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The catechol-O-methyltransferase Val[158]Met polymorphism modulates fronto-cortical dopamine turnover in early Parkinson's disease: a PET study

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Cognitive deficits occur in up to 30% of patients with early Parkinson's disease, some of which are thought to result from dysfunction within the fronto-striatal dopaminergic network. Recently, it has been shown that a common functional polymorphism (Val[158]Met) in the catechol-O-methyltransferase (*COMT*) gene is associated with changes in executive performance in tasks that have a fronto-striatal basis. This is thought to relate to changes in cortical dopamine levels as catechol-O-methyltransferase is the main mode of inactivation for dopamine in frontal areas. However to date, no study has investigated dopamine turnover as a function of this genetic polymorphism in Parkinson's disease. We, therefore, set out to investigate *in vivo* changes in presynaptic dopamine storage in patients with idiopathic Parkinson's disease as a function of the catechol-O-methyltransferase Val[158]Met polymorphism using ^{18}F-DOPA positron emission tomography. Twenty patients with Parkinson's disease (10 homozygous for Val/Val and 10 for Met/Met catechol-O-methyltransferase polymorphisms) underwent ^{18}F-DOPA positron emission tomography using a prolonged imaging protocol. The first dynamic scan was acquired from 0 to 90 min (early), and the second scan (late) from 150 to 210 min post-intravenous radioligand administration. Patients were matched for age, sex, verbal IQ, disease duration and severity of motor features. ^{18}F-DOPA influx constants (Ki) were calculated and compared for frontal and striatal regions. Late scan mean frontal and striatal Ki values were significantly reduced in both Parkinson's disease groups relative to early scan Ki values. Met/Met patients had significantly higher late scan Ki values compared with their Val/Val counterparts in anterior cingulate, superior frontal and mid-frontal regions but early frontal Ki values were not different between the two groups. As late Ki values reflect rates of dopamine metabolism to 3,4-dihydroxyphenylacetic acid and homovanillic acid, our results indicate that Met homozygotes have higher presynaptic dopamine levels in frontal regions than Val homozygotes, which may help to explain how this genotypic variation may influence the fronto-striatal cognitive deficits of Parkinson's disease.

Keywords: gene; F-DOPA; PET; Parkinson
Abbreviation: COMT = catechol-O-methyltransferase

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Introduction

Parkinson's disease is a neurodegenerative condition affecting 1% of the population over the age of 60 years and is clinically characterized by limb bradykinesia, rigidity, tremor and postural instability associated with dopaminergic neuronal loss in the nigro-striatal tract. However, non-motor features are now increasingly being recognized as significant aspects of the disorder, having the greatest impact on patient and carer quality of life in later disease (Martinez-Martin, 2007; Politis *et al*., 2010). Of these non-motor aspects of Parkinson's disease, cognitive deficits are a major issue with up to 80% of patients eventually dementing if they live for 20 years or longer, while more subtle cognitive dysfunction can be seen in ~30% in earlier cases (Foltynie *et al*., 2004*a*; Aarsland *et al*., 2009; Elgh *et al*., 2009). The nature of these deficits varies but fronto-striatal executive problems are common and seem to have a different natural history compared with other cognitive problems (Williams-Gray *et al*., 2008).

The basis for these fronto-striatal deficits is currently unresolved, but may well have a basis in the dopaminergic networks that innervate these areas and in particular how dopamine is handled at the synaptic level in the cortex and striatum. Striatal dopamine levels are mainly regulated by dopamine transporters, which take up the released transmitter from the synaptic cleft. In the frontal lobe, there are low levels of dopamine transporters and instead catechol-O-methyltransferase (*COMT*) has been shown to be mainly responsible for the regulation of synaptic dopamine levels, inactivating it by methylation (Karoum *et al*., 1994; Matsumoto *et al*., 2003; Tunbridge *et al*., 2004).

A common functional polymorphism in the *COMT* gene exists resulting in a substitution of valine for methionine at codon 158 (Val^{158}Met), which in turn causes a 40% increase in the enzymic activity in the prefrontal cortex in Val homozygotes (Scanlon *et al*., 1979; Lotta *et al*., 1995; Chen *et al*., 2004). These changes have been associated with phenotypic features in some cognitive aspects of Parkinson's disease. In early stage Parkinson's disease, the high COMT activity genotype (Val/Val homozygotes), presumed to cause lower dopamine levels in the frontal cortex, is associated with a better performance on the Tower of London planning task compared with a low COMT activity genotype (Met/Met) (Foltynie *et al*., 2004). This relationship reverses as disease becomes more severe and higher levodopa doses are administered (Williams-Gray *et al*., 2008).

