Psychological Medicine (2011), **41**, 2331–2338. © Cambridge University Press 2011
doi:10.1017/S0033291711000341

ORIGINAL ARTICLE

Striatal dopamine synthesis capacity in twins discordant for schizophrenia

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Background. Elevated striatal dopamine synthesis capacity is thought to be fundamental to the pathophysiology of schizophrenia and has also been reported in people at risk of psychosis. It is therefore unclear if striatal hyperdopaminergia is a vulnerability marker for schizophrenia, or a state feature related to the psychosis itself. Relatives of patients with schizophrenia are themselves at increased risk of developing the condition. In this study we examined striatal dopamine synthesis capacity in both members of twin pairs discordant for schizophrenia.

Method. *In vivo* striatal dopamine synthesis capacity was examined using fluorine-18-L-dihydroxyphenylalanine (18F-DOPA) positron emission tomography (PET) scans in seven twin pairs discordant for schizophrenia and in a control sample of 10 healthy control twin pairs.

Results. Striatal 18F-DOPA uptake was not elevated in the unaffected co-twins of patients with schizophrenia ($p=0.65$) or indeed in the twins with schizophrenia ($p=0.89$) compared to the control group. Levels of psychotic symptoms were low in the patients with schizophrenia who were in general stable [mean (S.D.) Positive and Negative Syndrome Scale (PANSS) total = 56.8 (25.5)] whereas the unaffected co-twins were largely asymptomatic.

Conclusions. Striatal dopamine synthesis capacity is not elevated in symptom-free individuals at genetic risk of schizophrenia, or in well-treated stable patients with chronic schizophrenia. These findings suggest that striatal hyperdopaminergia is not a vulnerability marker for schizophrenia.

Received 21 September 2010; Revised 9 February 2011; Accepted 14 February 2011; First published online 22 March 2011

Key words: Dopamine, imaging, schizophrenia, twin study.

Introduction

Ten studies have investigated pre-synaptic striatal dopaminergic function in schizophrenia through quantification of the uptake of the positron emission tomography (PET) radiotracers l-[β-^{11}C]DOPA or 6-[^{18}F]fluoro-L-DOPA (18F-DOPA). Eight out of the 10 studies reported elevated striatal DOPA uptake in patients with schizophrenia, including all of the studies in patients in the acute psychotic phase of the illness (reviewed in Howes *et al*. 2009*a*). The two studies that did not report an elevation were in chronic, remitted patients (Dao-Castellana *et al*. 1997; Elkashef *et al*. 2000). Overall, these studies support the hypothesis that striatal hyperdopaminergia is important in the pathogenesis of psychosis in schizophrenia (Cannon *et al*. 1998; Howes & Kapur, 2009). However, it is not clear whether striatal hyperdopaminergia is a vulnerability marker present in people at risk for developing schizophrenia as well as in the disorder, or is simply a state marker associated with psychotic symptoms. The term vulnerability marker is used here to convey an association with increased risk of developing the disorder.

The heritability of schizophrenia is approximately 80% (Cannon *et al*. 1998; Cardno & Gottesman, 2000; Sullivan *et al*. 2003) and the neurotransmitter basis of the genetic vulnerability to schizophrenia has been examined using PET. In one study, unaffected monozygotic (MZ) co-twins of patients with schizophrenia exhibited increased caudate dopamine D2 receptor density compared to unaffected dizygotic (DZ) co-twins and healthy control twins (Hirvonen *et al*. 2005). A more recent study examining striatal dopamine synthesis capacity in first-degree relatives of patients with schizophrenia found that this group had higher striatal 18F-DOPA uptake values than unrelated controls at

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low genetic risk (Huttenen *et al*. 2008). Furthermore, elevated striatal dopaminergic function has also been reported in people who are vulnerable to schizophrenia because they have prodromal signs of the disorder (Howes *et al*. 2009*b*), or because they have schizotypal personality disorder (Abi-Dargham *et al*. 2004). These findings suggest that hyperactivity of the striatal dopaminergic system is also present in individuals at risk for schizophrenia. By reference to data from unrelated patients with schizophrenia, Huttenen *et al*. (2008) proposed that the elevation in 18F-DOPA uptake they observed in unaffected first-degree relatives of patients with schizophrenia was of the same magnitude as that in schizophrenia. However, because they did not image the relative with schizophrenia for comparison, it is unclear if this is the case. This is an important point because if the dopaminergic elevation was of the same magnitude, then this would imply that hyperdopaminergia is a vulnerability marker and not directly related to the onset of schizophrenia itself.

