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The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort

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Cognitive abnormalities are common in Parkinson's disease, with important social and economic implications. Factors influencing their evolution remain unclear but are crucial to the development of targeted therapeutic strategies. We have investigated the development of cognitive impairment and dementia in Parkinson's disease using a longitudinal approach in a population-representative incident cohort (CamPaIGN study, *n* = 126) and here present the 5-year follow-up data from this study. Our previous work has implicated two genetic factors in the development of cognitive dysfunction in Parkinson's disease, namely the genes for catechol-*O*-methyltransferase (*COMT* Val^{158}Met) and microtubule-associated protein tau (*MAPT*) H1/H2. Here, we have explored the influence of these genes in our incident cohort and an additional cross-sectional prevalent cohort (*n* = 386), and investigated the effect of *MAPT* H1/H2 haplotypes on tau transcription in post-mortem brain samples from patients with Lewy body disease and controls. Seventeen percent of incident patients developed dementia over 5 years [incidence 38.7 (23.9–59.3) per 1000 person-years]. We have demonstrated that three baseline measures, namely, age ⩾72 years, semantic fluency less than 20 words in 90 s and inability to copy an intersecting pentagons figure, are significant predictors of dementia risk, thus validating our previous findings. In combination, these factors had an odds ratio of 88 for dementia within the first 5 years from diagnosis and may reflect the syndrome of mild cognitive impairment of Parkinson's disease. Phonemic fluency and other frontally based tasks were not associated with dementia risk. *MAPT* H1/H1 genotype was an independent predictor of dementia risk (odds ratio = 12.1) and the H1 versus H2 haplotype was associated with a 20% increase in transcription of 4-repeat tau in Lewy body disease brains. In contrast, *COMT* genotype had no effect on dementia, but a significant impact on Tower of London performance, a frontostriatally based executive task, which was dynamic, such that the ability to solve this task changed with

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disease progression. Hence, we have identified three highly informative predictors of dementia in Parkinson's disease, which can be easily translated into the clinic, and established that *MAPT* H1/H1 genotype is an important risk factor with functional effects on tau transcription. Our work suggests that the dementing process in Parkinson's disease is predictable and related to tau while frontal-executive dysfunction evolves independently with a more dopaminergic basis and better prognosis.

Keywords: Parkinson's disease; dementia; cognitive deficits; microtubule-associated protein tau; catechol-*O*-methyltransferase

Abbreviations: *COMT* = the gene coding for catechol-*O*-methyltransferase; gDNA = genomic DNA; *MAPT* = the gene coding for microtubule-associated protein tau; MCI = mild cognitive impairment; OR = odds ratio; PIGD = postural instability and gait disturbance; PRM = Pattern Recognition Memory; SRM = Spatial Recognition Memory; TOL = Tower of London

Introduction

Although Parkinson's disease is classically defined as a movement disorder, cognitive abnormalities including dementia are a common feature (Aarsland *et al*., 2003) and have a major impact on quality of life (Schrag *et al*., 2000), survival (Buter *et al*., 2008) and the need for nursing home placement (Aarsland *et al*., 2000), with important implications for the cost of care. An understanding of the evolution and neural basis of cognitive dysfunction in Parkinson's disease is essential both prognostically and for the development of targeted therapeutic strategies, especially given the recent interest in the concept of mild cognitive impairment (MCI) in Parkinson's disease as a precursor of dementia (Caviness *et al*., 2007).

Pathological changes in Parkinson's disease occur in a predictable sequence, with Lewy body deposition in the nigrostriatal system during the early stages and pathological changes within the cortex occurring later (Braak *et al*., 2002). The cognitive correlates of these changes appear to be frontostriatal executive deficits and dementia, leading to assumptions that the former evolve into the latter, and indeed executive dysfunction has been described as a key clinical component of Parkinson's disease dementia (Dubois and Pillon, 1997; Emre *et al*., 2007). Our own work, however, suggests otherwise. Through longitudinal investigation of an incident population-based cohort of Parkinson's disease patients (the CamPaIGN cohort), we have previously described two types of cognitive dysfunction in the early stages of the disease, which differ in terms of their prognosis. While frontostriatal executive deficits were indeed found to be common in early disease, they did not appear to evolve into dementia over 3.5 years of follow-up, whereas more posterior cortically based deficits did (Williams-Gray *et al*., 2007*a*). In addition, there appeared to be genetic influences on these cognitive deficits. In particular, a common functional polymorphism in the catechol-*O*-methyltransferase gene (*COMT* $Val^{158}Met$), which alters the activity of this dopamine-regulating enzyme by 40% in human prefrontal cortex (Chen *et al*., 2004), impacts on both performance (Foltynie *et al*., 2004*b*) and underlying frontal brain activation (Williams-Gray *et al*., 2007*b*, 2008) during executive tasks in Parkinson's disease patients. In contrast, a commonly inverted genomic region containing the microtubule-associated protein tau gene (*MAPT*, H1 haplotype) was strongly associated with dementia risk over 3.5 years of follow-up in our incident cohort (Goris *et al*., 2007). Hence, it seems that executive deficits in Parkinson's disease are mediated, at least in part, by variations in dopaminergic activity in frontal regions, while the dementing process is influenced by genetic variation of tau, a protein that is strongly implicated, together with alpha-synuclein, in protein aggregation during Parkinson's disease (Galpern and Lang, 2006). However, despite apparent epidemiological and genetic differences, it remains unclear whether the executive dysfunction of Parkinson's disease and the dementing process are truly dissociable.

Furthermore, there is little direct evidence for a mechanism by which the *MAPT* genotype predisposes to protein aggregation and dementia in Parkinson's disease. Disruption in relative amounts of transcription of tau isoforms with three or four microtubule-binding domains (3- or 4-repeat tau) has been demonstrated in the tauopathies (Hutton *et al*., 1998, Chambers *et al*., 1999) and, more recently, in Parkinson's disease (Tobin *et al*., 2008). Other work has suggested that *MAPT* H1 or H1 subhaplotypes result in an increased expression of total tau or of 4-repeat tau (Kwok *et al*., 2004; Rademakers *et al*., 2005; Caffrey *et al*., 2006; Myers *et al*., 2007), although this has not been demonstrated in Parkinson's disease brain to date.

We now report the 5-year follow-up of our incident Parkinson's disease cohort, validating and extending our previous findings of the clinical and genetic predictors of dementia. In addition, we have more fully investigated the basis and significance of frontostriatal task performance using both this incident group of patients and a larger cross-sectional cohort, comprising over 500 Parkinson's disease patients in total. Finally, we have sought to explore the link between *MAPT* genotype, tau transcription and dementia using post-mortem Lewy body disease brain.

Materials and methods

Subjects

Subjects included an incident community-based population-representative cohort of patients with Parkinson's disease ($n = 126$) (Foltynie *et al*., 2004*a*; Williams-Gray *et al*., 2007*a*), as well as prevalent patients recruited from the Parkinson's disease Research Clinic at the Cambridge Centre for Brain Repair ($n = 386$). All met United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank diagnostic criteria (Gibb and Lees, 1988) and provided written consent for genetic analysis of their DNA. Approval from the Local Research Ethics Committee was obtained.

Clinical assessment

All patients underwent a comprehensive battery of clinical and neuropsychological tests as used previously (Foltynie *et al*., 2004*a*; Williams-Gray *et al*., 2007*a*) on at least one occasion. These included the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987), the Beck Depression Inventory (Beck *et al*., 1961), the Schwab and England scale of functional independence (Schwab and England, 1969), the 30 item Minimental State Examination (MMSE) (Folstein *et al*., 1975), the National Adult Reading Test (NART, a measure of verbal IQ) (Nelson and O'Connell, 1978), a test of phonemic fluency for words starting with the letters F, A and S for 1 min each (Benton, 1968), a test of semantic fluency for animals in a 90 s period (Goodglass, 1972) and selected neuropsychological tests from the computerized Cambridge neuropsychological test automated battery (CANTAB) including pattern and spatial recognition memory (PRM and SRM) (Sahakian *et al*., 1988) and the 'one-touch' Tower of London (TOL) (Owen *et al*., 1995). In addition, patients within the incident cohort completed a pentagon copying test derived from the MMSE, scored using a 0–2 rating scale modified from Ala *et al*. (2001) as previously described and used (Williams-Gray *et al*., 2007*a*). Patients were classified in terms of motor phenotype as 'tremor dominant', 'mixed' or 'postural instability and gait disturbance' (PIGD) on the basis of tremor and PIGD scores derived from the motor subsection of the UPDRS (Zetusky *et al*., 1985). Doses of dopaminergic medication at the time of assessment were recorded and converted to equivalent levodopa doses using the formula previously adopted (Williams-Gray *et al*., 2007*a*). All clinical and neuropsychological assessments were performed with patients taking their usual medications and, if motor fluctuations were apparent, assessments were conducted in the peak 'on' state where possible.