The reason for these changing responses is postulated to relate to the presence in the early stages of Parkinson's disease of a compensatory hyperdopaminergic state within the frontal cortex. The possession of the low activity COMT genotype aggravates the situation and worsens task performance. Functional MRI studies have corroborated the above findings: Williams-Gray *et al*. (2008) reported that patients with Parkinson's disease with the Met/Met genotype failed to adopt typical preferential attention shifting strategies, and this was associated with lower activation blood oxygen level-dependent signals in the Met group (compared with Val homozygotes) in the dorsolateral prefrontal cortex. Similar neuroimaging findings were also seen in early Parkinson's disease during performance on the Tower of London planning task, with underactivation of a fronto-parietal network (Williams-Gray *et al*., 2007). However, while these cortical activation data suggest that COMT may be having its effect at a frontal level through changes in synaptic dopamine concentrations, this has not been explicitly investigated and formed the basis of this new study.

^{18}F-DOPA PET is an *in vivo* marker of both aromatic amine decarboxylase and COMT activities. Initially, radiolabelled ^{18}F-DOPA is taken up by neutral amino acid transporters and decarboxylated to form ^{18}F-dopamine, which is subsequently methylated by COMT and oxidized by monoamine oxidase B to form DOPAC (3,4-dihydroxyphenylacetic acid) (Garnett *et al*., 1983; Martin *et al*., 1989, Brooks *et al*., 1990). Administration of a peripheral COMT inhibitor (entacapone) and decarboxylase inhibitor (carbidopa) prior to imaging results in a marked decrease in peripheral methylation and decarboxylation of ^{18}F-DOPA and increases its bioavailability for entry into the brain, along with a reduction in non-specific background radioactivity (Ishikawa *et al*., 1996; Leger *et al*., 1998).

Previous ^{18}F-DOPA PET studies have proposed the use of a prolonged imaging protocol to detect changes in dopamine turnover (Ruottinen *et al*., 2001; Ceravolo *et al*., 2002) as this better characterizes central COMT activity. In our study, we therefore performed two separate ^{18}F-DOPA PET scans following tracer administration: an 'early' scan taking place 0–90 min after tracer injection, and a 'late' scan taking place 150–210 min after tracer injection. We hypothesized that there would be no difference in ^{18}F-DOPA influx constant between the two genotypes during the early scan as this period mainly reflects tracer influx and central DOPA decarboxylase activity (Patlak *et al*., 1983). However, in the late scan we should detect differences in central COMT activity with the Met/Met group and its associated lower COMT activity showing a higher ^{18}F-DOPA influx constant compared with the Val/Val group. We hypothesized that these changes would be most evident in frontal regions (superior frontal, mid-frontal, inferior frontal regions, orbitofrontal cortex as well as anterior cingulate) due to the abundance of COMT (and the relative lack of dopamine transporter) in this region, whereas the rate of decline of ^{18}F-DOPA influx would be similar in the striatum for both groups as dopamine clearance at this site is regulated by dopamine transporters.

Materials and methods

Participants

Twenty patients with Parkinson's disease with known homozygosity for the COMT Val^{158}Met polymorphism were recruited from the Cambridge Centre for Brain Repair for the study. These patients underwent initial motor, cognitive and affective assessments. Inclusion criteria for this study were as follows: a diagnosis of Parkinson's disease according to the UK PDS Brain Bank Criteria with a disease duration of <6 years, mild to moderate disease (Hoehn and Yahr $\leqslant 2.5$), no evidence of dementia (Mini-Mental State Examination <26) nor depressive symptoms [Beck depression Inventory (II) score $\leqslant 16$] (Table 1). Informed consent was obtained from all participants in accordance with the Declaration of Helsinki agreement and approval was obtained from the Hammersmith and Queen Charlotte's Hospitals Research

Table 1 Clinical demographic details of patients

	Genotype		*P*-value
	Val/Val	Met/Met	
Frequency (male:female)	10 (7:3)	10 (6:4)	0.660
Age	60.6 (9.7)	66.2 (7.6)	0.168
Disease duration (years)	3.5 (1.7)	2.7 (1.4)	0.220
UPDRS (III) motor	26.8 (12.1)	25.6 (8.5)	0.811
Hoehn and Yahr	1.89 (0.33)	1.80 (0.42)	0.615
Total LEDD (mg/day)	384.4 (246.7)	455.0 (202.1)	0.508
Number of patients on dopamine agonist	4	4	1.00
Dopamine agonist levodopa equivalent daily dose (mg/day)	120.0 (142.0)	200.0 (277.13)	0.43
Number of patients on levodopa	6	8	0.36
Amount of levodopa (mg/day)	253.3 (215.9)	247.0 (184.6)	0.95
MMSE	29.6 (0.7)	29.6 (0.5)	1.00
BDI (II)	7.8 (6.4)	7.3 (3.4)	0.84
NART PVIQ	114.3 (8.2)	120.2 (4.4)	0.08

Values represent mean (SD). *P*-value obtained from student two sample *t*-test.
BDI(II) = Beck Depression Inventory, second edition; LEDD = levodopa equivalent daily dose; MMSE = 30 point Mini-Mental State Examination; NART PVIQ = National adult reading test predicted verbal Intelligence Quotient; UPDRS = Unified Parkinson's Disease Rating Scale.

