TECHNICAL COMMENTARY

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Positron emission tomography

Introduction

Positron emission tomography (PET) is a nuclear based imaging technique that utilises a radioactive tracer to visualise functional brain activity. The radioisotopes tracers are coupled with a biological molecule such as glucose, which is used during cellular metabolism and can be used to highlight areas with changes in metabolic activity.

Method

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

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

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an 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 24 systematic reviews that met our inclusion criteria[3-26].

- 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

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activation in the anterior cingulate cortex, temporal lobe, parietal cortex, lingual gyri, insula and the amygdala.

- 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 emotion processing tasks, moderate and moderate to low quality evidence suggests decreased activation in the amygdala, parahippocampus, superior frontal gyrus and middle occipital gyrus. There is also lower magnitude of activation in the fusiform gyrus, lentiform nucleus, and parahippocampal gyrus. During explicit (effortful) emotion tasks, there is decreased activation in the fusiform gyrus, while during implicit (automatic) emotion tasks, there are decreases in the superior frontal and middle occipital gyri.
- During auditory hallucinations, moderate and moderate to low quality evidence suggests increased activation in Broca's area of the temporal lobe, insula, hippocampus, left parietal operculum, left and right postcentral gyrus, and left inferior frontal gyrus, and decreased activation of Broca's area, the left middle temporal gyrus, left premotor cortex, anterior cingulate cortex, and left superior temporal gyrus during external auditory stimulation.
- During cognitive tasks and rest periods, moderate to high quality evidence shows a medium to large effect of reduced functional activity in bilateral frontal lobes in people with schizophrenia. Moderate quality evidence suggests increased functional activity in the left temporal lobe during cognitive tasks, but no differences between patients and controls during rest periods.
- Moderate quality evidence suggests elevated striatal dopamine synthesis and release capacities and increased synaptic dopamine levels in people with schizophrenia. The finding for dopamine synthesis was apparent in treatment-responsive and treatment-naive patients, but not significant in treatment-resistant patients. There were no differences in dopamine D2/3 receptor or transporter availability. Within-group variability was similar for dopamine synthesis and release capacities, but there was greater variability in synaptic dopamine levels, and dopamine D2/3 receptor and transporter availability in the patient groups than in the control groups.
- Moderate quality evidence suggests greatest D2 receptor occupancy with haloperidol (92%), then risperidone, olanzapine, clozapine, quetiapine, aripiprazole, ziprasidone, and then amisulpride (85%).
- Moderate to low quality evidence suggests there may be an association between dopamine receptor occupancy and clinical improvement on the PANSS, following treatment with antipsychotic medications. Single ligands had significantly higher occupancy than dual ligands. Significant difference in occupancy rates between first- and second-generation antipsychotics was reported, when controlling for ligand type and modelling method.
- Moderate to low quality evidence suggests dopamine receptor occupancy may be different depending on first- or second-generation antipsychotic treatment.
- Moderate quality evidence suggests a small to medium-sized increase in translocator protein in people with schizophrenia when measured using binding potential, but not volume of distribution.

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. healthy controls.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate quality evidence (medium to large sample sizes, unable to assess precision and consistency, direct) 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 observational 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 observational 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 measured of heterogeneity is provided.
Precision in results§	No confidence intervals are provided.
Directness of results‖	Direct measures and comparison of functional activity.

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

Directness of results	Direct measures and comparison of functional activity.

Brugger SP, Angelescu I, Abi-Dargham A, Mizrahi R, Shahrezaei V, Howes OD

Heterogeneity of Striatal Dopamine Function in Schizophrenia: Meta-analysis of Variance

Biological Psychiatry 2020; 87: 215-24

View review abstract online

Comparison	**Striatal dopamine function in people with schizophrenia (measured by PET or SPECT) vs. controls.**
Summary of evidence	**Moderate quality evidence (medium to large samples, mostly inconsistent and precise, direct) suggests elevated striatal dopamine synthesis and release capacities, and increased synaptic dopamine levels in people with schizophrenia. The finding for dopamine synthesis was apparent in treatment-responsive and treatment-naive patients, but not significant in treatment-resistant patients. There were no differences in dopamine D2/3 receptor or transporter availability.** **Within-group variability was similar for dopamine synthesis and release capacities, but there was greater variability in synaptic dopamine levels, and dopamine D2/3 receptor and transporter availability in the patient groups than in the control groups.**

Dopamine synthesis capacity

A medium-sized, significant increase in dopamine synthesis capacity in people with schizophrenia;

15 studies, N = 410, g = 0.65, 95%CI 0.30 to 1.10, p = 0.004, I^2 = 76%

There was similar within-group variability in patient and control groups.

The result was similar in the subgroup analysis of treatment-responsive and treatment-naive patients, but not significant in treatment-resistant patients.

Dopamine release capacity

A medium-sized, significant increase in dopamine release capacity in people with schizophrenia;

6 studies, N = 172, g = 0.66, 95%CI 0.06 to 1.25, p = 0.03, I^2 = 79%

There was similar within-group variability in patient and control groups.

There were insufficient studies for a subgroup analysis of treatment status.
Synaptic dopamine levels
A medium-sized, significant increase in dopamine synthesis capacity in people with schizophrenia; 3 studies, N = 86, *g* = 0.78, 95%CI 0.34 to 1.73, *p* = 0.0006, I^2 = 0% There was greater within-group variability in patient groups than in control groups. There were insufficient studies for a subgroup analysis of treatment status.
Dopamine D2/3 receptor availability
There was no significant difference between groups; 34 studies, N = 970, *g* = 0.17, 95%CI -0.07 to 0.39, *p* = 0.14, I^2 = 76% There was greater within-group variability in patient groups than in control groups. The result was similar in the subgroup analysis of treatment-naive patients.
Dopamine transporter availability
There was no significant difference between groups; 15 studies, N = 566, *g* = -0.20, 95%CI -0.55 to 0.16, *p* = 0.28, I^2 = 71% There was greater within-group variability in patient groups than in control groups. The result was similar in the subgroup analysis of treatment-naive patients.

