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Attentional control in Parkinson's disease is dependent on COMT val^{158}met genotype

Caroline H. Williams-Gray,[1] Adam Hampshire,[2] Roger A. Barker[1,*] and Adrian M. Owen[2,*]

[1]Cambridge Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge and [2]MRC Cognition and Brain Sciences Unit, Cambridge, UK

*These authors contributed equally to this work.

Correspondence to: Caroline Williams-Gray, Cambridge Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, Forvie Site, Robinson Way, Cambridge, CB2 2PY, UK
E-mail: chm27@cam.ac.uk

Cognitive deficits occur even in the earliest stages of Parkinson's disease. Some such deficits are known to relate to dysfunction in dopaminergic frontostriatal networks, and may be influenced by a common functional polymorphism (val^{158}met) within the catechol *O*-methyltransferase (COMT) gene. Abnormal attentional shifting behaviour is an important and well-recognized cognitive problem in PD, but nonetheless its precise cognitive and neural basis remains unclear. Here we explored this impairment in an fMRI study employing a recently developed cognitive task designed to fractionate components of attentional control. We investigated the impact of the COMT val^{158}met genotype and dopaminergic medication on both patterns of behaviour and associated brain activation in 29 medicated patients with early PD. Genotype had a critical impact on task strategy: whilst patients with high activity COMT genotypes (val/val) adopted a typical approach of preferentially shifting attention within rather than between dimensions, those with low activity genotypes (met/met) failed to adopt such a strategy, suggesting an inability to form an attentional 'set'. Moreover, this behaviour was associated with significant underactivation across the frontoparietal attentional network. Furthermore, we demonstrated an interactive effect of COMT genotype and dopaminergic medication on task performance and BOLD response. Hence we have shown for the first time that attentional control in PD is critically determined by genetic and pharmacological influences on dopaminergic activity in frontoparietal networks. This has important implications for understanding the neurobiological basis of attentional control, and highlights the risk of medication-induced cognitive dysfunction in certain genotypic groups of PD patients, which may ultimately impact on clinical practice.

Keywords: Parkinson's disease; attentional set shifting; catechol *O*-methyl transferase; functional MRI; prefrontal cortex

Abbreviations: COMT = catechol *O*-methyltransferase; PD = Parkinson's disease; val = valine; met = methionine; ED = extradimensional; ID = intradimensional; PFC = prefrontal cortex; DLPFC = dorsolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex; PPC = posterior parietal cortex

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Introduction

Parkinson's disease (PD) is a common neurodegenerative disease which is defined clinically in terms of bradykinesia, rigidity, tremor and postural instability. However, cognitive symptoms also form an important part of the syndrome, with executive dysfunction being particularly prominent in early disease (Foltynie *et al.*, 2004a; Muslimovic *et al.*, 2005). The dysexecutive syndrome encompasses difficulty in planning, organizing and regulating goal-directed behaviour, similar to that seen in patients with frontal lesions, and is demonstrable on tasks of attentional control, planning and working memory (Owen *et al.*, 1992, 1995). The observed influence of dopaminergic medication on performance (Lange *et al.*, 1992; Owen *et al.*, 1995) together with functional imaging data (Owen *et al.*, 1998; Mattay *et al.*, 2002), supports the theory that the basis for the dysexecutive syndrome in PD lies within dopaminergic frontostriatal networks. However, whilst loss of nigrostriatal dopamine occurs by definition in all PD patients, not all patients exhibit neuropsychological evidence of dysfunction

in downstream frontostriatal networks (Lewis *et al.*, 2003a). Furthermore, the relationship between dopamine and executive function is complex, with levodopa administration being associated with an improvement in performance on certain executive tasks, and a deterioration in others (reviewed in Cools, 2006). Thus, the precise cognitive and neural bases for executive dysfunction in PD and its heterogeneity are not fully understood.

Some insight into this problem can be gained through exploiting the existence of a common functional polymorphism in catechol *O*-methyl transferase (COMT), an enzyme which plays a key role in regulating dopamine levels in cortical areas in particular (Karoum *et al.*, 1994; Gogos *et al.*, 1998; Mazei *et al.*, 2002) where, in contrast to the striatum, there are low numbers of dopamine transporters (Lewis *et al.*, 2001). The polymorphism results in a substitution of valine for methionine at codon 158 (val^{158}met), which is known to increase the thermostability of the protein and enzyme activity in blood and liver samples (Scanlon *et al.*, 1979; Weinshilboum and Dunnette, 1981; Boudikova *et al.*, 1990; Lotta *et al.*, 1995). Furthermore, Chen and colleagues recently measured mRNA expression, protein levels and enzyme activity in post-mortem human prefrontal cortex (PFC) and demonstrated a 40% increase in enzyme activity at 37°C in association with the val variant, mediated principally through altered protein integrity, whilst *in vitro* work provided further evidence for increased thermostability of the protein as the underlying mechanism for this functional change (Chen *et al.*, 2004). We have previously demonstrated that this functional polymorphism has phenotypic consequences in PD. Specifically, low activity COMT genotypes (met/met) leading to higher dopamine levels in the PFC, are associated with impaired performance during the Tower of London planning task (Foltynie *et al.*, 2004b) and a reduction in associated frontoparietal activation (Williams-Gray *et al.*, 2007*b*). When interpreted on the background of other studies demonstrating a hyperdopaminergic state in the PFC in early PD compared to healthy controls (Rakshi *et al.*, 1999; Kaasinen *et al.*, 2001), this work implies that further genetically determined elevations in prefrontal dopamine are detrimental to cognitive performance in PD patients, possibly due to an 'overload' effect whereby signal-to-noise ratios (SNR) are reduced (Foltynie *et al.*, 2004*b*). Hence it is unsurprising that the majority of studies investigating the impact of dopaminergic medication on executive performance have produced inconsistent results (Cools, 2006), given that this genetic influence has not been considered. Stratifying patients according to COMT genotype not only provides a convenient means of exploring the dopaminergic basis of executive deficits in PD, but is essential in order to interpret medication effects. In this study we have adopted such an approach in order to allow us to explore the neural basis of a key executive deficit in PD, namely the attentional set shifting impairment.

