Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix

Supplementary Background

A number of PET and SPECT imaging techniques have been used to study *in vivo* dopaminergic function in schizophrenia. Dopamine synthesis capacity can be indexed using two radiolabeled homologues of *l*-3,4-dihydroxy-phenylalanine (DOPA): [β-^{11}C]L-DOPA ([^{11}C]-DOPA) and 6-[^{18}F]fluoro-DOPA ([^{18}F]-DOPA).[1, 2] Brain metabolism of radiolabeled-DOPA parallels that of endogenous L-DOPA.[3] In dopamine neurons, these radiotracers are converted by aromatic L-amino acid decarboxylase (AADC) into [^{11}C]dopamine and 6-[^{18}F]fluoro-dopamine, respectively, and trapped in vesicles in the nerve terminals ready for release (see review[1]). AADC is a regulated enzyme and its activity in dopamine neurons is relative to other aspects of dopamine metabolism.[4] AADC is present in other monoaminergic neurons in addition to dopamine neurons.[5] Nevertheless, radiolabeled-DOPA uptake in the striatum is predominantly due to dopaminergic innervation, is highly correlated with striatal dopamine levels in post mortem brains, and responds to experimental manipulation of brain dopaminergic systems.[5-8]

The next stage of dopaminergic transmission is dopamine release into the synapse. Synaptic levels of dopamine can be indexed by imaging the effect of competition between dopamine and radiotracers which selectively bind to dopamine D2/3 receptors, such as [^{11}C]-raclopride, and [^{123}I]-iodobenzamide, on the availability of these receptors.[9] The competition model indicates that radiotracer binding will decrease when synaptic dopamine levels are increased, for example with dopamine release after amphetamine administration, and conversely that binding will increase when synaptic dopamine levels are reduced, for example after depletion of presynaptic dopamine stores achieved with alpha-*methyl*-paratyrosine (AMPT) administration (see reviews [9, 10]). Supporting this, *in vivo* animal studies show that specific binding by the radiotracer decreases monotonically with increasing dopamine levels measured by microdialysis.[11] Studies have shown that the competition model alone does not account for all of the observations yielded by these imaging paradigms, and that receptor trafficking likely plays a role, but nevertheless, changes in radiotracer binding are related to the overall net effects of these events, which are a direct consequence of the change in dopamine tone produced by pharmacological or other challenges.[12, 13]

Following its release, dopamine diffuses across the synapse to act on post-synaptic dopamine receptors. A large number of radiotracers have been developed to image D2 receptors, including benzamides (including [^{11}C]-raclopride, [^{18}F]-fallypride, [^{11}C]-FLB457 and [^{123}I]-iodobenzamides), ergot derivatives (including [^{76}Br]-bromolisuride) and the butyrophenones (including [^{18}F]-spiperone, [^{11}C]-spiperone, [^{76}Br]-bromospiperone, and [^{11}C]-NMSP).[9, 10] These do not distinguish D2 from D3 receptors or pre- from post-synaptic receptors and vary somewhat in their properties, including selectivity for D2/3 receptors over D4 receptors and kinetics (see[10] and discussion). Selective tracers are also available for D1 receptors and are being developed for D4 and D5 receptors.

Subcortical dopaminergic neurotransmission is predominantly terminated by dopamine diffusion out of the synapse and reuptake into the nerve terminal by dopamine transporters. Dopamine

transporters can be imaged using PET or SPECT radiotracers such as [^{123}I]-β-CIT, TRODAT, [11C]-cocaine, [11C]-methylphenidate, [18F]CFT ([18F]-WIN 35,428) and [^{11}C]-PE2I.[14]

Supplementary Methods

The following keywords were used in the database searches: “Positron Emission Tomography”, OR “PET”, OR “Single photon emission tomography”, OR “SPET”, OR “Single Photon Emission Computed Tomography” OR “SPECT”; AND “dopamine”, OR “dopamine release”, or “dopamine synthesis”, or “dopamine availability”, OR “dopamine transporter”, OR “dopamine reuptake”, OR “dopamine receptor”; AND “schizophrenia”, OR “psychosis”, OR “schizophreniform”.

The inclusion criteria were: peer-reviewed studies that reported an *in vivo* measure of striatal dopaminergic function in patients with a diagnosis of schizophrenia and in a healthy control group. We excluded case studies, reviews, studies of patients with co-morbid neurological diagnoses, and duplicate publications. The abstracts of all papers identified by the search were screened by OH, EK & JK to determine if they met inclusion criteria. If the abstract indicated the study potentially met inclusion criteria, or where there was any uncertainty, the full text of the paper was reviewed to identify studies that met all the inclusion criteria and to ensure they did not have any of the exclusion criteria. Where there was uncertainty, authors were contacted to confirm that no overlap in the studied participants existed between papers. Current antipsychotic treatment was an exclusion criterion for the studies of dopamine receptors, because this affects dopamine receptor binding potential.[15] Where antipsychotic treatment was stopped prior to scanning we looked for evidence that there was a sufficient wash-out period (at least 5 times longer than the half-life of the antipsychotic drug in plasma) such that residual antipsychotic occupancy of D2/3 receptors was unlikely.

Meta-analytic Procedure

The statistical analysis of the extracted data was conducted using the R statistical programming language version 2.10.1 with the packages ‘rmeta’ and ‘metafor’.[16] Most studies reported data for the whole striatum. However, some only reported data for striatal sub-regions (caudate nucleus and putamen) without reporting values for the whole striatum. In order to achieve higher comparability between studies where data for the whole striatum was not available, an effect size for the whole striatum was calculated.

For studies where data for the whole striatum was not available, the effect size for the whole striatum was calculated by averaging the means of the dopaminergic index in putamen and caudate nucleus weighted by their volume to reflect the relatively larger contribution of the putamen to the overall striatal volume. Where volumes were not reported, the following volumes, derived from healthy controls (n=34, mean age=32.5 (SD=8.8) years), were used: mean (SD) volume (mm^3): putamen=8805 (994), caudate=5562 (865)). When estimating the standard deviation of this striatal measure, we accounted for the dependency of measures in striatal subregions by assuming a correlation of r = 0.5 between measures in striatal sub-regions.

We investigated the validity of this approach by using two studies included in the meta-analysis where data were available for the putamen and caudate and for the whole striatum.[17, 18] We evaluated the intra-class correlation coefficient (ICC) for the whole striatal values determined by combining data from the caudate and putamen as described above and the values for the whole striatum reported in these studies using a mixed effects two-way ANOVA.[19] The ICC was high

(ICC=+0.98, F(24,24)=94.3, p<0.0001, 95%-CI for ICC: 0.95 to 0.99), indicating that our approach to combining regions gives an accurate estimate of the whole striatal values.

The standardized effect sizes of the individual studies were entered in a random-effects meta-analytic model [20, 21], which does not assume homogeneity amongst studies. The summary effect sizes (Cohen's *d)* were computed using a restricted maximum-likelihood estimator.[22] 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 due to heterogeneity rather than chance.[23] I^2 values of 25%, 50%, and 75% can be interpreted as indicating low, moderate and high heterogeneity respectively.[23]

Where there was a significant difference between patients and controls in the meta-analysis, a sensitivity analysis was conducted using the leave-one-out approach, which re-runs the meta-analysis repeatedly with a different study excluded on successive iterations.

We evaluated potential sources of heterogeneity in the effect sizes and the influence of possible confounding factors in the following ways. The potential effects of publication year and the age of subjects was evaluated using meta-regression.[20] Additionally, to investigate the influence of antipsychotic treatment, where there were ≥5 studies in a group, we re-ran the meta-analyses separately for studies grouped by antipsychotic treatment (drug-naïve/ drug-free or currently receiving drug treatment). Where there were <5 studies in a group we plotted the individual effect sizes but did not enter them into a meta-analysis because this becomes unreliable with a small numbers of studies. We used the same approach to investigate whether the different radiotracer imaging methods used contributed to heterogeneity (see Supplementary Tables 1-6 for the groupings).

