

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 “SPET” OR “Single Photon Emission Computed 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 (SPET) 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.²⁰

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,²¹ data were presented combined and, where available, separately for patients who had previously received antipsychotic treatment and for patients who were antipsychotic-naïve 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.²² The

R statistical programming language²³ version 2.10.1 on Mac OS-X (version 10.6.8) with the package ‘metafor’²⁴ was used to conduct meta-analyses as well as power calculations.²⁵ 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,^{26,27} which does not assume homogeneity among studies. The summary effect sizes (Cohen’s d) were computed using a restricted maximum-likelihood estimator.²⁸ Heterogeneity was assessed in the studies by calculating the I^2 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.²⁹ As a guideline, I^2 values of 0–40% indicate heterogeneity that is not important, 30–60% moderate heterogeneity, 50–90% substantial heterogeneity and 75–100% considerable heterogeneity²⁹ (for further details see Higgins & Green³⁰). 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.²⁶ 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.³¹ 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 (BP_{ND}). The BP_{ND} 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_P or BP_F respectively.³² The BP_{ND}, BP_P and BP_F are all proportional to the concentration of receptors available to be bound in the tissue of interest.³² As all the studies reported BP_{ND} and only two studies reported BP_P and BP_F, we used BP_{ND} 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.*³³ was excluded as there was sample overlap with Lehrer *et al.*³⁴ Also there was sample overlap between Yasuno *et al.*,³⁵ Yasuno *et al.*³⁶ and Suhara *et al.*³⁷ Only Suhara *et al.*³⁷ was included as the thalamic region used was closest to that of other studies in the available literature. For Talvik *et al.*³⁸ and Talvik *et al.*³⁹ 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*³⁸ in the meta-analysis of the temporal cortex and Talvik *et al*³⁹ for the meta-analysis of the thalamus to maximise sample size and to avoid potential sample overlap. Kegeles *et al*⁴⁰ applied the simplified reference tissue model (SRTM) and a two-tissue compartmental model to the imaging data and reported D_2/D_3 BP_{ND} for both. As most other studies in this analysis applied an SRTM approach, we selected these data from Kegeles *et al*⁴⁰ to ensure the modelling approach was the same across studies. Kegeles *et al*⁴⁰ reported D_2/D_3 BP_{ND} 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 BP_{ND} 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 ($z = -0.6727$, $P = 0.5011$) 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*⁴⁰ or Glenthøj *et al*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 $0-89.38\%$). The studies of medication-naïve participants showed effect sizes of 0.35 ,⁴¹ -0.62 ³⁹ and -0.77 .³⁷ However, there were too few studies of medication-naïve 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 $0-67.2\%$, 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 $d = -0.42$,⁴⁰ $d = -0.33$ ⁴⁴ and $d = 0.0$.⁴⁵ The studies in drug-naïve participants reported comparable effect sizes of $d = 0.49$,³⁷ $d = -0.12$ ⁴¹ 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 a 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-naïve patients there was still no significant effect ($d = -0.04$, 95% CI -1.31 to 1.22 , $z = -0.0628$, $P = 0.9$, $I^2 = 88.59\%$, 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 BP_{ND} 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 BP_{ND} in patients with schizophrenia³⁶ and two reported no significant change.^{38,44} One study reported a significant decrease of D_2/D_3 BP_{ND} in the uncus.⁴⁴ There were no significant changes reported in the entorhinal cortex,⁴⁰ the hippocampus,^{37,40,44} the amygdala,^{40,44} the prefrontal cortex,^{36,38,41} the occipital cortex,³⁷ the parietal cortex,³⁶ the insula⁴⁰ or the globus pallidum.⁴³

Dopamine synthesis capacity

Four studies investigated presynaptic dopamine synthesis capacity outside the striatum.⁴⁶⁻⁴⁹ These studies report data from 58 healthy controls and 53 patients in 12 different regions (Fig. 4(a)). There were significant changes in two regions in one study. This study reported a significant decrease in the middle frontal cortex and a significant increase in the posterior cingulate.⁴⁸

