Review article

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

Joseph Kambeitz, Anissa Abi-Dargham, Shitij Kapur and Oliver D. Howes

Background
The hypothesis that cortical dopaminergic alterations underlie aspects of schizophrenia has been highly influential.

Aims
To bring together and evaluate the imaging evidence for dopaminergic alterations in cortical and other extrastriatal regions in schizophrenia.

Method
Electronic databases were searched for in vivo molecular studies of extrastriatal dopaminergic function in schizophrenia. Twenty-three studies (278 patients and 265 controls) were identified. Clinicodemographic and imaging variables were extracted and effect sizes determined for the dopaminergic measures. There were sufficient data to permit meta-analyses for the temporal cortex, thalamus and substantia nigra but not for other regions.

Results
The meta-analysis of dopamine D2/D3 receptor availability found summary effect sizes of \( d = -0.32 \) (95% CI, -0.68 to 0.03) for the thalamus, \( d = -0.23 \) (95% CI, -0.54 to 0.07) for the temporal cortex and \( d = 0.04 \) (95% CI, -0.92 to 0.99) for the substantia nigra. Confidence intervals were wide and all included no difference between groups. Evidence for other measures/regions is limited because of the small number of studies and in some instances inconsistent findings, although significant differences were reported for D2/D3 receptors in the cingulate and uncus, for D1 receptors in the prefrontal cortex and for dopamine transporter availability in the thalamus.

Conclusions
There is a relative paucity of direct evidence for cortical dopaminergic alterations in schizophrenia, and findings are inconclusive. This is surprising given the wide influence of the hypothesis. Large, well-controlled studies in drug-naive patients are warranted to definitively test this hypothesis.

Declaration of interest
O.D.H. has consulted for and/or spoken at events organised by AstraZeneca, Bristol-Myers Squibb, Janssen, Eli Lilly, Roche and Sunovion. A.A.-D. has consulted or given lectures for Sunovion, Shire, and Bristol-Myers Squibb/Otsuka. S.K. has received grant support from AstraZeneca and GlaxoSmithKline and has served as consultant and/or speaker for AstraZeneca, Bioline, Bristol-Myers Squibb/Otsuka, Eli Lilly, Janssen (Johnson & Johnson), Lundbeck, Neuro-Search, Pfizer, Roche, Servier, and Solvay/Wyeth.

Schizophrenia affects about 1% of the population,\(^1\) and is a major cause of global disease burden.\(^2\) The investigation of the biological underpinnings of the disease are crucial steps to the rational development of more effective treatments for the illness.\(^3,4\) The dopamine hypothesis of schizophrenia has been an enduring theory of the neurobiology underlying the disorder.\(^5,6\) In its earliest instance it was a biochemical hypothesis (increased dopamine transmission) without a precise molecular or anatomical specificity. In the past two decades the hypothesis has been refined to enhance its molecular and anatomical specificity. The newer conceptualisation of the hypothesis aims to systematically review the extrastriatal molecular imaging evidence for cortical dopaminergic alterations underlie aspects of schizophrenia has been highly influential.\(^7\) The in vivo investigation of extrastriatal dopamine function has been technologically more complicated, not least because dopaminergic projections to other regions are sparse compared with the striatum. However, the development of high-affinity selective tracers such as \([11C]\)-FLB 457,\(^14\) \([18F]\)-fallypride,\(^15\) \([123I]\)-epidepride\(^16\) and \([11C]\)-(+)4-propyl-9-hydroxynaphthoxazine (PHNO)\(^17\) has enabled the in vivo investigation of D2/D3 receptors in extrastriatal regions, and the tracers \([11C]\)-NNC and \([11C]\)-SCH23390 have enabled this for D1 receptors.\(^18,19\) Besides dopamine receptors, tracers with specific binding to the dopamine transporter or that use radiolabelled-dihydroxyphenylalanine (DOPA) to index dopamine synthesis capacity have been used to investigate different aspects of dopaminergic neurotransmission in extrastriatal regions.\(^20\) We recently conducted a meta-analysis of striatal dopaminergic function in schizophrenia.\(^2\) This found that presynaptic dopamine function – specifically dopamine synthesis capacity, dopamine release and baseline synaptic dopamine levels – were highly significantly elevated in schizophrenia with a large effect size (Cohen’s \(d = 0.8\)). There was also an elevation in D2/D3 receptor availability but this was relatively small (Cohen’s \(d = 0.24\)) and inconsistent. In contrast there was no evidence of an alteration in dopamine transporter or D1 receptor availability. We now aim to systematically review the extrastriatal molecular imaging findings in schizophrenia and, where there are sufficient studies, conduct a meta-analysis to evaluate the evidence for dopaminergic dysfunction outside of the striatum.
Method

