Chemical Alterations – Dopamine

Introduction

Dopamine is a neurotransmitter that is important for emotional and cognitive processing in the brain, particularly rewarding and pleasurable stimuli or experiences.

Alterations of the dopamine system have been suggested in schizophrenia. This may be assessed as changes in levels of dopamine or its metabolites, or as changes in levels or activity of the mechanical components of the dopamine system, such as the receptors that ‘receive’ dopamine, or the transporters that ‘remove’ it. Reviews included in this table reflect evidence from functional brain imaging investigations into biochemical activity across the whole brain.

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. As part of a wider search for all topics included in the library, reviews assessing dopamine alterations in schizophrenia 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. The decision to include or exclude reviews was conducted in duplicate by two independent reviewers with any disagreements settled by discussion. All quality assessments and data extraction have been completed in duplicate by two reviewers who were not masked to review authors.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (formerly the QUOROM statement) which describes a preferred way to present a meta-analysis [1]. Reviews were assigned a low, medium or high possibility of reporting bias* depending on how many items were checked. For instance, a low possibility of bias would be assigned to reviews checking over 66% of items, a medium possibility between 33 and 66% and a high possibility would be given to reviews checking less than 33%. Reviews rated as having a high possibility of reporting bias 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 randomized controlled trials (RCT) may be downgraded to moderate, low or very 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
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are solely the opinion of staff of the Schizophrenia Research Institute.

Results
See table below for a detailed summary of the available evidence pertaining to dopamine. We found five systematic reviews that met our inclusion criteria [3-7].

See PRISMA checklist for review quality assessments.

Conclusions
• High quality evidence suggests that presynaptic dopamine synthesis and activity is significantly increased in people with schizophrenia compared to controls.
• Inconsistent, moderate quality evidence suggests receptor availability may also be increased, with no difference in dopamine transporter levels.
• Moderate to low quality evidence suggests dopamine receptor occupancy may be different depending on first or second generation antipsychotic treatment.
• Moderate to low quality evidence suggests there may be an association between D₂ receptor occupancy (measured by SPECT alone) and clinical improvement on PANSS, following treatment with antipsychotic medications.
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*Fusar-Poli, P, Meyer-Lindenberg A.*

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


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<table>
<thead>
<tr>
<th>Comparison</th>
<th>Density of dopamine transporter (measured by PET or SPECT) in people with schizophrenia compared to controls</th>
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<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (inconsistent, precise, direct) suggests no difference in dopamine transporter levels in the striatum of people with schizophrenia compared to controls.</td>
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</table>

**Presynaptic dopamine transporter density**

13 studies, N = 349

No significant difference in dopamine transport density in the striatal pre-synaptic terminals of people with schizophrenia compared to controls

\[ d = -0.244, 95\% CI -0.676 to 0.188, p = 0.269, \]

\[ Q = 44.075, p < 0.001, I^2 = 75.082\% \]

This difference remained 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 \( (p = 0.389) \).

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Inconsistent</th>
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<tbody>
<tr>
<td>Precision in results</td>
<td>Precise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
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</tbody>
</table>
Fusar-Poli, P, Meyer-Lindenberg A.

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

View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Dopamine synthesis capacity (measured by PET or SPECT) in people with schizophrenia compared to controls</th>
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</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>High quality evidence (consistent, precise, direct) shows increased dopamine synthesis capacity in the striatum of people with schizophrenia compared to controls</td>
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</table>

Presynaptic dopamine synthesis capacity

11 studies, N = 244

Large effect size suggests a significant increase in dopamine synthesis capacity in the striatal presynaptic terminals of people with schizophrenia compared to controls

$$d = 0.867, \text{95%CI 0.594 to 1.140, } p < 0.001,$$

$$Q = 19.19, \ p = 0.078, I^2 = 39.17\%$$

This difference remained when only studies considering striatal subregions were included:

- Caudate: $$d = 0.569, \text{95%CI 0.176 to 0.961, } p = 0.005$$
- Putamen: $$d = 0.643, \text{95%CI 0.098 to 1.189, } p = 0.021$$

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 ($p = 0.299$).