Genotyping

DNA was extracted from peripheral blood samples using standard phenol/chloroform techniques. Genotyping for rs4680 (*COMT* Val^{158}Met) and rs9468 (tagging *MAPT* H1 versus H2 haplotype) was performed using an allelic discrimination assay and run on an HT7900 detection system (Applied Biosystems).

CamPaIGN follow-up

The original CamPaIGN cohort comprised 239 patients with incident Parkinsonism of whom 159 were diagnosed with idiopathic Parkinson's disease (Foltynie *et al*., 2004*a*). At 3.5 years, the idiopathic Parkinson's disease cohort comprised 126 surviving patients in whom diagnoses had been revalidated using the UKPDS Brain Bank criteria. Attrition rates up to 3.5 years were relatively low (15% mortality, 7% lost to follow-up; see Williams-Gray *et al*., 2007*a*). Further follow-up was now conducted over a 9 month period between September 2006 and May 2007, approximately 5 years from diagnosis.

Dementia was diagnosed on the basis of a MMSE of less than or equal to 24 and fulfilment of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for dementia as previously (Williams-Gray *et al*., 2007a). The application of DSM-IV criteria was standardized where possible. Criterion A, requiring memory impairment plus impairment of at least one other 'higher cortical function', was evaluated using pre-defined cut-off values on our neuropsychological test battery. These cut-offs represented a score 1 SD below the mean in age-matched control cohorts, as described in Williams-Gray *et al*. (2007*a*) [14/20 for SRM, 16/20 for PRM and 8/14 for the TOL (number correct); 25 words in 3 min for phonemic fluency and 16 words in 90 s for semantic fluency]. A cut-off of <2 was used for the pentagon copying test as described previously (Williams-Gray *et al*., 2007*a*). Criterion B, relating to impairment of occupational and social functioning, required a functional independence score on the Schwab and England scale of $\leqslant$60% (denoting an inability to perform certain activities of daily living), although some subjective judgement was required to determine whether this disability was attributable to cognitive rather than motor impairment. Dementia incidence was estimated using the person-years method; that is, by dividing the number of cases of dementia by the number of 'at risk' person-years of follow-up. For cases of incident dementia, time of dementia onset was assumed to be the midpoint of the interval between assessments (Aarsland *et al*., 2001; Williams-Gray *et al*., 2007*a*).

The relationship between potential predictor variables (baseline clinical/neuropsychological scores, *COMT* and *MAPT* genotypes) and cognitive decline (change in MMSE per year) over 5 years was evaluated using the same bivariate and multivariate methods as previously (Williams-Gray *et al*., 2007a). Specifically, non-categorical variables were dichotomized at the median, and between-group comparisons of mean change in MMSE per year were made using Student *t*-tests or one-way analysis of variance (ANOVA) as appropriate. Baseline variables or genotypes significantly associated with cognitive decline in these bivariate analyses ($P \leqslant 0.05$) were entered into a multivariate regression analysis using a backward stepwise method (criteria for removal of variables $P > 0.10$) with 'change in MMSE per year' as the dependent variable, the aim being to identify the most important determinants of cognitive decline. The impact of these predictors on dementia risk was subsequently explored using logistic regression analysis. Dementia status based on cumulative data collected over the 5 year follow-up period was used as the dependent variable. Variables significantly associated with cognitive decline over 5 years in bivariate analyses were selected for entry into the logistic regression model and a backward stepwise method was employed as previously.

Cross-sectional analyses

The relationship between *COMT* genotype and cognitive performance was explored in the whole cohort (incident and prevalent) using bivariate and multivariate analyses. The primary outcome of interest was the impact of *COMT* genotype on performance of the TOL, a test of planning and working memory with a predominantly frontostriatal basis (Owen *et al*., 1996; Dagher *et al*., 1999). Further to the well-established inverted U-shaped function relating prefrontal function to dopaminergic activity (Goldman-Rakic *et al*., 2000), we had a strong *a priori* hypothesis that the impact of *COMT* genotype would alter with disease progression. Hence, subgroup analyses were performed to examine the effect of *COMT* genotype on TOL score in 'early' versus 'later' disease. Subgroups were defined on the basis of disease duration by dichotomizing at the median.

Different *COMT* geneotypes and Tower of London test performance over time

The hypothesis that different *COMT* genotypes would have differential effects on longitudinal changes in executive function, was investigated in the incident cohort by comparing mean change in TOL score per year over the 5 year follow-up period across genotypic groups using non-parametic (Kruskall–Wallis) tests.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 11.5.

Tau transcription in post-mortem brains

The Parkinson's Disease Society brain bank (Imperial College, London) provided anonymous brain tissue from the frontal cortex (Brodmann's area 46) of 61 cases with Lewy body disease (idiopathic Parkinson's disease or dementia with Lewy bodies) and 17 controls with no histopathological evidence of neurodegenerative disease. Brain samples were flash-frozen, unfixed and maintained at −80°C. DNA was prepared using the Qiagen DNeasy kit. Samples were genotyped for the *MAPT* H1/H2 polymorphism (rs9468) using Taqman Assays-by-Design single nucleotide polymorphism assay C_7 563 752_10 on a 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). H1/H2 heterozygotes were selected for by an allele-specific real-time PCR expression assay allowing comparison of relative amounts of transcription from variant alleles in a single sample, thus controlling for differences in RNA yield.

RNA was extracted from 300 mg samples of cortical grey matter with an initial homogenization in Trizol reagent (Invitrogen) followed by column purification using the RNeasy mini kit (Qiagen) and treatment with DNAase (Roche Diagnostics) to ensure no contamination by genomic DNA (gDNA). RNA yield was determined by spectrophotometry. cDNA was synthesized using Superscript≈ III reverse transcriptase (Invitrogen) using random hexamers as primers.

Allele-specific real-time PCR analysis was conducted on cDNA from H1/H2 heterozygotes utilizing the primer/probe sets previously used by Myers *et al*. (2007). The primers have been designed to span exon 9, contained in all tau transcript isoforms, and exon 10, present only in 4-repeat containing transcripts. The two probes used took advantage of allele-specific sequence differences in 3-repeat and 4-repeat transcripts selectively to label these transcripts as originating from either the H1 or H2 allele. Probes were 5′ labelled with either carboxyfluorescein (FAM) or VIC.

Samples were analysed using a 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). All reactions were repeated six times and relative quantification data analysed using standard delta–delta cycle-threshold methods.

To control for potential allele-specific differences in probe binding, efficiency reactions were repeated using genomic DNA from H1/H2 heterozygotes. As the starting quantity of H1 and H2 are equal when gDNA is used, a non-zero value for delta cycle-threshold would indicate a probe-specific effect upon the amplification efficiency of the PCR reaction. In practice, we found a non-zero delta cycle-threshold (Supplementary Table 5) and, therefore, evidence for such an effect. By repeating the RT–PCR reaction with serial dilutions of genomic DNA, we constructed a standard log plot of cycle-threshold value versus relative concentration of starting material which enabled quantification of the PCR amplification efficiency for each allele independently using a standard method.

Results

A total of 126 incident and 386 prevalent patients were recruited (see Table 1 for patient details). Genotype frequencies did not differ significantly from the predictions of the Hardy Weinberg equilibrium ($P > 0.05$). Among the post-mortem samples, 17 H1/H2 heterozygotes were identified for the allele-specific transcription analysis including 10 cases with Lewy body disease and 7 controls.