Search and selection strategy

The entire PubMed, PsycINFO and MEDLINE electronic databases were searched from 1 January 1950 up to 31 December 2012. Initially, studies were screened based on a search using a comprehensive search term |("Positron Emission Tomography" OR "PET" OR "Single photon emission tomography" OR "SPECT") AND ("dopamine") AND ("schizophrenia" OR "psychosis" OR "psychotic" OR "schizophreniform") AND ("thalamus" OR "thalamic" OR "cingulate" OR "cortex" OR "frontal" OR "prefrontal" OR "temporal" OR "parietal" OR "midbrain" OR "substantia nigra" OR "hippocampus" OR "amygdala") AND (1950:2012/12/31[DP])). Only publications in peer-reviewed journals in English language were considered.

To be included in the meta-analysis a paper needed to report in vivo positron emission tomography (PET) or single photon emission computed tomography (SPECT)/single photon emission tomography (SPECT) imaging findings of extrastriatal dopaminergic function in patients with schizophrenia and a control group with sufficient data to enable the mean and standard deviations for both groups to be calculated. Studies were excluded if healthy controls had any neurological or psychiatric disease or if patients had any neurological condition or psychiatric disease other than a psychotic disorder. Current antipsychotic treatment was an exclusion criterion for the studies of D2/D3 receptors, because it is clear this affects dopamine receptor binding potential.

Where the studies reported overlapping samples, the paper reporting the largest sample size was used and the other paper excluded to prevent double counting. For the region of the brain sampled, if two papers reported different definitions of regions applied to the same data, the paper reporting the regional definition closest to that used by other papers in the meta-analysis was used to ensure greatest comparability. As prior antipsychotic treatment may influence dopaminergic indices, data were presented combined and, where available, separately for patients who had previously received antipsychotic treatment and for patients who were antipsychotic-naive to enable findings to be compared.

Data extraction

The main outcome measure was the difference in the dopaminergic imaging parameter between healthy controls and patients with schizophrenia. The following additional information was extracted from all the studies: names of the authors, year of publication, population characteristics of the healthy control and patient groups (group size, age, gender, antipsychotic use, diagnosis, symptom ratings), characteristics of the imaging (radiotracer, other methodological factors reported), scanner characteristics (scanner type and resolution), and modelling method. The data were extracted by one author (J.K.) and checked twice additionally to assure accuracy. In case of uncertainties data were checked by another author (O.D.H.) and consensus reached. As there are no established criteria for assessing the quality of molecular imaging studies, we have summarised methodological aspects of each study to enable individual judgements to be made (see online Tables DS1 and DS2).

Data analysis

A minimum of five studies was required to proceed with the meta-analysis as findings become less reliable with fewer studies. The R statistical programming language version 2.10.1 on Mac OS-X (version 10.6.8) with the package ‘metafor‘ was used to conduct meta-analyses as well as power calculations. A significance level of P<0.05 (two-tailed) was used for all analyses.

The standardised effect sizes of the individual studies were entered in a random-effects meta-analytic model, which does not assume homogeneity among studies. The summary effect sizes (cohen’s d) were computed using a restricted maximum-likelihood estimator. Heterogeneity was assessed in the studies by calculating the P value, which is a sample size independent measure that describes the percentage of total variation across studies that is as a result of heterogeneity rather than chance.