In this study we investigated striatal 18F-DOPA uptake in twin pairs discordant for schizophrenia to test the hypothesis that unaffected members of twin pairs discordant for schizophrenia would show elevations in striatal 18F-DOPA uptake of a similar magnitude to their schizophrenic co-twin.

Method

Subjects

One MZ and six DZ twin pairs discordant for schizophrenia were recruited [mean age 43 (S.D. = 12) years, age range 30–63 years, 71% male]. Twin zygosity was established by DNA analysis. A control group of 10 DZ normal twin pairs was also recruited [mean (S.D.) age 39 (14) years, age range 25–62 years, 50% male]. A power calculation using the effect size of the increase in 18F-DOPA uptake from a previous study of patients with schizophrenia at the same centre indicated that a minimum sample size of six twin pairs was required (McGowan *et al*. 2004). All volunteers gave written informed consent for the study, which was approved by the Hammersmith Research Ethics Committee and the Administration of Radioactive Substances Advisory Committee, UK.

All subjects with schizophrenia met DSM-IV criteria for the disorder. Healthy control volunteers were required to have no personal history of psychiatric illness or any first-degree relatives with schizophrenia. The patients with schizophrenia were taking antipsychotic medication as follows: risperidone depot 37.5 mg/twice weekly ($n = 1$), risperidone tablets 2 mg bd ($n = 1$), olanzapine 15 mg ($n = 1$), flupenthixol depot 80 mg/twice weekly ($n = 1$), amisulpiride (200 mg od, $n = 1$ and 200 mg bd, $n = 1$) and aripiprazole 20 mg ($n = 1$). The mean chlorpromazine equivalent dose of treatment was 216 mg (range 200–366 mg; for equivalent dose calculation, see Woods, 2003). The patients with schizophrenia were taking the following additional medication: temazepam 10 mg/day ($n = 1$), procyclidine 10 mg/day ($n = 1$), and a combination of fluoxetine 20 mg/day and diazepam 5 mg/day ($n = 1$). Patients were asked to omit their regular medication on the morning of the PET scan. One of the healthy co-twins was taking propranolol 80 mg and escitalopram 10 mg for anxiety. None of the other volunteers was taking or had taken any psychotropic medication. Urine drug testing confirmed that none of the volunteers had taken illicit drugs prior to the scan. Subjects were asked not to smoke on the day of the scan.

Clinical measures

All subjects were assessed at the time of scanning using the Positive and Negative Syndrome Scale (PANSS; Kay *et al*. 1987) for schizophrenia (Table 1). The presence of psychiatric diagnoses was assessed using the Structured Clinical Interview for DSM-IV (SCID; Spitzer *et al*. 1992). Demographic and recreational substance use variables were assessed by clinical interview.

PET scanning and image analysis

PET data were acquired using the ECAT/EXACT3D PET scanner (Siemens/CTI, USA). High-resolution images of the whole brain were reconstructed from 95 planes with a slice spacing of 2.425 mm. The scanner has a spatial resolution of 4.8 ± 0.2 mm and a sensitivity of 69 cps/Bq/ml. Approximately 150 MBq of 18F-DOPA was administered by bolus intravenous injection 30 s after the start of the emission scan. The emission data were acquired in list mode over 95 min and rebinned into 26 time frames (comprising a 30-s background frame, four 60-s, three 120-s, three 180-s and finally 15 300-s frames) and reconstructed using the three-dimensional (3D) reprojection algorithm.

Image analysis

A frame-by-frame realignment and denoising method was used to correct for head movement in the scanner (Turkheimer *et al*. 1999). Non-attenuation corrected images were used to reduce the influence of redistribution of radiotracer producing erroneous realignments (Dagher *et al*. 1998). These images are considered to be more useful for the realignment algorithm because they include a significant scalp signal in comparison to attenuation corrected images

https://doi.org/10.1017/S0033291711000341 Published online by Cambridge University Press

Table 1. *Actual PANNS scores and marginal mean differences of planned comparisons between groups on PANSS and K_i values*