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Consistent</th>
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<tbody>
<tr>
<td>Precision in results</td>
<td>Mostly precise</td>
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<tr>
<td>Directness of results</td>
<td>Direct</td>
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</table>

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

Archives of General Psychiatry, 2012. epub April, p. 1-11
View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Dopamine function (measured by PET or SPECT) in people with schizophrenia compared to controls</th>
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</thead>
<tbody>
<tr>
<td><strong>Summary of evidence</strong></td>
<td>High quality evidence (consistent, precise, direct) suggests that presynaptic dopamine function is significantly increased in people with schizophrenia compared to controls. Inconsistent evidence suggests receptor availability may also be increased, but there was no difference in transporter levels.</td>
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</table>

**Presynaptic dopamine function**

17 studies, N = 482
Large effect size suggests significantly elevated dopamine activity in schizophrenia patients compared to controls
\[ d = 0.79, 95\%CI 0.52 \text{ to } 1.07, \ p < 0.001, \ i^2 = 39.92\% \]
The results did not differ when the analysis was conducted only on drug-free or drug-naïve patients
\[ d = 0.69, 95\%CI 0.36 \text{ to } 1.01, \ p = 0.001, \ i^2 = 46.46\% \]

**Dopamine transporter levels**

11 studies, N = 284
Small effect size suggests no significant difference in dopamine transporter levels between schizophrenia and controls
\[ d = -0.34, 95\%CI -0.75 \text{ to } 0.07, \ p = 0.10, \ i^2 = 64\% \]

**Dopamine receptor availability**

22 studies, N = 661
Small effect size suggests significantly elevated dopamine receptor levels in unmedicated schizophrenia patients compared to controls
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\[ d = 0.26, \quad 95\% CI \ 0.001 \text{ to } 0.52, \quad p = 0.049, \quad I^2 = 63.93\% \]

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>Consistent for presynaptic dopamine function.</th>
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</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>Precise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
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</tbody>
</table>

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


View review abstract online

Comparison 1

Comparison of dopamine D2/D3 receptor occupancy in the striatum and temporal cortex of schizophrenia patients compared to healthy controls following first and second generation antipsychotic administration. 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 (direct, small to moderate sample size, unable to assess precision and consistency) suggests dopamine receptor occupancy may be different depending on first or second generation antipsychotic treatment

Low quality evidence (indirect, unable to assess sample size, precision and consistency) 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
### D<sub>2</sub>/D<sub>3</sub> receptor occupancy
Measured by PET and SPECT

| Striatal occupancy following first generation antipsychotic administration: N = 28, 74% ± 12% | t = 8.8, p < 4x10<sup>-13</sup> |
| Striatal occupancy following second generation antipsychotic administration: N = 115, 49% ± 21% |
| 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% |

**Ratio of striatal/temporal occupancy**
- First generation antipsychotics: 96 ± 24%
  - t = 8.8, p < 4x10<sup>-13</sup>
- Second generation antipsychotics: 74 ± 35%
  - t = 8.8, p < 4x10<sup>-13</sup>

### 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 D<sub>2</sub>/D<sub>3</sub>: 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 (EPSE)

*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 (STRM) 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. $F = 37, p = 0.00000005$

<table>
<thead>
<tr>
<th>Consistency in results</th>
<th>No measure of consistency reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results</td>
<td>CIs not reported for all outcomes, precise for subgroup analyses 4 and 5</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct comparison of receptor occupancy, indirect comparison of antipsychotic doses</td>
</tr>
</tbody>
</table>

Yilmaz Z., Zai C.C., Hwang R., Mann S., Arenovich T., Remington G., Daskalakis Z.J.

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

[View review abstract online](http://www.schizophreniaresearch.org.au)

<table>
<thead>
<tr>
<th>Comparison</th>
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<tr>
<td>Association between PET/SPECT 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</td>
</tr>
<tr>
<td>Note: this review combines PET and SPECT studies</td>
</tr>
</tbody>
</table>
Summary of evidence

Low to moderate quality evidence (unable to assess consistency, direct) suggests there may be an association between D₂ 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 they 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

However, 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 D₂ 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 D₂ receptor occupancy and PANSS change scores.

Consistency in results

Unable to assess

Precision in results

Precise for PANSS, unable to assess correlation outcomes

Directness of results

Direct
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Explanation of acronyms

ANCOVA = analysis of covariance statistical test, BPRS = Brief psychiatric rating scale, CI = Confidence Interval, D₂ = dopamine receptor, d = Cohen’s d and g = Hedges’ g = standardized mean differences (see below for interpretation of effect sizes), F = ratio of between sample variance and within sample variance, N = number of participants, p = statistical probability of obtaining that result (p < 0.05 generally regarded as significant), PANSS = positive and negative syndrome scale, PET = positron emission tomography, r = correlation coefficient, SPECT = Single-photon emission computed tomography
Explanation of technical terms

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

† 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 randomized trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardized 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 moderate effect, and 0.8 and over represents a large effect [8].

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 large effect is considered if RR > 2 or < 0.5 and a very large effect if RR > 5 or < 0.2[9]. 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 unforeseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardized (b) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable,
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statistically controlling for the other independent variables. Standardized 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.

§ 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[9].

‖ 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.

The PET and SPECT topics were reviewed by Dr Melissa Green

School of Psychiatry, University of New South Wales; Black Dog Institute, Prince of Wales Hospital, Sydney NSW

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