Publication bias was evaluated by inspection of the funnel plot for evidence of asymmetry. A funnel plot is a plot of each study's effect size on the x-axis against its standard error (1/precision). Publication bias is suggested if trials in the left hand corner (small precision and small effect size) are omitted, creating a degree of asymmetry in the funnel plot. Publication bias was further evaluated using a regression test for funnel plot asymmetry, and the trim-and-fill analysis, which provides an estimate of the meta-analysis if there has been publication bias.[24, 25]

Supplementary Results

Dopamine transporter- sub-group analyses

We repeated the meta-analysis including only studies of patients who were drug-naive (6 studies). This showed no significant difference between patients and controls (*d*=-0.44; 95%-CI: -0.99 to 0.12, z=-1.54, p=0.12, I^2=69.28%, 95%-CI for I^2: 25.48 to 93.81%). There was no significant difference in illness duration between drug-naive subjects (mean (sd) =13 (11) months) and subjects taking antipsychotic drugs (mean (sd) = 150 (43) months; t=4.44, df=1.04 (corrected for unequal variances), p=0.13). There were too few studies of patients currently taking neuroleptics (n=4) or of drug-free patients (n=1) to enable separate meta-analysis and insufficient studies in each group to enable a separate meta-analysis for the different radiotracer imaging approaches used.

Dopamine receptor- sub-group analyses

Studies were grouped into those of patients who had never received antipsychotic treatment (drug naive) and those including patients who had received previous antipsychotic drug treatment (prior treatment). The antipsychotic-naïve group (n=6 studies) showed no significant difference between patients and controls (see Supplementary Figure 6, *d*=0.27, 95%-CI: -0.57 to 1.11, z=0.62, p=0.53, I^2=86.08%, 95%-CI of I^2: 63.02 to 97.88 %). However, the prior treatment group (n=15 studies) showed evidence of an elevation in D2/3 receptors in patients (*d*=0.28, 95%-CI: 0.03 to 0.52, z=2.20, p=0.03, I^2=40.96%, 95%-CI of I^2: 0 to 76.44%). The duration of illness was significantly longer in the prior treatment patients (mean (sd)=124 (63) months) than in drug-naive patients (mean (sd)= 15 (4) months, t = -4.21, df=5.1 (corrected for unequal variances), p=0.008).

The effect sizes for the different radiotracer imaging methods used are shown in Supplementary Figure 7. The meta-analysis was re-run separately for the studies that used a benzamide and for those that used a butyrophenone radiotracer (there were too few studies to enable this for those using ergot derivative radiotracers). There was no significant difference between patients and controls in the studies using a benzamide radiotracer (n=14; *d*=0.13, 95%-CI: -0.19 to 0.44, z=0.78, p=0.44, I^2=63.26%, 95%-CI of I^2: 63.26 to 89.40%). There was, however, a significant elevation in the patients in the studies that used a butyrophenone radiotracer (n=5; *d*=0.71, 95%-CI: 0.14 to 1.28, z=2.44, p=0.01, I^2=60.85%, 95%-CI of I^2: 0 to 94.52 %). There was no significant difference in duration of illness between studies using benzamides (mean (sd) = 75 (79) months) and those using butyrophenones radiotracers (mean (sd) = 129 (44) months, t=1.23, df=3.2 (corrected for unequal variances), p=0.3).

Given that most of the studies that used butyrophenone radiotracers included patients who had received prior antipsychotic treatment, prior treatment and radiotracer used were potentially confounded. To explore this we excluded the studies that had used butyrophenones, and repeated the meta-analysis of the remaining studies of patients who had received prior antipsychotic treatment (n=11). This found no significant difference between patients and controls (*d*=0.09, 95%-CI: -0.13 to 0.32, z=0.81, p=0.41; Supplementary Figure 6), and low heterogeneity (I^2=0%, 95%-CI of I^2: 0 to 42.11 %).

Dopamine D1 receptors

We identified six studies that measured striatal D1 receptor availability in patients with schizophrenia, although two studies included patients who were taking antipsychotic drugs at the time of scanning.[26-31] Three of the studies, comprising 43 patients in total (23 antipsychotic free and 20 antipsychotic naive), found no difference in striatal D1 availability[27-29], whilst two, comprising 15 patients in total (all taking antipsychotic drugs) found a reduction[26, 30], and one found a trend-level increase in antipsychotic-naïve patients (n=12) that was not present in previously treated but drug free patients (n=13). Although the investigators in the two studies that found a reduction selected patients who were taking antipsychotic drugs with relatively low affinity for D1 receptors, antipsychotic occupancy of D1 receptors cannot be excluded and could explain the reduction in these two studies. There were too few studies of drug free patients to enable a meta-analysis of striatal D1 availability in schizophrenia.

Meta-analysis for striatal sub-regions

To evaluate whether our analyses for the whole striatum were obscuring important sub-regional differences, we repeated the meta-analysis for striatal sub-regions where sufficient data were available (a minimum of five studies). There were sufficient studies to enable this for the caudate and putamen, but not for the nucleus accumbens or for functional sub-divisions of the striatum.

Pre-synaptic dopaminergic function studies

Caudate:

Eight studies provided data for the caudate. The meta-analysis of these studies found no significant difference between patients and controls (d=0.37, z=1.57, p=0.12, 95%-CI: -0.09-0.82, I2=54.04%, 95%-CI of I2: 0-90.74%).

Putamen:

Eight studies provided data for the putamen. The meta-analysis of these studies found a significant elevation in schizophrenia, with an effect size of *d*=0.51 (z=2.71, p=0.007, 95%-CI: 0.14-0.88, I2=29.98%, 95%-CI of I2: 0-80.07%).

Dopamine transporter studies

Caudate:

Eight studies provided data for the caudate. The meta-analysis of these studies found no significant difference between patients and controls (*d*=-0.43, z=-1.60, p=0.11, 95%-CI: -0.95 to -0.09, I2=65.09%, 95%-CI of I2: 20.25 to -91.48%).

Putamen:

Eight studies provided data for the putamen. The meta-analysis of these studies found no significant difference between patients and controls (*d*=-0.4, z=-1.41, p=0.16, 95%-CI: -0.95 to -0.15, I2=68.97%, 95%-CI of I2: 28.83-92.51%).

Dopamine D2/3 receptor availability

Caudate:

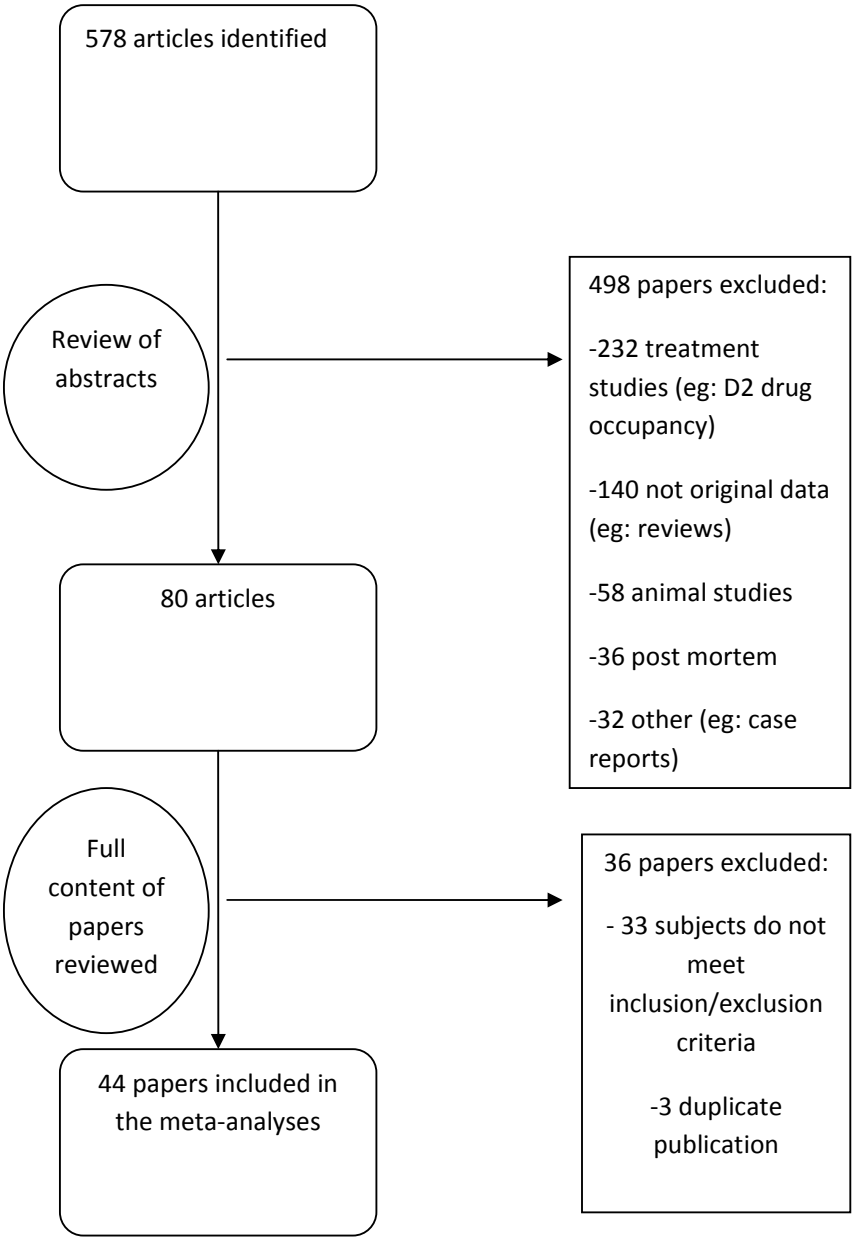
Five studies provided data for the caudate. The meta-analysis of these studies found no significant difference between patients and controls (*d*=0.32, z=0.96, p=0.33, 95%-CI: -0.33 to -0.97, I2=78%, 95%-CI of I2: 36.98-97.48%).