Measure	DC twins with schizophrenia ($n=6$) Mean (S.D.)	Non-psychotic DC twins ($n=6$) Mean (S.D.)	Control twins ($n=20$) Mean (S.D.)
PANSS total	56.8 (25.4)	30.5 (1.3)	30.1 (0.5)
PANSS positive	13.5 (6.7)	7.2 (0.4)	7 (0)
PANSS negative	15 (4.9)	7 (0)	7 (0)
PANSS general	28.3 (14.2)	16.3 (0.8)	16.1 (0.4)
Marginal mean differences	**DC twins with schizophrenia *versus* control twins Mean difference (p value)**	**Non-psychotic DC twins *versus* control twins Mean difference (p value)**	**DC twins with schizophrenia *versus* non-psychotic DC twins Mean difference (p value)**
PANSS total	**26.07548 (<0.0005)**	0.2715708 (0.598)	**0.2715708 (<0.0005)**
PANSS positive	**5.995143 (0.003)**	0.0048574 (0.982)	**5.990285 (0.003)**
PANSS negative	**7.88137 (<0.0005)**	−0.0242269 (0.609)	**−0.0242269 (<0.0005)**
PANSS general	**12.158 (0.002)**	0.338823 (0.338)	**11.81917 (0.004)**
K_i value for whole striatum	0.0000748 (0.859)	−0.0002147 (0581)	0.0002895 (0.425)
K_i value for whole R striatum	0.00 (0.591)	0.00 (0.491)	0.00 (0.217)
K_i value for whole L striatum	0.00 (0.770)	0.00 (0.463)	0.00 (0.638)
K_i value for associative striatum	0.0003312 (0.490)	−0.0000544 (0.893)	0.0003856 (0.338)
K_i value for limbic striatum	−0.0005923 (0.423)	−0.0003689 (0.582)	−0.0002234 (0.782)
K_i value for sensorimotor striatum	0.0000354 (0.936)	−0.0002905 (0.387)	0.0003259 (0.421)

PANNS, Positive and Negative Syndrome Scale; DC, discordant; S.D., standard deviation; R, right; L, left.
Bold indicates significance.

(Bose *et al*. 2008). Frames were realigned to a single, 'reference' frame acquired 7 min post-injection using a mutual information algorithm and the transformation parameters were then applied to the corresponding attenuation-corrected dynamic images (Studholme *et al*. 1997).

These realigned frames were then summated, creating a movement-corrected dynamic image to be used in the analysis. Standardized regions in Montreal Neurologic Institute (MNI) space were defined in the cerebellum (the reference region) using a probabilistic atlas and in the whole striatum delineated using previously described criteria to create a region of interest (ROI) map (Hammers *et al*. 2003; Martinez *et al*. 2003). SPM5 (www.fil.ion.ucl.ac.uk/spm) was then used to normalize the ROI map together with the tracer-specific (18F-DOPA) template (the template aids normalization) to each individual PET summation image (McGowan *et al*. 2004). This non-linear transformation procedure allowed ROIs to be placed automatically on individual 18F-DOPA PET dynamic images. An example of this is shown in Fig. 2. Striatal subdivisions were delineated as described previously generating limbic (LS), associative (AST) and sensorimotor (SMST) subregions of the whole striatal ROI (Martinez *et al*. 2003). These 'functional' subdivisions reflect the topographical arrangement of corticostriatal projections. Projections to the LS are from limbic areas such as the hippocampus and amygdala, projections to the AST originate in associative areas such as the dorsolateral prefrontal cortex, and projections to the SMST come from motor and related areas such as the primary motor cortex, premotor cortex and supplementary motor cortex. Influx constants (K_i values) for the whole striatal ROI and the functional subdivisions were calculated relative to uptake in the reference region for left and right sides combined using a Patlak graphical approach (Patlak *et al*. 1983).

Voxel-based statistical image analyses were performed to confirm the results obtained from the conventional ROI analysis. Wavelet-based kinetic modeling was deployed to the scans to produce maps of the uptake constant for 18F-DOPA (K_i) using the cerebellum as a reference region. It has been documented that wavelet-based methodology increases the signal-to-noise ratio of K_i maps for 18F-DOPA by a factor of three without significant loss of resolution (Turkheimer *et al*. 2006). Statistical analyses of parametric images were performed using SPM5 (Wellcome Department of Cognitive Neuroscience, London, UK) and Matlab6.5 (Mathworks, USA). An explicit anatomical mask confining the analyses to striatal areas was used. The results of the voxel-based analysis were analyzed corrected for multiple comparisons