As a guideline, P values of 0–40% indicate heterogeneity that is not important, 30–60% moderate heterogeneity, 50–90% substantial heterogeneity and 75–100% considerable heterogeneity (for further details see Higgins & Green). Pre-specified analyses to evaluate potential sources of bias and sensitivity analyses were conducted as follows. To examine the potential effect of prior antipsychotic treatment, the analysis was repeated for subgroups defined by treatment history (antipsychotic-naïve or previously treated) to determine whether this influenced the findings. The potential effects of publication year, gender and the age of participants was evaluated using meta-regression.

To account for differences in precision, studies were weighted by their sample size before being entered in a regression model with the variable of interest as a predictor for the standardised effect sizes.

Publication bias was evaluated by inspection of the funnel plot (a plot of effect sizes on the x-axis against standard error (1/precision)) for evidence of asymmetry. Publication bias is suggested if studies with small precision and small effect size are absent. Publication bias was further evaluated using Egger's test.

To assess the influence of individual studies on the estimated summary effect size, a post hoc leave-one-out approach was applied by re-running the meta-analysis after leaving out one different individual study at successive iterations.

Results

After initial identification of 242 articles, 219 articles were excluded (see online Fig. DS1 for reasons for excluding studies). This resulted in a sample of 23 studies of extrastriatal dopamine in schizophrenia including 13 studies of D2/D3 receptors, 4 studies of D1 receptors, 5 studies of dopamine synthesis capacity and 1 study of dopamine transporter availability. The most commonly used outcome measure was the binding potential relative to the non-displaceable compartment (BPND). The BPND is the equilibrium ratio of the concentration of specifically bound radioligand relative to the sum of the free and non-specifically bound radioligand, estimated from activity in a reference region. Alternatively the equilibrium ratio relative to either the total or free (unbound) concentration of radioligand in plasma can be used, denoted as BP_T or BP_R respectively.

The BPND, BP_T and BP_R are all proportional to the concentration of receptors available to be bound in the tissue of interest. As all the studies reported BPND and only two studies reported BP_T and BP_R, we used BPND for the meta-analyses. For the meta-analysis of thalamic D2/D3 receptors some studies reported results of overlapping samples, in which case the study with the largest sample was selected for inclusion. Thus, Buchsbaum et al was excluded as there was sample overlap with Lehrer et al. Also there was sample overlap between Yasuno et al and Suhara et al. Only Suhara et al was included as the thalamic region used was closest to that of other studies in the available literature. For Talvik et al and Talvik et al there appeared to be sample overlap. As attempts...
to contact the authors to verify this were unsuccessful, we included only one of both studies in each meta-analysis. We included Talvik et al.\textsuperscript{38} in the meta-analysis of the thalamic cortex and Talvik et al.\textsuperscript{39} for the meta-analysis of the thalamus to maximise sample size and to avoid potential sample overlap. Kegeles et al.\textsuperscript{40} applied the simplified reference tissue model (SRTM) and a two-tissue compartmental model to the imaging data and reported D_{2}/D_{3} BPND for both. As most other studies in this analysis applied an SRTM approach, we selected these data from Kegeles et al.\textsuperscript{40} to ensure the modelling approach was the same across studies. Kegeles et al.\textsuperscript{40} reported D_{2}/D_{3} BPND values corrected for partial volume effects. These were entered in the analysis rather than uncorrected values.

The characteristics of the participants for the included studies are shown in Table DS1 and the imaging methods are summarised in Table DS2. There were sufficient studies to conduct separate meta-analyses for the D_{2}/D_{3} receptor availability in the thalamus, the substantia nigra and for the temporal cortex. There were too few studies to enable reliable meta-analysis of findings for other regions or for other measures of dopaminergic function – for these studies we have plotted the individual effect sizes to aid comparison and evaluation of trends and summarised the findings below.