Putamen:

Five studies provided data for the putamen. The meta-analysis of these studies found no significant difference between patients and controls (*d*=0.02, z=0.13, p=0.9, 95%-CI: -0.3 to -0.34, I2=0%, 95%-CI of I2: 0-90.88%).

Supplementary Figures

eFigure 1: Flowchart showing how the papers were identified for inclusion



*Notes:

Presynaptic dopaminergic function: one paper[32] combined data from two previous studies[33, 34] with new data from an additional study. As this is the most complete data set, we used this report in the main meta-analysis but include data from the other studies in sub-analyses where there is no overlap in subjects, and for this reason these papers are also reported in the Tables. One study was

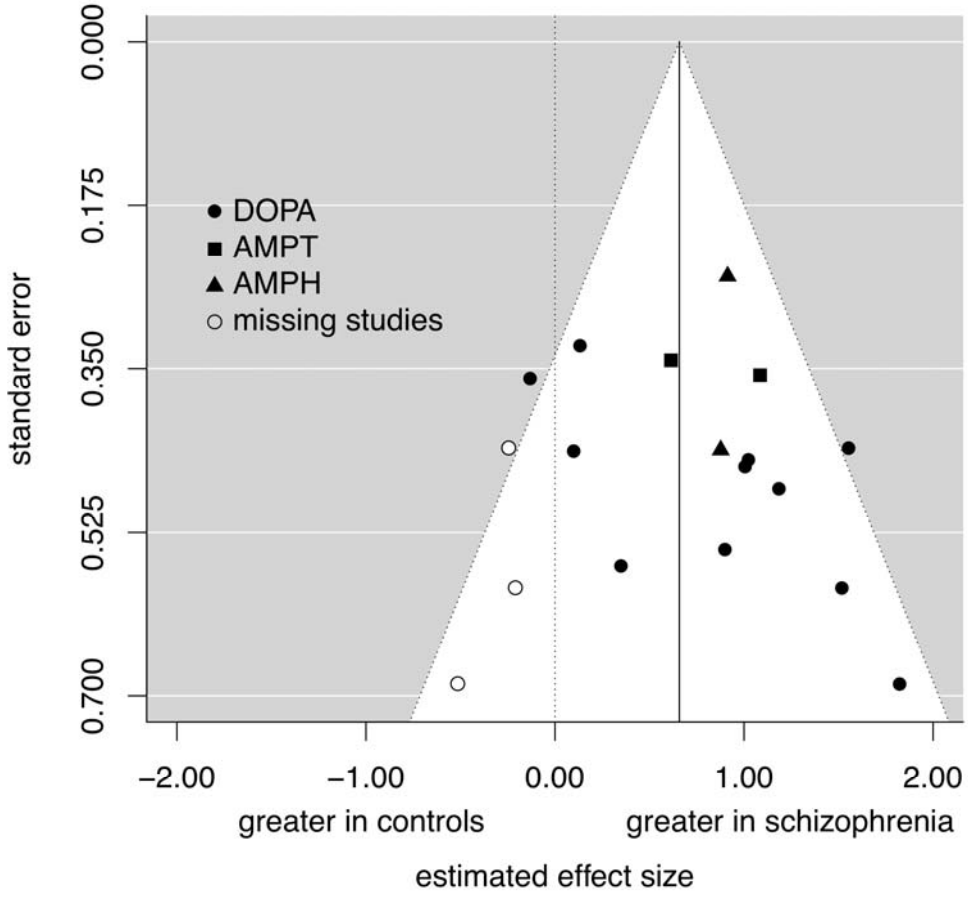
of patients with schizophrenia and their well siblings. This study was excluded because the comparator group was related to the patients.[35]

Dopamine transporter availability: One study was excluded because the patients had a co-morbid neurological disorder associated with dopamine neuron loss (parkinson's disease) in addition to schizophrenia[36], and another was excluded as data were only reported as percentage of control values without reporting actual values.[37]

Dopamine receptor availability: one paper[38] combined data from one previous study[39] with additional new data and was used as it is the most complete data set. One study included subjects who were scanned 7 days after stopping antipsychotic treatment, and was excluded from the main analysis because of the risk of residual antipsychotic occupancy of D2/3 receptors (see above), but was included in a further sensitivity analysis.[40]

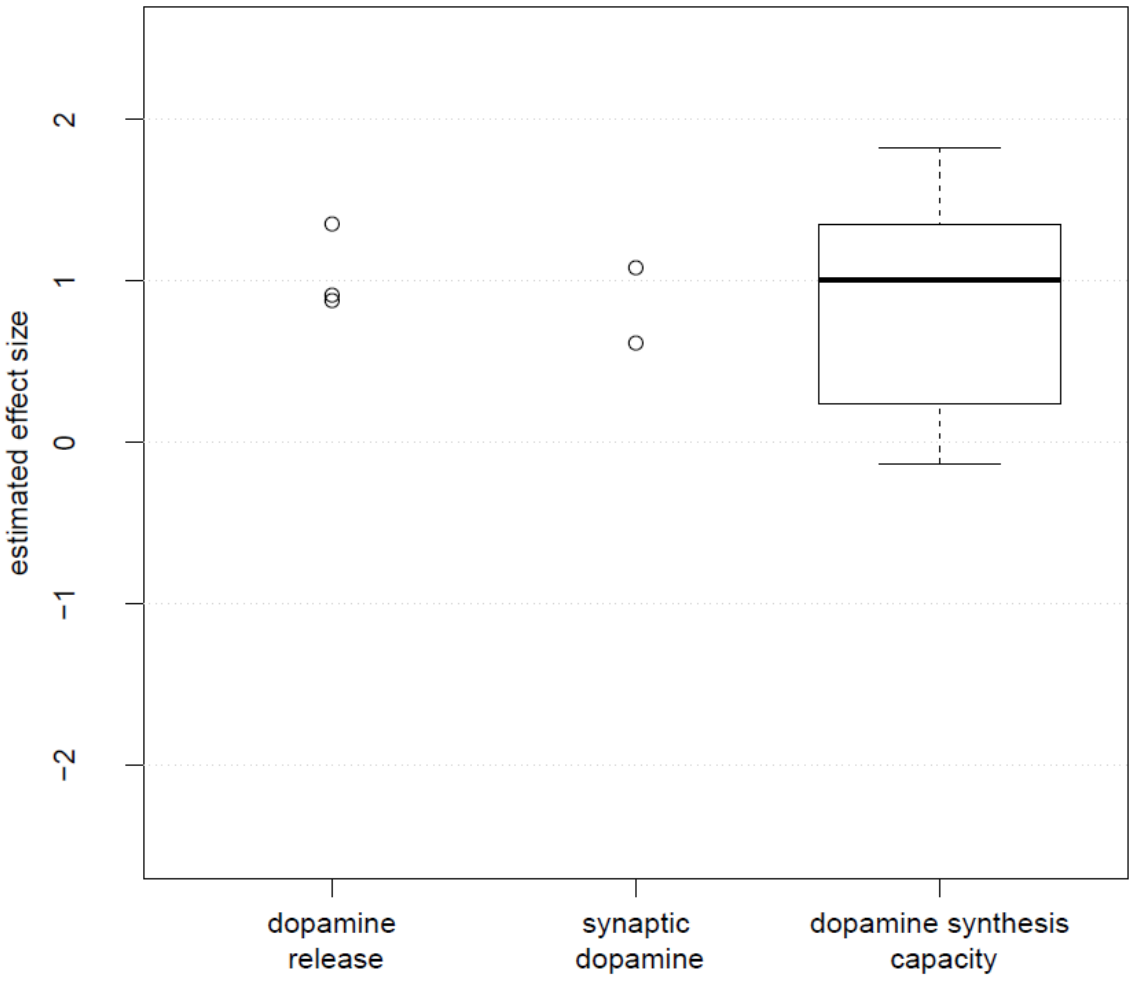
eFigure 2

Studies of presynaptic dopaminergic function: Funnel plot showing the effect sizes for each study (studies using radiolabeled DOPA [filled circles]; alphamethyl-*para*-tyrosine [AMPT; filled squares] to index synaptic dopamine levels; amphetamine [AMPH; filled triangles] to index dopamine release) and potentially missing studies (open circles) based on the trim-and-fill analysis, which assumes the effect sizes follow a normal distribution.



