

D₂ Dopamine Receptor Binding in the Basal Ganglia of Antipsychotic-Free Schizophrenic Patients

An ¹²³I-IBZM Single Photon Emission Computerised Tomography Study

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We used SPECT to examine striatal D₂ receptor binding in 20 antipsychotic-free DSM-III-R schizophrenic patients and 20 age- and sex-matched normal controls. Dynamic single-slice SPECT, at a slice chosen to include the basal ganglia, began immediately following intravenous injection of 185 MBq of ¹²³I-IBZM. A semiquantitative approach was used to generate indices of specific D₂ receptor binding in the basal ganglia. There was no overall elevation of D₂ receptor binding between patients and controls. A male sex-specific left lateralised asymmetry of striatal D₂ receptor binding was found in the patient group. Age-dependent decline of striatal D₂ receptors was confirmed in controls, but not in patients. These results suggest that alterations in striatal D₂ receptor distribution and density do occur in schizophrenia, and possibly reflect wider disruptions in prefrontal–striatal–limbic circuits.

It has long been proposed that dopaminergic overactivity could be the substrate for psychotic symptoms (Crow, 1980). Pharmacological studies implicate a role for post-synaptic D₂ receptors in the pathophysiology of schizophrenia. *In vitro* studies of striatal D₂ binding have directly correlated D₂ receptor blockade and clinical antipsychotic potency (Creese *et al.*, 1976; Seeman *et al.*, 1976; Peroutka & Snyder, 1980). *In vivo* studies of schizophrenic patients showed that ten chemically distinct classes of antipsychotics produced 65–85% striatal D₂ receptor occupancy (Farde *et al.*, 1989). A double-blind, placebo-controlled study of the α - and β -isomers of flupenthixol showed clinical antipsychotic efficacy only for the β -isomer, 1000 times more potent at the D₂ receptor site than the α -isomer (Johnstone *et al.*, 1978).

Post-mortem evidence is more controversial. Although increases in striatal D₂ receptor density and sensitivity in antipsychotic-treated, and some untreated, schizophrenic patients have been reported, it is unclear whether these increases are an artefact of chronic neuroleptic treatment (Owen *et al.*, 1978; Clow *et al.*, 1980; Lee & Seeman, 1980; Mackay *et al.*, 1982). Neurochemical asymmetry of striatal D₂ receptors has also been described post-mortem; Reynolds *et al.* (1987) found a mean 19% increase in D₂ receptor binding in the right putamen of 16 antipsychotic-treated schizophrenic patients compared with 11 controls. An increase in dopamine concentrations in the left amygdala was previously demonstrated in a series of 19 treated patients (Reynolds, 1983).

Positron emission tomography (PET) and single photon emission computerised tomography (SPECT)

now permit corroboration of necropsy findings and pharmacological studies, by mapping activity from radiolabelled ligands specific for the D₂ receptor in the living brain. Crawley *et al.* (1986) first reported an 11% elevation of D₂ receptor density in 12 antipsychotic-free schizophrenic patients with ⁷⁷Br-spiperone SPECT, and a single fixed gamma camera. Similarly, the Johns Hopkins PET group found clear-cut elevation of D₂ receptors in the basal ganglia in samples of 10, 18 and 23 never-medicated schizophrenic patients using ¹¹C-N-methylspiperone (NMSP) (Wong *et al.*, 1986, 1989; Tune *et al.*, 1992). However, contradictory findings were reported by other groups. Farde *et al.* (1990) found no elevation in D₂ receptors in a PET study of 18 never-medicated patients and 20 healthy controls with the highly specific D₂ ligand, ¹¹C-raclopride. Their finding was substantiated by two smaller PET studies, employing similar methodology and ⁷⁶Br-labelled ligands, bromospiperone and bromolisuride, in samples of nine and ten never-medicated patients respectively (Martinot *et al.*, 1990, 1991).

Subtle disturbances of D₂ receptor status have also been characterised *in vivo*. Farde *et al.* (1990) found that significant left-lateralised asymmetry of striatal D₂ receptor binding occurred in schizophrenic patients (asymmetry was not assessed by other PET groups) and Martinot *et al.* (1991) showed a linear decline in D₂ receptor density with age in controls but not in patients.

In view of these conflicting results, the hypothesis that an *in vivo* elevation of striatal D₂ receptor binding is a fundamental abnormality in schizophrenia,

remains unproven. Clarifying these anomalies is of crucial importance in helping to provide markers for the disease, in understanding its pathogenesis and in assisting in the design of novel antipsychotic drugs.

We therefore used the selective D₂ receptor ligand ¹²³I-iodobenzamide (IBZM) and SPECT to estimate and compare striatal D₂ receptor binding in 20 schizophrenic patients (17 never-medicated and 3 antipsychotic-free (for >5 years)) and 20 normal controls.

Method

Ethical permission for the study and permission to administer radioactive substances was obtained from the local hospital ethics committee and the Administration of Radioactive Substances Advisory Committee.

Initially, 25 patients were recruited for the study from the Maudsley Hospital, which is located in an inner-city area assessing and treating local and national psychiatric referrals. Of these patients, 14 (70%) were from the emergency clinic (self- or police referral), 3 (15%) came via national tertiary referral (from other psychiatric hospitals) and 3 (15%) by direct referral to the research group from other hospital clinics.

The DSM-III-R criteria (American Psychiatric Association, 1987) for a diagnosis of schizophrenia had to be fulfilled. In addition, patients had either never taken antipsychotic medication or had received no such treatment for at least six months before entry into the study. Diagnosis and evidence of treatment was established by the following:

- clinical interview by a trained psychiatrist (LP)
- interview with independent witnesses (family practitioner, relatives, friends, employers)
- detailed assessment by an independent multi-disciplinary clinical team.

Patient follow-up was for a minimum of six months. Illness duration was defined as the length of illness prior to the scanning date by the criterion of first onset of positive or negative psychotic symptoms that could be independently corroborated. Patients also had to be able to give informed consent for a scan and be safe and co-operative for scanning procedures.

Exclusion criteria were the following: evidence of primary substance use disorder or chronic use of psychoactive substances clearly associated with psychotic episodes; concomitant serious physical illness.

When the above criteria were applied, one patient was excluded due to loss of follow-up information (so DSM-III-R criteria could not be met) and two patients were excluded due to evidence of substance use disorder. Two never-medicated schizophrenic patients were excluded from the main analysis due to scanner gantry malfunction during their scans. Thus, the final sample consisted of 20 antipsychotic-free patients (17 never-medicated and 3 antipsychotic-free >5 years). Their clinical characteristics are summarised in Table 1.