Ethics Committee. Permission to administer ^{18}F-DOPA was obtained from the Administration of Radioactive Substance Advisory Committee (ARSAC) of the Department of Health, UK. ^{18}F-DOPA was manufactured and supplied by Hammersmith Imanet.

Genotyping

Genotyping was performed using standard methods as previously described (William-Gray *et al*., 2008). Briefly, DNA was extracted from a peripheral venous sample using standard phenol/chloroform methods. A single nucleotide polymorphism rs4680 (COMT Val^{158}Met) was genotyped using a TaqMan® SNP genotyping assay on a 7900HT Sequence Detection System (Applied Biosystems) according to the manufacturer's instructions.

Clinical assessments

Patients attended for clinical assessment at the Hammersmith Hospital on a weekday morning after withholding their anti-parkinsonian medication overnight. Patients were instructed to avoid smoking, alcohol and caffeinated beverages for at least 12 h prior to attending. The clinical assessment included a full medical history, and clinical examination that included the Unified Parkinsons Disease Rating Scale (III) motor score and Hoehn and Yahr. All assessments were performed by the same clinician to reduce inter-operator variability. On the day of scanning, each patient's regular anti-parkinsonian medication was recorded and converted to an equivalent levodopa dose for ease of comparison based on a formula previously adopted (Brodsky *et al*., 2003; Williams-Gray *et al*., 2007). Briefly, equivalent levodopa dose = [levodopa ($\times$ 1.2 if COMT inhibitor) ($\times$ 1.2 if 10 mg of selegiline OR $\times$ 1.1 if 5 mg selegiline)] + [pramipexole $\times$ 400] + [ropinirole $\times$ 40] + [cabergoline $\times$ 160], all doses in milligrams. Patients also completed the National Adult Reading Test (NART), a measure of premorbid verbal IQ.

Positron emission tomography scanning procedures

Patients were premedicated with 150 mg of carbidopa and 400 mg of entacapone 1 h prior to the injection of ^{18}F-DOPA. Carbidopa is a peripheral amino acid decarboxylase inhibitor, and entacapone is a peripheral COMT inhibitor. They both act to increase the bioavailability of ^{18}F-DOPA to the brain improving the signal to noise ratio of the scans (Sawle *et al*., 1994; Cumming *et al*., 1995).

PET scans were performed using the ECAT/EXACT HR 962 (Siemens/CTI) 3D PET camera with a total axial field of view of 15.5 cm. This camera has a mean image transaxial resolution (3D mode) over a 10-cm radius field of view (from the centre) of 6.0 $\pm$ 0.5 mm (mean $\pm$ SD) and an axial resolution of 5.0 $\pm$ 0.8 mm (Brix *et al*., 1997). To correct for attenuation, a 10-min transmission scan was carried out before emission scanning. A mean dose of 215 $\pm$ 5.3 MBq of ^{18}F-DOPA was administered as an intravenous bolus over 10 s. Dynamic data were acquired in 26 time frames over 90 min for the first scan period (early scan). The subjects were positioned such that the orbitomeatal line was parallel to the transaxial plain of the tomography and head position was maintained with a soft strap across the forehead to minimize head movement. The exact position where the cross-hair laser light from the scanner fell on the patient's forehead was marked with a waterproof marker pen to facilitate repositioning of the patient for the subsequent scan. Following completion of the early scan, patients were removed from the scanner for 60 min and subsequently repositioned and data acquired in six time frames from 150 to 210 min post injection. In real time, the second scan started 2.5 h post injection of ^{18}F-DOPA (late scan). To allow for changes in head position between early and late time frames, a second 10-min transmission scan was performed at the end of the late scan to facilitate accurate attenuation correction of the late emission images.