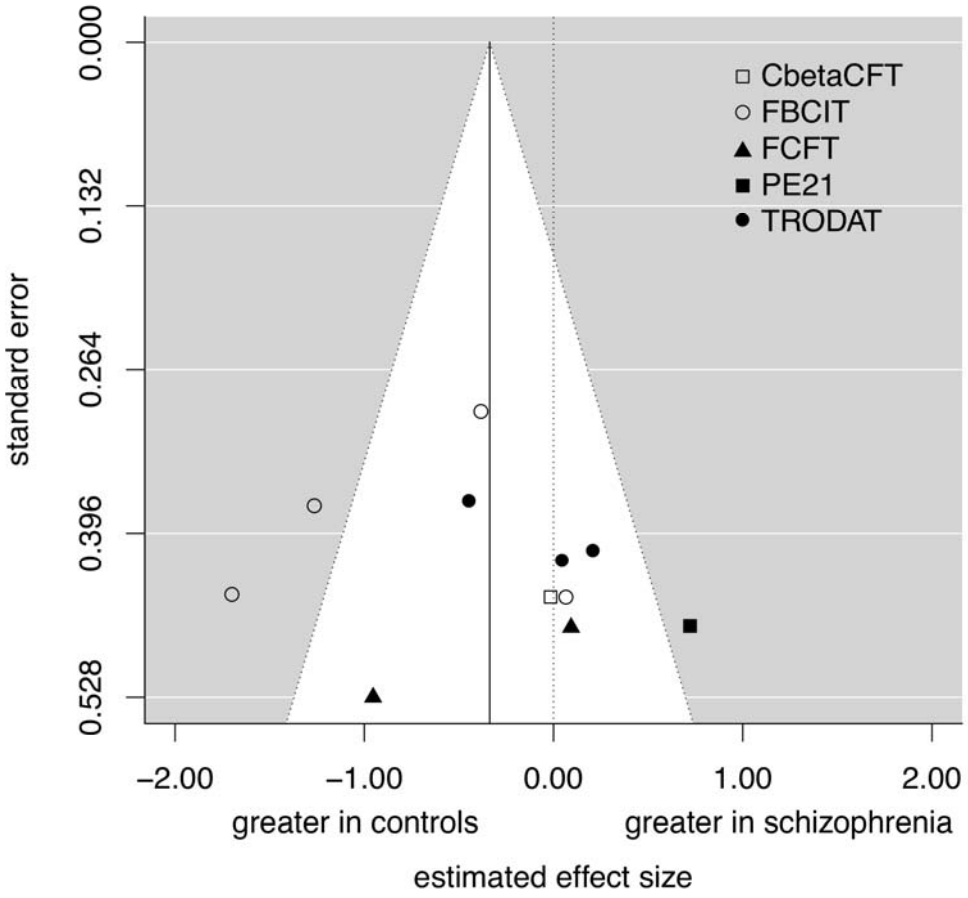
eFigure 3

Studies of presynaptic dopaminergic function: Showing the effect sizes by imaging approach used in the studies. Where n>4 studies in a group, the effect sizes are summarised using a boxplot (in the boxplot in the boxplot the band is the median and the whiskers indicate the lowest and highest data points that are within 1.5 * the inter-quartile range, and data outside this range (circles if present) are regarded as potential outliers), otherwise the effect size for each study is plotted). Studies using change in radiotracer binding following AMPT or amphetamine are grouped as 'synaptic dopamine' and 'dopamine release' respectively (effect sizes shown for Laruelle et al 1999, which combines 3 dopamine release studies and is used in the main meta-analysis as it is the most complete data-set; Breier et al, 1997; and Abi-Dargham et al 2009, although this latter study is not included in the main meta-analysis because the subjects also took part in the Abi-Dargham et al 2000 AMPT study). Studies using radiolabeled DOPA radiotracers are in the 'dopamine synthesis capacity' group



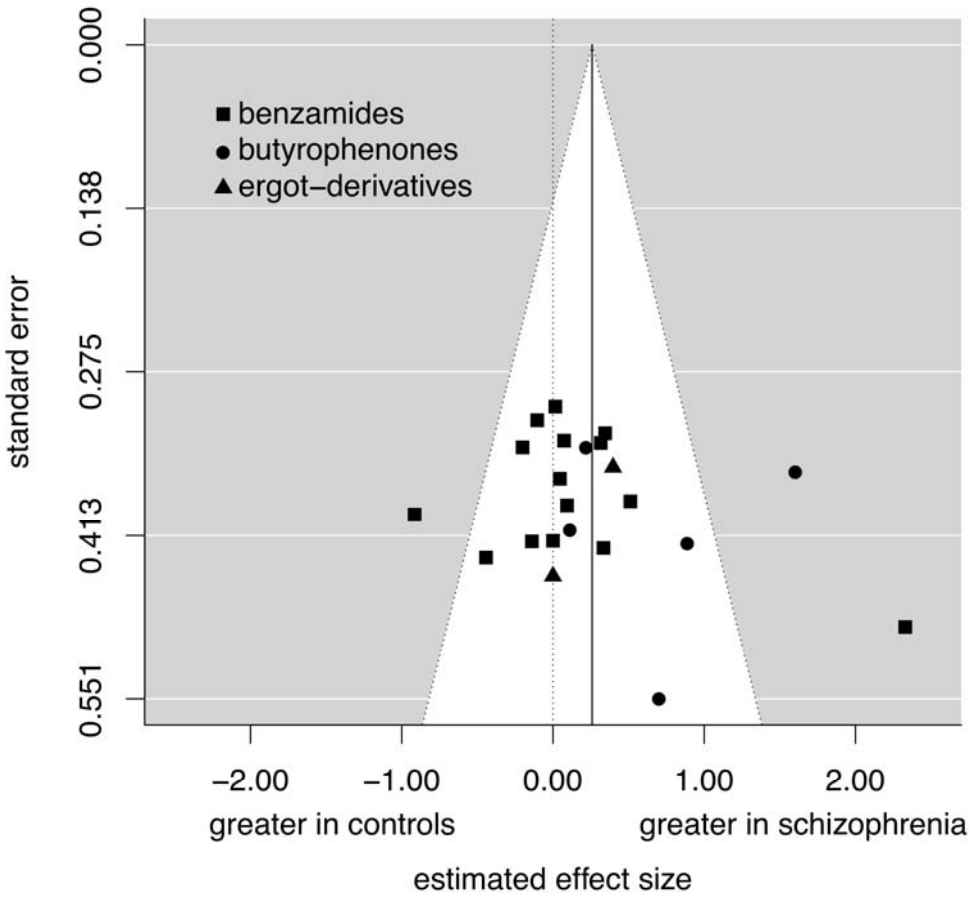
eFigure 4

Studies of the dopamine transporter: Funnel plot showing the effect sizes for each study (studies using TRODAT [filled circles]; PE2I [filled square]; FCFT [filled triangle];FBCIT [open circles]; CbetaCFT [open square]).