Twenty-two healthy controls matched for age, sex, and handedness were recruited from the community. Controls

Table 1
Clinical data

Patients	DSM-III-R subtype	24-item BPRS ¹ score	Illness duration
1	Paranoid	46	12 months
2	Paranoid	69	3 months
3	Undifferentiated	62	2 months
4	Disorganised	55	12 months
5	Catatonic	67	6 months
6	Disorganised	69	6 months
7	Paranoid	77	3 years
8	Undifferentiated	61	10 months
9 ²	Paranoid	31	8 years
10 ²	Paranoid	54	12 years
11 ²	Undifferentiated	53	11 years
12	Disorganised	62	12 months
13	Paranoid	59	16 months
14	Disorganised	69	3 years
15	Paranoid	61	5 months
16	Schizophreniform	61	>3 months
17	Undifferentiated	53	2 years
18	Paranoid	72	2 years
19	Paranoid	61	3 years
20	Paranoid	57	3 years
Mean	-	60	36 months

- Brief Psychiatric Rating Scale (Overall & Gorham, 1962).
- No antipsychotic for >5 years.

completed a general screening questionnaire, a checklist on drug and alcohol use and the Annett scale for handedness (Annett, 1970). Those with a history of, or current, serious mental or physical illness, or substance use disorder were excluded from the study. Two controls were excluded due to malpositioning during the scan. Thus the final sample was 20 healthy controls.

Symptom ratings

Presence and severity of psychotic symptoms were rated with the 24-item Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) within 72 hours of scanning. Other ratings were handedness by the Annett scale (Annett, 1970); drug and alcohol use by a checklist (including DSM-III-R criteria for substance abuse or dependence); pre-morbid IQ by the National Adult Reading Test (Nelson, 1982) and a verbal fluency task.

¹²³I IBZM SPECT

The scanning protocol has been described elsewhere (Costa *et al*, 1990; Verhoeff *et al*, 1990; Pilowsky *et al*, 1992a). Images were acquired with an SME 810 SPECT brain scanner. This is a high-resolution, multidetector single-slice scanner, which permits the study of radiopharmaceutical changes within a chosen slice over time. The in-plane spatial resolution is 7–9 mm full width at half maximum, with an average slice thickness of 12.5 mm. Scanning took place at a level chosen to include the basal ganglia (BG: head of caudate and putamen), 30 mm above the orbitomeatal plane.

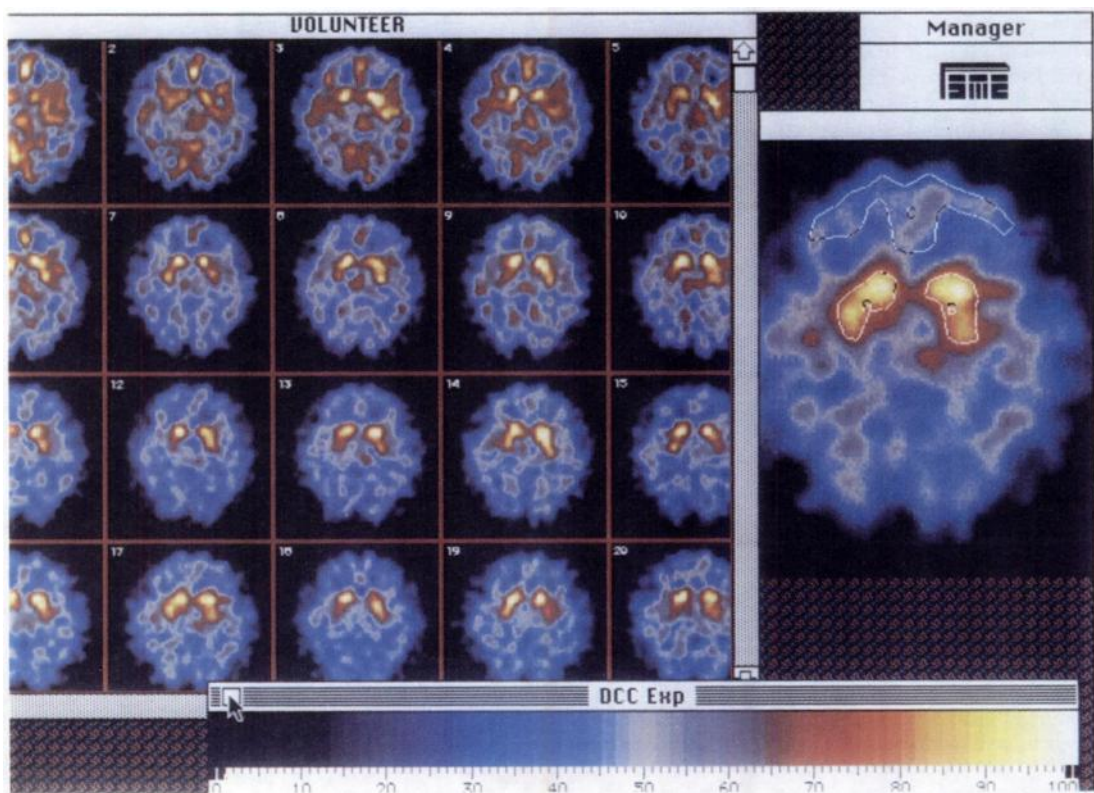


Fig. 1 A typical control scan showing concentration of radioactivity in the basal ganglia, with washout of activity from the frontal cortex over time. Regions of interest are shown (enlarged scan, right) for slice 17 (bottom left) (85 minutes after injection) over the frontal cortex and basal ganglia at 50% and 75% isocontours respectively.

Continuous single-slice data acquisition began immediately after intravenous injection of 185 MBq ^{123}I -IBZM (specific activity 104–259 GBq/ μmol) flushed with 20 ml normal saline. Following injection the intravenous cannula was withdrawn. Head position was monitored constantly throughout the scan. If movement was detected, the slice was excluded from analysis. Acquisition time per slice was five minutes. All subjects were scanned for at least 80–100 minutes, providing 16–20 data points on the time-activity curve per subject. Figure 1 shows a typical control scan.

To minimise interobserver variation, scans were analysed blind to diagnostic status by the same rater (LP). A standardised isocontour approach was employed, with the aid of semi-automated contour-finding software (SME 810 version 2.51). For each scan, irregular regions of interest were drawn around the frontal cortex at the 50% radioactivity isocontour and around each of the left and right basal ganglia at the 75% radioactivity isocontour (clearly outlining the striata).

Regions were initially drawn on the slice best visualising each structure (at 15 minutes after injection for the frontal

cortex and at 80 minutes after injection for the striata (Fig. 1)). The 'templates' for regions of interest (ROIs) thus defined were applied unchanged to each slice of the subject's scan, and the radioactive density within each region was calculated (giving mean density in counts/pixel).

Over 90% agreement has been obtained between independent raters for semiquantitative measures generated by this method (Verhoeff *et al*, 1990). This image-analysis technique also corrects for interindividual differences in spatial relationships of cerebral landmarks. There was no significant difference in the areas of basal ganglia ROIs between the patient and control groups or between right and left sides within subjects, and ROI area was not correlated with mean density within the ROI in either group.

