < 0.01$, Q$p < 0.01$ *Decreased activity in relatives in;* Right middle frontal gyrus (BA9; whole brain studies): Talairach coordinates 34, 36, 34 Right inferior frontal gyrus (BA44; whole brain studies): Talairach coordinates 52, 10, 18 *Increased activity in relatives in;* Right frontopolar (BA10; whole brain studies): Talairach coordinates 32, 50, 10 Left inferior parietal lobe (BA40; whole brain studies): Talairach coordinates -40, -60, 44 Right thalamus (ROI studies): Talairach coordinates 4, -10, 10 Left thalamus (ROI studies): Talairach coordinates -10, -20, 4	
Consistency in results	Inconsistent for reaction time, consistent for accuracy.
Precision in results	Precise
Directness of results	Direct

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

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

Schizophrenia Bulletin 2013; doi:10.1093/schbul/sbt063

View review abstract online

Comparison	**Localised brain regions associated with neurological soft signs in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, direct, unable to assess precision or consistency) suggests people with schizophrenia showed reduced activation in the 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. *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 *Patients alone - 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 - 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	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct

Explanation of acronyms

ALE = Activation Likelihood Estimate for Gaussian smoothed foci, CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences, DLPFC = dorsolateral prefrontal cortex, FDR = False Discovery Rate correction for multiple comparisons, FWHM = full width at half maximum, applied as a smoothing kernel, KS3 = Kolmogorov-Smirnov test for homogeneity of distributions, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), 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, vs. = versus

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials 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[47].

† 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[47].

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[48]. 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;

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

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