Impaired ability to shift attention between stimuli (i.e. shift attentional 'set') is a well-established part of the dysexecutive syndrome in PD and is likely to have important consequences for everyday activities requiring cognitive multitasking. However, this deficit remains poorly understood, in part because tasks traditionally used to examine set shifting ability, such as the Wisconsin card sorting test (Grant and Berg, 1948), confound several behavioural components whose neuroanatomical and neurochemical bases may differ. The CANTAB ID/ED shift task, which was developed in an attempt to isolate the set-shifting process (Downes *et al.*, 1989), indicates a particular deficit in extradimensional (ED) shifting (between stimulus dimensions) rather than intradimensional (ID) shifting (within stimulus dimensions) in PD (Downes *et al.*, 1989; Owen *et al.*, 1992, 1993). Nonetheless, this shifting deficit still remains poorly defined due to the persistent problem of confounding of multiple cognitive processes at the ED shift stage of this task.

Previous attempts to explore the neurochemical basis of attentional shifting deficits in PD have relied on pharmacological modulation of dopamine levels and have produced inconsistent results (Downes *et al.*, 1989; Owen *et al.*, 1992; Lange *et al.*, 1992; Owen *et al.*, 1993; Lewis *et al.*, 2005; Slabosz *et al.*, 2006). The neuroanatomical basis of the deficit is also uncertain. Whilst functional imaging studies in healthy controls have demonstrated that switching between tasks is mediated by the PFC (Dove *et al.*, 2000; Sohn *et al.*, 2000; Cools *et al.*, 2002), there is a paucity of literature examining the neural basis of the attentional shifting deficit in PD. Furthermore, most previous neuroimaging studies have focused on behaviour induced by externally imposed cues, rather than examining internally generated shifts in attention, which are arguably much more relevant for everyday life, influencing an individual's ability to make decisions and solve problems independently.

Here, we have employed a recently developed cognitive task (Hampshire and Owen, 2006), derived from the CANTAB ID/ED task, to examine for the first time internally guided attentional shifting in PD and its neural basis. This task involves working out by a process of trial and error which object is the target in a stimulus set consisting of two faces and two buildings (Fig. 1). The subject makes a series of self-directed ID (e.g. face to face) and ED (e.g. face to building) shifts during this working out period. The task allows the constituent components of attentional control, including responding to novel stimuli, shifting attention both intra- and extra-dimensionally, inhibiting the response to a previously relevant stimulus, and responding to positive and negative feedback, to be examined separately without the confounding which complicates the original CANTAB ID/ED task. Furthermore, the subject's focus of attention is monitored and used to define switching events, rather than attentional switches being imposed externally by the experimental paradigm,