Positron emission tomography data analysis

Analysis of PET data was performed using an *a priori* defined region of interest approach. It has been shown from a number of studies that F-DOPA uptake in extrastriatal areas (including frontal regions) in both patients with Parkinson's disease and healthy individuals can be quantified and compared across groups of subjects (Moore *et al*., 2003, 2008; Politis *et al*., 2012). ^{18}F-DOPA dynamic scans underwent frame-by-frame realignment for movement correction (Montgomery

et al., 2006). All frames of each dynamic ^{18}F-DOPA scan were summed to produce an addition (ADD) image reflecting both tracer delivery and specific uptake. The summed images were normalized into standard stereotaxic Montreal Neurological Institute (MNI) space with a normal ^{18}F-DOPA PET template (Meyer *et al.*, 1999) (already in MNI space) using Statistical Parametric Mapping (SPM2) software (www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 6.5. This technique allowed for standardization of brain position and shape to best facilitate tracing of an object map. The *a priori* regions of interest were drawn manually with guidance from a well-established probabilistic brain atlas developed in-house (Duvernoy, 1999; Gousias *et al.*, 2008). Regions that were traced included the left and right superior frontal, mid-frontal, and inferior frontal gyri, anterior cingulate, orbitofrontal cortex, caudate, putamen and ventral striatum. These regions were chosen as they form part of a fronto-striatal cognitive network. Regions of interest for all the scans were traced by the same clinician to reduce inter-operator variability and bias. The object map used for the early scan was employed for the late scan of the same patient. Each object map was applied to the dynamic images and the ^{18}F-DOPA net influx constant (Ki) values for each individual region were computed using RPM in ANALYZE 8.1 software (Mayo clinic). Both early and late scans were orientated in the same PET space and normalized to the same template. Each plane of the summed image with the superimposed object map was inspected to ensure correct placement.

^{18}F-DOPA net influx constants (Ki; units: ml/min/g) were calculated using the Patlak graphical approach (Patlak *et al.*, 1983). A reference region input function representing non-specific tissue uptake was used to generate Ki values and was obtained by sampling the cerebellum and occipital cortex (previously validated in Brooks *et al.*, 1990). The Ki values for each of the left and right regions were averaged to provide a mean value for statistical analysis.

Statistical analysis

Statistical analyses were performed with SPSS version 20 for Macintosh. For all comparisons, variance homogeneity and normal distribution were tested with Bartlett and Kolmogorov–Smirnov tests. The Student two-tailed *t*-test was used to test for differences in clinical demographics between the two groups (Table 1). To compare Ki influx constants for different regions of interest in early and late scans in each group of patients, ANOVA was employed, where the Bonferroni correction was applied to compare selected pairs *post hoc*, e.g. when comparing superior frontal Ki values during early and late scans in the Val/Val group (Supplementary Tables 1 and 2). To compare Ki influx constants for different regions of interest between the two groups (Met/Met versus Val/Val) for early and late scans, analysis of covariance was employed to control for the effect of age as a covariate (Table 2 and Supplementary Table 3). The alpha level was set at $P < 0.05$.

Results

Patients

The two groups of patients were matched for disease duration, age, gender, predicted verbal IQ and Unified Parkinson's Disease Rating Scale measures. There were equal numbers of patients in both groups taking a dopamine agonist ($n = 4$), the levodopa equivalent daily dose of their dopamine intake, the amount of levodopa and the total daily dose of dopamine replacement therapy were not significantly different between the two groups. None of the patients were depressed, demented or on centrally acting COMT inhibitors (Table 1).

Comparison of early and late ^{18}F-DOPA scans

^{18}F-DOPA influx constants (Ki) were significantly reduced in both frontal and striatal regions during the late scan compared with the early scan (Fig. 1 and Supplementary Tables 1 and 2).

Comparison of the early ^{18}F-DOPA scans between COMT Val^{158}Met genotypes

We found no significant early scan (0–90 min) Ki differences between the two groups of patients for frontal and striatal regions of interest using ANCOVA comparing Ki values across all *a priori* defined regions of interest (Supplementary Table 3 and Supplementary Figs 1 and 2].

Comparison of the late ^{18}F-DOPA scans between COMT Val^{158}Met genotypes

Patients with Parkinson's disease with Met/Met homozygosity had higher late scan (150–210 min) Ki values compared with patients with Val/Val homozygosity. When interrogated with analysis of covariance, significant differences were seen in the superior frontal, mid-frontal gyri, anterior cingulate cortex and orbitofrontal cortex. Ki values for the inferior frontal were also lower in the Val/Val group compared with Met/Met homozygotes but the difference was not significant (Table 2, Figs 2, 3 and 4).

Discussion

This study is the first to investigate resting basal dopamine turnover, as reflected by ^{18}F-DOPA uptake in frontal cortex, as a function of the COMT Val^{158}Met polymorphism in patients with early stage idiopathic Parkinson's disease. Using a prolonged scanning protocol, we found that subjects who were Met/Met homozygotes had significantly higher mean late Ki values in the superior frontal, mid-frontal, anterior cingulate and orbitofrontal cortex compared with Val/Val patients, indicating a relatively higher level of frontal presynaptic dopamine storage by the Met/Met homozygotes. There was also a trend for mean Ki values to be higher for the inferior frontal gyrus and orbitofrontal cortex in the Met/Met group compared with the Val/Val group, but these differences were no longer significant after a correction for multiple comparisons.