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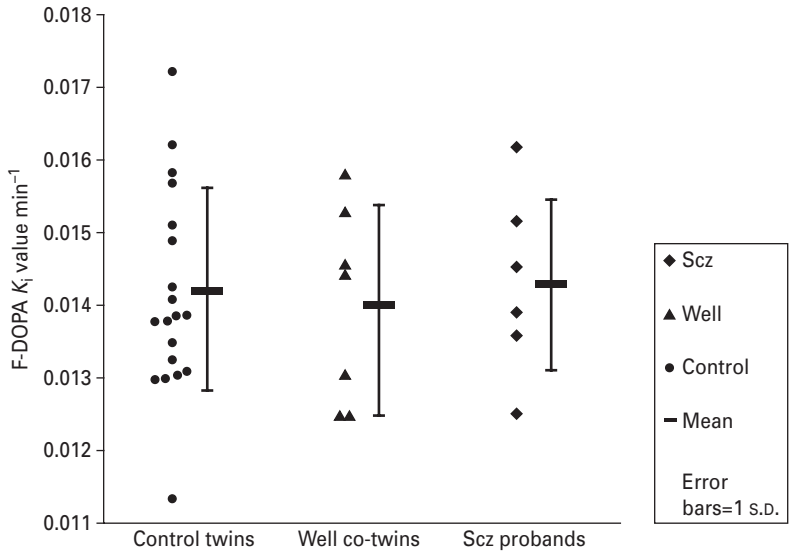

Fig. 1. Comparison of whole (left and right sides combined) striatal 18F-DOPA uptake constants (K_i/min).

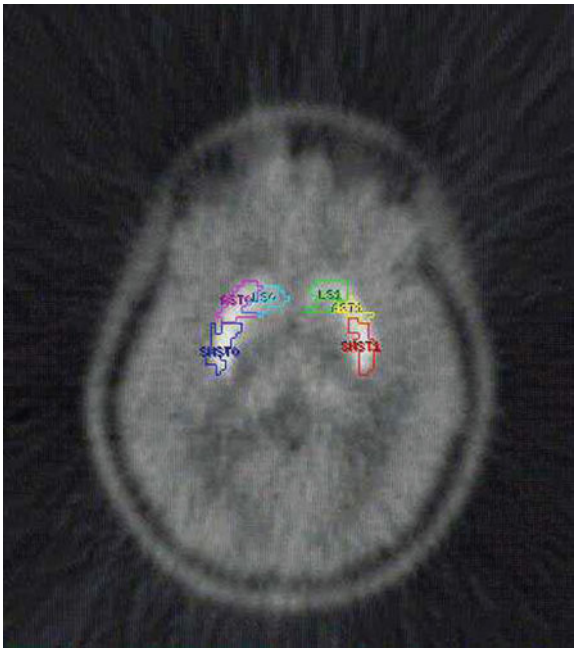

Fig. 2. A single subject's summated positron emission tomography (PET) image with the normalized region of interest (ROI) map of the striatal functional subdivisions. LS, limbic striatum; AST, associative striatum; SMST, sensorimotor striatum; 1, left side; 0, right side.

($p < 0.05$, family-wise error rate) and using a liberal threshold value of $p < 0.001$ (uncorrected).

Statistical analysis

We investigated whether patients and their healthy co-twins differed from controls on radiochemical, demographic and clinical measures, and whether 18F-DOPA uptake in healthy co-twins was intermediate between patients and unrelated healthy controls, using a regression analysis in Stata version 10 statistical software (Stata Corp, USA). Planned contrasts were performed to test our hypotheses by comparing discordant patients and their non-psychotic co-twins with each other and against unrelated healthy DZ control twins.

Familial correlations violate the assumption of independence made in standard regression models. Generalized estimating equations (GEEs) were used to account for the lack of independence; specifically, an exchangeable correlation structure was assumed to account for the within-family correlation. GEEs provide unbiased estimates of the marginal effects, even if the assumed correlation structure is misspecified (Hardin & Hibe, 2003; Rabe-Hesketh & Skrondal, 2010). To safeguard against a possible misspecification in the variance/covariance matrix, we used robust Hubert White sandwich estimators to adjust standard errors, and hence confidence intervals and p values (Williams, 2000).