CamPaIGN follow-up

The cohort comprised of 126 patients following the 3.5 year assessment. The current round of follow-up was conducted at a mean (SD) time from diagnosis of 5.2 (0.4) years. Seventeen of the 126 died prior to this visit. Four withdrew consent to participate in further clinical assessment, but underwent a telephone interview and review of hospital case notes, thus allowing us to assess whether dementia was likely. One hundred and five were fully assessed, following which a further 4 were excluded, 2 due to resolution of symptoms off dopaminergic medication and 2 due to evolution of symptoms leading to a change in diagnosis, while the remaining 101 still met UKPDS Brain Bank criteria.

Dementia incidence

Figure 1 summarizes outcomes in terms of dementia status among the 122 incident Parkinson's disease patients (following the retrospective exclusion of the four non-Parkinson's patients identified at this 5.2 years of follow-up) at both 3.5 and 5.2 years. All were non-demented at diagnosis. Twenty-one incident dementia cases were identified cumulatively over 5.2 years of follow-up, corresponding to a dementia incidence estimate of 38.7 per 1000 person-years of observation (95% confidence intervals 23.9–59.3).

In 13 individuals with a confirmed Parkinson's disease diagnosis, outcome in terms of dementia status could not be established beyond 3.5 years due to death. An adjustment for mortality can

Table 1 Demographic, clinical and genotypic characteristics of the Parkinson's disease cohorts

	Incident	Prevalent	Combined
n	126	386	512
Gender (% male)	56	61	60
Age (years)	69.5 (9.9)[a]	65.4 (10.9)	66.2 (10.8)
Disease duration (years)	0.2 (0.3)[a]	4.5 (5.2)	3.5 (4.8)
UPDRS motor subscore	25.5 (11.9)[a]	24.1 (14.8)	24.4 (14.2)
MMSE	28.1(1.5)[a]	28.1 (2.4)	28.1 (2.2)
NART (verbal IQ)	109.3 (10.1)[a]	112.0 (9.9)	111.4 (9.9)
Dopaminergic therapy (%)	48[a]	82	74
MAPT H1/H1: H2 carrier	73:37	248:126	321:163
COMT Val/Val: Val/Met: Met/Met	30:53:29	86:198:103	116:251:132

Values are expressed as mean (SD) with the exception of gender and genotype.
a At baseline assessment.

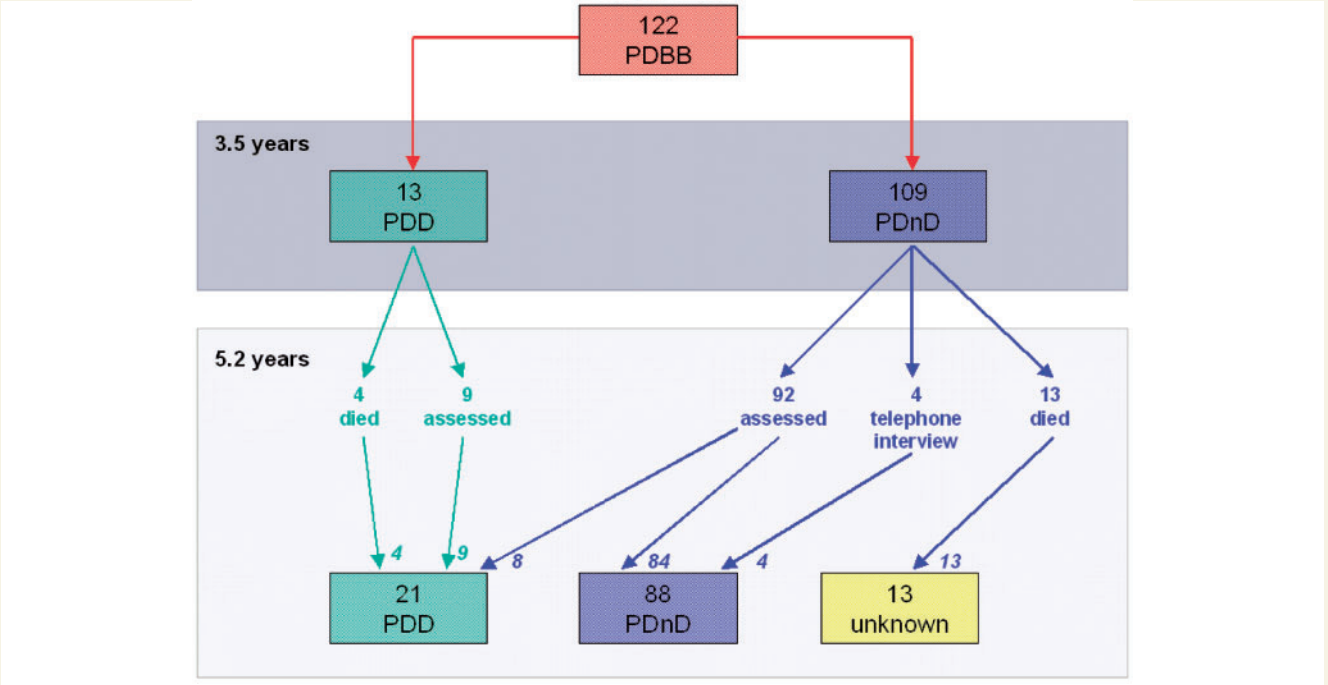

Figure 1 Longitudinal outcomes in terms of dementia status in the 122 incident Parkinson's disease patients meeting UKPDS Brain Bank diagnostic criteria (PDBB). Follow-up was conducted at two time-points, at 3.5 years (Williams-Gray *et al*., 2007*a*) and 5.2 years from diagnosis. PDD = indicates Parkinson's disease with dementia; PDnD = indicates Parkinson's disease without dementia.

be made to the dementia incidence estimate if it is assumed that first, a similar proportion of these 13 patients developed dementia between 3.5 and 5.2 years of follow-up assessments as in the assessed group, that is 8.3%, or one additional case; and second, the time-point of development of dementia in this individual is the mid-point of the mean interval between the 3.5 years of follow-up visit and death for the 13 deceased patients. Applying this adjustment does not alter the 5.2 years of dementia incidence estimate significantly 37.0 (25.5–61.8) per 1000 person-years, respectively.

Risk factors for cognitive decline

MMSE scores declined at a mean rate of -0.3 ± 0.1 points per year over the 5.2 years (range +0.9 to −5.1). Bivariate analyses suggested that age $\geqslant 72$, a non-tremor dominant motor phenotype, a UPDRS motor score greater than and equal to 25, a semantic fluency score less than 20, lower pentagon copying score ($0 < 1 < 2$) and *MAPT* H1/H1 genotype were associated with a more rapid rate of cognitive decline ($P < 0.05$, Table 2). These variables were selected for inclusion in a multivariate analysis using a backward stepwise method, which identified poor semantic fluency ($b = -0.37$, $P = 0.04$), inaccurate pentagon copying ($b = -0.37$, $P = 0.02$) and *MAPT* H1/H1 genotype ($b = -0.41$, $P = 0.02$) as significant predictors of subsequent cognitive decline over 5.2 years, independently of older age ($b = -0.52$, $P = 0.003$) (Supplementary Table 1).

Risk factors for dementia

MAPT genotype had a clear impact on dementia outcome over the 5.2 years of follow-up period, with all but one of the patients developing dementia carrying the H1/H1 genotype. Twenty-eight per cent (18/65) of H1/H1 individuals developed dementia, versus 3% (1/34) of H2 carriers ($P = 0.003$, Fisher's exact test). In contrast, dementia frequencies across *COMT* genotypic groups were similar ($P = 0.12$).

Logistic regression analysis confirmed that in addition to *MAPT* genotype, older age and poor performance on semantic fluency and pentagon copying tests at diagnosis were significant independent predictors of dementia risk within 5.2 years (Table 3). These variables are particularly useful in terms of their predictive capacity in combination. Considering the clinical predictors alone, 8/11 patients with all three clinical risk factors developed dementia within 5.2 years of follow-up versus 1/34 of those with no such risk factors, corresponding to an odds ratio (OR) of 88 (8-962). Of the 8 patients who carried the 'at risk' *MAPT* genotype in addition to all 3 clinical risk factors, 6 developed dementia versus none of the 15 patients without any of these risk factors, corresponding to a positive predictive value of 75% and negative predictive value of 85.7% for all 4 risk factors (versus less than 4 risk factors) and a positive predictive value of 22.6% and negative predictive value of 100% for possession of at least one risk factor versus no risk factors.

