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The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S. Arch Gen Psychiatry. 2012 Aug;69(8):776-86.

Supplementary tables 1-6.

Supplementary table 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
pet dopamine (AMPT)	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

The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S. Arch Gen Psychiatry. 2012 Aug;69(8):776-86.

Supplementary tables 1-6.

	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

Supplementary table 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	15 (15/0)	37.3 (6.4)	8	37.3 (6.3)	All SZ	DSM-IV	psychoactive	na	3 naive, 6 free for	PANSS:	PANSS:	PANSS:

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Supplementary tables 1-6.

	2007			(8/0)				medication		≥6 months	80.2 (4.7)	15.4 (3.5)	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	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)

The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S. Arch Gen Psychiatry. 2012 Aug;69(8):776-86.

Supplementary tables 1-6.

								dependence, severe medical conditions					

[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

The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S. Arch Gen Psychiatry. 2012 Aug;69(8):776-86.

Supplementary tables 1-6.

Supplementary table 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

The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S. Arch Gen Psychiatry. 2012 Aug;69(8):776-86.

Supplementary tables 1-6.

Supplementary table 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	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	na	20 naïve	na	PANSS: 30.65 (7.65)	PANSS: 29.50 (6.45)

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Supplementary tables 1-6.

2008							abuse, CNS comorbidity					

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

Supplementary table 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+	ECAT EXACT HR+	4.1	BP_{ND}	Cerebellum

The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S. Arch Gen Psychiatry. 2012 Aug;69(8):776-86.

Supplementary tables 1-6.

			infusion				
	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

The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S. Arch Gen Psychiatry. 2012 Aug;69(8):776-86.

Supplementary tables 1-6.

Supplementary table 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	14 years	1 naïve, 14 free for ≥21 days	BPRS: 37(3)	PANSS: 16.6 (1.7)	PANSS: 14.9 (1.5)

The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S. Arch Gen Psychiatry. 2012 Aug;69(8):776-86.

Supplementary tables 1-6.

								or dependence, severe medical condition					
	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:undiffer-	Age<18 or >25 years old, marked positive symptoms,	na	8 naïve, 2 free for ≥ 4 months	na	SAPS: 19.1 (13.8)	SANS: 87.2 (14.2)

The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S. Arch Gen Psychiatry. 2012 Aug;69(8):776-86.

Supplementary tables 1-6.

							entiated/di-sorganised sub-types, SANS score>55	lifetime neuroleptic exposure >1 month, unable to remain medication free for 1 week before scan					

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

References:

1. Reith, J.*, et al.* Elevated dopa decarboxylase activity in living brain of patients with psychosis. *Proc.Natl.Acad.Sci U.S.A* **91**, 11651-11654 (1994).
2. Hietala, J.*, et al.* Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. *Lancet* **346**, 1130-1131 (1995).
3. Dao-Castellana, M.H.*, et al.* Presynaptic dopaminergic function in the striatum of schizophrenic patients. *Schizophr.Res* **23**, 167-174 (1997).
4. Hietala, J.*, et al.* Depressive symptoms and presynaptic dopamine function in neuroleptic-naive schizophrenia. *Schizophr.Res* **35**, 41-50 (1999).
5. Lindstrom, L.H.*, et al.* Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(beta-11C) DOPA and PET. *Biol.Psychiatry* **46**, 681-688 (1999).
6. Elkashef, A.M.*, et al.* 6-(18)F-DOPA PET study in patients with schizophrenia. Positron emission tomography. *Psychiatry Res* **100**, 1-11 (2000).
7. Meyer-Lindenberg, A.*, et al.* Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. *Nat.Neurosci.* **5**, 267-271 (2002).
8. McGowan, S., Lawrence, A.D., Sales, T., Quested, D. & Grasby, P. Presynaptic dopaminergic dysfunction in schizophrenia: a positron emission tomographic [18F]fluorodopa study. *Arch.Gen.Psychiatry* **61**, 134-142 (2004).
9. Kumakura, Y.*, et al.* Elevated [18F]fluorodopamine turnover in brain of patients with schizophrenia: an [18F]fluorodopa/positron emission tomography study. *J Neurosci.* **27**, 8080-8087 (2007).
10. Nozaki, S.*, et al.* Regional dopamine synthesis in patients with schizophrenia using L-[beta-(11)C]DOPA PET. *Schizophr.Res* **108**, 78-84 (2009).
11. Howes, O.D.*, et al.* Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Arch Gen Psychiatry* **66**, 13-20 (2009).
12. Laruelle, M.*, et al.* Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc Natl Acad Sci U S A* **93**, 9235-9240 (1996).
13. Breier, A.*, et al.* Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. *Proc.Natl.Acad.Sci U.S.A* **94**, 2569-2574 (1997).
14. Abi-Dargham, A.*, et al.* Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am J Psychiatry* **155**, 761-767 (1998).