D₁ receptor availability

There were four studies of D₁ receptor availability including a total of 55 patients and 68 controls and reporting results for 15 different regions^{21,50-52} (summarised in Fig. 4(b)). There were three reports of significant changes in the prefrontal cortex, and one report of no significant change. Abi-Dargham *et al*⁵² reported a significant increase in prefrontal D₁ BP_{ND} in patients with schizophrenia. However, Okubo *et al*⁵⁰ report a significant decrease. Both of these studies included drug-naïve and previously drug-treated patients. The most recent study reported a significant elevation in D₁ receptor availability in antipsychotic-naïve patients, but no difference from controls in previously antipsychotic-treated patients.²¹ No other extrastriatal regions showed

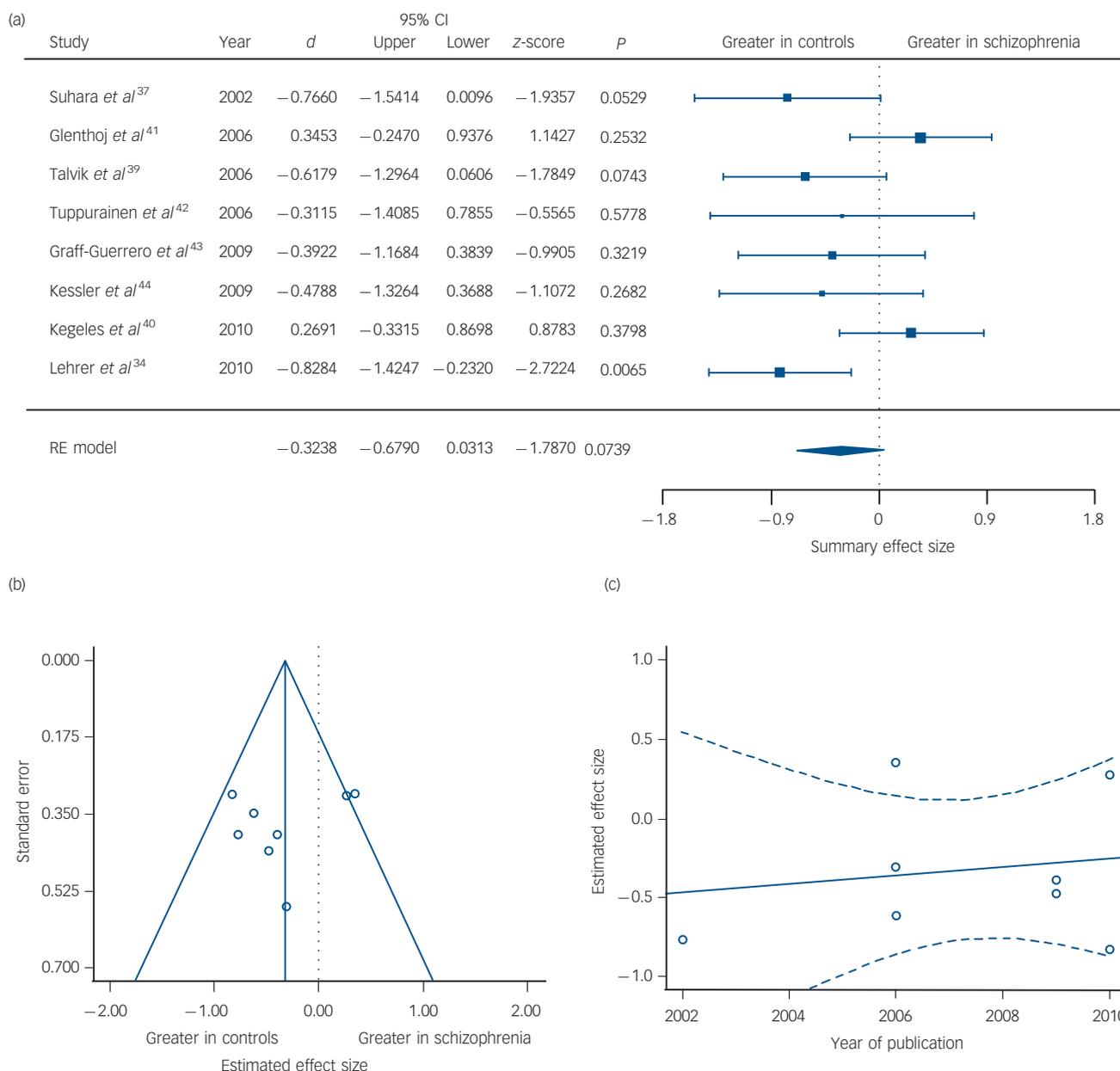


Fig. 1 (a) Forrest plot, (b) funnel plot and (c) meta-regression with year of publication of meta-analysis of thalamic D₂/D₃ BP_{ND}.