COMT and cognitive function

TOL scores and *COMT* genotypes were available for a total of 425 patients from both the incident and prevalent cohorts for cross-sectional analysis. Two hundred and eighty seven of these were previously included in our original study implicating *COMT* genotype as a determinant of TOL performance in Parkinson's

Table 2 Bivariate comparisons of baseline demographic, clinical and neuropsychological variables versus rate of cognitive decline over 5.2 years (change in MMSE per year) in the incident cohort, using Student *t*-test (two categories) or ANOVA (more than two categories)

Variable	Change in MMSE/year Mean (SD)	*P*-value
Age		
<72	−0.04 (0.38)	0.001
⩾72	−0.68 (1.16)	
Gender		
Male	−0.36 (0.76)	0.69
Female	−0.29 (1.02)	
Motor phenotype[a]		
Tremor dominant	−0.06 (0.44)	0.003
Mixed/PIGD	−0.55 (1.07)	
UPDRS motor score		
<25	−0.08 (0.61)	0.006
⩾25	−0.56 (1.03)	
Equivalent levodopa dose		
0	−0.32 (0.99)	0.49
1–250	−0.46 (0.72)	
251–500	−0.53 (0.94)	
501–750	−0.03 (0.33)	
751–1000	−0.01 (0.31)	
NART (IQ)		
<111	−0.37 (0.80)	0.54
⩾111	−0.26 (0.93)	
Phonemic fluency (F-A-S)		
<33	−0.43 (0.82)	0.31
⩾33	−0.24 (0.94)	
Semantic fluency (animals)		
<20	−0.69 (1.16)	0.001
⩾20	−0.03 (0.38)	
PRM score		
<19	−0.55 (1.13)	0.09
⩾19	−0.19 (0.67)	
SRM score		
<15	−0.54 (1.15)	0.13
⩾15	−0.22 (0.66)	
TOL score		
<11	−0.37 (0.81)	0.09
⩾11	−0.12 (0.61)	
Pentagon copying score		
0	−1.44 (0.87)	0.003
1	−0.52 (1.59)	
2	−0.22 (0.67)	
Beck depression score		
<7	−0.23 (0.89)	0.29
⩾7	−0.42 (0.87)	
COMT genotype		
Val/Val	−0.55 (1.28)	0.32
Val/Met	−0.20 (0.64)	
Met/Met	−0.33 (0.82)	
MAPT genotype		
H1/H1	−0.54 (1.02)	0.0003
H2 carrier (0.04) (0.46)		

Continuous variables are dichotomized at the median, with the exception of levodopa dose, which is stratified into five subgroups.
a Preliminary analyses suggested similar rates of cognitive decline in PIGD and mixed subgroups; hence, these were combined into a single subgroup for analysis.

disease (cohort 1) (Foltynie *et al*., 2004*b*) and so an initial analysis of *COMT* genotype and cognitive function confined to newly recruited individuals ($n = 138$, cohort 2) was performed. This confirmed that an increasing number of Met alleles had a significant negative impact on TOL score (*b* coefficient = −0.73, $P = 0.04$) after adjustment for potential confounding factors in a multivariate model (Supplementary Table 2). Repetition of this analysis with MMSE, semantic fluency, phonemic fluency, PRM and SRM as dependent variables demonstrated no significant effect of *COMT* genotype on any other cognitive measure.

Cohorts 1 and 2 were well matched in terms of demographic and clinical characteristics as well as *COMT* genotype distributions (Supplementary Table 3); hence, data from the two cohorts were combined ($n = 425$) prior to subgroup analysis to investigate whether the impact of genotype on TOL performance differed with disease duration. Subjects were stratified around the median disease duration of 1.6 years into 'early' and 'later' disease groups. There was a clear dissociation of the *COMT*–TOL relationship in 'early' (Pearson's $r = -0.21$) versus 'later' disease ($r = 0.10$) ($P = 0.001$, Fisher's test; see Fig. 2A). In 'early' disease, there was a significant decline in mean TOL score with an increasing number of Met alleles ($P = 0.007$, one-way ANOVA), whereas in 'later' disease, no significant relationship was found ($P = 0.35$).

Multivariate regression analyses confirmed a dissociation of the *COMT* effect on TOL performance in 'early' (*b* coefficient = −0.80, $P = 0.005$) and 'later' disease (*b* coefficient = 0.22, $P = 0.55$) (Table 4). Furthermore, overall analysis of the combined cohort revealed a significant interaction between '*COMT* Met alleles' and 'disease duration' (*b* coefficient = 1.1, $P = 0.02$), further supporting the conclusion that the relationship between *COMT* genotype and TOL score in the whole sample was dependent on disease progression (Table 4).

In addition, of the 101 incident patients assessed at the 5.2 year visit, TOL scores were available at both baseline and follow-up in 70 individuals, the remaining patients being unable to complete the test on one or both occasions due to fatigue or difficulty comprehending the task instructions. There was a significant effect of *COMT* genotype on mean change in TOL score per year (Kruskall–Wallis test, $P = 0.017$). Specifically, performance in Met homozygotes tended to improve with disease progression, in contrast to performance in Val homozygotes or heterozygotes (Fig. 2B).

Effect of *MAPT* haplotype on tau transcription

In cases with Lewy body disease at post-mortem, there was a 20% (1.2-fold) increase in the quantity of 4-repeat containing transcript originating from the H1 versus the H2 allele ($P = 0.02$), which was not seen in control brains. Total tau transcription, by contrast, was not significantly different between the two alleles in either group (Table 5 and Supplementary Table 4).

Table 3 Logistic regression model with dementia outcome over the 5.2 year period from diagnosis as the dependent variable

Variable	*b* coefficient	*P* value	OR (exp^b)	95% CIs for OR	
				Lower	Upper
Constant	−9.57	<0.001	0	–	–
MAPT H1/H1 genotype	2.50	0.03	12.14	1.26	117.36
Age ⩾72	1.57	0.03	4.81	1.14	20.23
Semantic fluency <20	1.93	0.02	6.89	1.30	36.55
Pentagon copying (0 versus 1 versus 2)	1.02	0.05	2.78	1.001	7.73
Non-TD motor phenotype	1.37	0.09	3.93	0.79	19.57

Baseline variables significantly associated with cognitive decline in bivariate analyses ($P \leqslant 0.05$, see Table 2) were entered into the model and a backward stepwise method was employed to exclude non-significant variables. Model parameters: −2 Log Likelihood = 56.87, Cox and Snell $R^2 = 0.33$, Chi-squared statistic = 39.53, $P < 0.001$. CI = confidence interval; non-TD = non-tremor dominant; exp^b = exponential of b coefficient.