**D_{2}/D_{3} receptor availability**

**Thalamus**

Eight studies comprising 138 patients with schizophrenia and 126 healthy controls met inclusion criteria for the meta-analysis. The summary effect size for thalamic D_{2}/D_{3} BPND between patients with schizophrenia and healthy controls was $d = -0.32$ but did not reach significance (95% CI $-0.68$ to 0.03, $z = -1.787$, $P = 0.07$, $I^2 = 48.79\%$, 95% CI 0–84.25%, see Fig. 1(a)). Inspection of the funnel plot (Fig. 1(b)) and Egger’s test ($z = -0.7627$, $P = 0.5011$) did not show evidence for publication bias. The sensitivity analysis for the thalamus showed a significant summary effect size for two out of eight iterations. There was a significant summary effect size when Kegeles et al.\textsuperscript{40} or Glenthoj et al.\textsuperscript{41} were excluded from the meta-analysis. Meta-regression analysis did not show evidence for an effect of year of publication ($\beta = 0.0275$, $F(1,6) = 0.1591$, $P = 0.7038$, see Fig. 1(c)), gender ($\beta = 1.257$, $F(1,4) = 0.1675$, $P = 0.7033$) or age ($\beta = 0.0695$, $F(1,5) = 0.3863$, $P = 0.5615$) on the estimated summary effect size. Restricting the meta-analysis to the five studies that included participants with previous exposure to antipsychotic medication showed a non-significant effect size of $d = -0.34$ (95% CI $-0.78$ to 0.1, $z = -1.5058$, $P = 0.1$, $I^2 = 42.83\%$, 95% CI $-0.89$–39.38%). The studies of medication-naive participants showed effect sizes of 0.35,\textsuperscript{41} -0.62\textsuperscript{39} and -0.77.$^{37}$ However, there were too few studies of medication-naive participants to permit meta-analysis.

**Temporal cortex**

We included six studies in the meta-analysis comprising 84 patients with schizophrenia and 86 healthy controls. There was no evidence for a reduction in D_{2}/D_{3} availability in the temporal cortex in patients with schizophrenia ($d = -0.23$, 95% CI $-0.54$ to 0.07, $z = -1.5097$, $P = 0.1$, $I^2 = 0\%$, 95% CI $-0.67$–2.72%, see Fig. 2(a)). Inspection of the funnel plot (Fig. 2(b)) and Egger’s test ($z = 0.6917$, $P = 0.4891$) did not show evidence for publication bias. The sensitivity analysis for the temporal cortex did not show a significant summary effect size in any of the six iterations. Meta-regression analysis did not show evidence for an effect of year of publication ($\beta = 0.0297$, $F(1,4) = 0.7138$, $P = 0.4458$, see Fig. 2(c)), gender ($\beta = -1.1818$, $F(1,3) = 2.2341$, $P = 0.2319$) or age ($\beta = 0.0535$, $F(1,4) = 1.4834$, $P = 0.2902$) on the estimated summary effect size. The meta-analysis of the temporal cortex included three studies in drug-free patients that reported effect sizes of $d = -0.42$,$^{30}$ $d = -0.33$\textsuperscript{44} and $d = 0.6$.$^{21}$ The studies in drug-naive participants reported comparable effect sizes of $d = 0.49$,$^{37}$ $d = -0.12$,$^{31}$ and $d = 0.27$.$^{38}$ The small number of studies did not allow further analysis of the moderating effect of medication in this region.