Data analysis

Labelled IBZM binds stereoselectively and reversibly to central D_2 receptors (Kung *et al*, 1989) and is almost entirely broken down to polar metabolites which do not

re-enter the brain and compete for D₂ receptor binding. Areas rich in D₂ receptors (where specific binding predominates; e.g. striatum) take a relatively long time to reach peak uptake and show slow washout of the ligand. Areas with few or no D₂ receptors (i.e. where binding is mainly non-specific; e.g. frontal cortex (FC)) show rapid uptake and rapid washout of the ligand. Activity in these regions measured serially over time with a dynamic single-slice scanning protocol may then be expressed on a time-activity saturation curve. During the first period of acquisition (approximately 0–40 minutes after injection) relatively little specific binding occurs, and what is seen is the distribution of tracer proportional to cerebral blood flow. Over the latter portion of the curve (60–100 minutes after injection) this component decreases and detected activity is predominantly specific or non-specific binding of ¹²³I-IBZM.

Semiquantitative estimation of the saturable component of D₂ binding was performed over the 60–80 minutes after injection. This component is obtained by the mean ratio or difference between the BG and FC signal. Analysis of the time-activity curves was according to the method of Matthews *et al* (1990), which validates the mean of several points on a serial-measurements curve for significance over a time of interest. Primate and human studies with ¹²³I-IBZM SPECT have demonstrated that plateau between uptake and washout (i.e. equilibrium and, therefore, peak specific binding) occurs within 60–100 minutes (Kung *et al*, 1989; Costa *et al*, 1990). The frontal cortex is an appropriate reference region for non-specific binding as D₂ receptor numbers are negligible in this region and of the same order

as those present in the cerebellum (Farde *et al*, 1988; Camps *et al*, 1989; Brucke *et al*, 1991).

Semiquantitative estimation of D₂ receptor availability for ¹²³I-IBZM binding was performed on the decay-corrected time-activity curves at maximum stable plateau between tracer uptake and washout (60–100 minutes after injection) (Kung *et al*, 1989; Alavi *et al*, 1989). The assumptions underlying the method have been outlined in a previous paper (Pilowsky *et al*, 1992a) and are briefly that, during plateau

- (a) basal ganglia density (BG) = estimate of total binding = specific + non-specific binding + free ligand
- (b) frontal cortex density (FC) = estimate of background activity = non-specific binding + free ligand.

Two indices of the saturable component of D₂ binding (an *in vivo* approximation to specific binding) in each subject were obtained: first, the ratio index

mean BG : FC ratio over 60–80 minutes after injection which corrects for interscan differences in instrumentation, filter setting and attenuation correction, and secondly, the subtraction index

mean [(BG – FC)/FC] × 100 over 60–80 minutes after injection

which addresses interindividual variations in percentage injected dose by normalising the measure and expressing it as a percentage of background activity.

The same results were obtained by both ratio and subtraction indices of specific D₂ binding. An index of relative left laterality in striatal D₂ binding was obtained in each subject by subtracting the right specific binding index from the left.

Table 2
Demographic and binding data

Patients				Controls			
Age: years	Sex	Specific binding indices		Age: years	Sex	Specific binding indices	
		Right striatum	Left striatum			Right striatum	Left striatum
34	M	62.8	71.3	42	M	57.8	66.8
34	F	73.9	78.9	37	F	60.6	60.5
25	M	66.9	82.5	34	F	63.3	66.0
18	M	82.7	82.4	30	M	84.8	86.1
21	M	55.7	64.8	28	M	70.5	60.6
33	F	81.9	76.1	28	F	50.1	55.9
25	M	59.5	62.7	29	M	71.7	75.7
27	F	67.2	72.7	26	F	76.4	89.2
51	M	70.6	81.7	48	M	44.7	45.7
52	F	73.7	78.2	33	F	76.0	78.9
34	M	76.2	88.9	22	F	75.6	80.7
25	M	62.6	68.6	28	M	50.9	42.5
37	F	57.2	48.3	34	M	70.6	71.8
29	F	73.1	79.1	22	F	96.9	102.0
28	M	59.9	63.0	21	M	63.5	70.8
29	F	58.7	54.3	25	F	67.2	63.5
33	F	42.7	63.7	46	M	54.2	57.4
27	M	73.0	79.2	35	M	76.9	70.7
32	F	55.2	60.3	29	F	61.8	79.5
26	M	68.6	64.0	22	M	80.3	83.9
Range 18–52, median 29	11 M, 9 F	Mean 66.1, s.e. 2.2	Mean 70.9, s.e. 2.4	Range 21–48, median 29	11 M, 9 F	Mean 67.7, s.e. 2.9	Mean 70.4, s.e. 3.3

Statistics

As regards overall group effects on right and left striatal D₂ binding indices, analysis of variance (ANOVA) was used to assess differences between groups and between sides, and group-by-side interactions.

As regards laterality indices (left-minus-right striatal D₂ binding), ANOVA was used to assess differences between groups and between sexes, and group-by-sex interactions. *Post hoc* (hypothesis-testing) unpaired *t*-tests were subsequently used to compare laterality between male patients and male controls and between female patients and female controls. Confidence intervals at the 95% level (95% CI) were calculated for the mean differences in laterality for the male and female patient and control groups.

Linear regression and Pearson's correlation coefficient were used to assess the relationships within the patient group, between binding indices and total BPRS scores, negative- and positive-symptom subscale scores, and illness duration, and the relationships in both patient and control groups between age and binding indices.

Results

Demographic and binding data for patients and controls are shown in Table 2.

Mean BG:FC ratios obtained in the patient group were 1.65 (s.e. 0.027, 95% CI 1.60–1.70) and 1.71 (s.e. 0.024, 95% CI 1.65–1.75) on the right and left sides respectively. In the control group, mean ratios were 1.68 (s.e. 0.029,

Table 3
Mean left-minus-right striatal D₂ binding difference (left laterality index) for male and female patients and controls

	Males	Females
Patients	6.15 (95% CI 2.5 to 9.75) (<i>n</i> = 11)	3.11 (95% CI 2.69 to 8.91) (<i>n</i> = 9)
Controls	0.57 (95% CI -3.0 to 4.2) (<i>n</i> = 11)	5.37 (95% CI 0.97 to 9.77) (<i>n</i> = 9)

ANOVA shows case-by-sex interaction $F = 3.255$, *d.f.* = 1, $P = 0.08$.