Error bars represent 95% confidence intervals; RE model, random-effects model.

significant changes in D₁ 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 regions⁵³ (Fig. 4(d)). This study reports a significant increase in the thalamus but no significant change in the substantia nigra.

Discussion

D₂/D₃ receptor availability

Our meta-analyses showed small, non-significant reductions in D₂/D₃ 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 D₂/D₃ receptor availability in extrastriatal regions but there may be a small reduction in D₂/D₃ availability in the thalamus. The

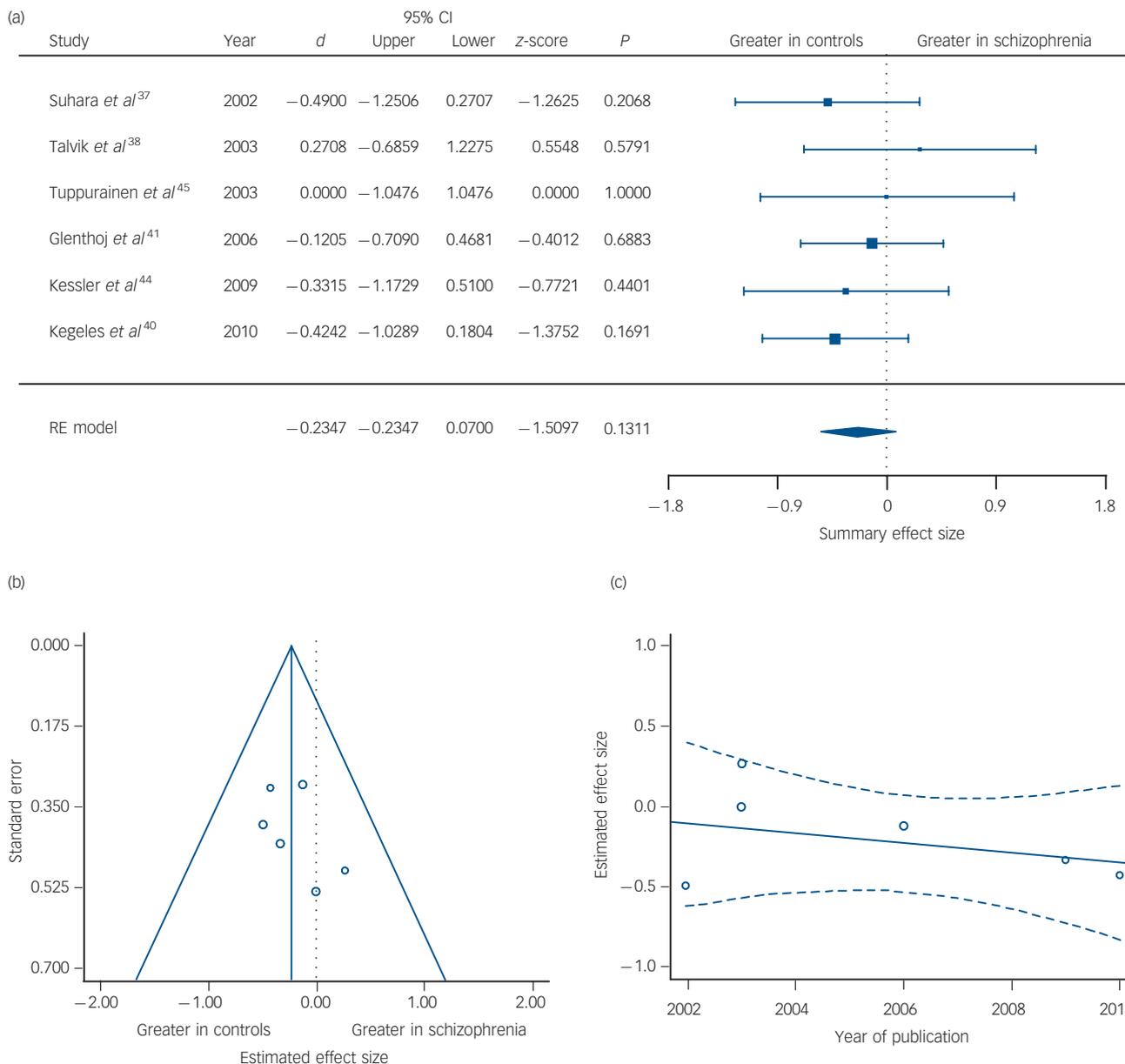


Fig. 2 (a) Forrest plot, (b) funnel plot and (c) meta-regression with year of publication of meta-analysis of temporal D₂/D₃ BP_{ND}. Error bars represent 95% confidence intervals; RE model, random-effects model.

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,³⁵ other studies report the opposite relationship^{38,44} or no relationship in these regions.⁴¹

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.⁵⁴ 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,⁵⁵ 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-hydroxytryptamine (5HT_{2A}) receptors.⁵⁶ In the absence of more selective D₁ tracers, blocking studies using selective 5HT_{2A} 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-naïve 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,⁵⁷ indicating that measurement is reliable and suggesting that further investigation