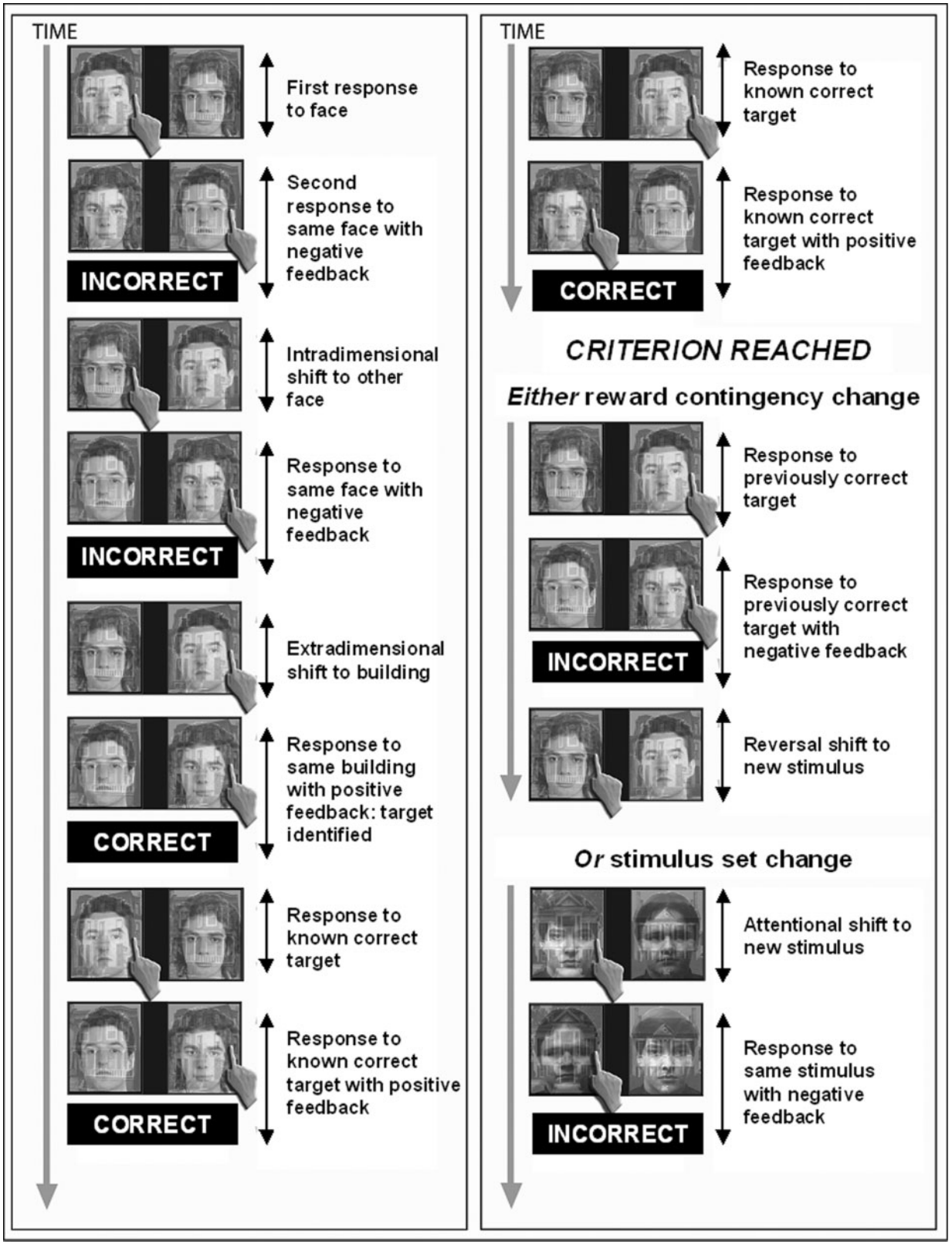

Fig. 1 A typical sequence of events during the experimental task. The subject is instructed to work out by a process of trial and error which is the correct target amongst a compound stimulus set comprising two faces superimposed on two buildings. Responses are guided by positive or negative feedback provided after every second response. Once the correct target is identified, the subject continues to respond to the known target, as per prior instruction. After six correct responses (three 'correct' feedback messages), either a change of reward contingency occurs, such that the previous target is no longer correct and the subject is required to shift attention to a previous non-target ('reversal') or a new stimulus set is presented and the process of working out the correct target begins again ('set change').

thus the problem-solving strategy adopted by the individual can be examined. The task has been validated in healthy controls, in whom individual components of attentional control have been shown to reliably activate neuroanatomically discrete regions of the frontoparietal attentional network (Hampshire and Owen, 2006).

We directly compared performance, fMRI activation patterns and the impact of dopaminergic medication during this attentional control task in two matched groups of PD patients, differing only in whether they possessed high (val/val) or low (met/met) activity COMT genotypes. Our aim was to define the neural basis of attentional control dysfunction in PD through delineating the impact of genetically and pharmacologically based variation in dopamine levels on behaviour and associated brain activation.

Methods

Subjects

Inclusion criteria for the study were a diagnosis of PD according to the UK Parkinson's Disease Society Brain Bank criteria (Gibb and Lees, 1988), a disease duration of less than 6 years from diagnosis, homozygosity for the COMT val^{158}met polymorphism, mild to moderate disease stage (Hoehn and Yahr stage $\leqslant$2.5), no significant cognitive deficit [Minimental State Examination (MMSE) score $\geqslant$26] and no major depression (Beck depression score $\leqslant$18; Beck *et al.*, 1988). Patients were also assessed using the Unified Parkinson's disease rating scale (UPDRS) and completed the National Adult Reading Test (NART), a measure of verbal IQ, prior to scanning.

Each subject's current dopaminergic drug regime was recorded and converted to an equivalent levodopa dose to facilitate comparison between patients using the following formula based on those previously adopted in the literature (Brodsky *et al.*, 2003; Williams-Gray *et al.*, 2007a). Equivalent levodopa dose = [levodopa ($\times$1.2 if COMT inhibitor) ($\times$1.2 if 10 mg selegiline OR $\times$ 1.1 if 5 mg selegiline)] + [pramipexole $\times$ 400] + [ropinirole $\times$ 40] + [cabergoline $\times$160] + [pergolide $\times$ 200] + [bromocriptine $\times$ 10] + [lisuride $\times$ 160], all doses in milligrams. No patients were taking acetylcholinesterase inhibitors. All testing was performed with patients taking their usual medications.

Written informed consent was obtained from all participants. Ethical approval for the study was granted by Cambridge Research Ethics Committee, UK.

Genotyping

DNA was extracted from peripheral blood samples using standard phenol/chloroform methods. SNP rs4680 (COMT val^{158}met) was genotyped using a Taqman SNP Genotyping Assay on a 7900HT Sequence Detection System (Applied Biosystems).