The relationship between whole striatal K_i values and symptom scores was explored using Pearson's product moment correlation coefficient. Intraclass correlation coefficients (ICCs) for striatal K_i values were calculated for the healthy control twin group and the discordant twin group.

Results

Demographic data and clinical characteristics

No significant differences existed between groups on age ($\chi^2 = 0.38$, df = 2, $p = 0.825$), gender ($\chi^2 = 3.17$, df = 2,

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$p=0.205$), cigarette ($\chi^2=1.00$, df = 2, $p=0.607$), cannabis ($\chi^2=2.97$, df = 2, $p=0.227$) and alcohol ($\chi^2=0.09$, df = 2, $p=0.954$) use. The cannabis use was occasional in all subjects, and at least 12 months had elapsed between last use and the PET scan. There were no current stimulant users in any of the groups. In the pairs discordant for schizophrenia, the mean duration of discordance was 15 ± 13 years.

As expected, there was a significant effect of group on current psychotic symptom ratings (see Table 1). There was no relationship between whole striatal K_i values and age in any group (unwell twins, $r=-0.4$, $p=0.4$; well co-twins, $r=-0.5$, $p=0.9$; healthy controls, $r=0.018$, $p=0.94$) or overall ($r=-0.7$, $p=0.7$).

Striatal dopaminergic function

We found no significant group effects on K_i values for any of the ROIs examined (Table 1, Fig. 1). There was also no significant effect of group when the left and right striata were analyzed separately. Excluding the MZ twin pair made no difference to the findings. The voxel-based analyses corroborated the ROI analysis findings, with no significant differences between groups when corrected for multiple comparisons, and this remained the case even when the liberal threshold ($p<0.001$, uncorrected) was used. Within the schizophrenia group, there was no significant correlation between the severity of symptoms as indexed by the total PANNS score and whole striatal K_i values ($r=-0.1$, $p=0.59$) or K_i values in the AST ($r=-0.05$, $p=0.77$), SMST ($r=-0.1$, $p=0.54$) or LS ($r=-0.15$, $p=0.4$) subdivisions. The ICCs for the normal and discordant twin pairs were low and of similar magnitude (for the whole striatum; normal pairs = 0.087, discordant pairs = 0.094).

Discussion

We did not find evidence of increased striatal dopamine synthesis in the well co-twins from twin pairs discordant for schizophrenia compared with healthy control twins, in contrast to a previous finding in first-degree relatives of patients with schizophrenia (Huttunen *et al*. 2008). None of the unaffected co-twins of schizophrenia patients in our study had symptoms with a PANNS rating of >2 on any item (a PANSS rating of ⩾3 indicates a definite symptom whereas 1 indicates the symptom is absent and 2 indicates questionable pathology/upper extreme of normal limits). As the unaffected co-twins in our study were asymptomatic whereas relatives in the previous study had appreciable symptom levels (mean PANSS score = 39.8, median 39, range 30–63), one possible interpretation of these findings is that elevated dopamine synthesis capacity is linked to the development of psychotic symptoms rather than a vulnerability to psychosis *per se*.

The absence of a correlation between whole striatal K_i values and age is unexpected but consistent with some (Eidelberg *et al*. 1993; Ishikawa *et al*. 1996; Sawle *et al*. 1990) but not all previous studies (Bhatt *et al*. 1991; Cordes *et al*. 1994; Martin *et al*. 1989). Nevertheless, age is not a potential confound in this study because the main comparison is between the patients and their well co-twins who are the same age.

The probability that any of the discordant pairs will become concordant for schizophrenia in the future is low as an average of 15 years had elapsed since the onset of the illness in the probands (Belmaker *et al*. 1974). We cannot exclude the possibility that the well co-twins in this study had not inherited the risk genes for schizophrenia, bearing in mind that our mostly DZ group only share 50% of genes with their co-twin with schizophrenia. We included both DZ and MZ twins in the primary analysis because our main hypothesis was that familial vulnerability to schizophrenia was associated with elevated striatal dopamine synthesis capacity, as suggested by Huttunen *et al*. (2008). Excluding the MZ twins made no difference to our finding. ICC values were similar in both twin groups suggesting that having a co-twin with schizophrenia does not alter concordance in 18F-DOPA K_i values.