Consistency in results	Inconsistent, apart from synaptic dopamine levels.
Precision in results	Precise, apart from synaptic dopamine levels and dopamine release.
Directness of results	Direct

Davidson LL, Heinrichs RW

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

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

View review abstract online

Positron emission tomography

Comparison	**Whole brain comparison of functional activation in people with schizophrenia patients vs. healthy controls.**
Summary of evidence	**Moderate to high quality evidence (large sample size, precise, mostly inconsistent, direct) shows a medium to large effect of reduced functional activity in bilateral frontal lobes in schizophrenia both during cognitive tasks and at rest compared to controls.** **Moderate quality evidence (large sample size, precise, inconsistent, direct) suggests increased functional activity in the left temporal lobe during cognitive tasks with no differences at rest.** **Moderate to low quality evidence (large sample size, inconsistent, imprecise, direct) suggests no differences in hippocampus functional activity.**
During cognitive tasks and at rest	
Total frontal lobe *During cognitive tasks: large effect suggests reduced activity in people with schizophrenia;* N = 879, *d* = -0.81, 95%CI -1.06 to -0.57, SD = 0.52, FSN = 142 *At rest: medium-sized effect suggests reduced activity in people with schizophrenia;* N = 971, *d* = -0.65, 95%CI -0.88 to -0.42, SD = 0.64, FSN = 176 Left frontal lobe *During cognitive tasks; Medium-sized effect suggests reduced activity in people with schizophrenia;* N = 390, *d* = -0.54, 95%CI -0.78 to -0.30, SD = 0.38, FSN = 53 *At rest: medium-sized effect suggests reduced activity in people with schizophrenia;* N = 617, *d* = -0.48, 95%CI -0.80 to -0.15, SD = 0.74, FSN = 87 Right frontal lobe *During cognitive tasks: medium-sized effect suggests reduced activity in people with schizophrenia;* N = 397, *d* = -0.54, 95%CI -0.90 to -0.18, SD = 0.53, FSN = 48 *At rest: small effect suggests reduced activity in people with schizophrenia;* N = 617, *d* = -0.43, 95%CI -0.74 to -0.12, SD = 0.72, FSN = 76 Left temporal lobe *During cognitive tasks: small effect suggests increased activity in people with schizophrenia;* N = 480, *d* = 0.43, 95%CI -0.16 to 1.01, SD = 0.82, FSN = 33 *At rest: no effect on activity;*	

N = 608, *d* = -0.13, 95%CI -0.50 to 0.23, SD = 0.76, FSN = 6 Right temporal lobe *At rest: no effect on activity;* N = 608, *d* = -0.05, 95%CI -0.49 to 0.38, SD = 0.90, FSN < 0.1 Left hippocampus *During cognitive tasks: no effect on activity;* N = 415, *d* = 0.13, 95%CI -0.69 to 0.43, SD = 0.78, FSN = 3 Right hippocampus *During cognitive tasks: no effect on activity;* N = 415, *d* = -0.07, 95%CI -0.60 to 0.46, SD = 0.74, FSN < 0.1	
Consistency in results	Significant heterogeneity reported for all outcomes except left and right frontal lobes during task.
Precision in results	Precise for all outcomes except left and right hippocampus.
Directness of results	Direct measures and comparison of functional activity.

Fusar-Poli P, Meyer-Lindenberg A

Striatal presynaptic dopamine in schizophrenia, part I: meta-analysis of Dopamine Active Transporter (DAT) density

Schizophrenia Bulletin 2013; 39(1): 22-32

View review abstract online

Comparison	**Density of dopamine transporter (measured by PET or SPECT) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, inconsistent, precise, direct) suggests no difference in dopamine transporter levels in the striatum of people with schizophrenia compared to controls.**
Presynaptic dopamine transporter density	

No significant difference in dopamine transport density in the striatal pre-synaptic terminals of people with schizophrenia compared to controls; 13 studies, N = 349, *d* = -0.244, 95%CI -0.676 to 0.188, *p* = 0.269, Q = 44.075, *p* < 0.001, I^2 = 75.082% *The results remained non-significant when only studies considering striatal subregions were included:* Caudate: *d* = -0.197, 95%CI -0.564 to 0.133, *p* = 0.431 Putamen: *d* = -0.187, 95%CI -0.661 to 0.153, *p* = 0.549 There were also no significant effects of any potential moderating variables including radiotracer type (*p* = 0.602), year of publication (*p* = 0.927), participant age (*p* = 0.301), duration of illness (*p* = 0.468), symptom severity (*p* = 0.452), antipsychotic exposure (*p* = 0.171), or gender (*p* = 0.389).

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct comparisons and measures of functional activity

Fusar-Poli P, Meyer-Lindenberg A

Striatal presynaptic dopamine in schizophrenia, part II: meta-analysis of [^{18}F/^{11}C]-DOPA PET studies

Schizophrenia Bulletin 2013; 39(1): 33-42

View review abstract online

Comparison	**Dopamine synthesis capacity (measured by PET or SPECT) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium-sized sample, consistent, precise, direct) shows increased dopamine synthesis capacity in the striatum of people with schizophrenia compared to controls.**

Presynaptic dopamine synthesis capacity
Large effect size suggests a significant increase in dopamine synthesis capacity in the striatal pre-synaptic terminals of people with schizophrenia compared to controls; 11 studies, N = 244, *d* = 0.867, 95%CI 0.594 to 1.140, *p* < 0.001, Q = 19.19, *p* = 0.078, I^2 = 39.17%

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This difference remained when only studies considering striatal subregions were included: Caudate: *d* = 0.569, 95%CI 0.176 to 0.961, *p* = 0.005 Putamen: *d* = 0.643, 95%CI 0.098 to 1.189, *p* = 0.021 There were also no significant effects of any potential moderating variables including radiotracer type (*p* = 0.701), year of publication (*p* = 0.727), participant age (*p* = 0.856), duration of illness (*p* = 0.736), symptom severity (*p* = 0.783), antipsychotic exposure (*p* = 0.501), or gender (*p* = 0.299).