Experimental design

The task required subjects to work out which was the correct target in a stimulus set consisting of two faces and two buildings through a process of trial and error. The four stimuli were presented as two compound stimulus sets on the right- and left-hand side of the screen; each set consisted of a face and a building superimposed on one another (Fig. 1). A full description of the task has been published elsewhere (Hampshire and Owen, 2006). Briefly, subjects were asked to select a target using a button box in their right hand to indicate whether their selection was on the left or right of the screen. Following their response, the face-building combinations were reversed, and subjects were asked to respond to their chosen target a second time, thus allowing the experimenter to track the subject's focus of attention. After two responses, feedback was presented on the screen indicating whether the choice was correct or incorrect. If incorrect, the subject selected a new target, at this moment performing either an ID shift (i.e. face to face) or an ED shift (i.e. face to building). The partial feedback design allowed the attentional shift to be modelled in isolation (first response), with confounding from feedback information occurring only during the second response. This cycle continued until the correct target was identified. Subjects had received prior instruction indicating that once they had worked out the target, they should continue to respond to this until informed that it was no longer the target. This process of responding to a known target provided a control condition for contrasting with working out. After six correct responses, a target change occurred. Either entirely new compound stimuli were presented ('set change') or the reward contingency of the existing stimuli changed such that the previous target now became a non-target, thus the subject received negative feedback alerting them to switch to a different target ('reversal').

Subjects performed 2 $\times$ 16 min runs of the task in the scanner, with a short rest period in between. The number of trials varied between subjects as the task was response-driven. All subjects underwent a training session prior to scanning to ensure that they understood the requirements of the task.

Data acquisition

Patients were scanned at the MRC Cognition and Brain Sciences Unit, Cambridge, using a 3 Tesla Siemens TIM Trio MRI scanner. Eight hundred and eighty T2-weighted echo-planar images depicting blood oxygen-level-dependent (BOLD) signal were acquired during each 16 min run, the first 18 of which were discarded to avoid T1-equilibrium effects. Each image consisted of 21 slices of 4 mm thickness with a 1 mm interslice gap, with an in-plane resolution of 3.2 $\times$ 3.2 mm^2. The TR was 1.1 s. Slices were angled away from the orbits to avoid signal dropout due to magnetic susceptibility inhomogeneity. Stimuli were presented on a computer screen with a resolution of 1024 pixels which was visualized using a mirror positioned within the scanner at a viewing distance of 90 mm, such that 37 pixels subtended a visual angle of 1°.

Data analysis

Behavioural performance on the task was measured in two ways. First, the mean number of errors whilst searching for the correct target was recorded for each of the four possible types of problem encountered, i.e. problems requiring an ID shift following a set change, an ED shift following a set change, an ID shift following a reversal of reward contingency, and an ED shift following a reversal of reward contingency. Secondly, mean response times were recorded for each of five types of subject response, namely ID shifts whilst working out the correct target, ED shifts whilst working out the correct target, first response following a set change, first response following a reversal of reward contingency,

and response to a known correct target. Repeated measures ANOVA was used to compare performance between genetic subgroups (full details described in 'Results' section). Further subgroup analyses were subsequently performed to examine the effects of levodopa dose on behavioural performance in val/val and met/met individuals, again using repeated measures ANOVA. We included age as a covariate given that our previous work has suggested that increasing age is associated with deterioration in performance on the task (Slabosz *et al.*, unpublished data).

Imaging data was analysed using SPM 5 (Wellcome Department of Imaging Neuroscience, UCL, UK). Preprocessing was undertaken with the aa version 1 batch system using aarecipe_general_ver02.m (http://imaging.mrc-cbu.cam.ac.uk/imaging/AutomaticAnalysisManualReference). Images were subject motion corrected, slice time acquisition corrected, co-registered to the structural MPRAGE, normalized to the standard Montreal Neurological Institute echo-planar imaging template using the SPM 5 normalization/segment routine, and smoothed with an 8 mm full width at half maximum Gaussian kernel.

The BOLD response was modelled to the onset times and durations of a number of events. Four of these involved the subject shifting their focus of attention, namely (i) 'ID shifts' whilst actively working out the target, (ii) 'ED shifts' whilst actively working out the target, (iii) switching attention to an object not previously seen following a change in stimulus set ('set change') and (iv) switching attention away from a previous target to a previous non-target following a change in reward contingency ('reversal'). The fifth event was responding to a target that was known to be correct, as positive feedback had been received ('known correct'). Finally, trials immediately followed by positive or negative feedback were modelled separately. Onsets were the time of appearance of the stimuli on the screen. For non-feedback events, durations were measured to the time of the button box response whereas for feedback events, durations were measured through the response to the time of disappearance of the feedback message from the screen.

Given that multiple genetic and non genetic factors are likely to contribute to complex cognitive processes, it was anticipated that any effects of a single genetic polymorphism on BOLD response would be small (Goldberg and Weinberger, 2004); hence we attempted to optimise sensitivity for detecting such changes using the following three-step strategy.

(1) In the whole patient group, we identified those regions specifically involved in the task by performing a group level analysis of three contrasts of interest. The first, which allowed brain areas activated during solution search to be identified, involved contrasting all events whilst actively working out the target (ID shifts, ED shifts, set changes, reversals and events followed by positive or negative feedback) with 'known correct' events. The second was intended to isolate the extradimensional component of switching, and involved contrasting ED shifts with ID shifts, which were identical in all respects other than this dimensional difference. The third involved contrasting reversal events with set change events, to isolate the reversal component of shifting. Following the extraction of these contrast images for each individual, group level random effects analysis was performed using an initial threshold of $P = 0.005$. Where necessary, a more stringent threshold of $P = 0.05$ following false discovery rate (FDR) correction for whole brain mass was applied to enable areas of greatest activation to be identified with more precision.
(2) ROIs were defined on the basis of this analysis as 5 mm radius spheres at peak height co-ordinates within each cluster of signal change.
(3) Using the contrast of all events whilst working out the target (ID shifts, ED shifts, set changes, reversals and responses with positive and negative feedback) versus baseline (rest), which was expected to generate maximal signal change, we modelled our task-specific ROIs for each individual subject using the MARSeille Boîte A Région d'Intérêt (Marsbar) toolbox (Brett *et al.*, 2002). ROI data was extracted for a cross-group comparison between COMT val/val and met/met subgroups using repeated measures ANOVA with levodopa dose and age as covariates (SPSS version 11.5).