**Substantia nigra**

We included five studies in the meta-analysis comprising 61 patients with schizophrenia and 72 healthy controls. There was no significant difference between patients with schizophrenia and healthy controls ($d = 0.04$, 95% CI $-0.92$ to 0.99, $z = 0.075$, $P = 0.9$, $I^2 = 84.8\%$, 95% CI 52.89–98.49%, see Fig. 3(a)). Inspection of the funnel plot (Fig. 3(b)) and Egger’s test ($z = -0.79$, $P = 0.43$) did not show evidence for publication bias. The sensitivity analysis for the substantia nigra did not show a significant summary effect size in any of the five iterations. Meta-regression did not show evidence for an effect of year of publication ($\beta = 0.1649$, $F(1,3) = 0.3381$, $P = 0.6018$, see Fig. 3(c)), gender ($\beta = -0.6768$, $F(1,3) = 0.0375$, $P = 0.8587$) or age ($\beta = 0.0085$, $F(1,3) = 0.0008$, $P = 0.9793$) on the estimated summary effect size. Also after excluding the one study of drug-naive patients there was still no significant effect ($d = -0.04$, 95% CI $-1.31$ to 1.22, $z = -0.0628$, $P = 0.9$, $I^2 = 88.99\%$, 95% CI $60.53$–99.28%).

**Findings in the other regions**

There were seven studies with a total of 109 patients and 120 controls investigating D_{2}/D_{3} BPND in 11 other extrastriatal regions. The effect sizes for these regions are shown by study in Fig. 4. Out of three studies of the anterior cingulate, one reported a significant decrease of D_{2}/D_{3} BPND in patients with schizophrenia\textsuperscript{46} and two reported no significant change.\textsuperscript{38,44} One study reported a significant decrease of D_{2}/D_{3} BPND in the uncus.\textsuperscript{64} There were no significant changes reported in the entorhinal cortex,\textsuperscript{40} the hippocampus,\textsuperscript{37,44} the amygdala,\textsuperscript{40,44} the prefrontal cortex,\textsuperscript{37,44,41} the occipital cortex,\textsuperscript{44} the parietal cortex,\textsuperscript{46} the insula\textsuperscript{45} or the globus pallidum.\textsuperscript{43}
significant changes in $D_1$ BP$_{ND}$ in schizophrenia in any of these studies.

Dopamine transporter availability
One study investigated dopamine transporter availability outside the striatum in 12 healthy controls and 8 patients for two regions (Fig. 4(d)). This study reports a significant increase in the thalamus but no significant change in the substantia nigra.

Discussion

**D$_2$/D$_3$ receptor availability**
Our meta-analyses showed small, non-significant reductions in D$_2$/D$_3$ receptor availability in the thalamus ($d = -0.32$, $P = 0.07$) and temporal cortex ($d = -0.23$, $P = 0.1$) in schizophrenia and no significant difference between patients and controls in the substantia nigra ($d = 0.04$, $P = 0.9$). Although these were not statistically significant, it is important to note that the summary estimates were relatively imprecise and the confidence intervals for the thalamus and temporal cortex included moderate–large reductions as well as very small elevations. Furthermore, the leave-one-out sensitivity analysis for the thalamus found that the reduction was significant on two iterations, indicating that the meta-analysis was sensitive to the inclusion of two individual studies, and that the lack of significance should not be considered as conclusively excluding a reduction. This sensitivity could reflect differences in methodology or sample characteristics (see later) and indicates the need for further large studies to conclusively address the issue. Although there were too few studies to permit meta-analysis in other regions, the majority of studies found no significant differences in patients, and where there were significant decreases this was either a sole finding or not replicated in other studies. Thus, overall there do not appear to be marked alterations in D$_2$/D$_3$ receptor availability in extrastriatal regions but there may be a small reduction in D$_2$/D$_3$ availability in the thalamus. The