The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S. Arch Gen Psychiatry. 2012 Aug;69(8):776-86.

Supplementary tables 1-6.

15. Laruelle, M., Abi-Dargham, A., Gil, R., Kegeles, L. & Innis, R. Increased dopamine transmission in schizophrenia: relationship to illness phases. *Biol Psychiatry* **46**, 56-72 (1999).
16. Abi-Dargham, A., Giessen, E.V., Slifstein, M., Kegeles, L.S. & Laruelle, M. Baseline and Amphetamine-Stimulated Dopamine Activity Are Related in Drug-Naive Schizophrenic Subjects. *Biol.Psychiatry* (2009).
17. Abi-Dargham, A*., et al.* Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc Natl Acad Sci U S A* **97**, 8104-8109 (2000).
18. Kegeles, L.S*., et al.* Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. *Archives of general psychiatry* **67**, 231-239 (2010).
19. Arakawa, R*., et al.* Increase in thalamic binding of [(11)C]PE2I in patients with schizophrenia: a positron emission tomography study of dopamine transporter. *Journal of psychiatric research* **43**, 1219-1223 (2009).
20. Hsiao, M.C., Lin, K.J., Liu, C.Y., Tzen, K.Y. & Yen, T.C. Dopamine transporter change in drug-naive schizophrenia: an imaging study with 99mTc-TRODAT-1. *Schizophrenia research* **65**, 39-46 (2003).
21. Laakso, A*., et al.* Striatal dopamine transporter binding in neuroleptic-naive patients with schizophrenia studied with positron emission tomography. *The American journal of psychiatry* **157**, 269-271 (2000).
22. Lavalaye, J*., et al.* Dopamine transporter density in young patients with schizophrenia assessed with [123]FP-CIT SPECT. *Schizophrenia research* **47**, 59-67 (2001).
23. Laruelle, M*., et al.* Dopamine and serotonin transporters in patients with schizophrenia: an imaging study with [(123)I]beta-CIT. *Biological psychiatry* **47**, 371-379 (2000).
24. Mateos, J.J*., et al.* Decreased striatal dopamine transporter binding assessed with [123I] FP-CIT in first-episode schizophrenic patients with and without short-term antipsychotic-induced parkinsonism. *Psychopharmacology* **181**, 401-406 (2005).
25. Mateos, J.J*., et al.* Lower striatal dopamine transporter binding in neuroleptic-naive schizophrenic patients is not related to antipsychotic treatment but it suggests an illness trait. *Psychopharmacology* **191**, 805-811 (2007).
26. Yang, Y.K*., et al.* Associated alterations of striatal dopamine D2/D3 receptor and transporter binding in drug-naive patients with schizophrenia: a dual-isotope SPECT study. *The American journal of psychiatry* **161**, 1496-1498 (2004).
27. Yoder, K.K*., et al.* Dopamine transporter density in schizophrenic subjects with and without tardive dyskinesia. *Schizophrenia research* **71**, 371-375 (2004).
28. Schmitt, G.J*., et al.* Dual-isotope SPECT imaging of striatal dopamine: first episode, drug naive schizophrenic patients. *Schizophrenia research* **101**, 133-141 (2008).
29. Crawley, J.C*., et al.* Uptake of 77Br-spiperone in the striata of schizophrenic patients and controls. *Nucl.Med.Commun.* **7**, 599-607 (1986).
30. Martinot, J.L*., et al.* Striatal D2 dopaminergic receptors assessed with positron emission tomography and [76Br]bromospiperone in untreated schizophrenic patients. *The American journal of psychiatry* **147**, 44-50 (1990).