Table 1 Demographic and clinical characteristics of genetic subgroups

Variable	COMT genotype	
	val/val ($n = 16$)	met/met ($n = 13$)
Age	64.8 (10.4)	64.0 (9.4)
Gender (male:female)	10:6	8:5
Disease duration (years)	4.0 (2.0)	3.3 (1.6)
UPDRS motor score	23.0 (10.8)	26.8 (10.0)
MMSE	28.9 (1.2)	28.8 (0.7)
Beck depression score	7.3 (4.0)	6.5 (4.8)
NART (verbal IQ)	114.2 (6.9)	114.5 (6.6)
Equivalent levodopa dose (mg)	593.8 (468.7)	611.2 (456.1)

Note: Mean (SD) is tabulated unless otherwise stated. Between-group comparisons using Student's *t* or Chi-squared tests as appropriate revealed no significant differences ($P > 0.05$).

Results

Thirty-two patients with early PD were recruited to the study (17 val/val, 15 met/met), of whom three were excluded due to difficulty comprehending the instructions for the task (1 val/val, 2 met/met). Hence 16 val and 13 met homozygotes were included. The subgroups were well-matched in terms of demographic and clinical characteristics (Table 1).

Behavioural performance

Comparison of number of errors made whilst searching for the correct target during each of the four possible problem types (ED shift + set change, ED shift + reversal, ID shift + set change, ID shift + reversal) indicates a clear difference between the behavioural patterns adopted in the two genotypic groups (Fig. 2). Three-way repeated measures ANOVA with genotype as a between-subject factor and shift type (ID versus ED) and target change (set change versus reversal) as within-subject factors revealed no main effect of genotype on number of errors ($F = 0.13$, $P = 0.73$), but a significant interaction between shift type and genotype ($F = 9.53$, $P = 0.005$). Specifically, val/val individuals made fewer errors during ID problems than ED problems, thus exhibiting a similar response

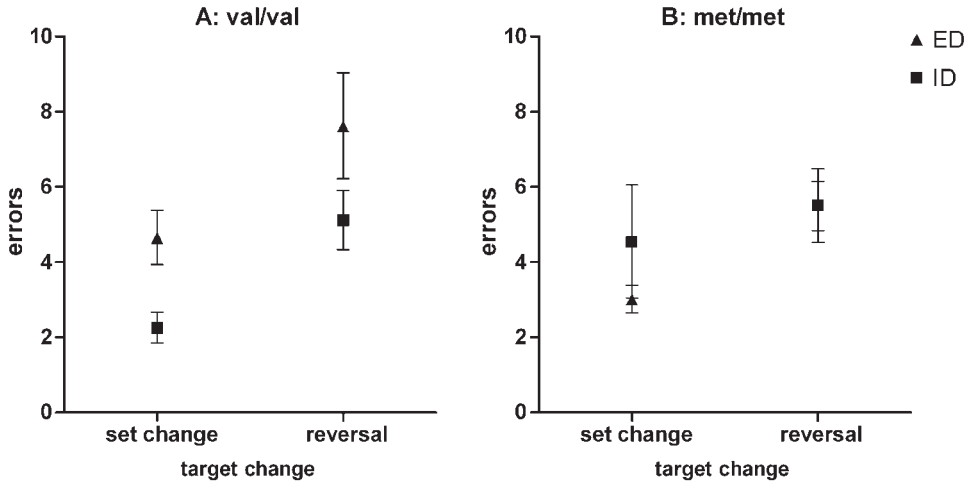

Fig. 2 Mean number of errors whilst searching for the correct target stratified according to whether the problem follows a change in stimulus set or a reversal of reward contingency, and according to whether an ID or ED shift is required in (**A**) val homozygotes and (**B**) met homozygotes.

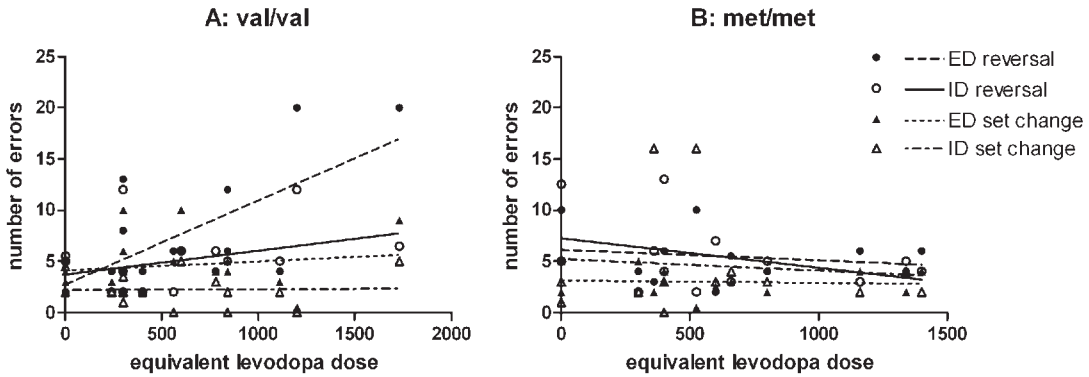

Fig. 3 Relationship between mean number of errors whilst searching for the correct target and levodopa dose in (**A**) val homozygotes and (**B**) met homozygotes. Linear regression lines are shown. Only the regression line for ED reversal problems in the val/val group differs significantly from zero ($F = 12.08$, $P = 0.004$).

pattern to controls (Hampshire and Owen, 2006), whereas met/met individuals adopted a different pattern of behaviour, performing equivalently whether an ID or ED shift was required. The effect of target change on number of errors was similar across both groups, with more errors being made during reversal problems than set change problems ($F = 11.05$, $P = 0.003$; no target change*genotype interaction). This is similar to the pattern seen in controls (Hampshire and Owen, 2006), presumably reflecting the increased cognitive demands of inhibiting responses to a previously relevant object.