^{18}F-DOPA is an analogue of L-DOPA and a marker for presynaptic dopamine integrity. Regional concentrations of F-DOPA initially reflect the activity of aromatic amine decarboxylase and later, COMT. As such, ^{18}F-DOPA PET provides a marker for the *in vivo* investigation of catecholamine turnover. Our study has

Table 2 Mean regional Ki values during late scan for the two groups of COMT polymorphisms

Regions of interest	Ki influx constants during late scan for Val/Val and Met/Met groups		*F*-score *F*(1,17)	*P*-value	Partial η^2 value
	Val/Val	Met/Met			
Superior frontal	0.252 (0.139)	0.516 (0.228)	0.127	0.018*	0.285
Middle frontal	0.266 (0.129)	0.616 (0.295)	0.078	0.015*	0.302
Inferior frontal	0.279 (0.140)	0.493 (0.253)	0.068	0.081	0.168
Anterior cingulate	0.401 (0.192)	0.743 (0.229)	0.553	0.004*	0.386
Orbitofrontal cortex	0.341 (0.124)	0.579 (0.208)	0.086	0.019*	0.283
Caudate	2.262 (1.888)	3.522 (1.637)	0.566	0.101	0.150
Putamen	3.330 (1.872)	2.915 (1.415)	0.567	0.472	0.031
Ventral striatum	2.795 (2.289)	4.083 (2.197)	0.593	0.164	0.110

All numerical values are multiplied by a factor of 1000 for ease of interpretation. Values represent mean (SD). Statistical significance calculated using analysis of covariance, controlling for the effect of age as a covariate between Val/Val and Met/Met groups.
*Statistical significance, $P < 0.05$.

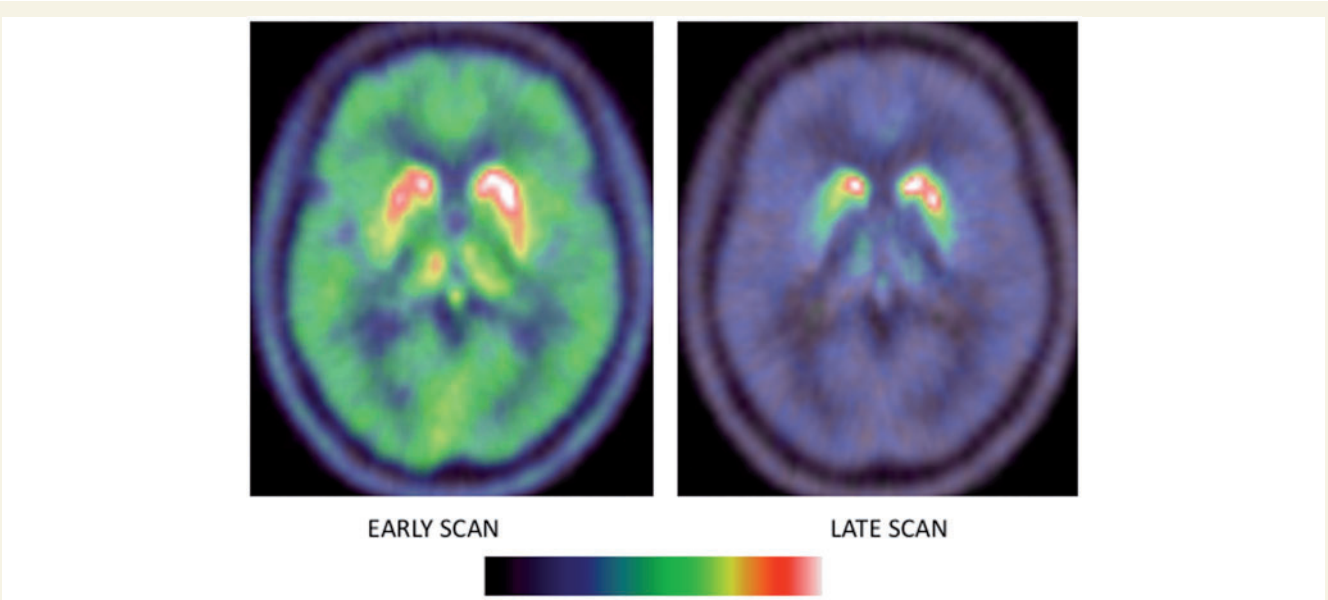

Figure 1 Representative ^{18}F-DOPA PET images of a patient during early and late scan. *Left*: early scan (0–90 min), *right:* late scan (150–210 min).