**Table 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>$d$</th>
<th>Upper (Lower)</th>
<th>z-score</th>
<th>$P$</th>
<th>Greater in controls</th>
<th>Greater in schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suhara et al$^{37}$</td>
<td>2002</td>
<td>-0.7660</td>
<td>-1.5414 (0.0096)</td>
<td>-1.9357</td>
<td>0.0529</td>
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<td>Glenthoj et al$^{41}$</td>
<td>2006</td>
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<td>-0.2470 (0.9376)</td>
<td>1.1427</td>
<td>0.2532</td>
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<td>Talvik et al$^{39}$</td>
<td>2006</td>
<td>-0.6179</td>
<td>-1.2964 (0.0606)</td>
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<tr>
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<td>-0.3115</td>
<td>-1.4085 (0.7855)</td>
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<td>0.5778</td>
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<td></td>
</tr>
<tr>
<td>Graff-Guerrero et al$^{43}$</td>
<td>2009</td>
<td>-0.3922</td>
<td>-1.1684 (0.3839)</td>
<td>-0.9905</td>
<td>0.3219</td>
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</tr>
<tr>
<td>Kessler et al$^{44}$</td>
<td>2009</td>
<td>-0.4788</td>
<td>-1.3264 (0.3688)</td>
<td>-1.1072</td>
<td>0.2682</td>
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</tr>
<tr>
<td>Kegeles et al$^{40}$</td>
<td>2010</td>
<td>0.2691</td>
<td>-0.3315 (0.8698)</td>
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<td>0.3798</td>
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<tr>
<td>Lehrer et al$^{34}$</td>
<td>2010</td>
<td>-0.8284</td>
<td>-1.4247 (0.2320)</td>
<td>-2.7224</td>
<td>0.0065</td>
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</tr>
</tbody>
</table>

**Fig. 1**

(a) Forrest plot, (b) funnel plot and (c) meta-regression with year of publication of meta-analysis of thalamic D$_2$/D$_3$ BP$_{ND}$.

Error bars represent 95% confidence intervals; RE model, random-effects model.
clinical significance of a small reduction in D2, if it is present, is not clear, and, although one study does report a significant correlation between lower D2/D3 receptor availability in subregions of the thalamus and higher symptom severity, other studies report the opposite relationship or no relationship in these regions.

**D1 receptor availability**

There were too few studies to permit meta-analysis and findings were inconsistent across studies. A factor that could underlie the inconsistency is suggested by a study in rats comparing the effects of dopamine depletion on the binding of the two tracers used. This found that although dopamine depletion increased, as expected, the binding of [11C]-NNC, it paradoxically decreased the binding of [11C]-SCH23390. Thus, if this also occurs in humans, low cortical dopamine levels in schizophrenia would be associated with opposite effects on the binding of these tracers. Additionally, antipsychotic treatment has been found to reduce D1 receptor density, indicating that prior antipsychotic treatment could be confounded in some studies. A further complicating issue is that both the tracers used in the studies show appreciable binding to 5-hydroxytrptamine (5HT2A) receptors. In the absence of more selective D1 tracers, blocking studies using selective 5HT2A or D1 compounds would enable the D1 specific signal to be evaluated. In summary, the available data of frontal D1 binding are limited and further studies in drug-naive patients are warranted.

**Dopamine transporter availability**

There has been remarkably little investigation of dopamine transporter availability in vivo outside of the striatum. The two findings were of a significant increase in dopamine transporter availability in the thalamus and no difference in the substantia nigra. Also, it is noteworthy that the tracer used shows good test-retest characteristics in both regions, indicating that measurement is reliable and suggesting that further investigation...
is warranted, particularly in the thalamus given the potential reduction in D_2/D_3 receptor availability here.

**Dopamine synthesis capacity**

The majority of findings indicate there was no significant alteration in cortical dopamine synthesis capacity in schizophrenia, although there was both a large effect size reduction in one frontal cortical region and a large effect elevation in the posterior cingulate in the same study. However, the findings in the frontal cortex, and the negative findings in the temporal cortex and amygdala need to be considered in the context of the relatively low reliability of imaging dopamine synthesis capacity in these regions^6^ and evidence that radiolabelled DOPA does not give a specific PET signal in cortical regions^2^.

Importantly, Cropley et al^3^ found that there was greater uptake of [18F]-DOPA in white matter than grey matter in frontal cortex, and that partial volume correction for white matter reduced the [18F]-DOPA uptake rate constant while increasing its variability. Thus, the cortical findings, both positive and null, need to be considered with these major caveats in mind.