Further analysis was performed to examine the influence of levodopa dose on performance in each genetic subgroup. Amongst val/val patients, increasing dose was associated with an overall impairment of performance (Fig. 3A). Repeated measures ANOVA confirmed a main effect of dose on number of errors ($F = 5.69$, $P = 0.03$), as well as significant interactions between shift type and dose ($F = 8.05$, $P = 0.01$) and target change and dose ($F = 6.28$, $P = 0.03$), and a three-way interaction between shift type, target change and dose ($F = 6.64$, $P = 0.02$) demonstrating that this effect was most pronounced for the most difficult 'ED reversal' problems (Fig. 3A). In the met/met group, there was no overall effect of levodopa dose on number of errors ($F = 2.16$, $P = 0.17$), and no interaction between shift type and dose or target change and dose (Fig. 3B). Inclusion of age as an additional covariate in these analyses did not significantly change these observations.

In terms of response times (Fig. 4), for all four event types whilst working out the target (ID shift, ED shift, first response following set change, first response following reversal), there was a clear trend towards impaired performance in the met/met versus the val/val group ($F = 3.45$, $P = 0.07$, two-way repeated measures ANOVA with genotype as between-subject factor and event type as within-subject factor). There was no interaction between

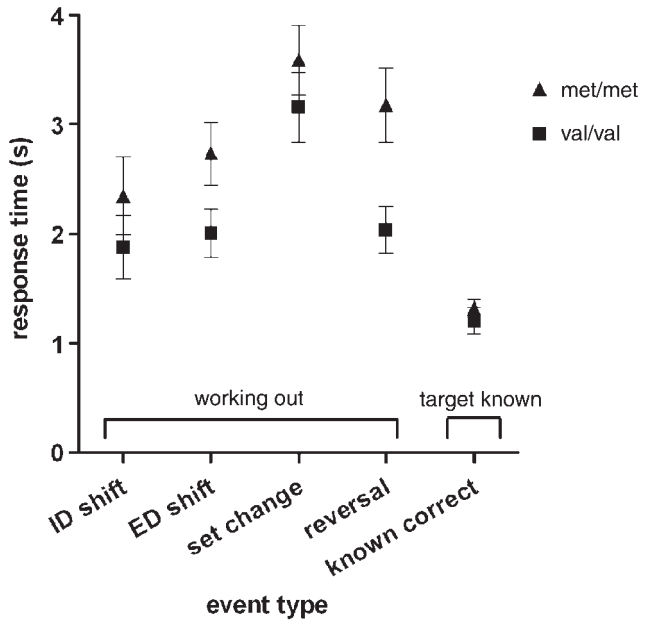

Fig. 4 Response times stratified according to event type and COMT genotype. Event types include those where the subject was actively working out the target, namely an internally driven ID shift, an internally driven ED shift, a first response following a set change, or a first response following a reversal of reward contingency, as well as those where the subject was responding to a known target.

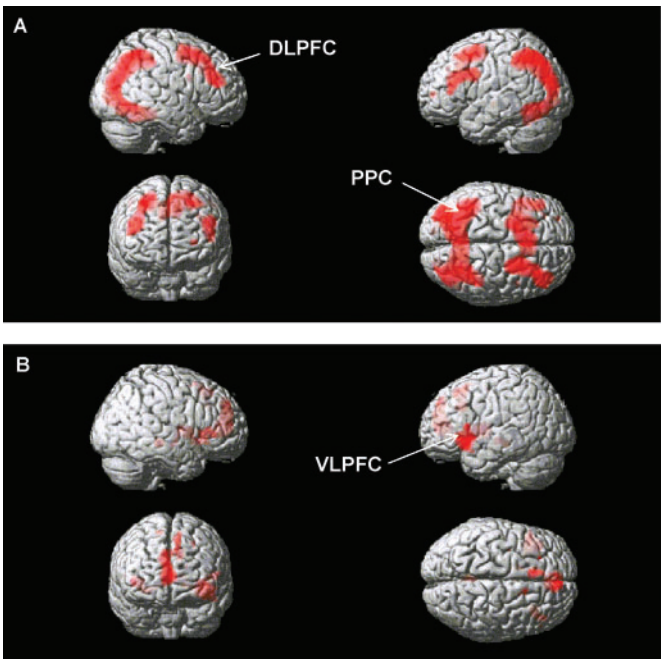

Fig. 5 BOLD signal change during key contrasts across all subjects ($n = 29$) rendered onto canonical brain images. (**A**) 'Working out' versus 'known correct' events; activation above a threshold of $P = 0.05$ following FDR correction for whole brain volume is shown. (**B**) 'ED shifts' versus 'ID shifts'; activation above a threshold of $P = 0.005$ uncorrected is shown. Approximate positions of peak height signal change used to define ROIs are indicated.