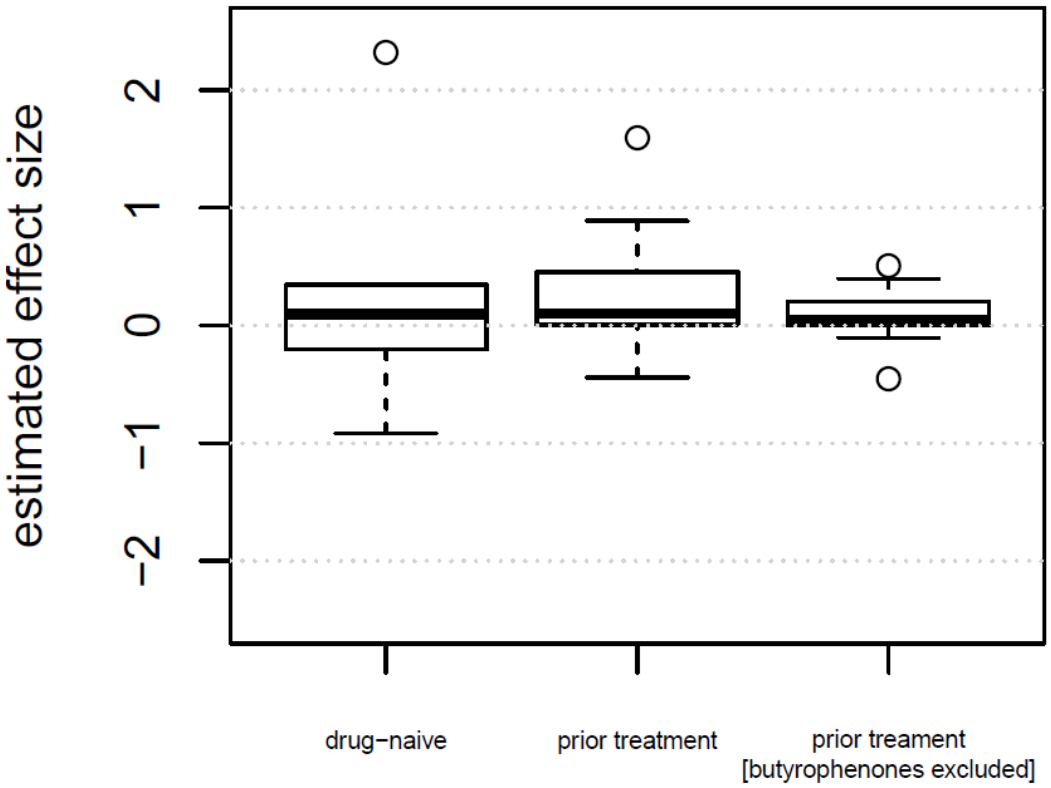
eFigure 5

Studies of D2 receptor availability: Funnel plot showing the effect sizes for each study



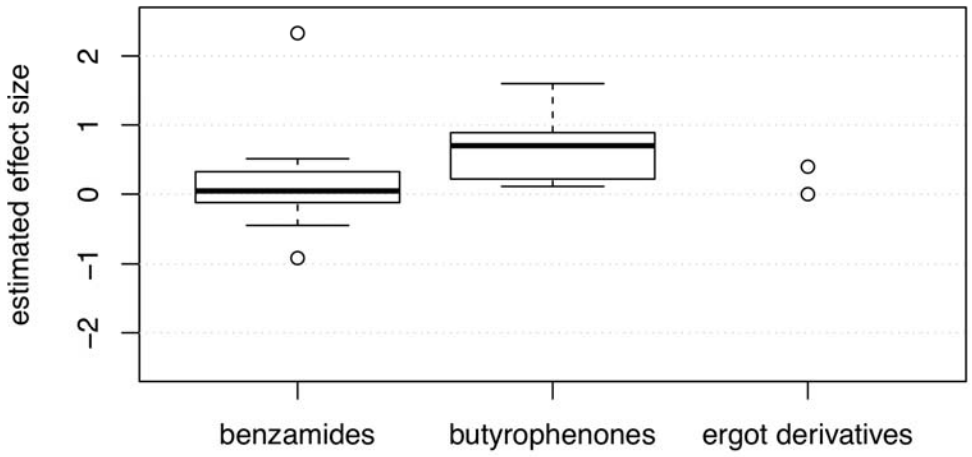
eFigure 6

Studies of D2 receptor availability: Boxplots of the effect sizes for studies by antipsychotic treatment history (in the boxplots the band is the median and the whiskers indicate the lowest and highest data points that are within 1.5 * the inter-quartile range, and data outside this range (circles if present) are regarded as potential outliers).



eFigure 7

Studies of D2 receptor availability: Effect sizes by class of radiotracer used in the studies. Where n>4 studies in a group the effect sizes are summarised using a boxplot (the band is the median and the whiskers indicate the lowest and highest data points that are within 1.5 * the inter-quartile range, and data outside this range (circles if present) are regarded as potential outliers)



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eTable 1. Methodological characteristics of the studies of presynaptic dopaminergic function

	Author	PET Tracer	Imaging approach	Radio-tracer delivery	Drugs administered prior to scanning	Scanner Type	Resolution (FWHM mm)	Outcome Measure	Reference region
Radiolabelled DOPA studies	Reith et al 1994[1]	[^{18}F]Fluoro-L-DOPA	single scan	bolus	-	PC-2048B; Scanditronix	na	k_3	cortex
	Hietala et al 1995[2]	[^{18}F]Fluoro-L-DOPA	single scan	bolus	-	ECAT 931/08-12	na	k_i	occipital cortex
	Dao-Castellana et al 1997[3]	[^{18}F]Fluoro-L-DOPA	single scan	bolus	-	ECAT-Siemens 953-B	6.26	k_i	occipital cortex
	Hietala et al 1999[4]	[^{18}F]Fluoro-L-DOPA	single scan	bolus	Carbidopa: 100 mg, 1.5h pre-scanning	ECAT 931/08-12	na	k_i	occipital cortex
	Lindstroem et al 1999[5]	[^{11}C]DOPA	single scan	bolus	-	GEMS PC2048-15B	5	k_i	occipital cortex
	Elkashef et al 2000[6]	[^{18}F]Fluoro-L-DOPA	single scan	bolus	Carbidopa: 150 mg amino acid infusion	2048-15B; Scanditronix	6.5	uptake ratio (striatum/ ref)	occipital cortex
	Meyer-Lindenberg et al 2002[7]	[^{18}F]Fluoro-L-DOPA	single scan	bolus	Carbidopa: 100 mg	PC-2048-153; Scanditronix	6.5	k_i	occipital cortex
	McGowan et al 2004[8]	[^{18}F]Fluoro-L-DOPA	single scan	bolus	Carbidopa: 150 mg, Entacapone: 400 mg	HR++/966 EXACT; CTI PET Systems	4.8	k_i	occipital cortex
	Kumakura et al 2007[9]	[^{18}F]Fluoro-L-DOPA	single scan	bolus	Carbidopa: 2mg/kg, 1h pre-scanning	ECAT EXACT 47, Siemens	na	k_{in}^{app}	cerebellum
	Nozaki et al 2009[10]	[^{11}C]DOPA	single scan	bolus	-	ECAT/EXACT HR; CTI-Siemens	7.5	k_i	occipital cortex
	Howes et al 2009[11]	[^{18}F]Fluoro-L-DOPA	single scan	bolus	Carbidopa: 150 mg, Entacapone: 400 mg	HR++/966 EXACT; CTI PET Systems	4.8	k_i	cerebellum
Dopamine release (amphetamine) studies	Laruelle et al 1996[12]	[^{123}I]IBZM	two scan (baseline and active)	bolus+ infusion	active scan: 0.3 mg/kg amphetamine IV bolus	PRISM 3000 Picker	11	ΔBP	occipital cortex
	Breier et al 1997[13]	[^{11}C]Raclopride	two scan (baseline and active)	bolus+ infusion	active scan: 0.2 mg/kg amphetamine	General Electric Advance	6	ΔBP	cerebellum
	Abi-Dargham et al 1998[14]	[^{123}I]IBZM	two scan (baseline and active)	bolus+ infusion	active scan: 0.3 mg/kg amphetamine IV bolus	PRISM 3000 Picker	11	ΔBP	occipital cortex
	Laruelle et al 1999[15]	[^{123}I]IBZM	two scan (baseline and active)	bolus+ infusion	active scan: 0.3 mg/kg amphetamine IV bolus	PRISM 3000 Picker	11	ΔBP	occipital cortex
	Abi-Dargham et al 2009[16]	[^{123}I]IBZM	two scan (baseline and active)	bolus+ infusion	active scan: 0.3 mg/kg amphetamine IV bolus	na	na	ΔBP	average of frontal and occipital cortex
Synaptic dopamine (AMPT) studies	Abi-Dargham et al 2000[17]	[^{123}I]IBZM	two scan (baseline and active)	bolus+ infusion	active scan: 8g AMPT[1] PO over 2 days	PRISM 3000 Picker	11	ΔBP	average of frontal and occipital cortex
	Kegeles et al 2010[18]	[^{11}C]Raclopride	two scan (baseline and active)	bolus+ infusion	active scan: 12.9-16.9 mg/kg AMPT[1] PO over 2 days	ECAT/EXACT HR; CTI-Siemens	4.4/ 4.1	ΔBP	cerebellum

[1]alpha-methyl-*para*-tyrosine; $K_{3\ (K3^D)}$=relative activity of dopa decarboxylase, K_i=utilization rate constant of DOPA relative to a reference region; K_{in}^{app}=net blood-brain DOPA clearance, BP=binding potential, FWHM=full width half maximum

eTable 2. Subject characteristics of the studies of presynaptic dopaminergic function