Consistency in results	Consistent
Precision in results	Mostly precise
Directness of results	Direct comparisons and measures of functional activity

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. healthy controls.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate to low quality evidence (small sample, unable to assess precision or consistency, direct) 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 observational 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 centre of mass (7, 44, -13), cluster volume 472mm^3	

Right middle and inferior frontal gyrus: Talairach centre of mass (33, 37, 28), cluster volume 1200mm^3 Left middle frontal gyrus: Talairach centre of mass (-33, 35, 23) , cluster volume 1736mm^3 Right inferior frontal gyrus and insula: Talairach centre of mass (38, 16, 5) , cluster volume 936mm^3 *Significantly increased activity in people with schizophrenia;* Left middle frontal gyrus: Talairach centre of mass (-44, 42, -3) , cluster volume 560mm^3 Right superior frontal gyrus: Talairach centre of mass (4, 57, 26) , cluster volume 264mm^3 Cingulate cortex: Talairach centre of mass (-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 measures and comparison of functional activity.

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. healthy controls: voxel based comparison.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate quality evidence (medium-sized sample, unable to assess precision or consistency, direct) suggests no difference in frontal or non-frontal lobe functional activity during neurocognitive tasks between people with schizophrenia and healthy controls.**
Neurocognitive tasks; working memory, executive function, vigilance tasks combined	
Frontal lobe activity; 14 observational studies, N = 319 *No significant difference observed in frontal lobe activity;*	

Kolmogorov-Smirnov test (KS3) = 0.16, *p* = 0.94	
Non-frontal lobe; 14 observational studies, N = 319 *No significant difference observed in non-frontal lobe activity;* KS3 = 0.14, *p* = 0.98	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct measures and comparison of functional activity.

Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S

The nature of dopamine dysfunction in schizophrenia and what this means for treatment: Meta-analysis of imaging studies

Archives of General Psychiatry 2012; 69(8): 776-786

View review abstract online

Comparison	**Dopamine function (measured by PET or SPECT) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, some inconsistency, precise, direct) suggests a large effect of increased striatal presynaptic dopamine function, and a small effect of increased receptor availability in people with schizophrenia compared to controls. There are no difference in dopamine transporter levels.**
Presynaptic dopamine function	
Large effect size suggests significantly elevated dopamine activity in schizophrenia patients compared to controls; 17 studies, N = 482, *d* = 0.79, 95%CI 0.52 to 1.07, *p* < 0.001, I^2 = 39.92% *The results did not differ when the analysis was conducted only on drug-free or drug-naïve patients;* *d* = 0.69, 95%CI 0.36 to 1.01, *p* = 0.001, I^2 = 46.46%	

Dopamine transporter levels	
Small effect size suggests no significant difference in dopamine transporter levels between schizophrenia and controls; 11 studies, N = 284, *d* = -0.34, 95%CI -0.75 to 0.07, *p* = 0.10, I^2 = 64%	
Dopamine receptor availability	
Small effect size suggests significantly elevated dopamine receptor levels in unmedicated schizophrenia patients compared to controls; 22 studies, N = 661, *d* = 0.26, 95%CI 0.001 to 0.52, *p* = 0.049, I^2 = 63.93%	
Consistency in results	Some inconsistency
Precision in results	Precise
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, unable to assess precision or consistency, direct) 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: (-48 10 7), 1312mm^3 , ALE 1.84x10^{-3}	

Anterior insula: (-42 0 6) 1240mm^3, ALE 1.78x10^{-3} Precentral gyrus: (-54 0 14) 488mm^3, ALE 1.46x10^{-3} Hippocampus/parahippocampus: (-24 -32 -4) 1664mm^3, ALE 1.90x10^{-3} Anterior insula: (44 6 -4) 964mm^3, ALE 1.66x10^{-3} Frontal operculum: (42 12 -10) 265mm^3, ALE 1.29x10^{-3} Superior temporal gyrus: (-54 -44 16) 800mm^3, ALE 1.59x10^{-3} Supramarginalis gyrus: (-52 -20 15) 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 measures of functional activity.

Kambeitz J, Abi-Dargham A, Kapur S, Howes OD

Alterations in cortical and extrastriatal subcortical dopamine function in schizophrenia: Systematic review and meta-analysis of imaging studies

British Journal of Psychiatry 2014; 204(6): 240-249

View review abstract online

Comparison	**Cortical and extrastriatal D2/D3 receptor availability (measured by PET or SPECT) in unmedicated people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, some inconsistency and imprecision, direct) suggests no differences in D2/D3 receptor availability in the thalamus and temporal cortex of people with schizophrenia compared to controls.** **Moderate to low quality evidence (medium-sized samples, inconsistent, imprecise, direct) also suggests no differences in D2/D3 receptor availability in the substantia nigra.**
D2/D3 receptor availability **Binding potential relative to the non-displaceable compartment**	
Thalamus *No significant differences between groups in D_2/D_3 receptor availability;*	

8 studies, N = 264, *d* = -0.32, 95%CI -0.68 to 0.03, *p* = 0.07, I^2 = 49%

Authors report that the effect became significant when the only 2 studies with positive effect sizes were excluded from the analysis.

Subgroup analysis of 5 studies of participants with previous exposure to antipsychotic medication showed a non-significant effect size (*d* = -0.34). There were too few studies of drug-naïve patients for meta-analysis (k = 3), and effect sizes from these studies ranged from -0.77 to 0.35.

Temporal cortex

No significant differences between groups in D_2/D_3 receptor availability;

6 studies, N = 170, *d* = -0.23, 95%CI -0.54 to 0.07, *p* = 1.00, I^2 = 0%

Effect sizes in studies of drug-free or drug-naïve patients ranged from -0.42 to 0.49.