We also found no elevation of striatal 18F-DOPA uptake in the twins with schizophrenia. However, none of our patients was acutely unwell at the time of scanning. Thus our finding is consistent with previous findings that elevated dopaminergic function in schizophrenia is particularly associated with the acute development of psychotic symptoms (Laruelle *et al*. 1999). Furthermore, a study examining striatal dopamine synthesis capacity in the prodrome to schizophrenia found evidence of an increase in dopamine synthesis with the development of acute psychosis (Howes *et al*. 2011). It is possible that the absence of elevated striatal dopamine synthesis in our patients and relatives at rest reflects normal tonic presynaptic tonic dopamine release. However, phasic dopamine release in response to stress or a reward could be elevated and may potentially represent a vulnerability marker.

Our study was powered to detect a between-group difference in mean striatal K_i values of 0.0011/min (the effect size we have reported previously in patients scanned on the same scanner; Howes *et al*. 2009*b*). However, we cannot exclude the possibility of smaller between-group differences, although the data do not give any indication of differences. Although our

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sample was recruited from general clinics, its relatively small sample size means it is possible we have recruited an unusual subgroup of patients, which could limit the generalizability of the findings to schizophrenia. All of the patients had received long-term treatment with antipsychotic medication prior to the scan and, although subjects omitted treatment on the day of the scan itself, it remains possible that dopamine synthesis was influenced by prior treatment. However, the data in the literature on the effect of antipsychotic medication on dopamine synthesis capacity are equivocal. One study reported a reduction in F-DOPA uptake following 5 weeks pre-treatment with haloperidol (Grunder *et al*. 2003). Two studies found no change in dopamine synthesis capacity after a single dose of risperidone (Mamo *et al*. 2004; Ito *et al*. 2009), although an increase was found in the putamen but not the caudate following 3 days of haloperidol (Vernaleken *et al*. 2005). Another possibility is that antipsychotic treatment-induced structural changes might have influenced our results. The literature suggests that the striatal nuclei may increase in size following chronic antipsychotic use (Navari & Dazzan, 2009; Smieskova *et al*. 2009). This would, if anything, mitigate against our finding because, as larger structures are less susceptible to partial volume effects (Rousset *et al*. 1998), the schizophrenia group would be less susceptible to underestimation of striatal dopamine synthesis capacity. Studies in drug-naïve discordant twins would help to exclude an effect of medication.

Conclusions

Striatal dopamine synthesis capacity is not elevated in stable patients with chronic schizophrenia or in their unaffected co-twins. These findings suggest that genetic vulnerability to psychosis and a shared *in utero* environment are not associated with elevation in dopamine synthesis capacity *per se*. It can also be inferred that striatal hyperdopaminergia is related to the active psychotic phase of the illness, rather than being a vulnerability marker for schizophrenia.

Acknowledgements

This study was funded by a Wellcome Trust Clinical Training Fellowship awarded to P.S. and by the Medical Research Council, Clinical Sciences Centre. We acknowledge infrastructure support from the National Institute for Health Research Biomedical Research Centre for Mental Health at the South London and Maudsley National Health Service Foundation Trust and the Institute of Psychiatry, King's College London.

Declaration of Interest

None.

References

Abi-Dargham A, Kegeles LS, Zea-Ponce Y, Mawlawi O, Martinez D, Mitropoulou V, O'Flynn K, Koenigsberg HW, Van Heertum R, Cooper T, Laruelle M, Siever LJ (2004). Striatal amphetamine-induced dopamine release in patients with schizotypal personality disorder studied with single photon emission computed tomography and [^{123}I]iodobenzamide. *Biological Psychiatry* **55**, 1001–1006.

Belmaker R, Pollin W, Wyatt RJ, Cohen S (1974). A follow-up of monozygotic twins discordant for schizophrenia. *Archives of General Psychiatry* **30**, 219–222.

Bhatt MH, Snow BJ, Martin WR, Pate BD, Ruth TJ, Calne DB (1991). Positron emission tomography suggests that the rate of progression of idiopathic parkinsonism is slow. *Annals of Neurology* **29**, 673–677.

Bose SK, Turkheimer FE, Howes OD, Mehta MA, Cunliffe R, Stokes PR, Grasby PM (2008). Classification of schizophrenic patients and healthy controls using [18F] fluorodopa PET imaging. *Schizophrenia Research* **106**, 148–155.

Cannon TD, Kaprio J, Lonnqvist J, Huttunen M, Koskenvuo M (1998). The genetic epidemiology of schizophrenia in a Finnish twin cohort. A population-based modeling study. *Archives of General Psychiatry* **55**, 67–74.