	Authors	Controls		Patients									
		N (m/f)	Age mean (sd)/yr	N (m/f)	Age mean (sd)/yr	Diag-nosis [1]	Inclusion criteria for diagnosis	Exclusion criteria	Illness duration	Antipsychotic treatment	Total symptom score (mean [sd])	Positive symptom score (mean [sd])	Negative symptom score (mean [sd])
Radiolabelled DOPA studies	Reith et al 1994	13 (9/4)	36 (13)	5 (5/0)	38 (4)	All SZ	DSM-III-R	na	14 years	4 naïve, 1 free for >3 years	PANSS: 58 (na)	PANSS: 14 (3)	PANSS: 12 (2)
	Hietala et al 1995	8 (6/2)	27 (7)	7 (4/3)	26 (7)	All SZ	DSM-III-R	na	24 months	all drug naïve	PANSS: 81 (14)	na	na
	Dao-Castellana et al 1997	7 (na)	25 (5)	6 (na)	26 (9)	All SZ	DSM-III-R	neurological/ severe somatic disorders, alcoholism, toxicomania	6 years	2 naïve, 4 free for ≥4 months	PANSS: 94 (na)	PANSS: 21 (12)	PANSS: 33 (7)
	Hietala et al 1999	13 (8/5)	30.4 (9.4)	10 (4/6)	29.6 (8.8)	7 SZ, 3 SZD	DSM-III-R	na	7 months	All naïve	PANSS: 77.6 (na)	na	na
	Lindstroem et al 1999	10 (8/2)	na	12 (10/2)	31 (na)	All SZ	DSM-III-R	abnormality on CT, EEG or routine blood tests, positive urine drug screen	31.08 months	10 naïve, 2 drug free for >2 years	na	na	na
	Elkashef et al 2000	13 (8/5)	34.6 (10.75)	19 (15/4)	36.3 (na)	All SZ	DSM-III-R	medical/ neurological disorders, alcohol or drug abuse	17.3 years	10 taking drugs, 9 drug free	na	na	na
	Meyer-Lindenberg et al 2002	6 (5/1)	34 (na)	6 (5/1)	35 (na)	All SZ	DSM-III-R	na	na	all free for ≥6 weeks	na	na	na
	McGowan et al 2004	12 (12/0)	38.3 (7.1)	16 (16/0)	39.9 (11.3)	All SZ	DSM-IV	neurologic/serious physical illness, substance abuse	na	All on long-term drug treatment	CASH: 10.6 (na)	CASH: 4.2 (na)	CASH: 6.3 (na)
	Kumakura et al 2007	15 (15/0)	37.3 (6.4)	8 (8/0)	37.3 (6.3)	All SZ	DSM-IV	psychoactive medication	na	3 naive, 6 free for ≥6 months	PANSS: 80.2 (4.7)	PANSS: 15.4 (3.5)	PANSS: 23.6 (4.0)
	Nozaki et al 2009	20 (10/ 10)	35.1 (9.5)	18 (10/8)	35.6 (7.4)	All SZ	DSM-IV	brain disease, substance abuse, or episode of mood disorder	26.4 months	14 naïve, 4 free	PANSS: 79.2 (21.4)	PANSS: 22.6 (7.3)	PANSS: 17.1 (6.5)
	Howes et al 2009	12 (8/4)	24.3 (4.6)	7 (5/2)	36.0 (14.7)	All SZ	DSM-IV	neurologic/ medical illness, head injury, alcohol or drug abuse or dependence	na	2 naive, 5 free for >8 weeks	PANSS: 61.7 (31.0)	PANSS: 17.0 (7.0)	PANSS: 16.1 (10.0)

Dopamine release (amphetamine) studies	Laruelle et al 1996	15 (14/1)	41 (2)	15 (14/1)	42 (2)	All SZ	DSM-IV	other DSM-IV axis I diagnosis, substance abuse or dependence, severe medical condition	14 years	all free (mean free period=192 days)	BPRS: 37 (3)	PANSS: 16.1 (1.7)	PANSS: 14.9 (1.5)
	Breier et al 1997	12 (9/3)	29.2 (9.01)	11 (8/3)	32.4 (9.95)	All SZ	DSM-IV	illegal drug dependence and/or significant drug abuse, severe head trauma, significant medical condition	6.6 years	4 naive, 7 free for >14 days	BPRS: 28.8 (7.2)	BPRS: 6.7 (2.8)	na
	Abi-Dargham et al 1998	15 (12/3)	40 (11)	15 (12/3)	41 (9)	All SZ	DSM-IV	other DSM-IV axis I diagnosis, substance abuse or dependence, severe medical conditions	17 years (2 FE)	2 naive, 13 free	BPRS: 44 (11)	PANSS: 18.5 (5.1)	PANSS: 19.6 (7.0)
	Laruelle et al 1999	36 (32/4)	40 (9)	34 (28/6)	40 (9)	All SZ	DSM-IV	other DSM-IV axis I diagnosis, substance abuse or dependence, severe medical conditions	na	7 naive, 27 free for 104 days (mean)	na	PANSS: 17.5 (6.2)	PANSS: 16.8 (6.6)
	Abi-Dargham et al 2009	8 (6/2)	28 (8)	6 (4/2)	28 (8)	All SZ	DSM-IV	Na	FE	all drug naive	na	na	na
Synaptic dopamine (AMPT) studies	Abi-Dargham et al 2000	18 (11/7)	31 (8)	18 (11/7)	31 (8)	All SZ	DSM-IV	other DSM-IV axis I diagnosis, substance abuse or dependence, severe medical conditions	na	8 naïve, 10 free for 139 days (mean)	PANSS: FE: 71 (12) Chronic: 63 (11)	PANSS: 18.2 (6)	PANSS: 13.8 (5.4)
	Kegeles et al 2010	18 (13/5)	29 (7)	18 (13/5)	29 (8)	All SZ	DSM-IV	weight <50kg or> 115kg, other DSM-IV axis I diagnosis, substance abuse or dependence, severe medical conditions	na	6 naive, 4 free for ≥1 year, 8 free for ≥20 days	PANSS: 78.6 (20.6)	PANSS: 21.7 (7.1)	PANSS: 17.1 (5.9)

[1]SZ=schizophrenia, SZD=schizo-affective disorder

[2]merged patient sample including antipsychotic untreated and treated patients

[3]no significant difference between number of smokers in healthy and patients group

[4]includes all subjects from Laruelle et al. (1996), Abi-Dargahm et al. (1998) and 10 new subjects

[5]The AMPT data for these subjects is reported in Abi-Dargham et al. (2000)

AMPT=alpha-methyl-*para*-tyrosine, PANSS=Positive And Negative Syndrome Scale, FE=first episode of psychosis, BPRS=Brief Psychiatric

Rating Scale, CASH=Comprehensive Assessment of Symptoms and History , Chronic=multiple episode of psychosis, DSM=Diagnostic and Statistical Manual

eTable 3. Methodological characteristics of the studies of dopamine transporter availability

Author	PET Tracer	Radiotracer delivery	Scanner Type	Resolution (FWHM mm)	Outcome Measure	Reference region
Arakawa et al 2009[19]	[^{11}C]PE2I	bolus	ECAT EXACT HR+	Na	BP_{ND}	Cerebellum
Hisao et al 2003[20]	[^{99m}Tc]TRODAT-1	bolus	Siemens Multi-SPECT 3	Na	BP_{ND}	occipital cortex
Laakso et al 2000[21]	[^{18}F]CFT	bolus	ECAT 931/08-12(CTI)	Na	BP_{ND}	Cerebellum
Lavalaye et al 2001[22]	[^{18}F]CFT	bolus	ECAT 931/08-12(CTI)	Na	BP_{ND}	Cerebellum
Laruelle et al 2000[23]	[^{123}I]β-CIT	bolus	Picker PRISM 3000	9-11	BP_{ND}+1	occipital cortex
Lavalaye et al 2001[22]	[^{123}I]FP-CIT	bolus	Na	7.6	BP_{ND}	occipital cortex
Mateos et al 2005[24]	[^{123}I]FP-CIT	bolus	Helix, G.E.M.S.	10	BP_{ND}+1	occipital cortex
Mateos et al 2007[25]	[^{123}I]FP-CIT	bolus	Helix, G.E.M.S.	10	BP_{ND}+1	occipital cortex
Yang et al 2004[26]	[^{99m}Tc]TRODAT-1	bolus	GE Sigma CV-I	Na	BP_{ND}+1	cerebellum
Yoder et al 2004[27]	[^{11}C]β-CFT	bolus	Siemens ECAT 951R, EXACT HR+ (CTI)	Na	BP_{ND}	cerebellum
Schmitt et al 2008[28]	[^{99m}Tc]TRODAT-1	bolus	Picker PRISM 3000	Na	BP_{ND}	cerebellum

eTable 4. Subject characteristics of the studies of dopamine transporter availability