Substantia nigra

No significant differences between groups in D_2/D_3 receptor availability;

5 studies, N = 143, *d* = 0.04, 95%CI -0.92 to 0.99, *p* = 0.90, I^2 = 85%

Excluding one study of drug-naïve patients did not substantially change the effect (*d* = -0.04).

Meta-regression showed no effect of publication year, gender, or age in any analysis.

There was no evidence of publication bias.

Authors report that the evidence for other measures and regions is limited because of the small number of studies and some inconsistent findings, although individual studies have found significant differences in D2/D3 receptors in the cingulate and uncus, in D1 receptors in the prefrontal cortex, and in dopamine transporter availability in the thalamus.

Consistency in results	Some inconsistency
Precision in results	Some imprecision
Directness of results	Direct

Kompus K, Westerhausan R, Hugdahl K

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

Neuropsychologia 2011; 49: 3361-9

View review abstract online

Comparison	**Functional activation in people with schizophrenia during auditory**

	verbal hallucinations and during auditory stimulation tasks. **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, unable to assess precision or consistency, direct) 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: (-44 -2 6) 2656mm^3 Hippocampus: (-24 -32 -4) 1064mm^3 Postcentral gyrus: (-50 -24 40) 1016mm^3 Inferior parietal lobule: (32 -40 48) 960mm^3 Superior temporal gyrus: (-52 -22 16) 952mm^3 Inferior frontal gyrus: (40 12 16) 408mm^3 Middle temporal gyrus: (54 -32 -4) 368mm^3 Cerebellum: (20 -46 -16) 248mm^3 Superior frontal gyrus: (26 42 26) 240mm^3 Middle temporal gyrus: (58 -44 14) 200mm^3	
Auditory tasks	
11 studies, N = 384, showed reduced activation during auditory stimulation tasks in people with schizophrenia; Superior temporal gyrus: (-54 -8 0), 1824mm^3 Anterior cingulate cortex: (-10 0 40) 520mm^3 Thalamus: (12 -22 18) 520mm^3 Superior frontal gyrus: (24 50 14) 456mm^3 Retrosplenial/hippocampus: (-12 -38 10) 392mm^3	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.

Directness of results	Direct measures and comparison of functional activity.

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-sized samples, unable to assess precision or consistency, direct) 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: (-55 -19 16) 344mm^3

Left postcentral gyrus: (-49 -17 41) 256mm^3

Right postcentral gyrus: (36 -32 50) 216mm^3

Left inferior frontal gyrus: (-48 2 6) 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: (-56 -30 0), 424mm^3

Left premotor cortex: (-10 3 56) 376mm^3

Anterior cingulate cortex: (-4 26 31) 160mm^3 Anterior cingulate cortex: (-42 2 18) 152mm^3 Anterior cingulate cortex: (-9 4 37) 112mm^3 Left superior temporal gyrus: (-44 -22 0) 152mm^3	
Consistency in results	No measure of heterogeneity is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct measures and comparison of functional activity.

Lako IM, van den Heuvel ER, Knegtering H, Bruggeman R, Taxis K

Estimating dopamine D2 receptor occupancy for doses of 8 antipsychotics: a meta-analysis

Journal of Clinical Psychopharmacology 2013; 33(5): 675-81

View review abstract online

Comparison	**Dopamine D2 receptor occupancy according to antipsychotic type.** **Note: this review contains both PET and SPECT studies.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, unable to assess precision, direct) suggests greatest D2 receptor occupancy with haloperidol (91.9%), then risperidone, olanzapine, clozapine, quetiapine, aripiprazole, ziprasidone, and then amisulpride (85%).**
D2 receptor occupancy	
51 studies, N = 606 *Maximum occupancy for;* Haloperidol: 91.9%, 95%CI 86.1 to 97.8 Risperidone: 92.4%, 95%CI 81.8 to 100 Olanzapine: 96.5%, 95%CI 85.8 to 100 Clozapine: 61.7%, 95%CI 49.2 to 74.2 Quetiapine: 49.1%, 95%CI 18.7 to 79.6	

Aripiprazole: 86.9%, 95% CI 78.2 to 95.7 Ziprasidone: 82.9%, 95%CI 44.9 to 100 Amisulpride: 85.0%, 95%CI 68.5 to 100 Authors report that age, sex, and imaging method did not explain the heterogeneity observed across study results.	
Consistency in results	Authors report inconsistent results for haloperidol, risperidone, olanzapine, clozapine and amisulpride.
Precision in results	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 sample, unable to assess consistency or precision, direct) 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, 2048mm^3, 0.100 ALE

Left parahippocampal gyrus/amygdala: Talairach coordinates (-21, -5, -10), 8 foci, 784mm^3, 0.102 ALE

Right lentiform nucleus: Talairach coordinates (23, -4, -8), 8 foci, 728mm^3, 0.062 ALE

Right fusiform gyrus: Talairach coordinates (40, -47, -15), 8 foci, 672mm^3, 0.069 ALE

Right fusiform gyrus: Talairach coordinates (39, -65, -10), 5 foci, 416mm^3, 0.097 ALE

Right fusiform gyrus: Talairach coordinates (34, -73, -10), 3 foci, 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, 424mm^3, 0.061 ALE

Left insula: Talairach coordinates (-32, 20, 8), 3 foci, 312mm^3, 0.035 ALE

Right fusiform gyrus: Talairach coordinates (40, -42, -16), 2 foci, 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, 1768mm^3, 0.100 ALE

Left parahippocampal gyrus/amygdala: Talairach coordinates (-22, -5, -9), 8 foci, 464mm^3, 0.091 ALE

Right lentiform nucleus: Talairach coordinates (23, -4, -7), 7 foci, 424mm^3, 0.062 ALE

Right fusiform gyrus: Talairach coordinates (38, -64, -10), 6 foci, 408mm^3, 0.097 ALE