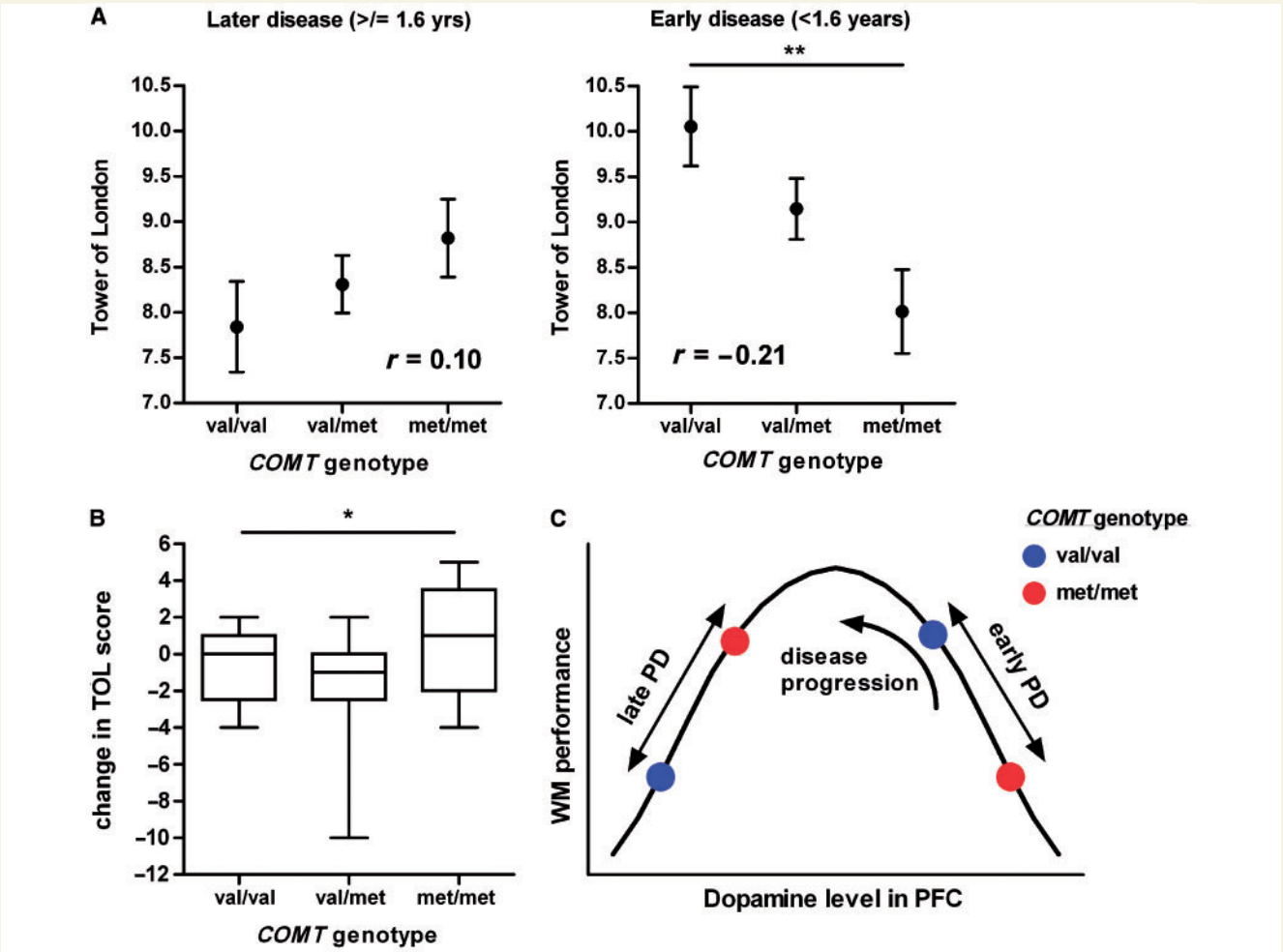

Figure 2 The relationship between *COMT* genotype and executive function, as measured using TOL performance, in Parkinson's disease is dependent on disease duration. (**A**) TOL scores (number of problems solved correctly on first attempt, maximum score 14) in patients with differing *COMT* genotypes in 'later' ($n = 203$) versus 'early' disease ($n = 222$). Dots and error bars represent mean ±SEM. **Indicates a significant between group difference at the $P < 0.005$ level. Comparison of Pearson's correlation coefficients (r) for the *COMT* versus TOL relationship using Fisher's test confirmed a significant dissociation between the slopes in 'early' versus 'later' disease subgroups ($P = 0.001$). (**B**) Change in TOL score per year in patients with differing *COMT* genotypes. TOL performance in Met homozygotes ($n = 18$) improved with disease progression, in contrast to performance in Val homozygotes ($n = 18$) or heterozygotes ($n = 34$). Means, interquartile ranges and minimum and maximum values are shown. *Indicates significance at the $P = 0.05$ level. (**C**) The hypothesized inverted U-shaped curve relating working memory [a predominantly frontal executive task] performance and dopaminergic activity in the prefrontal cortex (Goldman-Rakic *et al*., 2000), with position on the curve being determined by both disease state and *COMT* genotype. Early Parkinson's disease patients are postulated to be on the downslope of the curve with Val homozygotes being closer to the peak than Met homozygotes. As disease progresses, however, patients are expected to shift to the left. PD = Parkinson's disease; PFC = prefrontal cortex.

Table 4 Multivariate regression analysis with Tower of London score as the dependent variable

Variable	'Early' PD (<1.6 years)		'Later' PD (⩾1.6 years)		All patients	
	b coefficient	*P*-value	*b* coefficient	*P*-value	*b* coefficient	*P*-value
Constant	10.15	0.001	5.62	0.14	11.13	<0.001
COMT Met alleles	−0.78	0.007	0.28	0.46	−1.92	0.006
Gender	0.65	0.12	−0.10	0.99	0.42	0.33
Pre-morbid IQ	0.08	<0.001	0.08	0.004	0.08	<0.001
Age at assessment	−0.11	<0.001	−0.09	0.006	−0.10	<0.001
UPDRS motor score	−0.02	0.24	−0.22	0.25	−0.02	0.07
Equivalent levodopa dose	−0.001	0.14	−0.001	0.22	−0.001	0.07
Beck depression score	−0.18	<0.001	−0.03	0.48	−0.11	<0.001
Disease duration[a]	–	–	–	–	−2.00	0.001
*COMT** disease duration	–	–	–	–	1.13	0.02
Model statistics						
R^2	0.35	–	0.17	–	0.27	–
F	14.76		4.18		14.11	
P	<0.001		<0.001		<0.001	

In subgroups of patients with 'early' ($n = 201$) and 'later' disease ($n = 149$) and in the combined cohort ($n = 350$) with the inclusion of an interaction term to investigate whether the relationship between *COMT* Met alleles and TOL varies with disease duration (75 out of 425 patients were excluded from these analyses due to incomplete clinical data sets).
a Categorical variable: 'early' versus 'later' disease; PD = Parkinson's disease.

Discussion

Dementia is arguably one of the most distressing aspects of Parkinson's disease for the patient and carer and this study confirms that it is common, affecting 17% of our cohort within the first 5 years from diagnosis. This dementia incidence figure (38.7 per 1000 person-years) is approximately four times that estimated by the Medical Research Council (MRC) Cognitive Function and Ageing Study for the general UK population at a comparable age (10.3 per 1000 person-years at ages 70–74 years) (Matthews and Brayne, 2005). Previously, we reported that follow-up of an incident population-based Parkinson's disease cohort over 3.5 years identified four key factors, measurable at diagnosis, which were associated with increased rate of cognitive decline; namely older age (⩾72), poor semantic fluency (<20 animals in 90 s), inability to accurately copy an intersecting pentagons figure (Williams-Gray *et al*., 2007*a*) and the *MAPT* H1/H1 genotype (Goris *et al*., 2007). Importantly, we have now confirmed that these factors are associated with increased dementia risk at the 5.2 years of follow-up time-point. The first three of these factors are readily measurable within just a few minutes in the outpatient clinic and are extremely informative in their own right, with an estimated OR of 88. *MAPT* genotype, however, was found to be the strongest independent predictor of dementia (OR 12.1), and indeed all but one of those developing dementia carried the H1/H1 genotype. This work provides evidence that this *MAPT* H1 variant is the most important genetic factor contributing to Parkinson's disease dementia identified to date. Furthermore, we have shown for the first time that the H1 haplotype is associated with an increase in 4-repeat tau in brains with Lewy body disease, indicating that the *MAPT* association with dementia in Parkinson's disease may relate to changes in tau transcription.

Dementia incidence in this Parkinson's disease cohort is lower than estimates from previous prevalent studies (summarized in Williams-Gray *et al*., 2007*a*), which is not unexpected given that our study is the first to use an incident cohort. Nonetheless, it is possible that our figure is underestimated due to mortality. Although our mortality adjusted dementia incidence figure is not significantly different from our unadjusted figure, this adjustment relies on the assumption that individuals dement at the same rate in surviving and non-surviving groups, which may be invalid. In particular, some authors have suggested that dementia is associated with a higher mortality rate in Parkinson's disease (Louis *et al*., 1997). However, a longitudinal study following 250 prevalent Parkinson's disease patients over 5 years found no significant difference in survival between demented and non-demented groups (Nussbaum *et al*., 1998).