Further investigation of cortical dopamine synthesis would benefit from the development of more specific radiotracers.

**General methodological considerations**

Variation in the quality of studies is a potential source of bias in the meta-analyses. One important potential source of bias, particularly for small structures such as the substantia nigra, is the influence of partial volume effects. These become important for structures two to three times smaller than the resolution of the scanner.60,61 These effects include loss of signal in affected regions as well as spill-over from neighbouring structures. Where there is a loss of volume in a region, as there is in cortical regions in schizophrenia,62 this could bias group comparisons. Six of the studies examined whether there were differences in the volume of structures examined between the schizophrenia and controls

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>d</th>
<th>Upper</th>
<th>Lower</th>
<th>z-score</th>
<th>P</th>
<th>Greater in controls</th>
<th>Greater in schizophrenia</th>
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<td>2004</td>
<td>0.2741</td>
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<td>–1.7195</td>
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<tr>
<td>Graff-Guerrero et al^27</td>
<td>2009</td>
<td>–0.3922</td>
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<td>Kegeles et al^29</td>
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<td>0.2039</td>
<td>–0.3956</td>
<td>0.8034</td>
<td>0.6666</td>
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RE model: 0.0364 | –0.9162 | 0.9891 | 0.0750 | 0.9402

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Fig. 3  (a) Forrest plot, (b) funnel plot and (c) meta-regression with year of publication of meta-analysis of D_2/D_3 BPND in the substantia nigra. Error bars represent 95% confidence intervals; RE model, random-effects model.

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Kambeitz et al. discussed the impact of partial volume correction methods to reduce the impact of partial volume effects. When this was applied in the uncus, it was found that the use of partial volume correction methods could contribute to differences or, conceivably, result could either be that they cancel each other out or are additive. Studies using techniques that enable separate measurements of receptor density ($B_{\text{max}}$), affinity (1/$K_d$), where $K_d$ is the dissociation constant for the radiotracer from the receptor) and intrasynaptic dopamine levels are needed to disentangle these issues. Although most $D_1$/$D_2$ receptor radiotracers we included in the meta-analyses have similar affinity for $D_1$ and $D_2$ receptors, PHNO, as used in Graff-Guerrero et al., has a higher affinity for $D_2$ than $D_1$ receptors, which means it is relatively less sensitive to $D_2$ alterations. For the meta-analyses it is important to note that the sample sizes were modest and, as meta-analytic results are less stable with smaller sample sizes, consequently may change significantly with the addition of future studies. Furthermore, it is advisable not to solely rely on significance tests to interpret results, but to also consider the summary effect size estimate and associated confidence intervals.

### Table 1: Summary Effect Sizes for Different Regions

#### (a) Prefrontal Cortex

<table>
<thead>
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<th>Study</th>
<th>Estimated Effect Size</th>
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<tr>
<td>Nozaki et al. (DN &amp; DF)</td>
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<td>Lindström et al. (DN &amp; DF)</td>
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<td>Elkashef et al. (DN &amp; DF)</td>
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#### (b) Parietal Cortex

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<th>Study</th>
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<td>Okubo et al. (DN &amp; DF)</td>
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<td>Karlsson et al. (DN &amp; DF)</td>
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#### (c) Temporal Cortex

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<th>Study</th>
<th>Estimated Effect Size</th>
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<tbody>
<tr>
<td>Yasuno et al. (DN &amp; DF)</td>
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<td>Glenthoj et al. (DN &amp; DF)</td>
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<td>Talvik et al. (DN &amp; DF)</td>
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#### (d) Thalamus

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<th>Estimated Effect Size</th>
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<tr>
<td>Abid-Dargham et al. (DN &amp; DF)</td>
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**Fig. 4** Overview of the effect sizes found by (a) studies of presynaptic dopamine synthesis, (b) $D_1$ receptor studies, (c) $D_2$ receptor studies, and (d) dopamine transporter (DAT) studies for different extrastriatal regions.