Right fusiform gyrus: Talairach coordinates (40, -50, -15), 5 foci, 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, 368mm^3, 0.052 ALE

Right superior frontal gyrus: Talairach coordinates (9, 22, 51), 3 foci, 288mm^3, 0.051 ALE

Left parahippocampal gyrus/amygdala: Talairach coordinates (-26, -10, -13), 3 foci, 272mm^3, 0.060 ALE

Right middle occipital gyrus: Talairach coordinates (48, -72, 4), 2 foci, 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, 1840mm^3, 0.082 ALE Right fusiform gyrus: Talairach coordinates (40, -52, -14), 5 foci, 472mm^3, 0.068 ALE Right fusiform gyrus: Talairach coordinates (38, -64, -10), 5 foci, 432mm^3, 0.097 ALE Left amygdala: Talairach coordinates (-21, -7, -8), 6 foci, 368mm^3, 0.091 ALE Right lentiform nucleus: Talairach coordinates (22, -3, -5), 3 foci, 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, 312mm^3, 0.051 ALE Left parahippocampal gyrus/amygdala: Talairach coordinates (-26, -10, -14), 3 foci, 280mm^3, 0.060 ALE Right left parahippocampal gyrus/amygdala: Talairach coordinates (24, -8, -12), 3 foci, 280mm^3, 0.051 ALE Right middle occipital gyrus: Talairach coordinates (48, -72, 4), 2 foci, 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 measures and comparison of functional activity.

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

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

European Neuropsychopharmacology 2012; 22: 387-400

View review abstract online

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

Resting state
First-generation antipsychotics (high D2 affinity) One PET study (N = 24) compared patients treated with either sulpiride or chlorpromazine with healthy controls and found no difference in frontal cortex activation. One SPECT study (N = 25) found no difference in frontal activation between patients treated with haloperidol and healthy controls. One PET study (N unclear) found no effect of thiothixene over 4-6 weeks of treatment but found that haloperidol decreased frontal cortex activation after 406 weeks of treatment. A second study (N = 19) also found that haloperidol decreased frontal blood flow after three weeks of treatment. Another PET study (N = 12) showed that withdrawal of haloperidol resulted in increased glucose activity in the frontal cortex. However, one study (N = 11) found that haloperidol increased DLPFC activity but decreased VLPFC activity after 12 weeks of treatment with either haloperidol or 5 weeks of clozapine. *Second-generation antipsychotics (high D2 and 5-HT affinity)* One PET study (N = 13) found no effect of risperidone on brain changes after 3 weeks. A SPECT study (N = 24) found no pre-post effect of olanzapine on resting-state prefrontal brain activity. One study in 24 treatment-resistant patients found no overall effect of clozapine on brain activity, but clozapine-responders showed reductions of activity following treatment. This was supported by three further studies showing reductions of PFC activity after clozapine, but one small cross-over study (N = 10) found increases of activity following several months of clozapine.
Working memory
Second-generation antipsychotics One study (N = 10) showed increased activation during working memory in DLPFC when first-generation antipsychotics were substituted with risperidone. Another study (N = 25) showed that switching from first-generation antipsychotics to olanzapine also increased frontal cortex activation. However, one study (N = 20) found that olanzapine decreased prefrontal activation. One study (N = 25) found that frontal cortex activation also increased after quetiapine for 12 weeks. One study (N = 11) found no difference in activation when patients were switched from first-generation to aripiprazole for 3-4 weeks.
Learning
One study (N = 22) showed decreased activation during learning in DLPFC following haloperidol, but also found that olanzapine increased activation compared to baseline. However, another study (N = 15) found that haloperidol reduced activity in the PFC after 6 weeks, whereas sertindole increased metabolism.

Emotional processing
Second-generation antipsychotics One study (N = 12) found lanzapine reduced PFC activation during face processing after 4 weeks but increased it after 8 weeks. Activation also increased in another fMRI study (N = 16) during a monetary reward task following olanzapine. A PET study (N = 12) found that quetiapine over 22 weeks increased PFC activation during emotion processing. This was replicated in a second study (N = 12) after over 5 months of treatment.
Attention/executive function
First-generation antipsychotics One SPECT study (N = 24) showed reduced activation during auditory discrimination in DLPFC following fluphenazine. A second PET study (N = 22) also found that fluphenazine lowered glucose metabolism in the superior frontal cortex. Risperidone also decreased activation in the frontal cortex during a letter recognition task (N = 8) after 6 weeks, which was also associated with a decrease in positive symptoms. 8 weeks of clozapine had no effect on SPECT activation during a card sorting task (N = 21) but two studies (N = 21) found reductions following clozapine, and a third study (N = 10) found that substituting clozapine for risperidone extended the hypoactivation during the Stroop task.
Verbal fluency
Second-generation antipsychotics One study (N unclear) showed increased activation during verbal fluency (naming objects in a category) task following 4 weeks of amisulpride. A second study (N = 8) found increased activation during a verbal fluency task following 3 months of quetiapine.

Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct measures and comparison of functional activity.

Marques TR, Ashok AH, Pillinger T, Veronese M, Turkheimer FE, Dazzan P, Sommer IE, Howes OD

Neuroinflammation in schizophrenia: Meta-analysis of in vivo microglial

imaging studies

Psychological Medicine 2019; 49: 2186-96

View review abstract online

Comparison	**Translocator protein (measured by PET) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (small samples, some inconsistency, precise, direct) suggests a small to medium-sized increase in translocator protein in people with schizophrenia when measured using binding potential, but not volume of distribution.**

Translocator protein

A small to medium-sized, significant elevation in tracer binding in schizophrenia when binding potential was used as an outcome measure;

6 studies, N = 191, g = 0.31, 95%CI 0.02 to 0.60, p = 0.03, I^2 = 58%

The results were not significant after correcting for potential publication bias (g = 0.13).