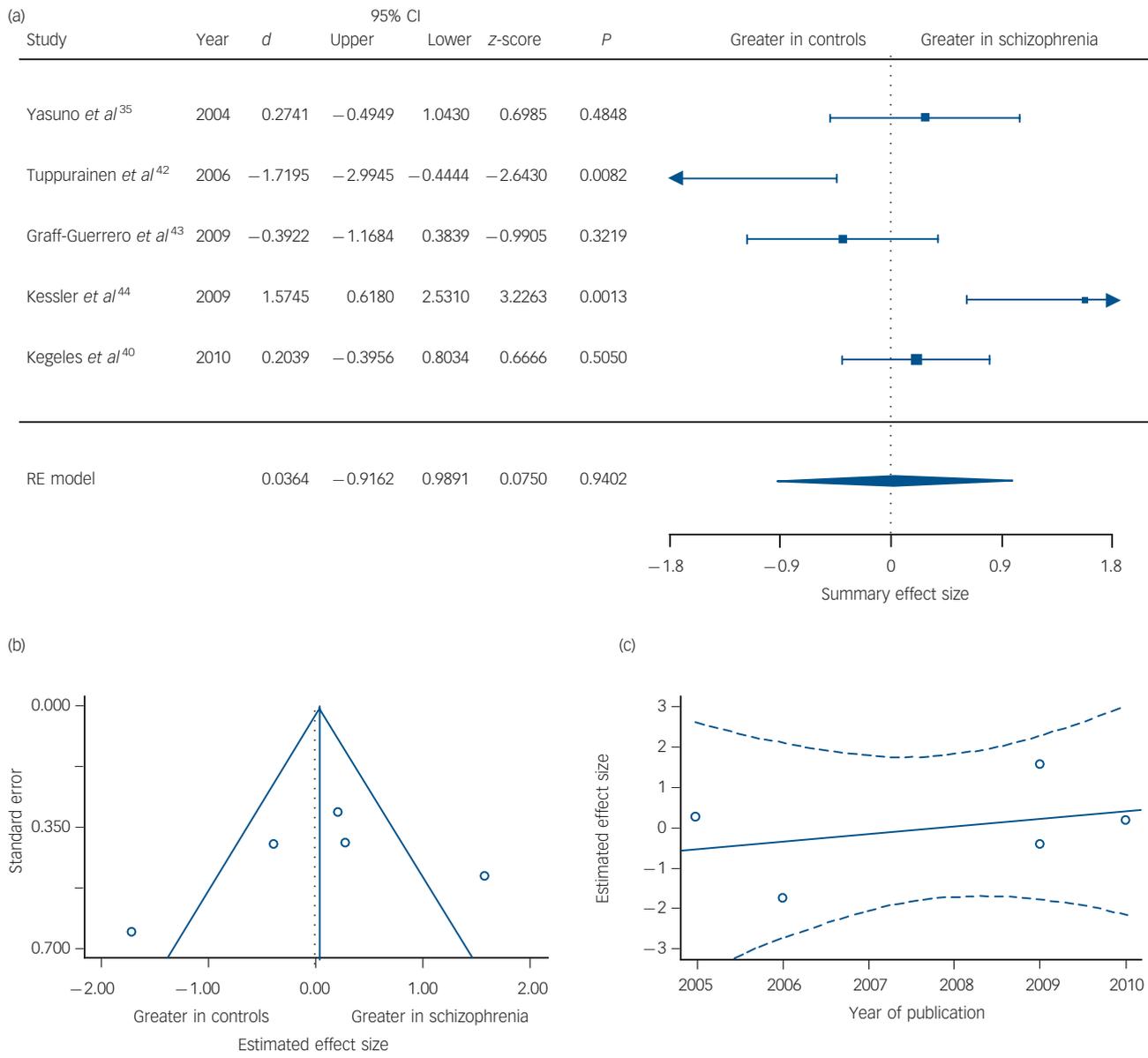


Fig. 3 (a) Forrest plot, (b) funnel plot and (c) meta-regression with year of publication of meta-analysis of D₂/D₃ BP_{ND} in the substantia nigra. Error bars represent 95% confidence intervals; RE model, random-effects model.

is warranted, particularly in the thalamus given the potential reduction in D₂/D₃ 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 regions⁵⁸ and evidence that radiolabelled DOPA does not give a specific PET signal in cortical regions.⁵⁹ Importantly, Cropley *et al*⁵⁹ 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