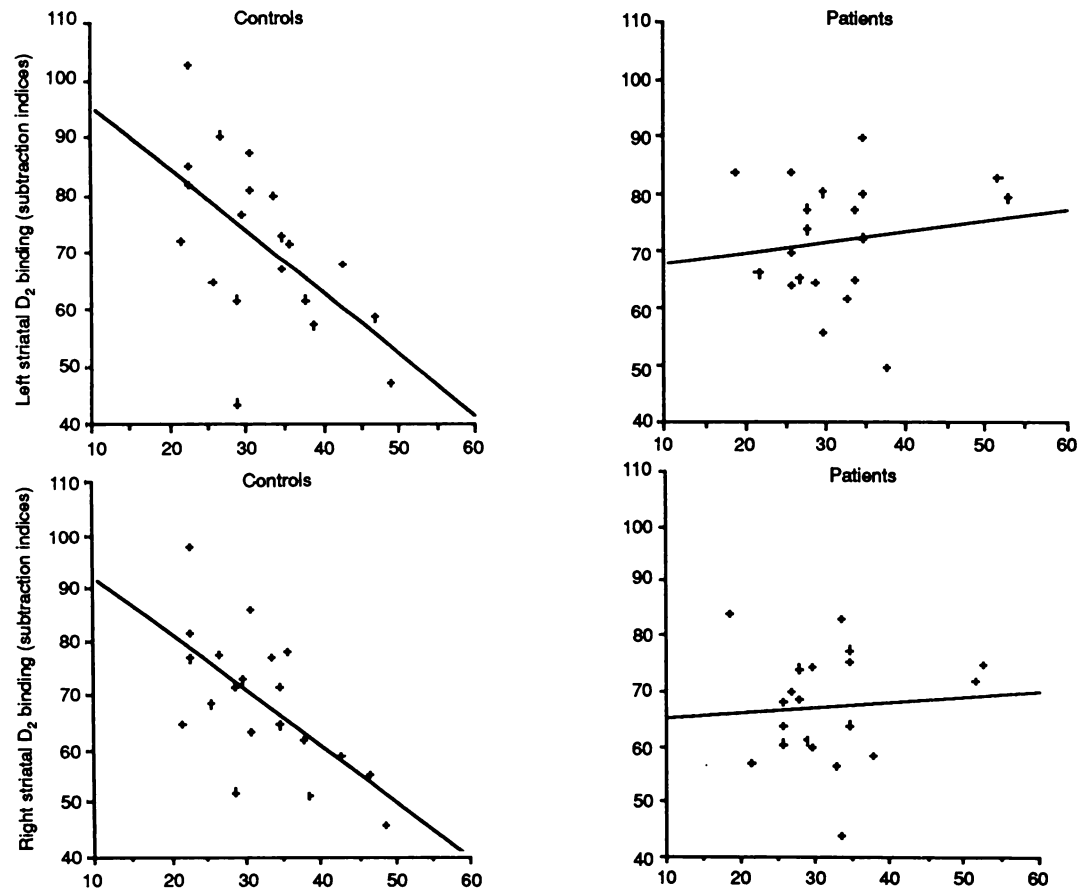


Fig. 2 Linear regression curves for binding data (subtraction indices) v. age in patients and controls in left and right striata. Regression coefficients (r^2) for the right striata 0.007 (patients) and 0.415 (controls), and for the left striata 0.022 (patients) and 0.338 (controls).

95% CI 1.62–1.74) and 1.70 (s.e. 0.033, 95% CI 1.64–1.76) on the right and left sides respectively.

Subtraction indices for patients on the right and left sides were 66.1 (s.e. 2.23, 95% CI 61.8–70.4) and 70.9 (s.e. 2.35, 95% CI 66.1–75.5), and for controls 67.7 (s.e. 2.90, 95% CI 62.0–73.3) and 70.4 (s.e. 3.27, 95% CI 64.0–74.8).

No significant differences were found between the patient and control groups on either side by either the ratio or the subtraction method.

There was no significant difference in laterality (left-minus-right binding) between the patient and control groups ($F=0.528$, NS). However, there was a significant difference in the mean left laterality index confined to males (5.57, 95% CI 0.40–10.76, $P=0.04$). ANOVA showed evidence of a case-by-sex interaction ($F=3.23$, $P=0.08$) (see Table 3): schizophrenic males showed much more laterality than their normal counterparts. There was no difference in mean left laterality indices between female patients and female controls (2.20, 95% CI –5.02 to 9.53).

No significant correlation was found between saturable D_2 binding and total BPRS score, BPRS positive- or negative-symptom subscale scores or duration of illness.

Figure 2 shows linear regression between D_2 binding data and age for the right and left striata in patients and controls. For the controls, age was negatively correlated with D_2 receptor binding in left ($r=0.561$, $P=0.01$, 95% CI –0.80 to 0.15) and right ($r=0.653$, $P=0.002$, 95% CI –0.79 to 0.11) striata. Patients did not show any correlation with age ($r=0.147$, NS, 95% CI –0.32 to 0.55 (left); $r=0.083$, NS, 95% CI –0.37 to 0.51 (right)).

Discussion

This is a study of a large number of never-medicated schizophrenic patients and controls examined with ^{123}I -IBZM SPECT. Left-sided striatal D_2 asymmetry, noted in the patient group by Farde *et al* (1990), is confirmed in this study, but is found to be specific to male patients compared with male controls (in whom there is little evidence of relative left laterality). The results verify PET studies which do not show overall elevations in striatal D_2 receptor binding in schizophrenic patients compared with controls (Farde *et al*, 1990; Martinot *et al*, 1990, 1991). In addition, we have substantiated earlier findings of a decline of striatal D_2 receptors with age in controls (Wong *et al*, 1984; Seeman *et al*, 1987; Martinot *et al*, 1991).

In the past five years, ^{123}I -IBZM SPECT has emerged as an increasingly useful tool for semi-quantitative evaluation of central D_2 receptor status. Studies have been performed in normal control groups (Alavi *et al*, 1989; Costa *et al*, 1990; Brucke *et al*, 1991; Seibyl *et al*, 1992), in differing disease states (Brucke *et al*, 1991; Costa *et al*, 1992), and following pharmacological intervention in animals (Innis *et al*, 1992) and humans (Costa *et al*, 1990; Pilowsky *et al*, 1992b; Ring *et al*, 1992). High-resolution,

brain-dedicated scanners provide images similar to those obtained by PET; and careful semiquantification with appropriate instrumentation, image analysis, comparison groups and research paradigms, is proving capable of substantiating and extending *in vivo* D_2 receptor research. The relatively low cost of SPECT (as well as its acceptability to the patient and its placement in routine clinical settings) permits replication of previous findings in more typical patient groups.

Thus, a novel SPECT imaging technique has corroborated and extended PET striatal D_2 receptor findings in a large, representative group of never-medicated and unmedicated schizophrenic patients.

Methodological considerations

Sample size power calculation (Young *et al*, 1983; Farde *et al*, 1990) suggests that a group of 20 patients and controls is well in excess of that needed to show the D_2 receptor elevation found by Wong *et al* (1986). Image analysis was semi-automated, standardised and blind to diagnostic status. Structural asymmetry of the basal ganglia has not been excluded in this study, but post-mortem and structural neuro-imaging studies do not reveal significant anatomical striatal asymmetry in schizophrenia. If anatomical rather than functional laterality was responsible for the detected asymmetry, ROI area would be directly related to density measured within the ROI, and significant asymmetry would appear in the patient group in the early, blood-flow portion of the time-activity curve (see Method). These possibilities were both excluded, confirming that the finding is indeed that of laterality in striatal D_2 receptor binding.