There was no significant difference when volume of distribution was used as the outcome measure;

6 studies, N = 226, g = -0.22, 95%CI -0.64 to 0.19, p = 0.30, I^2 = 53%

Authors report that five out of the six studies included in the binding potential meta-analysis used the first-generation tracer [11C]-PK11195, and the volume of distribution studies used second-generation tracers. Therefore, the difference between the findings could reflect tracer differences.

Consistency in results	Some inconsistency
Precision in results	Precise
Directness of results	Direct

McCutcheon R, Beck K, Jauhar S, Howes OD

Defining the Locus of Dopaminergic Dysfunction in Schizophrenia: A Meta-analysis and Test of the Mesolimbic Hypothesis

Schizophrenia Bulletin 2018; 44: 1301-11

View review abstract online

Comparison	**Presynaptic dopamine functioning (measured by PET) in people**

	with schizophrenia vs. controls.
Summary of evidence	**Moderate to high quality evidence (large sample, some inconsistency, precise, direct) suggests a medium-sized increase in presynaptic dopamine functioning in the striatum of people with schizophrenia, particularly in associative and sensorimotor regions.**
Presynaptic dopamine functioning	
A significant, medium-sized increase in presynaptic dopamine functioning in the striatum of people with schizophrenia; 21 studies, N = 582, g = 0.68, 95%CI 0.44 to 0.91, $p < 0.001$, I^2 = 42.5% There were similar increases in associative and sensorimotor, but not limbic, brain regions. There were no moderating effects of medication status, patient age, or symptom severity.	
Consistency in results	Some inconsistency
Precision in results	Precise
Directness of results	Direct

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

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

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

View review abstract online

Comparison 1	**Whole brain comparison of functional activation in people with schizophrenia vs. healthy controls: ALE analysis.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess precision or consistency, direct) 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, direct) 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 observational 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 centre of mass (-38, 30, 30), cluster volume 3096mm^3 Right middle frontal gyrus: Talairach centre of mass (32, 24, 42), cluster volume 712mm^3 Right medial frontal gyrus: Talairach centre of mass (6, 42, 18), cluster volume 1480mm^3 Right cingulate: Talairach centre of mass (2, 18, 34), cluster volume 1704mm^3 Right claustrum: Talairach centre of mass (26, 22, 2), cluster volume 1766mm^3 Left middle occipital gyrus: Talairach centre of mass (-42, -70, 6), cluster volume 416mm^3 Right inferior parietal lobule: Talairach centre of mass (36, -58, 42), cluster volume 792mm^3 Left claustrum: Talairach centre of mass (-28, 24, 0), cluster volume 880mm^3 Right putamen: Talairach centre of mass (20, -4, 14), cluster volume 448mm^3 Left mediodorsal thalamus: Talairach centre of mass (-4, -14, 10), cluster volume 1736mm^3 *Significantly increased activity in people with schizophrenia;* Left superior frontal gyrus: Talairach centre of mass (-8, -14, 68), cluster volume 440mm^3 Left superior frontal gyrus: Talairach centre of mass (-2, 52, 24), cluster volume 1320mm^3 Left inferior frontal gyrus: Talairach centre of mass (-40, 36, 12), cluster volume 656mm^3 Right medial frontal gyrus: Talairach centre of mass (8, 44, -12), cluster volume 424mm^3 Left precentral gyrus: Talairach centre of mass (-54, 4, 30), cluster volume 752mm^3 Left cingulate: Talairach centre of mass (-2, 10, 40), cluster volume 2208mm^3 Right superior temporal gyrus: Talairach centre of mass (38, -36, 6), cluster volume 584mm^3 Left inferior parietal lobule: Talairach centre of mass (-54, -42, 42), cluster volume 1200mm^3 Right lingual gyrus: Talairach centre of mass (14, -74, 6), cluster volume 800mm^3 Right insula: Talairach centre of mass (38, 16, 4), cluster volume 1136mm^3 Right amygdala: Talairach centre of mass (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 measures and comparison of functional activity.
Comparison 2	**Whole brain comparison of functional activation in people with schizophrenia vs. healthy controls: Co-occurring regions of activity change.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate quality evidence (large sample sizes, unable to assess precision or consistency, direct) suggests regions of co-occurring reduced activity in patients with schizophrenia include the middle and medial frontal cortex, as well as the cingulate cortex, mediodorsal thalamus and bilateral claustrum.** **Moderate quality evidence (large sample sizes, unable to assess precision or consistency, direct) suggests regions of co-occurring increased activity in patients with schizophrenia include the anterior cingulate cortex and the inferior parietal lobule.**
Executive function tasks	
41 studies, N = 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 centre of mass (-38, 30, 30), cluster volume 1456mm^3 Right middle frontal gyrus: Talairach centre of mass (6, 42, 18), cluster volume 696mm^3 Right anterior cingulate cortex: Talairach centre of mass (2, 18, 34), cluster volume 760mm^3 Left mediodorsal thalamus: Talairach centre of mass (-4, -14, 10), cluster volume 696mm^3 Left claustrum: Talairach centre of mass (-28, 24, 0), cluster volume 488mm^3 Right claustrum: Talairach centre of mass (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 centre of mass (-2, 10, 40), cluster volume 1256mm^3 Left inferior parietal lobule: Talairach centre of mass (-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 measures and comparison of functional activity.