Error bars represent 95% confidence intervals. Significant changes are indicated by * for $P<0.05$, ** for $P<0.01$ and *** for $P<0.001$. Previous treatment of the patient sample is indicated by DF for drug-free and DN for drug-naive. Please note that the significance level plotted in Fig. 4 has not been corrected for multiple comparisons.

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Implications and future directions

An updated version of the dopamine hypothesis proposes that negative and cognitive symptoms of schizophrenia are secondary to cortical hypodopaminergia, whereas psychotic symptoms are secondary to subcortical hyperdopaminergia. In the past two decades consistent in vivo evidence has accrued for subcortical hyperdopaminergia, with a large effect size elevation in striatal dopamine synthesis and release in schizophrenia and potentially sufficient specificity to be a biomarker. In contrast, our meta-analysis of dopamine studies in cortical regions highlights the relative paucity of in vivo studies to support the hypothesis of reduced cortical dopaminergic function. This is surprising given how influential the hypothesis of cortical hypodopaminergia has been and the central role of dopamine-blocking drugs in the treatment of schizophrenia.

Our finding of a small but not statistically significant reduction in D2/D3 receptor availability in the thalamus contrasts with our previous findings in the striatum, where there was a small but inconsistent elevation. One potential explanation for this inconsistency is that there are group differences in the volumes of these structures which, if they were smaller in schizophrenia, would lead to lower values due to partial volume effects (see above).

Our results indicate that the initial report of a large reduction in thalamic D2/D3 receptor availability appears to have moderated into a non-significant reduction with subsequent reports. However, as the confidence interval includes –0.6, it remains possible that there is a moderate–large effect size reduction in schizophrenia. Furthermore, given the finding of elevated thalamic dopamine transporter availability and the role of the thalamus in relaying sensory information, dopaminergic dysfunction here could plausibly play a role in the development of hallucinations and other psychotic symptoms. Thus, further investigation of thalamic dopamine function is warranted.

The substantia nigra is the location of the cell bodies of the dopamine neurons projecting to the striatum. As such the lack of alterations in dopamine transporter or D2/D3 availability in the nigra suggests there is no increase in dopamine neuron density or altered D2/D3 autoreceptor function underlying the striatal dopaminergic dysfunction seen in schizophrenia and its prodrome. Taken with evidence for altered dopamine synthesis capacity in the nigra, this suggests there is increased nigral dopamine function but no compensatory change in nigral D2/D3 receptors.

A fundamental issue that remains to be established is whether there is reduced cortical dopamine release in schizophrenia. Although the relatively lower density of dopamine receptors in cortical regions has made this more challenging to study than in the striatum, evidence from some studies, although not all, of the studies with high affinity D2/D3 selective radiotracers indicates that this is possible with sufficient reliability for group comparisons. There is, thus, the potential to test this unresolved aspect of the dopamine hypothesis in vivo in future studies. Finally, there has been relatively little in vivo investigation of the upstream and downstream regulation of dopaminergic signalling in schizophrenia; both of which are needed to understand the nature of dopaminergic dysfunction in the disorder.

Implications

Despite the wide influence of the cortical dopamine hypofunction hypothesis and the central role of dopamine blockade in the treatment of schizophrenia, there is relatively limited direct evidence of altered dopaminergic function in cortical and other extrastriatal regions in schizophrenia. In this context it is worth remembering that secondary indices (such as reduced blood flow or altered frontal activation) are not a substitute for direct evidence. The available data are inconclusive and further investigation is warranted to determine whether there are alterations in thalamic D2/D3 receptors, and in D1 receptor availability, dopamine synthesis capacity and dopamine transporter availability.

References


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

Joseph Kambeitz, Anissa Abi-Dargham, Shitij Kapur and Oliver D. Howes

BJP 2014, 204:420-429.
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