The demographic and clinical characteristics of our sample are representative of first-presentation schizophrenic patient samples (Loebel *et al*, 1992; Ram *et al*, 1992; Keshavan & Schooler, 1992) and compare with the Karolinska and Orsay samples (Farde *et al*, 1990; Martinot *et al*, 1991). All patients except one were actively psychotic at the time of scanning, with mean BPRS scores in the moderate to severe range. Although extremely distressed, violent or otherwise uncooperative patients were excluded, this factor affects all PET and SPECT scanning studies. DSM-III-R subtyping, and chronicity and severity of illness were not related to an increase in D_2 receptor number, and our sample was also representative of other studies in this regard (Farde *et al*, 1990; Martinot *et al*, 1991).

Previous studies

D_2 receptors in unmedicated and drug-naïve schizophrenic patients in comparison with controls have

been examined by three PET groups in five different studies (Wong *et al*, 1986; Farde *et al*, 1990; Martinot *et al*, 1990, 1991; Tune *et al*, 1992), yet no consensus has been reached. It is helpful to examine the various studies to determine which factors could account for the conflicting data. Broadly speaking, the differences may be due to the sample (patient and control subjects), instrumentation and scanning, radio-pharmaceutical characteristics, image analysis and modelling of tracer behaviour. Andreasen *et al* (1988) reviewed these areas exhaustively, and could not identify a single factor responsible for the divergent findings of the Johns Hopkins and Karolinska groups. Nevertheless, assuming technical and image-analytic factors remained the same for patient and control groups within each study, the most likely source of disagreement remains the nature of the subjects, or assumptions applied to the groups in mathematical modelling of receptor kinetics.

The patient samples in the five studies were very different. The Hopkins group examined an older, more chronic population than any subsequent study. We have shown a lack of decline of D₂ receptors with age in schizophrenic patients (see also Martinot *et al*, 1990, 1991); thus controlled comparisons with an older patient group may indeed show a relative elevation in D₂ receptor binding. However, Andreasen *et al* (1988) comment that the Wong *et al* (1986) control sample was younger than the patient sample, militating against this explanation.

Because ¹¹C-raclopride and ¹²³I-IBZM binding to D₂ receptors is competitive and reversible, and equilibrium (of tracer uptake and washout) occurs during the time of a single scan, simpler models, with fewer underlying assumptions, apply in the generation of specific binding indices. The ¹¹C-NMSP method used by Wong *et al* (1986) requires sophisticated two-scan imaging protocols and complex mathematical modelling of tracer behaviour to arrive at D₂ receptor B_{max} and K_d (indices of specific D₂ binding). Assumptions (e.g. distribution of haloperidol through the blood/brain barrier) which are not strictly true for both groups may also contribute to conflicting findings. The ligand ¹¹C-NMSP is less specific than the substituted benzamides, binding with equal affinity to 5-HT receptor subpopulations in the human putamen (Hall *et al*, 1990).

Seeman *et al* (1990) have suggested that substituted benzamide ligands (raclopride and IBZM) could underestimate D₂ receptors in the presence of endogenous dopamine, and so fail to detect elevated post-synaptic D₂ receptors in schizophrenic patients (in whom increased striatal endogenous dopamine has been demonstrated post-mortem (Mackay *et al*, 1982)). This hypothesis is not wholly tenable for the

following reasons: firstly, *in vitro* studies show that dopamine competes relatively poorly for D₂ binding with IBZM, with the same low order of competition as ketanserin (Kung *et al*, 1989); secondly, PET studies have shown displacement of spiperone derivatives by endogenous dopamine in humans and primates (Volkow *et al*, 1990; Dewey *et al*, 1991); thirdly, studies showing displacement of IBZM and raclopride by endogenous dopamine *in vivo* occurred in primates following doses of d-amphetamine (1–10 mg/kg administered intravenously) which would result in large pulses of dopamine acutely at the synapse (Young *et al*, 1991; Innis *et al*, 1992); fourthly, if the patient group had such levels of dopamine at the synapse, a significant decrease of D₂ receptor levels and an alteration in the slope of the time-activity uptake and washout curve relative to controls would occur, which was not the case in our own study or that of Farde *et al* (1990).

The weight of evidence from *in vivo* studies with four different radioligands in three different centres (Karolinska, Orsay and our own) (Farde *et al*, 1990; Martinot *et al*, 1990, 1991) does now suggest that overall striatal D₂ receptor elevation cannot be regarded as a consistent feature of schizophrenia. However, our data substantiate previous PET evidence showing derangements with age and symmetry in striatal D₂ receptor distribution (Farde *et al*, 1990; Martinot *et al*, 1990, 1991).

Relevance of findings to the dopamine hypothesis of schizophrenia

The dopamine hypothesis of schizophrenia proposes an overall excess of dopaminergic function, leading to schizophrenic symptoms (Crow, 1980). The most robust evidence for the hypothesis rests on the action of neuroleptic drugs in antagonising D₂ receptors (Seeman *et al*, 1976; Creese *et al*, 1976; Johnstone *et al*, 1978), and the capacity of dopamine-releasing agents to induce psychotic symptoms. Despite the pharmacological evidence, attempts to demonstrate elevation or hypersensitivity of D₂ receptor sites post-mortem and *in vivo* remain equivocal (Owens *et al*, 1978; Mackay *et al*, 1982; Wong *et al*, 1986; Farde *et al*, 1990). The majority of studies do not find consistent increases or decreases in dopamine or dopamine metabolites in the CSF, blood, or urine of schizophrenic patients (Early *et al*, 1989).

Arguing against the dopamine hypothesis, Hornykiewicz (1982) emphasised the irreducible two to three-week delay in onset of clinical antipsychotic effect, despite the relative immediacy of D₂ receptor antagonism. More recently, PET and SPECT studies have failed to demonstrate a direct relationship

between D₂ blockade and clinical effect *in vivo* in groups of antipsychotic responders and non-responders (Wolkin *et al.*, 1989; Coppens *et al.*, 1991; Pilowsky *et al.*, 1992b). The atypical drug clozapine has an extremely beneficial antipsychotic effect (Kane *et al.*, 1988), although it demonstrates a 50% decrease in D₂ receptor blockade compared with typical antipsychotics *in vivo* (Pilowsky *et al.*, 1992a; Farde *et al.*, 1992; Brucke *et al.*, 1992).

Although the above findings do not support a simple dopaminergic-excess model of schizophrenia, our data do not exclude a role for alterations in D₂ receptor number and distribution in the genesis of schizophrenic symptoms, particularly in the male patient group. Given the highly interconnected nature of cerebral function and structure, it is unlikely that such anomalies are primary or exist in isolation; it is more plausible that they reflect aberrations in other neurochemical systems, perhaps the result of structural lesions.