demonstrated that the low COMT activity associated with the Met allele of the COMT Val^{158}Met functional polymorphism is associated with a relative increase in ^{18}F-DOPA storage reflecting higher terminal dopamine levels in the frontal cortex compared with its Val allele counterpart. More importantly, this disparity of dopamine turnover in the frontal regions between the two groups of patients with Parkinson's disease was apparent at rest, independent of any involvement or active tasks, suggesting a fundamental difference in dopamine states at baseline. This emphasizes the critical role of the COMT Val^{158}Met functional polymorphism in regulating dopamine turnover in this anatomical region and its likely influence on frontal cognitive task processing.

Dopamine has long been known to modulate cortical striatal circuits and performance on executive tasks such as working memory. Administration of dopamine D_1 agonists and antagonists in animal studies have shown that the influence of dopamine on cognitive function is complex and non-linear; both too little (Sawaguchi and Goldman-Rakic, 1994) and too much (Zahrt *et al*., 1997) D_1 receptor stimulation can impair prefrontal cortex function in rats (Granon *et al*., 2000) and monkeys (Arnsten and Gondman-Rakic, 1998; Collins *et al*., 1998; Crofts *et al*., 2001). It has, therefore, been postulated that in the prefrontal cortex, the way in which dopamine modulates cortical processing is best modelled using an inverted U-shaped curve, where there is an optimal dopamine level for cognitive efficiency [Fig. 5; for a review, see Williams and Castner (2006)]. Functional magnetic resonance investigations in humans have revealed findings in keeping with this, by using tasks that activate prefrontal cortex function, and finding that prefrontal dopamine transmission operates within a limited optimal range for efficient cortical function (Cools *et al*., 2011).

Indeed, as COMT has a crucial role in the metabolism of synaptic dopamine in the frontal cortex due to the relative lack of

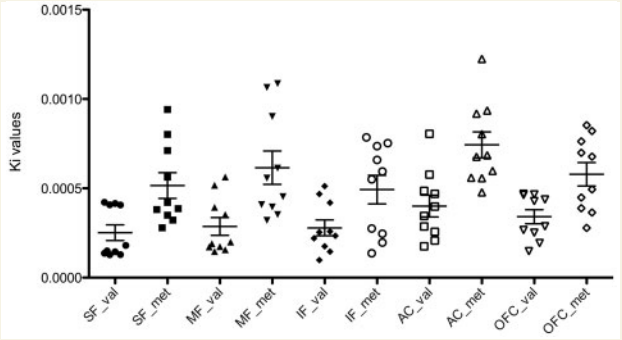

Figure 2 Scatter plot of ^{18}F-DOPA influx constant (Ki) of frontal regions during the late scan. AC = anterior cingulate; IF = inferior frontal gyrus; Met = Met/Met homozygote patients with Parkinson's disease; MF = mid-frontal gyrus; OFC = orbitofrontal cortex; SF = superior frontal gyrus; Val = Val/Val homozygote patients with Parkinson's disease.

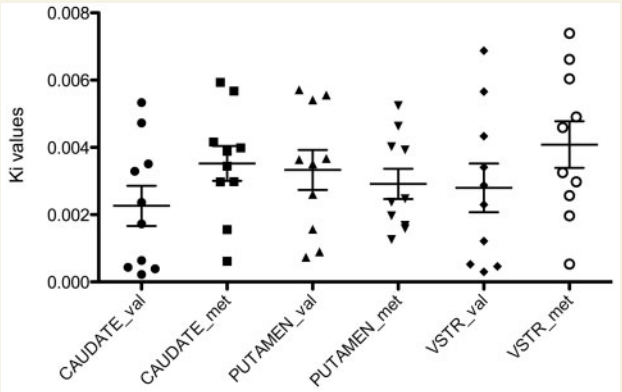

Figure 3 Scatter plot of ^{18}F-DOPA influx constant (Ki) of striatal regions during late scan. Met = Met/Met homozygote patients with Parkinson's disease; Val = Val/Val homozygote patients with Parkinson's disease.