The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S. Arch Gen Psychiatry. 2012 Aug;69(8):776-86.

Supplementary tables 1-6.

31. Tune, L.E.*, et al.* Dopamine D2 receptor density estimates in schizophrenia: a positron emission tomography study with 11C-N-methylspiperone. *Psychiatry Res.* **49**, 219-237 (1993).
32. Nordstrom, A.L., Farde, L., Eriksson, L. & Halldin, C. No elevated D2 dopamine receptors in neuroleptic-naive schizophrenic patients revealed by positron emission tomography and [11C]N-methylspiperone. *Psychiatry Res.* **61**, 67-83 (1995).
33. Okubo, Y.*, et al.* Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. *Nature* **385**, 634-636 (1997).
34. Farde, L.*, et al.* D2 dopamine receptors in neuroleptic-naive schizophrenic patients. A positron emission tomography study with [11C]raclopride. *Arch.Gen.Psychiatry* **47**, 213-219 (1990).
35. Hietala, J.*, et al.* Striatal D2 dopamine receptor characteristics in neuroleptic-naive schizophrenic patients studied with positron emission tomography. *Arch.Gen.Psychiatry* **51**, 116-123 (1994).
36. Talvik, M.*, et al.* Dopamine D2 receptor binding in drug-naive patients with schizophrenia examined with raclopride-C11 and positron emission tomography. *Psychiatry Res.* **148**, 165-173 (2006).
37. Pilowsky, L.S.*, et al.* D2 dopamine receptor binding in the basal ganglia of antipsychotic-free schizophrenic patients. An 123I-IBZM single photon emission computerised tomography study. *Br.J.Psychiatry* **164**, 16-26 (1994).
38. Pedro, B.M.*, et al.* Stereotypy, schizophrenia and dopamine D2 receptor binding in the basal ganglia. *Psychological medicine* **24**, 423-429 (1994).
39. Corripio, I.*, et al.* Striatal D2 receptor binding as a marker of prognosis and outcome in untreated first-episode psychosis. *Neuroimage.* **29**, 662-666 (2006).
40. Schmitt, G.J.*, et al.* Increase of striatal dopamine transmission in first episode drug-naive schizophrenic patients as demonstrated by [(123)I]IBZM SPECT. *Psychiatry research* **173**, 183-189 (2009).
41. Kessler, R.M.*, et al.* Dopamine D2 receptor levels in striatum, thalamus, substantia nigra, limbic regions, and cortex in schizophrenic subjects. *Biol.Psychiatry* **65**, 1024-1031 (2009).
42. Kegeles, L.S.*, et al.* Striatal and extrastriatal dopamine D2/D3 receptors in schizophrenia evaluated with [18F]fallypride positron emission tomography. *Biological psychiatry* **68**, 634-641 (2010).
43. Martinot, J.L.*, et al.* The estimated density of D2 striatal receptors in schizophrenia. A study with positron emission tomography and 76Br-bromolisuride. *The British journal of psychiatry : the journal of mental science* **158**, 346-350 (1991).
44. Martinot, J.L.*, et al.* Central D2 receptors and negative symptoms of schizophrenia. *The British journal of psychiatry : the journal of mental science* **164**, 27-34 (1994).
45. Andreasen, N.C.*, et al.* Workshop on schizophrenia, PET, and dopamine D2 receptors in the human neostriatum. *Schizophrenia bulletin* **14**, 471-484 (1988).