Relevance of the laterality findings to sex differences in schizophrenia

A number of studies have addressed the possibility of sex differences in schizophrenia. Male patients develop the disease at an earlier age, have an excess of soft neurological signs and show greater pre-morbid abnormalities in IQ, personality, and social adjustment (Rieder & Nichols, 1979; Foerster *et al.*, 1991a). Female patients respond more favourably to neuroleptics (Seeman, 1986), with greater remission rates and more positive and affective symptoms (Castle & Murray, 1991; Waddington *et al.*, 1992).

Males with schizophrenia are more likely to have a history of obstetric complications (Owens *et al.*, 1988; Nasrallah & Wilcox, 1989; Foerster *et al.*, 1991b). Structural-imaging studies show that ventricular enlargement occurs more often in males (Flaum *et al.*, 1990; Andreasen *et al.*, 1992). Magnetic resonance imaging (MRI) has shown decreased left hippocampal volume restricted to male patients (Bogerts *et al.*, 1990). In summary, the consensus from structural-imaging studies which have addressed this issue does point toward male, rather than female, patients demonstrating cerebral abnormalities when compared with sex-matched controls (Nasrallah & Wilcox, 1989; Castle & Murray, 1991). This study is the first to show a biochemical correlate of this sex difference; our data suggest that schizophrenia is associated with a change in laterality of striatal D₂ receptor binding in males but not in females.

The PET groups which have evaluated striatal D₂ receptor binding have either not examined binding

laterality or not appraised their data with regard to sex differences (Wong *et al.*, 1986; Martinot *et al.*, 1990, 1991; Farde *et al.*, 1990). PET and SPECT studies of blood flow and metabolism have noted laterality in schizophrenia, with increased blood flow to the left globus pallidus and left striatum (Early *et al.*, 1987; Liddle *et al.*, 1992; Kawasaki *et al.*, 1992), left temporal cortex (Liddle *et al.*, 1992) and left hemisphere generally (Gur *et al.*, 1985). Patients also fail to increase blood flow to the left frontal cortical regions during tasks which stimulate this region (Lewis *et al.*, 1992). These studies do not address the influence of sex differences on their findings, but, interestingly, nearly all the above studies (excluding Gur *et al.*, 1985) compare largely (if not exclusively) male patient and control groups.

We have shown a diagnosis-by-sex interaction by ANOVA in relative left laterality of striatal D₂ binding in male patients in comparison with controls which is on the boundaries of conventional levels of significance. Comparisons between patients and controls for males and females alone revealed a significant difference in males but not in females. This result for males is in accord with the above evidence of structural and functional imaging abnormalities in male patients, and clinical differences between male and female patients. Our results suggest that females do not show this laterality difference, although we accept that the diagnosis-by-sex interaction was of borderline significance. Given the small numbers of males and females involved in our study, it is an intriguing preliminary finding, requiring confirmation in larger samples.

The finding that D₂ receptors do not appear to decline with age in patients is consistent with PET data from one other study (Martinot *et al.*, 1990). It should be noted that the older patients in our sample had received treatment previously (though not within five years of the study), and thus relative D₂ receptor binding elevations may reflect supersensitivity. Nevertheless, it is a result which warrants future study. We are currently investigating an older, never-treated patient sample and matched controls to test this hypothesis.

There is a dopamine-rich fronto-limbic-striatal circuit, perturbations in which cause abnormalities in basal-ganglia D₂ receptors (Pycock *et al.*, 1980). It is suggested that this circuit is crucial for spontaneous initiation of action (Frith & Done, 1988), and is involved in higher cognitive functions including attention, internal monitoring of actions, internal generation of cognitions and executive motor planning (Frith & Done, 1988; Early *et al.*, 1989; Gray *et al.*, 1991); all of which may be impaired in schizophrenia.

Conclusion

Our finding of a left lateralised increase in striatal D₂ receptor binding in male schizophrenic patients, in the absence of an overall increase in D₂ receptor binding relative to controls, is consistent with three previous D₂ receptor PET studies (Farde *et al*, 1990; Martinot *et al*, 1990, 1991), and with neuropsychological, functional and structural-imaging evidence for lateralised deficits in schizophrenia, particularly affecting prefrontal and limbic regions. Further research will attempt to substantiate these findings in older patient and control groups, and correlate the neurochemical data with cognitive activity and behaviour on specific neuropsychological tasks (Gray *et al*, 1992; Pedro *et al*, 1992).