transporters in this region (Karoum *et al*., 1994; Huotari *et al*., 2002), it follows that any changes that affect the efficiency of this enzyme, such as the Val^{158}Met functional polymorphism, may in turn affect cognitive processes. In healthy subjects, an increasing number of Met alleles is associated with better performance on prefrontal functions (Malhotra *et al*., 2002; Blasi *et al*., 2005). Volunteers with the Val allele performed worse on the Wisconsin Cart Sorting Task, a test of attentional set shifting, and the N-back working memory task (de Frias *et al*., 2005; Caldu *et al*., 2007, Aguilera *et al*., 2008). This finding is supported by functional MRI studies, which report that healthy subjects with Val alleles show increased activation in prefrontal, dorsolateral and cingulate cortices (Goldberg *et al*., 2003; Blasi *et al*., 2005; de Frias *et al*., 2005; Bertolino *et al*., 2006; Mier *et al*., 2009) compared with Met alleles who demonstrated greater efficiency of prefrontal function as measured by the extent of activation on functional MRI in a working memory task. Results from these studies fit well with PET imaging studies in healthy subjects, where Val-carriers with relatively increased midbrain dopamine synthesis (as measured with ^{18}F-DOPA uptake) showed good correlations with N-back dorsolateral prefrontal cortical activation (measured with ^{15}O-H_2O) regional cerebral blood flow, while prefrontal activation in Met homozygotes positively correlated with midbrain dopamine synthesis (Meyer-Lindenberg *et al*., 2005). These results suggest that individuals with normal presynaptic dopaminergic integrity fit tightly to the left hand ascending side of the inverted-U dopamine curve.

In patients with schizophrenia, abnormalities in the frontocortical dopaminergic pathways have long been observed (Weinberger *et al*., 1988; Lisman *et al*., 1998; Egan *et al*., 2001; Harrison and Weinberger, 2005), but similar to healthy individuals, it is the Val carriers that predict worsening cognitive deficits compared with their met counterparts (Ramsey *et al*., 2002; Callicott *et al*., 2003). This is thought to be due to a relative hypodopaminergic state in the prefrontal cortex in schizophrenic subjects with a Val/Val genotype, and is supported by the observation of an improvement in cortical efficiency of schizophrenic patients with Val/Val genotype following administration of low doses of amphetamine, in comparison with the Met/Met counterparts (Mattay *et al*., 2003). In addition, a PET study with ^{15}O-H_2O demonstrated that patients with schizophrenia who possessed the Val allele showed reduced regional cerebral blood flow in the dorsolateral prefrontal cortex compared with healthy controls (Meyer-Lindenberg *et al*., 2005). In a separate study, the COMT Val genotype was related to worse performance on the Wisconsin Cart Sorting Task in patients with schizophrenia and accounted for 4% of the variance in frequency of perseverative errors (Egan *et al*., 2001). Furthermore, during functional MRI with a working memory task, Egan *et al.* (2001) found that Met allele load consistently showed a more efficient physiological response in the prefrontal cortex. Using the same cohort for family-based association analysis, they found a significant increase in transmission of the Val allele to the schizophrenic offspring. These data converge to suggest that the COMT Val allelic variant has a detrimental effect on prefrontal cortical function in patients with schizophrenia.

Interestingly, in medicated patients with Parkinson's disease this pattern is reversed, patients with Met alleles tend to perform worse on cognitive tasks compared with those with Val alleles. In the first study to look at this, Foltynie *et al*. (2004) showed that Val homozygotes with early Parkinson's disease perform better in the Tower of London planning tasks. A follow-up study by Williams-Gray *et al*. (2007, 2008) also showed, using a cognitive task to fractionate components of attentional control, that Met/Met patients treated with levodopa were impaired in attention shifting, in association with underactivation of frontoparietal regions on functional MRI. This may be because levodopa in the Met homozygotes means patients sit of the right hand side of the curve, which is associated with them being less efficient at tasks that activate this network.

In Parkinson's disease, our study is the first to provide *in vivo* evidence of a functional effect of the COMT Val^{158}Met polymorphism on prefrontal dopaminergic tone in a task-independent resting state in brain regions that are important in executive processing. This fundamental difference suggests that Met homozyotes with early Parkinson's disease have higher frontal dopamine