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

Seven studies contributing 40 foci

Significantly reduced activity in people with schizophrenia;

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

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

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

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

Right inferior parietal gyrus: cluster volume 1056mm^3, Talairach centre of mass (50, -48, 36)

Right lingual gyrus: cluster volume 1192mm^3, Talairach centre of mass (18, -86, 0)

Right posterior cingulate gyrus: cluster volume 896mm^3, Talairach centre of mass (4, -36, 32)

Four studies contributing 20 foci

Significantly greater activity in people with schizophrenia;

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

Left middle temporal gyrus: cluster volume 352mm^3, Talairach centre of mass (-44, -42, -8)

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

Left cingulate gyrus: cluster volume 1368mm^3, Talairach centre of mass (-2, 6, 38)

Left parahippocampal gyrus: cluster volume 304mm^3, Talairach centre of mass (-28, -50, -4)

Episodic retrieval

Ten studies contributing 76 foci

Significantly reduced activity in people with schizophrenia;

Left inferior frontal gyrus: cluster volume 3048mm^3, Talairach centre of mass (-40, 22, 20)

Left precentral gyrus: cluster volume 1064mm^3, Talairach centre of mass (-36, -2, 28)

Left middle frontal gyrus: cluster volume 888mm^3, Talairach centre of mass (-38, 32, 38)

Right anterior cingulate gyrus: cluster volume 888mm^3, Talairach centre of mass (4, 26, -6)

Left middle temporal gyrus: cluster volume 560mm^3, Talairach centre of mass (-56, -42, 0)

Right cuneus: cluster volume 2568mm^3, Talairach centre of mass (16, -86, 10)

Left thalamus: cluster volume 1496mm^3, Talairach centre of mass (-4, -8, 18)

Right thalamus: cluster volume 1448mm^3, Talairach centre of mass (8, -24, 10)

Right posterior cingulate gyrus: cluster volume 520mm^3, Talairach centre of mass (10, -52, 20)

Left cerebellum: cluster volume 1488mm^3, Talairach centre of mass (-24, -62, -42)

Right cerebellum: cluster volume 624mm^3, Talairach centre of mass (30, -80, -34)

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: cluster volume 1296mm^3, Talairach centre of mass (-28, -26, 66) Right medial frontal gyrus: cluster volume 1168mm^3, Talairach centre of mass (12, 44, 10) Right middle frontal gyrus: cluster volume 600mm^3, Talairach centre of mass (34, 36, -16) Right middle temporal: cluster volume 336mm^3, Talairach centre of mass (60, -58, 0) Right thalamus: cluster volume 792mm^3, Talairach centre of mass (26, -30, 6) Right parahippocampal gyrus: cluster volume not reported, Talairach centre of mass (20, -36, -4) *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 comparisons and measures of functional activity.

Stone JM, Davis JM, Leucht S, Pilowsky LS

Cortical dopamine D2/D3 receptors are a common site of action for antipsychotic drugs--an original patient data meta-analysis of the SPECT and PET in vivo receptor imaging literature

Schizophrenia Bulletin 2009; 35(4): 789-797

View review abstract online

Comparison	**Comparison of dopamine D2/D3 receptor occupancy in the striatum and temporal cortex of people with schizophrenia compared to healthy controls following first and second**

	generation antipsychotic medication. Indirectly compared to efficacy measurements of antipsychotics in separate patient groups. **Note – this review combines PET and SPECT in one analysis.**
Summary of evidence	**Moderate to low quality evidence (small samples, unable to assess precision and consistency, direct) suggests dopamine receptor occupancy may be different depending on first or second generation antipsychotic treatment.** **Lower quality evidence (indirect) is unclear about the relationship between receptor occupancy and drug effectiveness, side effects or measurement type. Single ligands had significantly higher occupancy than dual ligands. Significant difference in occupancy rates between first and second generation antipsychotics was reported, when controlling for ligand type and modelling method.**
D2/D3 receptor occupancy	
Fifteen studies were pooled to estimate the dopamine receptor occupancy Striatal occupancy following first generation antipsychotic administration: N = 28, 74% ± 12% Striatal occupancy following second generation antipsychotic administration: N = 115, 49% ± 21% t = 8.8, $p < 4x10^{-13}$ Temporal cortex occupancy following first generation antipsychotic administration: N not reported, 77% ± 12% Temporal cortex occupancy following second generation antipsychotic administration: N not reported, 67% ± 19% t = 3.5, $p = 0.001$ Ratio of striatal/temporal occupancy for first generation antipsychotics: 96 ± 24% Ratio of striatal/temporal occupancy for second generation antipsychotics: 74 ± 35% t = 3.7, $p < 0.001$	
Subgroup analysis 1: correlation to clinical efficacy *Indirect comparison using dose-response curve calculated from separate efficacy studies into first and second generation antipsychotics;* Occupancy correlated strongly with drug efficacy for temporal D2/D3: $r = 0.95$, $p < 0.001$ Also correlated striatal occupancy with drug efficacy: $r = 0.76$, $p = 0.046$	

Subgroup analysis 2: correlation to extrapyramidal side effects *Indirect comparison using dose-response curve calculated from separate efficacy studies into first and second generation antipsychotics;* Dose was correlated linearly with occupancy in the striatum, $r = 0.59$, $p = 0.004$, but not with temporal $r = 0.38$, p not significant EPSE are known to increase with dose and so are likely to be associated more with striatal dopamine	
Subgroup analysis 3: controlling for assessment method; Simplified Reference Tissue Modelling vs. Ratio modelling Significant difference in the two methods was seen in the temporal cortex, ratio modelling estimated 61% occupancy, SRTM estimated 78%. $F = 21.3$, $p = 0.04$ No significant difference was found in the occupancy estimates of both methods in the striatum The association of measurement method and drug type (typical vs. atypical) was zero for both regions	
Subgroup analysis 4: single vs. dual ligands Single ligand studies assess striatal and extrastriatal antipsychotic binding simultaneously, whereas dual ligand studies assess striatal and extrastriatal binding with different tracers on separate occasions In the striatum, single ligand binding had an 18% lower (95%CI 10 to 25%) occupancy estimate than dual ligands. $F = 22$, $p = 0.000007$ In the temporal cortex, single ligand binding had a 13% higher (95%CI 6 to 21%) occupancy estimate than dual ligands. $F = 13$, $p = 0.0006$	
Subgroup analysis 5: Occupancy ANCOVA with ligand type and modelling method covariates In the striatum, occupancy was estimated at 74%, 95%CI 66 to 82% for first generation antipsychotics. For second generation antipsychotics, occupancy was estimated at 47%, 95%CI 44 to 54% This is a significant difference of 27%, 95%CI 18 to 36% between the two classes of antipsychotics $F = 37$, $p = 0.00000005$	
Consistency in results	No measure of consistency is reported.
Precision in results	Confidence intervals are not reported for all outcomes, precise for subgroup analyses 4 and 5.
Directness of results	Direct comparison of receptor occupancy, indirect comparison of antipsychotic doses.