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References

- ALAVI, A., VELCHICK, M. G., KUNG, H. F., *et al* (1989) Imaging the basal ganglia in the human brain with I-123-IBZM: a new CNS D₂ receptor agent. *Journal of Nuclear Medicine*, **30**, 731.
- AMERICAN PSYCHIATRIC ASSOCIATION (1987) *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn, revised) (DSM-III-R). Washington, DC: APA.
- ANDREASEN, N. C., CARSON, R., DIKSIC, M., *et al* (1988) Workshop on schizophrenia, PET and dopamine D₂ receptors in the human neostriatum. *Schizophrenia Bulletin*, **14**, 471-485.
- , SWAYZE, V. W., FLAUM, M., *et al* (1992) Letter. *Archives of General Psychiatry*, **49**, 996-997.
- ANNETT, M. (1970) A classification of hand preference by association analysis. *British Journal of Psychology*, **61**, 303-321.
- BOGERTS, B., ASHTARI, M., DEGREEF, G., *et al* (1990) Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. *Psychiatry Research: Neuroimaging*, **35**, 1-35.
- BRUCKE, T., PODREKA, I., WENGER, S., *et al* (1991) Dopamine D₂ receptor imaging with SPECT: studies in different neuropsychiatric disorders. *Journal of Cerebral Blood Flow and Metabolism*, **11**, 220-228.
- , ROTH, J., PODREKA, I., *et al* (1992) Striatal dopamine D₂ blockade by typical and atypical neuroleptics. *Lancet*, **339**, 497.
- CAMPS, M., CORTES, R., GUEYE, B., *et al* (1989) Dopamine receptors in human brain: autoradiographic distribution of D₂ sites. *Neuroscience*, **28**, 275-290.
- CASTLE, D. & MURRAY, R. M. (1991) The neurodevelopmental basis of sex differences in schizophrenia. *Psychological Medicine*, **21**, 565-575.
- CLOW, A., THEODORU, A., JENNER, P., *et al* (1980) Changes in rat striatal dopamine turnover and receptor activity during one year's neuroleptic administration. *European Journal of Pharmacology*, **63**, 135-144.
- COPPENS, H. J., SLOOF, C. J., PAANS, A. M. J., *et al* (1991) High central D₂ dopamine receptor occupancy as assessed with positron emission tomography in medicated but therapy resistant patients. *Biological Psychiatry*, **29**, 629-634.
- COSTA, D. C., VERHOEFF, N. P. L. G., CULLUM, I., *et al* (1990) *In vivo* characterisation of 3-iodo-6-methoxybenzamide 123I in humans. *European Journal of Nuclear Medicine*, **16**, 813-816.
- , GEORGE, M. S., ELL, P. J., *et al* (1992) Dopamine D₂ receptor availability in patients with Gilles de la Tourette syndrome studied with SPET. In *Nuclear Medicine: Nuclear Medicine in Research and Practice* (eds H. A. E. Schmidt & R. Hofer). Stuttgart, New York: Schattauer.
- CRAWLEY, J. C., CROW, T. J., JOHNSTONE, E. C., *et al* (1986) Uptake of ⁷⁵Br-spiperone in the striata of schizophrenic patients and controls. *Nuclear Medicine Communications*, **7**, 599-607.
- CREESE, I., BURT, D. R. & SNYDER, S. H. (1976) Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science*, **192**, 481-483.
- CROW, T. J. (1980) Molecular pathology of schizophrenia: more than one disease process? *British Medical Journal*, **280**, 66-68.
- DEWEY, S. L., LOGAN, J., WOLF, A. P., *et al* (1991) Amphetamine induced decreases in (¹⁸F)-N-methylspiperidol binding in the baboon brain using positron emission tomography (PET). *Synapse*, **7**, 324-327.
- EARLY, T., REIMAN, E. M., RAICHEL, M. E., *et al* (1987) Left globus pallidus abnormality in never medicated patients with schizophrenia. *Proceedings of the National Academy of Science*, **84**, 561-563.
- , POSNER, M., REIMAN, E. M., *et al* (1989) Hyperactivity of the left striatopallidal projection. Part 1: Lower level theory. *Psychiatric Developments*, **2**, 85-108.
- FARDE, L., PAULI, S., HALL, H., *et al* (1988) Stereoselective binding of ¹¹C raclopride in the living human brain - a search for extrastriatal central D₂ receptors by PET. *Psychopharmacology*, **94**, 471-478.
- , WEISEL, F.-A., NORDSTROM, A.-L., *et al* (1989) D₁ and D₂ dopamine receptor occupancy during treatment with conventional and atypical neuroleptics. *Psychopharmacology*, **99**, S28-S31.
- , —, STONE-ELANDER, S., *et al* (1990) D₂ dopamine receptors in neuroleptic naive schizophrenic patients. *Archives of General Psychiatry*, **47**, 213-219.
- , NORDSTROM, A. L., WIESEL, F.-A., *et al* (1992) Positron emission tomographic analysis of central D₁ and D₂ receptor occupancy in patients treated with classical neuroleptics and clozapine. *Archives of General Psychiatry*, **49**, 538-544.
- FLAUM, M., ARNDT, S. & ANDREASEN, N. C. (1990) The role of gender in studies of ventricular enlargement in schizophrenia: a predominantly male effect. *American Journal of Psychiatry*, **147**, 1327-1332.
- FOERSTER, A., LEWIS, S., OWEN, M. J., *et al* (1991a) Premorbid personality in psychosis; effects of sex and diagnosis. *British Journal of Psychiatry*, **158**, 171-176.
- , —, —, *et al* (1991b) Low birth weight and a family history of psychosis predict poor premorbid functioning in psychosis. *Schizophrenia Research*, **5**, 3-20.
- FRITH, C. D. & DONE, D. J. (1988) Towards a neuropsychology of schizophrenia. *British Journal of Psychiatry*, **153**, 437-443.
- GRAY, J. A., FELDON, J., RAWLINS, N. P., *et al* (1991) The neuropsychology of schizophrenia. *Behavioural and Brain Sciences*, **14**, 1-84.
- GRAY, N. S., PEDRO, B. M., PILOWSKY, L. S., *et al* (1992) Dopamine D₂ receptor binding in drug naive schizophrenics: neuropsychology. *Journal of Psychopharmacology*, abstract book, August meeting 1992, 179.
- GUR, R. E., GUR, R. C. & SKOLNICK, B. E. (1985) Brain function in psychiatric disorder. III. Regional blood flow in unmedicated schizophrenics. *Archives of General Psychiatry*, **42**, 329-334.
- HALL, H., WEDEL, I., HALLDIN, C., *et al* (1990) Comparison of the *in vitro* receptor binding properties of N-[³H]methylspiperone and [³H]raclopride to rat and human brain membranes. *Journal of Neurochemistry*, **55**, 2048-2057.
- HORNEYKIEWICZ, O. (1982) Brain catecholamines in schizophrenia - a good case for schizophrenia. *Nature*, **299**, 484-486.