Cardno AG, Gottesman II (2000). Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. *American Journal of Medical Genetics* **97**, 12–17.

Cordes M, Snow BJ, Cooper S, Schulzer M, Pate BD, Ruth TJ, Calne DB (1994). Age-dependent decline of nigrostriatal dopaminergic function: a positron emission tomographic study of grandparents and their grandchildren. *Annals of Neurology* **36**, 667–670.

Dagher A, Gunn R, Lockwood G, Cunningham VJ, Grasby PM, Brooks DJ (1998). Measuring neurotransmitter release with PET: methodological issues. In *Quantitative Functional Brain Imaging with Positron Emission Tomography* (ed. R. Carson, M. Daube-Witherspoon and P. Herscovitch), pp. 449–454. Academic Press: San Diego.

Dao-Castellana MH, Paillere-Martinot ML, Hantraye P, Attar-Levy D, Remy P, Crouzel C, Artiges E, Feline A, Syrota A, Martinot JL (1997). Presynaptic dopaminergic function in the striatum of schizophrenic patients. *Schizophrenia Research* **23**, 167–174.

Eidelberg D, Takikawa S, Dhawan V, Chaly T, Robeson W, Dahl R, Margouleff D, Moeller JR, Patlak CS, Fahn S (1993). Striatal 18F-dopa uptake: absence of an aging effect. *Journal of Cerebral Blood Flow and Metabolism* **13**, 881–888.

Elkashef AM, Doudet D, Bryant T, Cohen RM, Li SH, Wyatt RJ (2000). 6-(18)F-DOPA PET study in patients with schizophrenia. Positron emission tomography. *Psychiatry Research* **100**, 1–11.

Grunder G, Vernaleken I, Muller MJ, Davids E, Heydari N, Buchholz HG, Bartenstein P, Munk OL, Stoeter P, Wong DF, Gjedde A, Cumming P (2003). Subchronic haloperidol downregulates dopamine synthesis capacity in the brain of schizophrenic patients in vivo. *Neuropsychopharmacology* **28**, 787–794.

Hammers A, Allom R, Koepp MJ, Free SL, Myers R, Lemieux L, Mitchell TN, Brooks DJ, Duncan JS (2003). Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. *Human Brain Mapping* **19**, 224–247.

Hardin JW, Hibe JM (2003). *Generalized Estimating Equations*. Chapman & Hall/CRC: Boca Raton, FL.

Hirvonen J, van Erp TG, Huttunen J, Aalto S, Nagren K, Huttunen M, Lonnqvist J, Kaprio J, Hietala J, Cannon TD (2005). Increased caudate dopamine D2 receptor availability as a genetic marker for schizophrenia. *Archives of General Psychiatry* **62**, 371–378.

Howes O, Bose S, Turkheimer F, Valli I, Egerton A, Stahl D, Valmaggia L, Allen P, Murray R, McGuire P (2011). Progressive increase in striatal dopamine synthesis capacity as patients develop psychosis: a PET study. *Molecular Psychiatry*. Published online: 1 March 2011. doi:10.1038/mp.2011.20.

Howes OD, Egerton A, Allan V, McGuire P, Stokes P, Kapur S (2009*a*). Mechanisms underlying psychosis and antipsychotic treatment response in schizophrenia: insights from PET and SPECT imaging. *Current Pharmacological Design* **15**, 2550–2559.

Howes OD, Kapur S (2009). The dopamine hypothesis of schizophrenia: version III – the final common pathway. *Schizophrenia Bulletin* **35**, 549–562.

Howes OD, Montgomery AJ, Asselin MC, Murray RM, Valli I, Tabraham P, Bramon-Bosch E, Valmaggia L, Johns L, Broome M, McGuire PK, Grasby PM (2009*b*). Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Archives of General Psychiatry* **66**, 13–20.

Huttunen J, Heinimaa M, Svirskis T, Nyman M, Kajander J, Forsback S, Solin O, Ilonen T, Korkeila J, Ristkari T, McGlashan T, Salokangas RK, Hietala J (2008). Striatal dopamine synthesis in first-degree relatives of patients with schizophrenia. *Biological Psychiatry* **63**, 114–117.