Van Snellenberg JX, Torres IJ, Thornton AE

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

Neuropsychology 2006; 20(5): 497-510

View review abstract online

Comparison	**Comparison of DLPFC activation during working memory tasks in people with schizophrenia vs. healthy controls.** **Note – this review combines PET and fMRI studies in one meta-analysis.**
Summary of evidence	**Moderate to high quality evidence (large samples, precise, unable to assess consistency, direct) 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 observational studies, N = 808, *d* = 0.20, 95%CI -0.05 to 0.44, *p* = 0.13 Left hemisphere DLPFC activation: 28 observational studies, N = 776, *d* = 0.23, 95%CI -0.05 to 0.51, *p* = 0.11 Right hemisphere DLPFC activation: 28 observational 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 comparisons and measures of functional activity.

Yilmaz Z, Zai CC, Hwang R, Mann S, Arenovich T, Remington G, Daskalakis ZJ

Antipsychotics, dopamine D2 receptor occupancy and clinical improvement in schizophrenia: a meta-analysis

Schizophrenia Research 2012; 140(1-3): 214-220

View review abstract online

Comparison	**Association between dopamine (D_2) receptor occupancy and clinical improvement following antipsychotic administration (olanzapine, risperidone, zotepine, haloperidol, ziprasidone, quetiapine, raclopride, aripiprazole, amisulpride, or clozapine) for at least 2 weeks.** **Note: this review combines PET and SPECT studies.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, unable to assess consistency, direct) suggests there may be an association between D_2 receptor occupancy (measured by SPECT alone) and clinical improvement on PANSS, following treatment with antipsychotic medications.**

Dopamine receptor occupancy

16 studies undertook PET/SPECT analysis following at least 2 weeks of antipsychotic medication.

Pre-post analysis of the effects of antipsychotic medications showed medications were associated with a large improvement in clinical symptoms;

PANSS: 17 effect sizes, N = 178, *d* = 1.36, 95%CI 1.13 to 1.60, *p* not reported

BPRS: 7 effect sizes, N = 78, *d* = 1.25, 95%CI 0.61 to 1.89, *p* not reported

D2 receptor occupancy did not predict antipsychotic response based on PANSS change scores;

17 effect sizes, N = 178, *r* = -0.067, CI not reported, *p* = 0.511

Exclusion of studies using clozapine,quetiapine and one outlier with D2 occupancy of over 80%, resulted in a significant relationship between D2 occupancy and greater PANSS improvement;

13 effect sizes, N unclear, *r* = 0.400, CI not reported, *p* < 0.001

D2 receptor occupancy did not predict antipsychotic response based on BPRS scores;

7 effect sizes, N = 78, *r* = 0.169, CI not reported, *p* = 0.092

This result did not change when one study using clozapine was excluded.

For those studies using SPECT only, a significant large correlation was found between D_2 receptor occupancy and better PANSS scores (excluding studies using clozapine, quetiapine and those

reporting >80% occupancy); 7 effect sizes, $r = 0.593$, $p < 0.001$ No studies (15 effect sizes) using PET found any correlation between D_2 receptor occupancy and PANSS change scores.	
Consistency in results	No measured of heterogeneity is provided.
Precision in results	Precise for PANSS, unable to assess correlation outcomes.
Directness of results	Direct measures and comparisons.

Zakzanis KK, Poulin P, Hansen KT, Jolic D

Searching the schizophrenic brain for temporal lobe deficits: a systematic review and meta-analysis

Psychological Medicine, 2000. 30(3): p. 491-504

View review abstract online

Comparison	**Temporal lobe functional activity in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to low quality evidence (small samples, unable to assess precision and consistency, direct) suggests reduction in functional activation of the temporal lobe in people with schizophrenia, however the authors suggest the average magnitude of this deficit is not sufficient to attribute any causative role in schizophrenia aetiology.**
Neurocognitive tasks	
Total temporal lobe *Significant, large effect size suggests decreased activity in people with schizophrenia;* 5 studies, (N = unclear), $d = 0.87$, SD = 1.1 Left temporal lobe *Significant, medium-sized effect suggests decreased activity in people with schizophrenia;* 1 study, N = 83, $d = 0.47$, SD = N/A Right temporal lobe *No differences in activity between patients and controls;*	

Positron emission tomography

1 study, N = 83, *d* = 0.14, SD= N/A Left temporal lobe showed significantly lower activity than right temporal lobe F= 3.11, *p*<0.05	
Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct measures and comparisons.

Explanation of acronyms

AFC = anterior frontal cortex, ALE = Activation Likelihood Estimate for Gaussian smoothed foci, β = coefficient, CI = confidence interval, CredInt = credible interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect sizes), DLPFC = dorsolateral prefrontal cortex, F= ratio of between sample variance and within sample variance, FDR = False Discovery Rate correction for multiple comparisons, FWHM = full width at half maximum, applied as a smoothing kernel, fMRI = Functional Magnetic Resonance Imaging, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), KS3 = Kolmogorov-Smirnov test for homogeneity of distributions, MNI = Montreal Neurological Institute system for stereotactic space, N = number of participants, N/A = not applicable, *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, SD = standard deviation, VLPFC = ventrolateral prefrontal cortex, vs. = versus

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Positron emission tomography

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias that involves selective reporting; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small.

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† Different effect measures are reported by different reviews.

ALE analysis (Activation Likelihood Estimate) refers to a voxel-based meta-analytic technique for functional imaging in which each 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[27].

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives which are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives which are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

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[28]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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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.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) which 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 considerable heterogeneity and over this is 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[29].

‖ 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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