Until we obtain post-mortem data, we cannot exclude the possibility that some of our dementia cases represent co-existing Alzheimer's disease, a condition in which tau pathology is well known to play a central role. However, the majority of studies have failed to find an association between the *MAPT* H1 haplotype and Alzheimer's disease risk (Russ *et al*., 2001; Green *et al*., 2002; Mukherjee *et al*., 2007; Abraham *et al*., 2009). Although one study has reported an association between a subhaplotype of *MAPT* H1 with Alzheimer's disease (Myers *et al*., 2005), this association was relatively weak with the at risk haplotype occurring in only 13.91% of patients compared with 8.51% of controls. Hence, it seems unlikely that a degree of misdiagnosis among our Parkinson's disease dementia cases could account for the observed *MAPT* association.

Importantly, this study clearly demonstrates that early deficits on frontostriatally based tasks are not related to subsequent dementia risk. The dissociation between semantic and phonemic fluency in terms of predicting dementia is a crucial finding in this respect, indicating that it is the semantic, temporal lobe component of the fluency task which is predictive of cognitive decline rather than the frontally based strategic retrieval common to both fluency tasks (Henry and Crawford, 2004). Furthermore, we have

shown that frontally based planning and working memory deficits (as assessed using the TOL task) are influenced by a common genetically determined variation in *COMT* activity, an effect presumably mediated through modulation of cortical dopamine levels (Slifstein *et al*., 2008). In contrast, deficits on tasks with a more temporal and parietal lobe basis, which do evolve into later occurring dementia, are not affected by *COMT* genotype, and furthermore *COMT* had no impact on dementia risk in our longitudinal analysis. Hence, it seems that this more posterior cortically based dementing process has a non-dopaminergic aetiology. Importantly, we have established for the first time that 'frontal executive' and 'posterior cortical' cognitive syndromes in Parkinson's disease are dissociable in terms of both their genetic basis and relationship to dementia (Fig. 3). This has implications for the definition of the MCI of Parkinson's disease (Caviness *et al*., 2007). In particular, it does not seem appropriate to label all mild cognitive deficits in Parkinson's disease as MCI, but this may be better defined in terms of the posterior cortically based deficits which herald dementia. In keeping with this, a recent study using a novel Parkinson's disease Cognitive Rating Scale (PD–CRS) in cognitively intact, cognitively impaired and demented Parkinson's disease groups has shown that Parkinson's disease dementia is characterized by the addition of cortical dysfunction upon fronto-subcortically based deficits (Pagonabarraga *et al*., 2008). Given the apparent importance of posterior cortically based deficits in the MCI and dementia of Parkinson's disease, it is crucial that instruments selected to evaluate cognition in this disease in future clinical trials adequately probe posterior cortical function (Kulisevsky and Pagonabarraga, 2009).

The mechanism underlying the association between *MAPT*, increased 4-repeat tau expression and dementia in Parkinson's disease remains speculative given that neuropathological data are not yet available for the majority of the CamPaIGN cohort. However, our hypothesis that protein aggregation, and in particular cortical Lewy body formation, is central to this association is supported by a number of lines of evidence. First, clinicopathological studies demonstrate an association between cortical Lewy body deposition and the development of dementia in Parkinson's disease (Aarsland *et al*., 2005). Second, tau and alpha-synuclein are known to co-localize within Lewy bodies in Parkinson's disease brains (Ishizawa *et al*., 2003). Third, tau and alpha-synuclein have been shown to interact and fibrillize synergistically *in vitro* (Giasson *et al*., 2003). Of course, other proteins may well be involved in the dementing process. A role for β-amyloidosis has been postulated, and certainly positron emission tomography (PET) studies have reported increased cortical uptake of the β-amyloid binding radioligand ^{11}C-pittsburgh compound B (PIB) in dementia with Lewy bodies relative to controls (Rowe *et al*., 2007; Edison *et al*., 2008; Gomperts *et al*., 2008). In Parkinson's disease dementia, however, raised cortical uptake of ^{11}C-PIB is an infrequent finding (Edison *et al*., 2008; Gomperts *et al*., 2008; Maetzler *et al*., 2008). The role of non-dopaminergic neurotransmitter deficits should also be considered. In particular, the cholinergic system has been heavily implicated in the dementia of Parkinson's disease, with functional PET studies reporting an even greater cholinergic deficit in cortical areas in Parkinson's disease dementia than in Alzheimer's disease of similar severity (Bohnen *et al*., 2003). Furthermore, direct comparison of

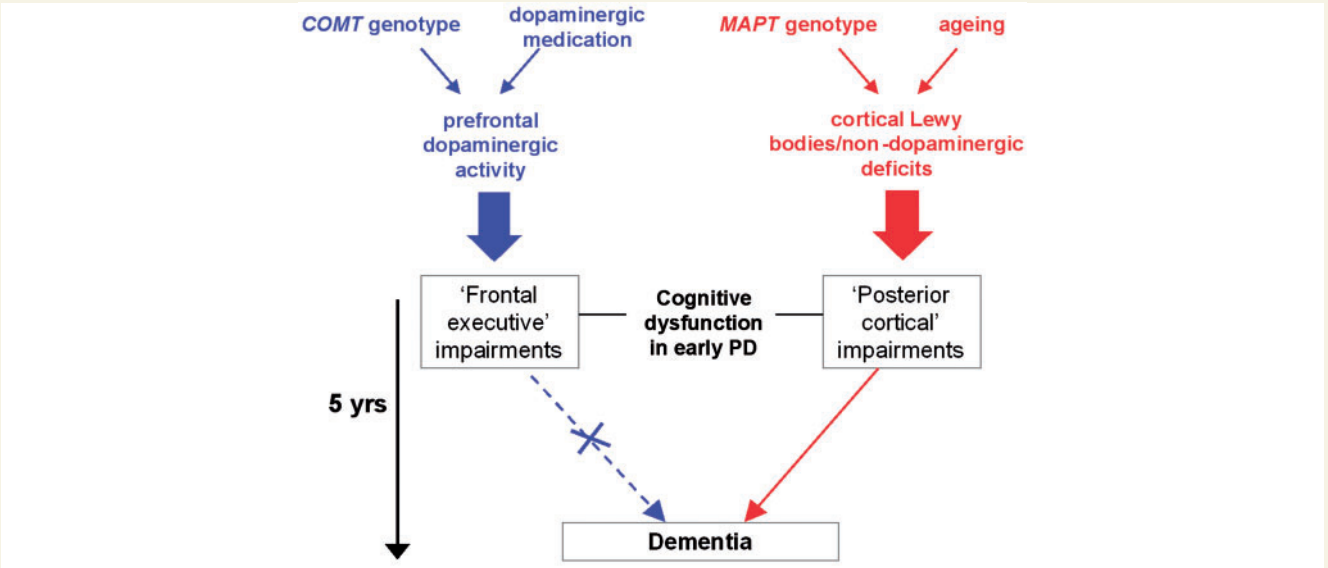

Figure 3 Schematic representation of hypothesized aetiological pathways leading to cognitive dysfunction in early Parkinson's disease and their relationship to the development of dementia 5 years later. 'Frontal executive' impairments in early disease appear to be a consequence of a hyperdopaminergic state in the prefrontal cortex, which is in turn modulated by *COMT* genotype and dopaminergic medication. These deficits are not associated with subsequent global cognitive decline and dementia over 5 years of follow-up. In contrast, it seems that early deficits on more posterior cortically based cognitive tasks, which do develop into subsequent dementia, do not have a dopaminergic basis. Rather, this work supports the hypothesis that they reflect Lewy body deposition in posterior cortical areas, which is in turn influenced by *MAPT* genotype and the ageing process; PD = Parkinson's disease.

Table 5 Ratio of tau transcripts originating from H1 versus H2 alleles in cases with pathologically proven Lewy body disease and controls

	Mean tau transcripts, H1: H2	
	Total tau (SD)	4R tau (SD)
Cases	1.0643 (0.0879) [$P = 0.164$]	1.1963 (0.0857) [$P = 0.02$]
Controls	0.9899 (0.4411) [$P = 0.566$]	1.0074 (0.1959) [$P = 0.924$]

Square brackets denote the result of one-sample *t*-tests.

cholinergic deficits in Parkinson's disease and Parkinson's disease dementia groups using MP4A PET revealed a regional difference within the parietal cortex in particular (Hilker *et al*., 2005). Thus, it is plausible that cholinergic deficits play a contributory role in the development of posteriorly based cognitive deficits and dementia in Parkinson's disease although we have not explicitly investigated this is this study.

