TECHNICAL COMMENTARY

Single-photon emission computed tomography

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Introduction

Single-photon emission computed tomography (SPECT) is a nuclear based imaging technique that uses radioactive tracers to visualise functional brain activity. SPECT imaging is frequently used in combination with anatomical imaging such as computed tomography (CT) or structural magnetic resonance imaging (MRI). Compared to positron emission tomography (PET) imaging, SPECT offers more limited spatial and temporal resolution, but is less expensive as it does not require a cyclotron in close proximity. The radioisotope 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 13 systematic reviews that met our inclusion criteria[3-15].

- 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

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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 (91.9%), then risperidone, olanzapine, clozapine, quetiapine, aripiprazole, ziprasidone, and then amisulpride (85%).
- Moderate to high quality evidence suggests significant reductions in functional activity in the whole brain of people with schizophrenia compared to healthy controls.
- 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 to low quality evidence suggests dopamine receptor occupancy is significantly different depending on first- or second-generation antipsychotic use. First generation antipsychotics were associated with significantly higher receptor occupancy in the striatum and temporal cortex.
- 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.

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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

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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

Chen KC, Yang YK, Howes O, Lee IH, Landau S, Yeh TL, Chiu NT, Chen PS, Lu RB, David AS, Bramon E

Striatal dopamine transporter availability in drug-naive patients with schizophrenia: a case-control SPECT study with [(99m)Tc]-TRODAT-1 and a meta-analysis

Schizophrenia Bulletin 2013; 39(2): 378-86

View review abstract online

Comparison	**Striatal dopamine transporter availability (measured by SPECT) in drug-naive people with schizophrenia and controls.**

Summary of evidence	**Moderate to high quality evidence (medium-sized sample, consistent, precise, direct) suggests no difference in striatal dopamine transporter availability between drug-naïve people with schizophrenia and controls.**
Striatal dopamine transporter availability	
No significant difference in striatial dopamine transport availability between drug-naive people with schizophrenia and controls; 6 studies, N = 293, *d* = -0.07, 95%CI -0.31 to 0.18, *p* = 0.60, *b* = 0.07, *p* = 0.61 There was no evidence of publication bias.	
Consistency in results	Consistent
Precision in results	Precise
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

Comparison	**Whole brain comparison of functional activation in people with schizophrenia patients vs. healthy controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, 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. There was increased functional activity in the left temporal lobe during cognitive tasks with no differences at rest. Moderate quality evidence (inconsistent and imprecise) finds 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 <u>Left frontal lobe</u> *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 <u>Right frontal lobe</u> *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 <u>Left temporal lobe</u> *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 <u>Right temporal lobe</u> *At rest: no effect on activity;* N = 608, *d* = -0.05, 95%CI -0.49 to 0.38, SD = 0.90, FSN < 0.1 <u>Left hippocampus</u> *During cognitive tasks: no effect on activity;* N = 415, *d* = 0.13, 95%CI -0.69 to 0.43, SD = 0.78, FSN = 3 <u>Right hippocampus</u> *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%

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

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

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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 were 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

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

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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 (small sample, 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.

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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

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

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 that olanzapine reduced PFC activation during face processing after 4 weeks but increased it after 8 weeks. Activation also increased in another fMRI study (N = 16) during a monetary reward task following olanzapine. A PET study (N = 12) found that quetiapine over 22 weeks increased PFC activation during emotion processing. This was replicated in a second study (N = 12) after over 5 months of treatment.
Attention/executive function

First-generation antipsychotics One SPECT study (N = 24) showed reduced activation during auditory discrimination in DLPFC following fluphenazine. A second PET study (N = 22) also found that fluphenazine lowered glucose metabolism in the superior frontal cortex. Risperidone also decreased activation in the frontal cortex during a letter recognition task (N = 8) after 6 weeks, which was also associated with a decrease in positive symptoms. 8 weeks of clozapine had no effect on SPECT activation during a card sorting task (N = 21) but two studies (N = 21) found reductions following clozapine, and a third study (N = 10) found that substituting clozapine for risperidone extended the hypoactivation during the Stroop task.
Verbal fluency
Second generation antipsychotics One study (N unclear) showed increased activation during verbal fluency (naming objects in a category) task following 4 weeks of amisulpride. A second study (N = 8) found increased activation during a verbal fluency task following 3 months of quetiapine.

Consistency in results	No measure of consistency is reported.
Precision in results	No confidence intervals are reported.
Directness of results	Direct measures and comparison 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.** **Low quality evidence (unclear sample size, unable to assess precision and consistency, 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.

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 and most precision, 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; 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

CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect sizes), F= ratio of between sample variance and within sample variance, N = number of participants, N/A = not applicable, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), SD = standard deviation, SPECT = Single-Photon Emission Computed Tomography, vs. = versus, WMD = weighted mean difference

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 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.

† Different effect measures are reported by different reviews.

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[16].

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

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[17]. 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

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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) 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 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[18].

‖ 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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