- INNIS, R. B., MALISON, R. T., AL-TIKRITI, M., *et al* (1992) Amphetamine stimulated dopamine release competes *in vivo* for 123I IBZM binding to the D2 receptor in nonhuman primates. *Synapse*, **10**, 177–184.
- JOHNSTONE, E. C., CROW, T. J., FRITH, C. D., *et al* (1978) Mechanisms of the antipsychotic effect in the treatment of acute schizophrenia. *Lancet*, *i*, 848–851.
- KANE, J., HONIGFELD, G., SINGER, J., *et al* (1988) Clozapine for the treatment resistant schizophrenic. *Archives of General Psychiatry*, **45**, 789–796.
- KAWASAKI, Y., SUZUKI, M., MAEDA, Y., *et al* (1992) Regional cerebral blood flow in patients with schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, **241**, 195–200.
- KESHAVAN, M. & SCHOOLER, N. R. (1992) First episode studies in schizophrenia: criteria and characterisation. *Schizophrenia Bulletin*, **18**, 491–513.
- KUNG, H. F., PAN, S., KUNG, M.-P., *et al* (1989) *In vitro* and *in vivo* evaluation of 123I IBZM: a potential CNS D-2 dopamine receptor imaging agent. *Journal of Nuclear Medicine*, **30**, 88–92.
- LEE, T. & SEEMAN, P. (1980) Elevation of brain neuroleptic/dopamine receptors in schizophrenia. *American Journal of Psychiatry*, **137**, 191–197.
- LEWIS, S. W., FORD, R. A., SYED, G. W., *et al* (1992) A controlled study of ^{99m}Tc-HMPAO single photon emission imaging in chronic schizophrenia. *Psychological Medicine*, **22**, 27–35.
- LIDDLE, P. F., FRISTON, K. J., FRITH, C. D., *et al* (1992) Patterns of cerebral blood flow in schizophrenia. *British Journal of Psychiatry*, **160**, 179–186.
- LOEBEL, A. D., LIEBERMAN, J. A., ALVIR, J. M. J., *et al* (1992) Duration of psychosis and outcome in first episode schizophrenia. *American Journal of Psychiatry*, **149**, 1183–1188.
- MARTINOT, J.-L., PERON-MAGNAN, P., HURET, J.-D., *et al* (1990) Striatal D2 dopaminergic receptors assessed with positron emission tomography and ⁷⁵Br bromospiperone in untreated schizophrenic patients. *American Journal of Psychiatry*, **147**, 44–50.
- , PALLIERE-MARTINOT, M. L., LOC'H, C., *et al* (1991) The estimated density of D2 striatal receptors in schizophrenia – a study with positron emission tomography and ⁷⁵Br-bromolisuride. *British Journal of Psychiatry*, **158**, 346–350.
- MATTHEWS, J. N. S., ALTMAN, D. G., CAMPBELL, M. J., *et al* (1990) Analysis of serial measurements in medical research. *British Medical Journal*, **300**, 230–235.
- NASRALLAH, H. A. & WILCOX, J. A. (1989) Gender differences in the aetiology and symptoms of schizophrenia – genetic vs brain injury factors. *Annals of Clinical Psychiatry*, **1**, 52–53.
- NELSON, H. E. (1982) *National Adult Reading Test (NART) for the Assessment of Premorbid Intelligence in Patients with Dementia: Test Manual*. Windsor: NFER-Nelson.
- OVERALL, J. E. & GORHAM, D. E. (1962) The Brief Psychiatric Rating Scale. *Psychological Reports*, **10**, 799–812.
- OWEN, F., CROSS, A. J., CROW, T. J., *et al* (1978) Increased dopamine receptor sensitivity in schizophrenia. *Lancet*, *ii*, 223–225.
- OWEN, M. J., LEWIS, S. & MURRAY, R. M. (1988) Obstetric complications and schizophrenia: computed tomography study. *Psychological Medicine*, **18**, 331–339.
- PEDRO, B. M., GRAY, N. S., PILOWSKY, L. S., *et al* (1992) Dopamine D2 receptor binding in schizophrenia: relationship to stereotypy. *Journal of Psychopharmacology*, abstract book, August meeting 1992, 267.
- PEROUTKA, S. J. & SNYDER, S. H. (1980) Relationship of neuroleptic drug effects at brain dopamine, serotonin, alpha-adrenergic and histaminergic receptors to clinical potency. *American Journal of Psychiatry*, **137**, 1518–1522.
- PILOWSKY, L. S., COSTA, D. C., ELL, P. J., *et al* (1992a) Clozapine, single photon emission tomography and the D2 dopamine receptor blockade hypothesis of schizophrenia. *Lancet*, **340**, 199–202.
- , —, —, *et al* (1992b) A ¹²³I-IBZM single photon emission tomography study of *in vivo* dopamine receptor occupancy in typical antipsychotic responders and non-responders. *British Journal of Pharmacology*, **107**, 68P.
- PYCOCK, C. J., KERWIN, R. W. & CARTER, C. J. (1980) Effects of lesion of cortical dopamine terminals on subcortical dopamine receptors in rats. *Nature*, **286**, 74–76.
- RAM, R., BROMET, E. J., EATON, W. W., *et al* (1992) The natural course of schizophrenia: a review of first admission studies. *Schizophrenia Bulletin*, **18**, 185–207.
- REYNOLDS, G. P. (1983) Increased concentrations and lateral asymmetry of amygdala dopamine in schizophrenia. *Nature*, **304**, 527–528.
- , CZUDEK, C., BZOWEJ, N., *et al* (1987) Dopamine receptor asymmetry in schizophrenia. *Lancet*, *i*, 979.
- RIEDER, R. O. & NICHOLS, P. L. (1979) Offspring of schizophrenics – III. Hyperactivity and neurological soft signs. *Archives of General Psychiatry*, **36**, 665–674.
- RING, H. A., TRIMBLE, M. R., COSTA, D. C., *et al* (1992) Effect of vigabatrin on striatal dopamine receptors: evidence in humans for interactions of GABA and dopamine systems. *Journal of Neurology, Neurosurgery and Psychiatry*, **55**, 758–761.
- SEEMAN, M. V. (1986) Current outcome in schizophrenia: women vs men. *Acta Psychiatrica Scandinavica*, **73**, 609–617.
- SEEMAN, P., LEE, T., CHOU-WONG, M., *et al* (1976) Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature*, **261**, 717–718.
- , BZOWEJ, N., GUAN, H.-C., *et al* (1987) Human brain dopamine receptors in children and aging adults. *Synapse*, **1**, 399–404.
- , NIZNIK, H. B. & GUAN, H.-C. (1990) Elevation of dopamine D2 receptors in schizophrenia is underestimated by radioactive raclopride. *Archives of General Psychiatry*, **47**, 1170–1172.
- SEIBYL, J. P., WOODS, S. W., ZOHGBI, S., *et al* (1992) Dynamic SPECT imaging of dopamine D2 receptors in human subjects with iodine-123-IBZM. *Journal of Nuclear Medicine*, **33**, 1964–1971.
- TUNE, L. E., WONG, D. F. & PEARLSON, G. (1992) Elevated dopamine 2 receptor density in 23 schizophrenic patients: a positron emission tomography study with ¹¹C N-methylspiperone. *Schizophrenia Research*, **22**, 147.
- VERHOEFF, N. P. L. G., COSTA, D. C., ELL, P. J., *et al* (1990) Dopamine D2-receptor imaging with dynamic I-123 IBZM SPET in patients with schizophrenia or HIV encephalopathy. In *Nuclear Medicine: the State of the Art of Nuclear Medicine in Europe* (eds H. A. E. Schmidt & J. B. Van der Schoot). Stuttgart, New York: Schattauer.
- VOLKOW, N. D., FOWLER, J. S., WOLF, A. P., *et al* (1990) Effects of chronic cocaine abuse on post synaptic dopamine receptors. *American Journal of Psychiatry*, **147**, 719–724.
- WADDINGTON, J. L., WELLER, M. P. I., CROW, T. J., *et al* (1992) Schizophrenia, genetic retrenchment and epidemiological renaissance. *Archives of General Psychiatry*, **49**, 990–994.
- WOLKIN, A., BAROUCHE, F., WOLF, A. P., *et al* (1989) Dopamine blockade and clinical response: evidence for two biological subgroups of schizophrenia. *American Journal of Psychiatry*, **146**, 905–908.
- WONG, D. F., WAGNER, H. N., DANNALS, R. F., *et al* (1984) Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. *Science*, **226**, 1391–1396.
- , WAGNER, H. N., JR, TUNE, L. E., *et al* (1986) Positron emission tomography reveals elevated D2 dopamine receptors in drug-naïve schizophrenics. *Science*, **234**, 1558–1563.

- , PEARLSON, G. D., YOUNG, L. T., *et al* (1989) Dopamine receptors are elevated in neuropsychiatric disorders other than schizophrenia. *Journal of Cerebral Blood Flow and Metabolism*, **9** (suppl. 1), S593.
- YOUNG, M. J., BRESNITZ, E. A. & STROM, B. L. (1983) Sample size nomograms for interpreting negative clinical studies. *Annals of Internal Medicine*, **99**, 248–251.
- YOUNG, L. T., WONG, D. F., GOLDMAN, S., *et al* (1991) Effects of endogenous dopamine on kinetics of [³H]N-methylspiperone and [³H]raclopride binding in the rat brain. *Synapse*, **9**, 188–194.

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