Authors	Controls		Patients									
	N (m/f)	Age mean (sd)/yr	N (m/f)	Age mean (sd)/yr	Diagn-osis [1]	Diagnostic inclusion criteria	Exclusion Criteria	Illness duration	Antipsychotic treatment	Total symptom score (mean [sd])	Positive symptom score (mean [sd])	Negative symptom score (mean [sd])
Arakawa et al 2009	12 (10/2)	33.2 (12.0)	8 (6/2)	36.5 (9.5)	All SZ	DSM-IV	substance abuse, brain disease or epilepsy	32.1 months	6 naïve, 2 free for >6 months	PANSS: 77.8 (18.8)	PANSS: 17.8 (4.8)	PANSS: 18.9 (6.5)
Hisao et al 2003	12 (2/10)	29.8 (8.6)	12 (2/10)	25.9 (7.7)	All SZ	DSM-IV	age <16 or >45 years old, other DSM-IV axis I diagnosis, substance abuse or dependence, severe medical conditions	0.8 years	12 naïve	na	na	Na
Laakso et al 2000	9 (6/3)	29.9 (5.6)	9 (6/3)	30.1 (7.0)	All SZ	DSM-III-R	Na	9 months	9 naïve	na	na	Na
Lavalaye et al 2001	8 (na)	35.3 (5.7)	8 (na)	37.1 (5.7)	All SZ	DSM-IV	Na	119 months	All on AP Tx.	na	na	Na
Laruelle et al 2000	22 (20/2)	39.0 (8.0)	24 (22/2)	41.0 (8.0)	All SZ	DSM-IV	age <18 or >55 years old, other DSM-IV axis I diagnosis, substance abuse or dependence, severe medical conditions	15 years	8 free for mean (sd)=18 (11) days, 16 on AP Tx.	na	na	Na
Lavalaye et al 2001	10 (7/3)	20.3 (0.5)	10 (9/1)	22.1 (3.7)	9 SZ, 1 SZD	DSM-IV	Na	33.5 months	10 naïve	na	PANSS: 22.8 (3.8)	PANSS: 18.9 (6.7)
Mateos et al 2005	10 (6/4)	27.0 (4.3)	20 (14/6)	26.0 (4.8)	All SZ	DSM-IV	CNS medications, CNS disorder, bipolar disorder, substance dependence	4.5 months	All on AP Tx.*	na	PANSS: 27.8(5.3)[#] 27.4(4.5)[$]	PANSS: 25.8 (4.3)[#] 24.4 (7.3)[$]
Mateos et al 2007	15 (8/7)	29.0 (7.0)	20 (14/6)	26.0 (5.0)	All SZ	DSM-IV	CNS medication, CNS disorder, bipolar disorder, substance dependence, positive drug screen (except for cannabis)	4 months	20 naïve*	na	PANSS: 28.25(9.43)[#] 30.75(3.84)[$]	PANSS: 22.63(6.50)[#] 24.17(8.71)[$]
Yang et al 2004	12 (9/3)	33.3 (12.9)	11 (6/5)	26.3 (10.2)	All SZ	DSM-IV	any medical or CNS diseases/head injury, antipsychotic, ECT, or lithium treatment, substance dependence	1.3 years	11 naïve	PANSS: 63.8 (10.8)	na	Na
Yoder et al 2004	10 (7/3)	45.0 (18.3)	10 (8/2)	40.5 (na)	All SZ	DSM-IV	Na	na	1 naïve, 1 free for 1 month, 8 on AP Tx	na	na	Na
Schmitt et al 2008	12 (9/3)	30.5 (7.98)	20 (18/2)	29.3 (6.51)	All SZ	DSM-IV/ICD-10	neuroleptic or antidepressant treatment, alcohol or illegal drug abuse, CNS comorbidity	na	20 naïve	na	PANSS: 30.65 (7.65)	PANSS: 29.50 (6.45)

SZD=schizo-affective disorder, CNS=central nervous system; *Patients were grouped by whether they showed antipsychotic-induced parkinsonism (#) or not ($) at the point of scanning or, in the case of antipsychotic naïve patients, to subsequent antipsychotic treatment

eTable 5. Methodological characteristics of the studies of dopamine receptor availability

	Author	PET Tracer	Radiotracer delivery	Scanner Type	Resolution (FWHM mm)	Outcome Measure	Reference region
Butyrophenones	Crawley et al 1986[29]	[^{76}Br]Bromospiperone	Bolus	IGE 400AT gamma camera	Na	BP_{ND}+1	Cerebellum
	Martinot et al 1990[30]	[^{76}Br]Bromospiperone	Bolus	LETI TTVO1	Na	BP_{ND}+1	Cerebellum
	Tune et al 1993[31]	[^{11}C]NMSP	Bolus	NeuroECAT PET	Na	B_{max}	Cerebellum
	Nordström et al 1995[32]	[^{11}C]NMSP	Bolus	Scanditronix PC 2048-15B	Na	B_{max}	Cerebellum
	Okubo et al 1997[33]	[^{11}C]NMSP	Bolus	PCT3600W40	Na	k_3	Cerebellum
Benzamides	Farde et al 1990[34]	[^{11}C]Raclopride	Bolus	PC-384-7B	Na	B_{max}	Cerebellum
	Hietala et al 1994[35]	[^{11}C]Raclopride	Bolus	ECAT 931/08-12	Na	B_{max}	Cerebellum
	Breier et al 1997[13]	[^{11}C]Raclopride	bolus+ infusion	GE Advance scanner	Na	BP_{ND}	Cerebellum
	Talvik et al 2006[36]	[^{11}C]Raclopride	Bolus	ECAT EXACT 47	4	BP_{ND}	Cerebellum
	Kegeles et al 2010[18]	[^{11}C]Raclopride	bolus+ infusion	ECAT EXACT HR+	4.1	BP_{ND}	Cerebellum
	Pilowsky et al 1994[37]*	[^{123}I]IBZM	Bolus	SME 810 SPECT brain scanner	7-9	BP_{ND}+1	frontal cortex
	Pedro et al 1994[38]*	[^{123}I]IBZM	Bolus	SME 810 SPECT brain scanner	na	BP_{ND}+1	frontal cortex

	Laruelle et al 1996[12]	[^{123}I]IBZM	bolus + infusion	PRISM 3000	11	BP_f	occipital cortex
	Knable et al 1997	[^{123}I]IBZM	Bolus	CERASPECT	11.5	BP_{ND}	occipital cortex
	Abi-Dargham et al 1998[14]	[^{123}I]IBZM	bolus + infusion	PRISM 3000	11	BP_f	occipital cortex
	Yang et al 2004[26]	[^{123}I]IBZM	Bolus	Na	Na	BP_{ND}+1	Cerebellum
	Corripio et al 2006[39]	[^{123}I]IBZM	Bolus	Helix, GEMS	Na	BP_{ND}+1	occipital cortex
	Abi-Dargham et al 2000[17]	[^{123}I]IBZM	bolus + infusion	PRISM 3000 XP	11	BP_{ND}	average of frontal and occipital regions
	Schmitt et al 2009[40]	[^{123}I]IBZM	Bolus	PRISM 3000 XP	Na	BP_{ND}	frontal cortex
	Kessler et al 2009[41]	[^{18}F]Fallypride	Bolus	GE Advance scanner	Na	BP_{ND}	Cerebellum
	Kegeles et al 2010[42]	[^{18}F]Fallypride	Bolus	ECAT EXACT HR+	Na	BP_{ND}	Cerebellum
Ergot derivatives	Martinot et al 1991[43]	[^{76}Br]Bromolisuride	Bolus	LETI TTVO1	Na	BP_{ND}+1	Cerebellum
	Martinot et al 1994[44]	[^{76}Br]Bromolisuride	Bolus	LETI TTVO1	na	BP_{ND}+1	Cerebellum

FWHM=full width half maximum; *there is potential subject overlap between these studies (attempts to contact the authors failed)—the meta-analysis is repeated excluding one study on www.schizoprenia.com.

eTable 6. Subject characteristics of the studies of dopamine receptor availability