genotype and event type. In contrast, there was no effect of genotype on response time when responding to a known target ($P = 0.51$, Student's t-test), suggesting specific slowing whilst problem solving in the met/met group. Further subgroup analysis to determine the impact of levodopa dose on response times whilst working out the target revealed no significant effect of dose in either val/val ($F = 0.22$, $P = 0.65$) or met/met groups ($F = 0.28$, $P = 0.61$), irrespective of adjustment for age.

fMRI activation during the task

In order to determine brain regions activated during specific components of the task, three contrasts of interest were examined in the whole patient group. During solution search (all 'working out' events contrasted with 'responding to known target' events) significant BOLD signal change ($P < 0.05$ following FDR correction for whole brain volume) was observed in the dorsolateral prefrontal and posterior parietal cortices bilaterally (DLPFC and PPC, Fig. 5A). The ED component of shifting (ED shift minus ID shift events) was associated with significant activation ($P < 0.005$) in the ventrolateral prefrontal cortex (VLPFC, Fig. 5B). The contrast of reversal and set change events, aimed at isolating the neural correlate of response inhibition, did not reveal the expected activation in the orbitofrontal cortex (Hampshire and Owen, 2006), presumably as a result of signal dropout in this area in a number of subjects.

Region of interest (ROI) analyses

ROIs were defined in the three key areas involved in the task, centred on co-ordinates of peak activation and reflected to the opposite hemisphere (DLPFC $X = +/-48$ $Y = 22$ $Z = 28$; VLPFC $X = +/-32$ $Y = 18$ $Y = -8$; PPC $X = +/-26$ $Y = -60$ $Z = 52$). Additional ROIs were defined anatomically in the caudate nuclei using the Marsbar ROI toolbox (Brett *et al.*, 2002; Tzourio-Mazoyer *et al.*, 2002). Although not activated by the task, the caudate nuclei constitute a central site of dopaminergic pathology in PD and previous work suggests that they may be relevant in terms of mediating executive performance in PD via their connections with the PFC (Lewis *et al.*, 2003*b*).

ROI analyses focussing on the areas activated during the task revealed underactivation in met compared to val homozygotes throughout the frontoparietal attentional network during 'working out' compared to baseline (Fig. 6A), a contrast selected to optimize power. There was no significant impact of genotype on BOLD response in the caudate nuclei. Repeated measures ANOVA with genotype as a between-subject factor, ROI and hemisphere as within-subject factors, equivalent levodopa dose and age as covariates and a genotype*dose interaction term, confirmed a significant main effect of genotype on cortical ROI activation ($F = 11.65$, $P = 0.002$) with no interaction between ROI and genotype or hemisphere and genotype. There were significant negative effects of increasing age

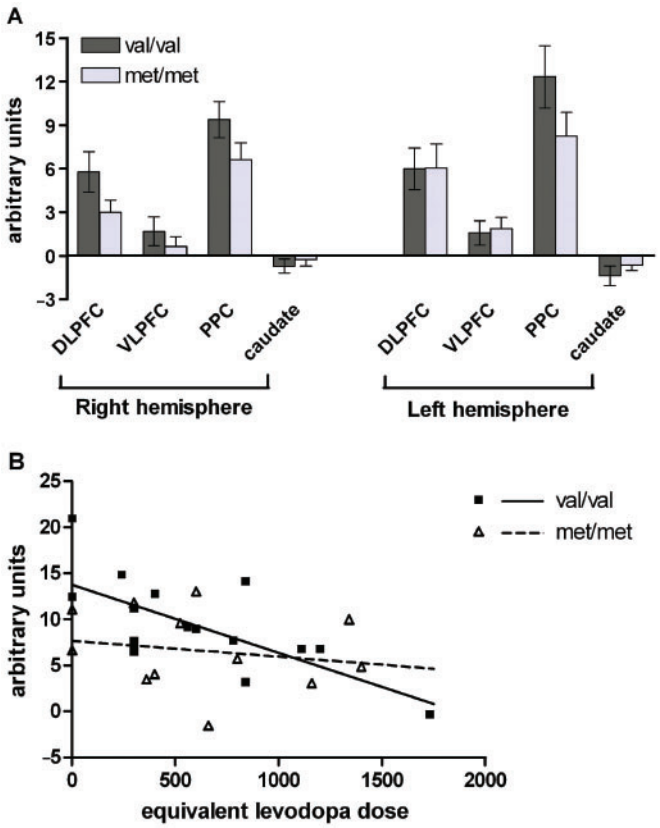

Fig. 6 BOLD signal change (arbitrary units) during 'working out' relative to baseline in val versus met homozygotes. (**A**) Activity in selected ROIs in the right and left hemispheres, where bars represent means +/− SEM. (**B**) Activity in the right PPC plotted as a function of equivalent levodopa dose, illustrating the direction of the interaction between COMT genotype and dose. Linear regression lines for each genotypic group are shown (val/val $F = 12.86$, $P = 0.003$; met/met $F = 0.39$, $P = 0.55$). Similar plots were obtained for all six ROIs.

($F = 9.45$, $P = 0.005$) and increasing levodopa dose ($F = 5.45$, $P = 0.03$) on activation, and a significant interaction between genotype and levodopa dose ($F = 9.47$, $P = 0.005$). The direction of this interaction is illustrated in Fig. 6B for the right PPC: whilst increasing levodopa dose was associated with a significant decrease in signal change in the val/val group, there was no effect of dose on activation in the met/met group. Similar plots were obtained for the five remaining ROIs.