We adopted the TOL as our primary measure of frontal executive function because it is a planning and working memory task that has been extensively used as a measure of executive function in Parkinson's disease (Owen *et al*., 1992, 1995), with minimal motor requirements (Owen *et al*., 1995). Furthermore, TOL performance is known not only to be sensitive to the manipulation of dopamine levels (Lange *et al*., 1992) but also to activate the prefrontal cortex reliably (Baker *et al*., 1996; Owen *et al*., 1996; Williams-Gray *et al*., 2007b). Our finding that the impact of the *COMT* Val^{158}Met polymorphism on cognitive function in our Parkinson's disease population was limited to performance on this test is in keeping with a locus of effect on dopamine levels in the prefrontal cortex due to the low numbers of dopamine transporters in this region (Gogos *et al*., 1998; Lewis *et al*., 2001; Mazei *et al*., 2002; Moron *et al*., 2002). Moreover, we have shown, for the first time, a dynamic relationship between *COMT* genotype and executive performance in Parkinson's disease. In 'early' disease, when dopaminergic activity appears to be upregulated in the prefrontal cortex (Bruck *et al*., 2006; Kaasinen *et al*., 2001; Rakshi *et al*., 1999), low *COMT* activity corresponding to further elevation of dopamine levels is detrimental to performance. In 'later' disease, when prefrontal dopamine levels fall (Brooks and Piccini, 2006), this effect disappears and may even reverse (Fig. 2A). These findings are consistent with the well-established hypothesis of an inverted U-shaped curve relating prefrontal dopaminergic activity and executive performance (Goldman-Rakic *et al*., 2000), and suggest that Parkinson's disease patients move from right to left on this putative curve as their disease progresses (Fig. 2C). Longitudinal data from our incident cohort provide further support for this theory in that the performance of Met homozygotes on the TOL planning task improved over the 5 year follow-up period, whereas the performance of Val carriers did not (Fig. 2B and C). Hence, our data suggest that early executive dysfunction in Parkinson's disease does not necessarily carry a poor prognosis, and has a basis that is more of the abnormalities of the dopaminergic networks than in the cortical Lewy body load.

The main strength of this study lies in the nature of the cohorts. Our cross-sectional Parkinson's disease cohort with genotypic and detailed cognitive profiles is, to our knowledge, the largest of its kind to date. The incident cohort is a community-based population-representative sample of patients, in whom the diagnosis of Parkinson's disease has been validated at two separate time-points to maximize diagnostic accuracy (Williams-Gray *et al*., 2007*a*), and thus represents a particularly valuable resource for monitoring the evolution of cognitive syndromes in typical idiopathic Parkinson's disease in the community. Limitations of the study include the unavoidable problem of attrition of the incident cohort over time, and the potential confounding effect of acetylcholinesterase inhibitors, although these were taken by only a minority of our patients (6% of the incident cohort at 5.2 years, and 1% of the prevalent cohort), and their impact on cognitive performance appears to be very modest (Emre *et al*., 2004).

In conclusion, our studies suggest that frontostriatal executive deficits and the dementia of Parkinson's disease are dissociable in terms of both their aetiology and clinical course. Executive deficits on the TOL task are influenced by *COMT* genotype as a function of disease duration, through a presumed effect of this genetic variant on prefrontal dopamine levels; but neither executive deficits nor *COMT* genotype predict progression to dementia. Rather, the dementing process is heralded by posterior cortically based cognitive deficits, and is heavily dependent on *MAPT* H1-H2 genotype, which, in turn, appears to influence the ratio of 4-: 3-repeat tau isoforms in the brain in Parkinson's disease, thus supporting the hypothesis that protein aggregation in cortical areas plays a key role in dementia evolution.

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Supplementary material

Supplementary material is available at *Brain* online.

References

Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol 2003; 60: 387–92.

Aarsland D, Andersen K, Larsen JP, Lolk A, Nielsen H, Kragh-Sorensen P. Risk of dementia in Parkinson's disease: a community-based, prospective study. Neurology 2001; 56: 730–6.

Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: a population-based prospective study. J Am Geriatr Soc 2000; 48: 938–42.

Aarsland D, Perry R, Brown A, Larsen JP, Ballard C. Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. Ann Neurol 2005; 58: 773–6.

Abraham R, Sims R, Carroll L, Hollingworth P, O'Donovan MC, Williams J, et al. An association study of common variation at the MAPT locus with late-onset Alzheimer's disease. Am J Med Genet B Neuropsychiatr Genet 2009 [Epub ahead of print].

Ala TA, Hughes LF, Kyrouac GA, Ghobrial MW, Elble RJ. Pentagon copying is more impaired in dementia with Lewy bodies than in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2001; 70: 483–8.

Baker SC, Rogers RD, Owen AM, Frith CD, Dolan RJ, Frackowiak RS, et al. Neural systems engaged by planning: a PET study of the Tower of London task. Neuropsychologia 1996; 34: 515–26.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561–71.

Benton AL. Differential behavioural effects of frontal lobe disease. Neuropsychologia 1968; 6: 53–60.

Bohnen NI, Kaufer DI, Ivanco LS, Lopresti B, Koeppe RA, Davis JG, et al. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. Arch Neurol 2003; 60: 1745–8.

Braak H, Del Tredici K, Bratzke H, Hamm-Clement J, Sandmann-Keil D, Rub U. Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). J Neurol 2002; 249 (Suppl 3): III/1–5.

Brooks DJ, Piccini P. Imaging in Parkinson's disease: the role of monoamines in behavior. Biol Psychiatry 2006; 59: 908–18.

Bruck A, Aalto S, Nurmi E, Vahlberg T, Bergman J, Rinne JO. Striatal subregional 6-[(18)F]fluoro-L-dopa uptake in early Parkinson's disease: a two-year follow-up study. Mov Disord 2006; 21: 958–63.

Buter TC, van den Hout A, Matthews FE, Larsen JP, Brayne C, Aarsland D. Dementia and survival in Parkinson disease: a 12-year population study. Neurology 2008; 70: 1017–22.

Caffrey TM, Joachim C, Paracchini S, Esiri MM, Wade-Martins R. Haplotype-specific expression of exon 10 at the human MAPT locus. Hum Mol Genet 2006; 15: 3529–37.

Caviness JN, Driver-Dunckley E, Connor DJ, Sabbagh MN, Hentz JG, Noble B, et al. Defining mild cognitive impairment in Parkinson's disease. Mov Disord 2007; 22: 1272–7.

Chambers CB, Lee JM, Troncoso JC, Reich S, Muma NA. Overexpression of four-repeat tau mRNA isoforms in progressive supranuclear palsy but not in Alzheimer's disease. Ann Neurol 1999; 46: 325–32.

Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am J Hum Genet 2004; 75: 807–21.

Dagher A, Owen AM, Boecker H, Brooks DJ. Mapping the network for planning: a correlational PET activation study with the Tower of London task. Brain 1999; 122 (Pt 10): 1973–87.

Dubois B, Pillon B. Cognitive deficits in Parkinson's disease. J Neurol 1997; 244: 2–8.

Edison P, Rowe CC, Rinne JO, Ng S, Ahmed I, Kemppainen N, et al. Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography. J Neurol Neurosurg Psychiatry 2008; 79: 1331–8.

Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, Deyn PP, et al. Rivastigmine for dementia associated with Parkinson's disease. N Eng J Med 2004; 351: 2509–18.

Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007; 22: 1689–707.

Fahn S, Elton RL. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. Recent developments in Parkinson's disease. Florham Park, NJ: MacMillan Healthcare Information; 1987. p. 153–63.

Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.

Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain 2004a; 127: 550–60.

Foltynie T, Goldberg TE, Lewis SG, Blackwell AD, Kolachana BS, Weinberger DR, et al. Planning ability in Parkinson's disease is influenced by the COMT val158met polymorphism. Mov Disord 2004b; 19: 885–91.

Galpern WR, Lang AE. Interface between tauopathies and synucleinopathies: a tale of two proteins. Ann Neurol 2006; 59: 449–58.

Giasson BI, Forman MS, Higuchi M, Golbe LI, Graves CL, Kotzbauer PT, et al. Initiation and synergistic fibrillization of tau and alpha-synuclein. Science 2003; 300: 636–40.

Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988; 51: 745–52.

Gogos JA, Morgan M, Luine V, Santha M, Ogawa S, Pfaff D, et al. Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. Proc Natl Acad Sci USA 1998; 95: 9991–6.

Goldman-Rakic PS, Muly EC 3rd, Williams GV. D(1) receptors in prefrontal cells and circuits. Brain Res Brain Res Rev 2000; 31: 295–301.

Gomperts SN, Rentz DM, Moran E, Becker JA, Locascio JJ, Klunk WE, et al. Imaging amyloid deposition in Lewy body diseases. Neurology 2008; 71: 903–10.

Goodglass H. The assessment of aphasia and related disorders. Philadelphia: Lea and Febiger; 1972.

Goris A, Williams-Gray CH, Clark GR, Foltynie T, Lewis SJ, Brown J, et al. Tau and alpha-synuclein in susceptibility to, and dementia in, Parkinson's disease. Ann Neurol 2007; 62: 145–53.

Green EK, Thaker U, McDonagh AM, Iwatsubo T, Lambert JC, Chartier-Harlin MC, et al. A polymorphism within intron 11 of the tau gene is not increased in frequency in patients with sporadic Alzheimer's disease, nor does it influence the extent of tau pathology in the brain. Neurosci Lett 2002; 324: 113–6.

Henry JD, Crawford JR. A meta-analytic review of verbal fluency performance following focal cortical lesions. Neuropsychology 2004; 18: 284–95.

Hilker R, Thomas AV, Klein JC, Weisenbach S, Kalbe E, Burghaus L, et al. Dementia in Parkinson disease: functional imaging of cholinergic and dopaminergic pathways. Neurology 2005; 65: 1716–22.

Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, et al. Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17. Nature 1998; 393: 702–5.

Ishizawa T, Mattila P, Davies P, Wang D, Dickson DW. Colocalization of tau and alpha-synuclein epitopes in Lewy bodies. J Neuropathol Exp Neurol 2003; 62: 389–97.

Kaasinen V, Nurmi E, Bruck A, Eskola O, Bergman J, Solin O, et al. Increased frontal [(18)F]fluorodopa uptake in early Parkinson's disease: sex differences in the prefrontal cortex. Brain 2001; 124: 1125–30.

Kulisevsky J, Pagonabarraga J. Cognitive impairment in Parkinson's disease: tools for diagnosis and assessment. Mov Disord 2009; 24: 1103–10.

Kwok JB, Teber ET, Loy C, Hallupp M, Nicholson G, Mellick GD, et al. Tau haplotypes regulate transcription and are associated with Parkinson's disease. Ann Neurol 2004; 55: 329–34.

Lange KW, Robbins TW, Marsden CD, James M, Owen AM, Paul GM. L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. Psychopharmacology 1992; 107: 394–404.

Lewis DA, Melchitzky DS, Sesack SR, Whitehead RE, Auh S, Sampson A. Dopamine transporter immunoreactivity in monkey cerebral cortex: regional, laminar, and ultrastructural localization. J Comp Neurol 2001; 432: 119–36.

Louis ED, Marder K, Cote L, Tang M, Mayeux R. Mortality from Parkinson disease. Arch Neurol 1997; 54: 260–4.

Maetzler W, Reimold M, Liepelt I, Solbach C, Leyhe T, Schweitzer K, et al. [11C]PIB binding in Parkinson's disease dementia. Neuroimage 2008; 39: 1027–33.

Matthews F, Brayne C. The incidence of dementia in England and Wales: findings from the five identical sites of the MRC CFA Study. PLoS Med 2005; 2: e193.

Mazei MS, Pluto CP, Kirkbride B, Pehek EA. Effects of catecholamine uptake blockers in the caudate-putamen and subregions of the medial prefrontal cortex of the rat. Brain Res 2002; 936: 58–67.

Moron JA, Brockington A, Wise RA, Rocha BA, Hope BT. Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines. J Neurosci 2002; 22: 389–95.

Mukherjee O, Kauwe JS, Mayo K, Morris JC, Goate AM. Haplotype-based association analysis of the MAPT locus in Late Onset Alzheimers disease. BMC Genet 2007; 8: 3.

Myers AJ, Kaleem M, Marlowe L, Pittman AM, Lees A, Fung HC, et al. The H1c haplotype at the MAPT Locus is associated with Alzheimer's disease. Hum Mol Genet 2005; 14: 2399–404.

Myers AJ, Pittman AM, Zhao AS, Rohrer K, Kaleem M, Marlowe L, et al. The MAPT H1c risk haplotype is associated with increased expression of tau and especially of 4 repeat containing transcripts. Neurobiol Dis 2007; 25: 561–70.

Nelson HE, O'Connell A. Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. Cortex 1978; 14: 234–44.

Nussbaum M, Treves TA, Inzelberg R, Rabey JM, Korczyn AD. Survival in Parkinson's disease: the effect of dementia. Parkinsonism Relat Disord 1998; 4: 179–81.

Owen AM, Doyon J, Petrides M, Evans AC. Planning and spatial working memory: a positron emission tomography study in humans. Eur J Neurosci 1996; 8: 353–64.

Owen AM, James M, Leigh PN, Summers BA, Marsden CD, Quinn NP, et al. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. Brain 1992; 115: 1727–51.

Owen AM, Sahakian BJ, Hodges JR, Summers BA, Polkey CE, Robbins TW. Dopamine-dependent frontostriatal planning deficits in early Parkinson's disease. Neuropsychology 1995; 9: 126–40.

Pagonabarraga J, Kulisevsky J, Llebaria G, Garcia-Sanchez C, Pascual-Sedano B, Gironell A. Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. Mov Disord 2008; 23: 998–1005.

Rademakers R, Melquist S, Cruts M, Theuns J, Del-Favero J, Poorkaj P, et al. High-density SNP haplotyping suggests altered regulation of tau gene expression in progressive supranuclear palsy. Hum Mol Genet 2005; 14: 3281–92.

Rakshi JS, Uema T, Ito K, Bailey DL, Morrish PK, Ashburner J, et al. Frontal, midbrain and striatal dopaminergic function in early and advanced Parkinson's disease A 3D [(18)F]dopa-PET study. Brain 1999; 122 (Pt 9): 1637–50.

Rowe CC, Ng S, Ackermann U, Gong SJ, Pike K, Savage G, et al. Imaging beta-amyloid burden in aging and dementia. Neurology 2007; 68: 1718–25.

Russ C, Powell JF, Zhao J, Baker M, Hutton M, Crawford F, et al. The microtubule associated protein Tau gene and Alzheimer's disease—an association study and meta-analysis. Neurosci Lett 2001; 314: 92–6.

Sahakian BJ, Morris RG, Evenden JL, Heald A, Levy R, Philpot M, et al. A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. Brain 1988; 111 (Pt 3): 695–718.

Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? lJ Neurol Neurosurg Psychiatry 2000; 69: 308–12.

Schwab RS, England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson MC, editors. Third Symposium on Parkinson's disease. Edinburgh: E&S Livingstone; 1969. p. 152–7.

Slifstein M, Kolachana B, Simpson EH, Tabares P, Cheng B, Duvall M, et al. COMT genotype predicts cortical-limbic D1 receptor availability measured with [11C]NNC112 and PET. Mol Psychiatry 2008; 13: 821–7.

Tobin JE, Latourelle JC, Lew MF, Klein C, Suchowersky O, Shill HA, et al. Haplotypes and gene expression implicate the MAPT region for Parkinson disease: the GenePD Study. Neurology 2008; 71: 28–34.

Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 2007a; 130: 1787–98.

Williams-Gray CH, Hampshire A, Barker RA, Owen AM. Attentional control in Parkinson's disease is dependent on COMT val 158 met genotype. Brain 2008; 131: 397–408.

Williams-Gray CH, Hampshire A, Robbins TW, Owen AM, Barker RA. Catechol O-methyltransferase val158met genotype influences fronto-parietal activity during planning in patients with Parkinson's disease. J Neurosci 2007b; 27: 4832–8.

Zetusky WJ, Jankovic J, Pirozzolo FJ. The heterogeneity of Parkinson's disease: clinical and prognostic implications. Neurology 1985; 35: 522–6.