Method	Authors	Controls		Patients									
		N (m/f)	Age mean (sd)/yr	N (m/f)	Age mean (sd)/yr	Diag-noses[1]	Diagnostic inclusion criteria	Exclusion Criteria	Illness duration (mean unless stated)	Antipsychotic treatment	Total symptom score (mean [sd])	Positive symptom score (mean [sd])	Negative symptom score (mean [sd])
Butyrophenones	Crawley et al 1986	13 (11/2)	41.2 (10.3)	12 (10/2)	44.3 (18.2)	11 SZ, 1 PD	na	Na	13.4 years	4 naïve, 8 free for ≥ 4 months	na	na	Na
	Martinot et al 1990	12 (na)	28.7 (10.3)	12 (12/0)	28.7 (8.7)	All SZ	DSM-III	age<18 year, female, patient unable to remain medication free for a week prior to scan	na	9 naïve, 3 free for > 1 year	na	CPRS: 42.6 (29.8)	CPRS: 57.6 (25.1)
	Tune et al 1993	17 (13/4)	39 (5.93)	25 (17/8)	34.88 (7.08)	All SZ	DSM-III-R	stroke, mental retardation, significant head trauma, seizure disorder, past ECT, stroke	8.16 years	18 naïve, 7 free for ≥ 4 months	BPRS: 47.2 (5.9)	BPRS: 13.0 (0.94)	BPRS: 7.08 (0.61) SANS: 37.79 (22.66)
	Nordström et al 1995	7 (7/0)	27.7 (6.8)	7 (5/2)	28.4 (5.7)	4 SZ, 3 SZD	DSM-III-R	physically healthy/history of organic brain disorder, head injury, alcohol or drug abuse	≥ 2 months	7 naïve	BPRS: 33 (4)	na	Na
	Okubo et al 1997	18 (na)	27.7 (5.6)	17 (na)	27.4 (5.9)	All SZ	ICD-10	Na	≥ 4 months	10 naïve, 7 free for ≥ 2 weeks	na	na	Na
Benzamides	Farde et al 1990	20 (10/10)	27.5 (4.9)	18 (10/8)	24.2 (3.3)	All SZ	DSM-III	organic brain disorder/ head injury, drug or alcohol abuse,	Median: 10 months[#]	18 naïve	CPRS subscale: 12.0 (3.7)	na	Na
	Hietala et al 1994	10 (6/4)	26.8 (7.3)	13 (9/4)	25.2 (6.8)	All SZ	DSM-III-R	long-term intensive psychotherapy, serious somatic illness	18.7 months	13 naïve	BPRS: 51.4 (18.9)	na	Na
	Breier et al 1997	12 (9/3)	29.2 (SE:2.6)	11 (8/3)	32.4 (SE:3.0)	All SZ	DSM-IV	drug dependence or significant drug abuse, severe head trauma, significant medical condition	6.6 years	6 naïve, 5 free for ≥ 14 days	BPRS: 28.8 (7.2)	na	Na
	Pilowsky et al 1994	20 (11/9)	31.0 (7.8)	20 (11/9)	31.0 (8.5)	All SZ	DSM-III-R	primary substance use disorder, serious physical illness	36 months	17 naïve, 3 free for > 5 years	na	na	Na
	Pedro et al 1994	15 (9/6)	33 (na)	12 (6/6)	33.5 (9.7)	All SZ	DSM-III-R	primary substance use disorder, serious physical illness	4.02 years	10 naïve, 2 free for ≥ 6 months	BPRS: 56.3 (10.2)	BPRS: 22.25 (7.07)	BPRS: 8.5 (5)
	Laruelle et al 1996	15 (14/1)	41 (SE: 2)	15 (14/1)	42 (SE:2)	All SZ	DSM-IV	other DSM-IV axis I diagnosis, substance abuse or dependence, severe medical condition	14 years	1 naïve, 14 free for ≥21 days	BPRS: 37(3)	PANSS: 16.6 (1.7)	PANSS: 14.9 (1.5)

	Knable et al 1997~	16 (11/5)	28.8 (7.8)	21 (18/3)	35.8 (9.0)	19 SZ, 2 SZD	DSM-IV	Na	14.5 years	1 naïve, 20 free for mean=25.6 days~	na	na	na
	Abi-Dargham et al 1998	15 (12/3)	40 (11)	15 (12/3)	41 (9)	All SZ	DSM-IV	other DSM-IV axis I diagnosis, substance abuse or dependence, severe medical conditions	17 years	2 naïve, 13 free for ≥22 days	BPRS: 44 (11)	PANSS: 18.5 (5.1)	PANSS: 19.6 (7.0)
	Abi-Dargham et al 2000	18 (11/7)	31 (8)	18 (11/7)	31 (8)	All SZ	DSM-IV	other DSM-IV axis I diagnosis, substance abuse or dependence, severe medical conditions	na	8 naïve, 10 free for 139 days (mean)	PANSS: 71 (12) (naïve) 63 (11) (free)	na	na
	Yang et al 2004	12 (9/3)	33.26 (12.93)	11 (6/5)	26.25 (10.22)	All SZ	DSM-IV	medical/ neurological diseases, ECT, lithium treatment, alcohol or substance dependence, or head injury	1.3 years	11 naïve	PANSS: 63.8 (10.8)	na	na
	Corripio et al 2006	18 (10/8)	24.2 (4.4)	11 (6/5)	25.6 (4.5)	All SZ	DSM-IV	substance abuse, neurological disease	na	11 naïve	PANSS: 71.1(11.4)	na	na
	Talvik et al 2006	17 (13/4)	Na	18 (9/9)	28.8 (10.5)	All SZ	DSM-IV	psychiatric comorbidity, head injury, drug addiction	≥ 1 year	18 naïve	PANSS: 80.4 (20.9)	PANSS: 21.9 (4.6)	PANSS: 20.1(9.6)
	Schmitt et al 2009	10 (5/5)	32.4 (12.73)	23 (19/4)	28.2 (6.23)	19 SZ, 2 SZD, 2 BP	DSM-IV/ICD-10	na	na	23 naïve	BPRS: 73.6 (na)	PANSS: 29.1 (na)	PANSS: 29.1 (na)
	Kessler et al 2009	11 (5/6)	31.6 (9.2)	11 (6/5)	30.5 (8.0)	All SZ	DSM-IV	significant medical conditions, substance abuse	na	4 naïve, 7 free for ≥ 3 weeks	BPRS (6 item scale): 28.8 (7.0)	SAPS: 9.8 (3.1)	SANS: 9.4 (4.0)
	Kegeles et al 2010	18 (13/5)	29 (7)	18 (13/5)	29 (8)	All SZ	DSM-IV	weight <50kg or> 115kg, other DSM-IV axis I diagnosis, substance abuse or dependence, severe medical conditions	na	6 naïve, 12 free for ≥ 20 days	PANSS: 78.61 (20.63)	PANSS: 21.72 (7.12)	PANSS: 17.17 (5.99)
	Kegeles et al 2010	22 (17/5)	26 (6)	21 (14/7)	31 (12)	All SZ	DSM-IV	medical illness, other DSM-IV Axis I diagnosis, substance abuse	na	5 naïve, 16 free for 191 days (mean)	PANSS: 64 (15)	na	na
Ergot derivatives	Martinot et al 1991	14 (14/0)	23 (4)	19 (12/7)	Men: 22(4) Female: 24(6)	All SZ	DSM-III	age <18 years old, schizophrenic disorder, unable to remain medication free for 1 week before scan	na	10 naive, 9 free for ≥ 6 months	na	na	na
	Martinot et al 1994	10 (na)	21 (2)	10 (na)	20 (2)	All SZ	DSM-III-R:undifferentiated/disorganised sub-types, SANS score>55	Age<18 or >25 years old, marked positive symptoms, lifetime neuroleptic exposure >1 month, unable to remain medication free for 1 week before scan	na	8 naïve, 2 free for ≥ 4 months	na	SAPS: 19.1 (13.8)	SANS: 87.2 (14.2)

PD: Psychotic depression; SZD: Schizo-affective disorder; BP: Brief Psychotic disorder; CPRS: Comprehensive Psychopathological Rating Scale; BPRS: Brief Psychiatric Rating Scale; PANSS: Positive And Negative Syndrome Scale; SAPS: Scale for the Assessment of Positive Symptoms; SANS: Scale for the Assessment of Negative Symptoms; ECT=electro-convulsive therapy

#=mean duration of illness was 1.9 years including the prodrome to the first psychotic episode, range: 1-72 months[45]; ~excluded from the main analysis because the antipsychotic wash-out 7 days in some patients

eReferences for eTable 6:

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