Ishikawa T, Dhawan V, Kazumata K, Chaly T, Mandel F, Neumeyer J, Margouleff C, Babchyck B, Zanzi I, Eidelberg D (1996). Comparative nigrostriatal dopaminergic imaging with iodine-123-beta CIT-FP/SPECT and fluorine-18-FDOPA/PET. *Journal of Nuclear Medicine* **37**, 1760–1765.

Ito H, Takano H, Takahashi H, Arakawa R, Miyoshi M, Kodaka F, Okumura M, Otsuka T, Suhara T (2009). Effects of the antipsychotic risperidone on dopamine synthesis in human brain measured by positron emission tomography with L-[beta-11C]DOPA: a stabilizing effect for dopaminergic neurotransmission? *Journal of Neurosciences* **29**, 13730–13734.

Kay SR, Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**, 261–276.

Laruelle M, Abi-Dargham A, Gil R, Kegeles L, Innis R (1999). Increased dopamine transmission in schizophrenia: relationship to illness phases. *Biological Psychiatry* **46**, 56–72.

Mamo D, Kapur S, Shammi CM, Papatheodorou G, Mann S, Therrien F, Remington G (2004). A PET study of dopamine D2 and serotonin 5-HT2 receptor occupancy in patients with schizophrenia treated with therapeutic doses of ziprasidone. *American Journal of Psychiatry* **161**, 818–825.

Martin WR, Palmer MR, Patlak CS, Calne DB (1989). Nigrostriatal function in humans studied with positron emission tomography. *Annals of Neurology* **26**, 535–542.

Martinez D, Slifstein M, Broft A, Mawlawi O, Hwang DR, Huang Y, Cooper T, Kegeles L, Zarahn E, Abi-Dargham A, Haber SN, Laruelle M (2003). Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: Amphetamine-induced dopamine release in the functional subdivisions of the striatum. *Journal of Cerebral Blood Flow and Metabolism* **23**, 285–300.

McGowan S, Lawrence AD, Sales T, Quested D, Grasby P (2004). Presynaptic dopaminergic dysfunction in schizophrenia: a positron emission tomographic [18F]fluorodopa study. *Archives of General Psychiatry* **61**, 134–142.

Navari S, Dazzan P (2009). Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. *Psychological Medicine* **39**, 1763–1777.

Patlak CS, Blasberg RG, Fenstermacher JD (1983). Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. *Journal of Cerebral Blood Flow and Metabolism* **3**, 1–7.

Rabe-Hesketh S, Skrondal A (2010). *Multilevel and Longitudinal Modeling using Stata*. Stata Press: College Station, TX.

Rousset OG, Ma Y, Evans AC (1998). Correction for partial volume effects in PET: principle and validation. *Journal of Nuclear Medicine* **39**, 904–911.

Sawle GV, Colebatch JG, Shah A, Brooks DJ, Marsden CD, Frackowiak RS (1990). Striatal function in normal aging: implications for Parkinson's disease. *Annals of Neurology* **28**, 799–804.

Smieskova R, Fusar-Poli P, Allen P, Bendfeldt K, Stieglitz RD, Drewe J, Radue EW, McGuire PK, Riecher-Rossler A, Borgwardt SJ (2009). The effects of antipsychotics on the brain: what have we learnt from structural imaging of schizophrenia? – a systematic review. *Current Pharmacological Design* **15**, 2535–2549.

Spitzer RL, Williams JB, Gibbon M, First MB (1992). The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Archives of General Psychiatry* **49**, 624–629.

Studholme C, Hill DL, Hawkes DJ (1997). Automated three-dimensional registration of magnetic resonance and positron emission tomography brain images by

multiresolution optimization of voxel similarity measures. *Medical Physics* **24**, 25–35.

Sullivan PF, Kendler KS, Neale MC (2003). Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Archives of General Psychiatry* **60**, 1187–1192.

Turkheimer FE, Aston JA, Asselin MC, Hinz R (2006). Multi-resolution Bayesian regression in PET dynamic studies using wavelets. *NeuroImage* **32**, 111–121.

Turkheimer FE, Brett M, Visvikis D, Cunningham VJ (1999). Multiresolution analysis of emission tomography images in the wavelet domain. *Journal of Cerebral Blood Flow and Metabolism* **19**, 1189–1208.

Williams RL (2000). A note on robust variance estimation for cluster-correlated data. *Biometrics* **56**, 645–646.

Woods SW (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. *Journal of Clinical Psychiatry* **64**, 663–667.