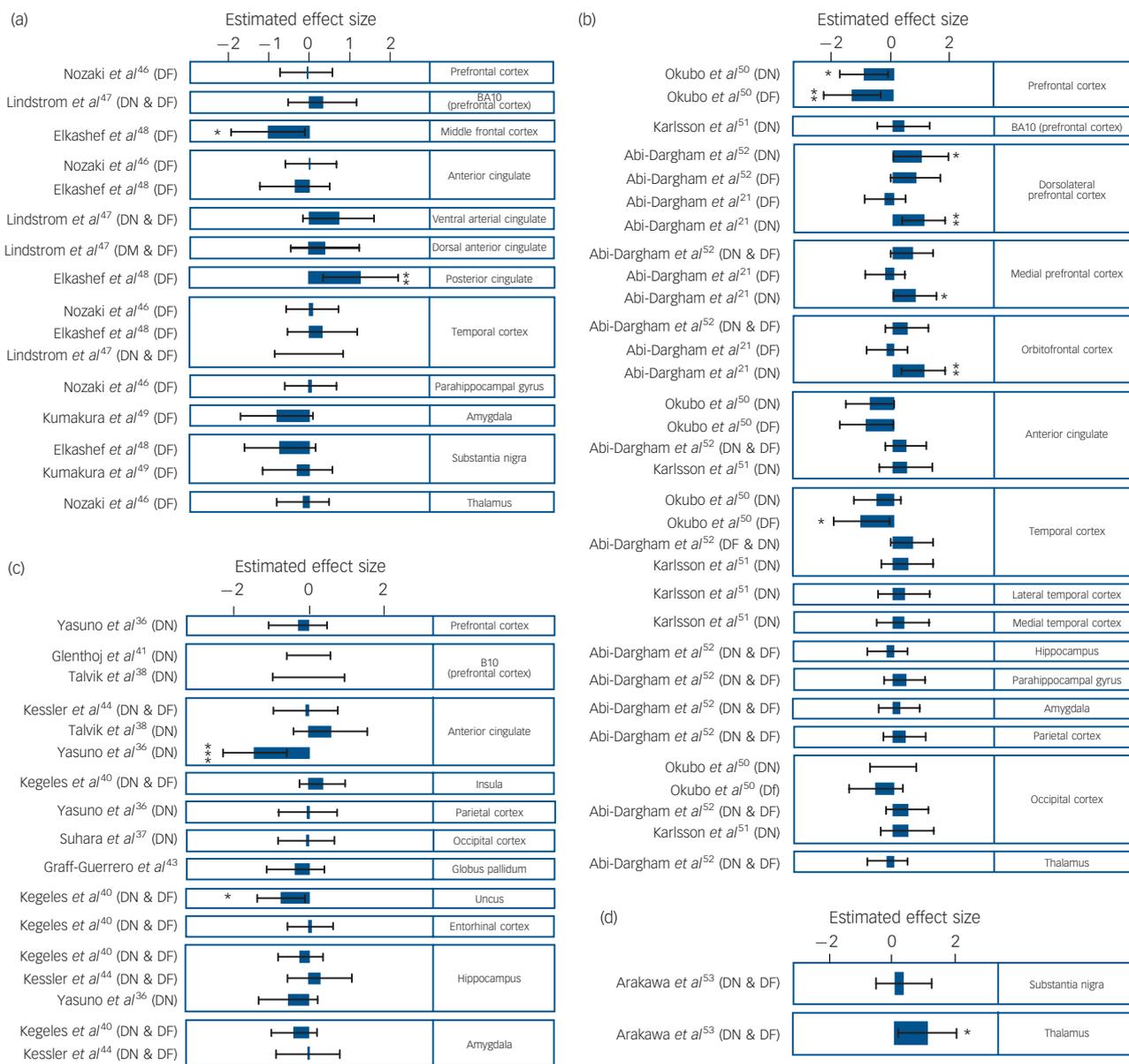


Fig. 4 Overview of the effect sizes found by (a) studies of presynaptic dopamine synthesis, (b) D₁ receptor studies, (c) D₂ receptor studies and (d) dopamine transporter (DAT) studies for different extrastriatal regions.

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.

group – four found no difference,^{24–27,51} and two found a significant difference.^{28,43} However, only one study⁴⁰ made use of partial volume correction methods to reduce the impact of partial volume effects.^{61,63} When this was applied in the uncus, for example, values changed markedly: there was a 109% increase in D₂/D₃ BP_{ND} in controls and an 88% increase in patients with schizophrenia.⁴⁰ Type of illness may also be important,⁶⁴ with evidence that patients whose condition is refractory do not show the same dopaminergic changes, for example, and this was not evaluated in the studies.

It is important to note that binding potential, the outcome measure in the receptor studies, depends on the density of receptors, affinity of the receptor for the radiotracer and occupancy by endogenous dopamine. Alterations in any one of these parameters could contribute to differences or, conceivably, if more than one parameter is affected in a condition, the net

result could either be that they cancel each other out or are additive.⁶⁵ Studies using techniques that enable separate measurements of receptor density (B_{max}), affinity ($1/K_d$; where K_d is the dissociation constant for the radiotracer from the receptor) and intrasynaptic dopamine levels^{66–68} are needed to disentangle these issues. Although most D₂/D₃ receptor radiotracers we included in the meta-analyses have similar affinity for D₂ and D₃ receptors, PHNO, as used in Graff-Guerrero *et al*,⁴³ has a higher affinity for D₃ than D₂ receptors,⁶⁹ which means it is relatively less sensitive to D₂ 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,⁷⁰ 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