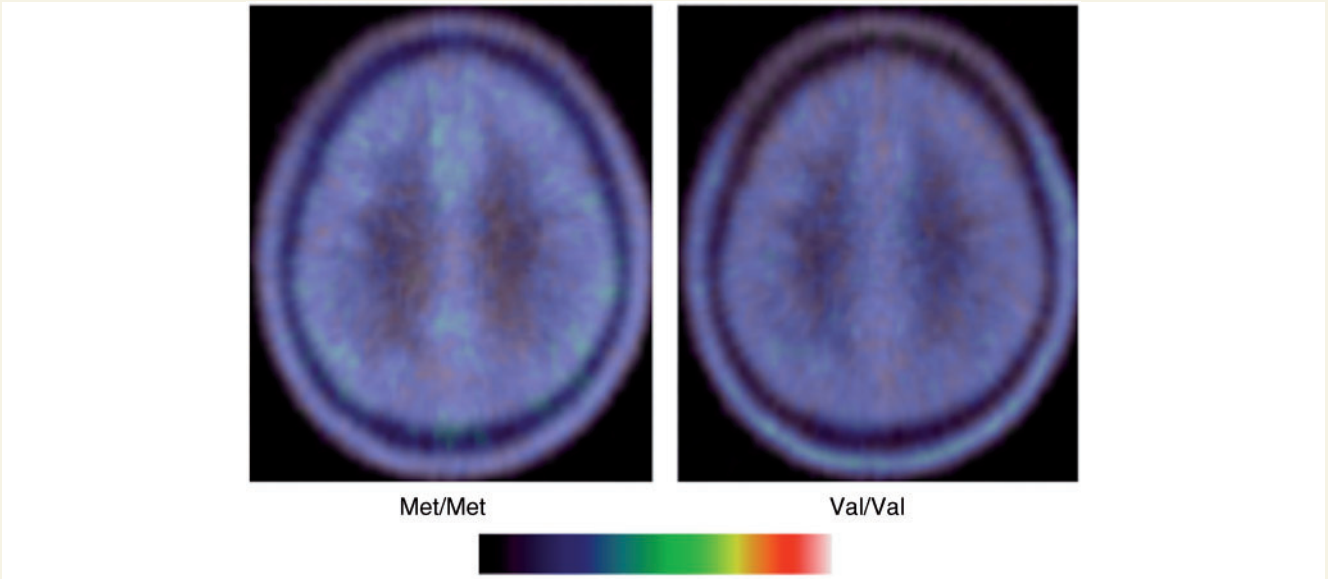

Figure 4 Representative ^{18}F-DOPA PET images of frontal cortex during late scan for Met and Val homozygotes. *Left*: Met homozygote patients with Parkinson's disease; *right*: Val homozygote patients with Parkinson's disease.

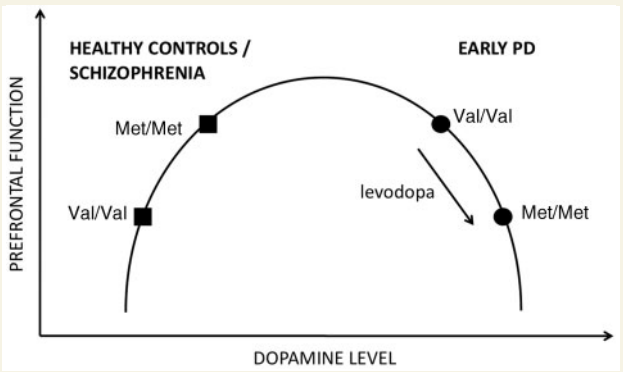

Figure 5 Inverted U-shaped curve between dopamine level and prefrontal function. One's position on the curve will be dependent on cognitive processes, disease states, genetic and environmental influences. Evidence suggests that Met allelic variants in health and schizophrenia operate better due to a more optimal level of prefrontal dopamine compared with their Val counterparts, while medicated patients with Parkinson's disease with Met allelic variants are pushed to the right side of the curve due to a hyperdopaminergic state. PD = Parkinson's disease.

levels when off medication, and while dopaminergic therapy is effective at replacing striatal losses and alleviating motor symptoms, the treatment may cause an excess of dopamine in the frontal cortical regions in Met homozygotes. This would be a problem especially in early Parkinson's disease, as other imaging studies have shown that there is a hyperdopaminergic state in the prefrontal cortex of such patients (Cools *et al*., 2010; Jahanshahi *et al*., 2010). This hyperdopaminergic state, pushing the patients towards the right descending side of the inverted U-shaped curve, could then account for some of their cognitive deficits as we have shown previously.

Understanding the precise role of dopamine in different parts of the fronto-striatal network and its influence on cognitive performance has important implications for the management of Parkinson's disease. Non-motor features of Parkinson's disease, such as cognitive decline, have an important influence on the quality of life of patients and their carers, as well as a social cost burden. It is, therefore, important to employ appropriate doses of pharmacological agents so as not to further worsen cognitive deficits, particularly for vulnerable patients with Parkinson's disease who carry the Met allele.

In the general population in Western Europe, it has been shown that Europeans have nearly equal frequencies of the two alleles (Palmatier *et al*., 1999). In an age of evidence-based practice, advocating the use of research evidence for best management of each individual patient, the notion of 'medication-by-genotyping' may be a feasible rationale towards a patient-centred approach to the optimal prescribing of dopamine replacement therapy to control motor symptoms while sustaining the best possible level of frontal cognitive function. In addition, our results indicate that it is imperative that future studies investigating frontal cognitive function should be stratified by COMT Val^{158}Met genotype, as this functional polymorphism has a significant effect on the baseline dopamine turnover.

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Supplementary material

Supplementary material is available at *Brain* online.

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