interval.⁷¹ This is particularly the case as the meta-analyses lacked power to detect small differences. Finally, we found evidence of moderate to large heterogeneity in our meta-analyses (indicated by I_2 values greater than 50%). However, the random-effects approach to meta-analysis we used is relatively robust to heterogeneity.³⁴

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.^{7,8} 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 schizophrenia⁹ and potentially sufficient specificity to be a biomarker.^{72,73} 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.⁷⁴

Our finding of a small but not statistically significant reduction in D_2/D_3 availability in the thalamus contrasts with our previous findings in the striatum, where there was a small but inconsistent elevation.⁹ One potential explanation for this inconsistency is that there are group difference 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 D_2/D_3 receptor availability³⁵ 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,⁷⁵ 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 D_2/D_3 availability in the nigra suggests there is no increase in dopamine neuron density or altered D_2/D_3 autoreceptor function underlying the striatal dopaminergic dysfunction seen in schizophrenia^{66,76–78} and its prodrome.^{79,80} Taken with evidence for altered dopamine synthesis capacity in the nigra,⁸¹ this suggests there is increased nigral dopamine function but no compensatory change in nigral D_2/D_3 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,⁶⁵ evidence from some,^{69,82–85} although not all,^{86–92} of the studies with high affinity D_2/D_3 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.^{93,94}

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 D_2/D_3 receptors, and in D_1 receptor availability, dopamine synthesis capacity and dopamine transporter availability.

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