No significant cross-group differences were detected using lower powered contrasts including 'ED shifting' versus baseline and 'reversal' versus baseline, as anticipated given that the effects of a single genetic variant on activation are likely to be small.

Discussion

In this study, we have clarified the nature and underlying neural basis of the attentional control deficit which commonly occurs in PD. We have demonstrated for the first time that both genetically determined and pharmacological variation in dopamine levels impact on set-shifting performance and corresponding BOLD activation in a frontoparietal attentional network. Our work confirms that this key executive skill has a dopaminergic basis, but reveals that the influence of dopamine is complex and non-linear.

The observed behavioural effects of COMT genotype on task performance are particularly interesting. We have previously demonstrated a detrimental effect of an increasing number of met alleles (i.e. lower COMT activity) on executive function in early PD using the Tower of London planning task (Foltynie *et al.*, 2004b). However, here, rather than observing a universal impairment across behavioural measures in met/met individuals, we identified a difference in the ID/ED response pattern in this group which suggests the adoption of an abnormal problem solving strategy. Typically, controls performing ID/ED shifting tasks preferentially shift attention within rather than between dimensions, and consequently identify the correct target with fewer errors when an ID shift is required rather than an ED shift (Hampshire and Owen, 2006). Amongst our PD patients, a similar pattern is seen in the val/val group. However, the met/met group perform equivalently in terms of number of errors whether an ID or ED shift is required, indicating that they do not form an attentional 'set' to the previously relevant stimulus dimension, but rather treat each problem independently (Fig. 2). This alternative strategy, although 'abnormal', is not actually detrimental in terms of number of errors overall whilst working out the target, and in fact remediates the ED shifting impairment classically observed in PD to some extent. However, in terms of the alternative performance measure of response time, there is a strong trend towards slower performance across all types of event involved in working out the target (ID shift, ED shift, response to set change and response to reversal) in met/met versus val/val patients (Fig. 4). Analysis of the fMRI data suggests that impaired ability to form an 'attentional set' and prolonged response times in met homozygotes reflects under-recruitment of the frontoparietal areas necessary for the task (Fig. 6A). Hence our data suggest that impaired attentional control in met versus val homozygotes in PD is due to reduced activity within the PFC, but also reveal that the pattern of attentional shifting impairments in PD is more complex and heterogeneous than the simple ED shifting deficit previously described in the literature.

Reversal learning, i.e. the ability to switch attention from a previous target to a previous non-target following a reversal of reward contingency, was not significantly influenced by COMT genotype in this study. A previous study in healthy controls administered the mixed dopamine and noradrenaline agonist methylphenidate produced analogous results: methylphenidate administration resulted in fewer ED shift errors associated with impaired speed of response, as in our met/met group, but did not influence errors during reversal learning (Rogers *et al.*, 1999).

These findings, together with evidence from lesion studies in animals (Roberts *et al.*, 1992, 1994), raise the possibility that ED shifting and reversal learning depend on dissociable neurochemical substrates, with the former being dopamine-dependent and the latter dopamine-independent. Conversely, Cools *et al.* (2001) have demonstrated that levodopa impairs reversal learning whilst improving task-switching performance, suggesting that dopamine influences both cognitive processes in PD, although in opposing directions. However, it should be borne in mind that the tasks employed by Cools *et al.* differed from ours in several respects, and in particular reversal learning was examined using probabilistic rather than total feedback, thus their results cannot be directly compared with ours.

A further important aspect of the current study is its capacity to examine the interaction between COMT genotype, an endogenous determinant of cortical synaptic dopamine levels, and exogenous dopaminergic medication. An increase in levodopa dose was associated with deterioration in certain aspects of performance, as anticipated, but also a complex interaction between medication dose and COMT genotype was clearly demonstrable. Specifically, in those with high activity COMT genotypes (val/val) and hence lower endogenous cortical dopamine levels, exogenous dopamine had a detrimental effect on performance through increasing the number of errors whilst searching for the target, whereas in those with higher endogenous cortical dopamine levels (met/met), additional exogenous dopaminergic stimulation had no effect (Fig. 3). The imaging data essentially mirrored these behavioural results: higher levodopa doses had a greater negative impact on activation in val compared to met homozygotes (Fig. 6B).

These data can be accommodated in the well-established hypothesis of an inverted U-shaped relationship between dopamine levels and prefrontal function (Fig. 7). The existence of such a relationship is supported by a wealth of evidence from both *in vivo* studies demonstrating non-linear effects of the iontophoretic application of D1 agonists as well as from behavioural and functional imaging studies in humans with genetically determined differences in prefrontal dopamine (reviewed in Williams and Castner, 2006). In healthy controls and patients with schizophrenia, an increasing number of met alleles is associated with improved prefrontal function (Egan *et al.*, 2001; Malhotra *et al.*, 2002; Blasi *et al.*, 2005), as predicted by the left-hand side of the inverted U-shaped curve. In contrast, our findings suggest a detrimental effect of elevated cortical dopamine levels on prefrontal function, thus supporting our previous suggestion that patients with early PD are on the right-hand side of this curve (Foltynie *et al.*, 2004*b*), consistent with the demonstration of a hyperdopaminergic state in the PFC in early PD (Rakshi *et al.*, 1999; Kaasinen *et al.*, 2001). The 'inverted U' model further suggests that the effect of dopaminergic medication will differ according to an individual's pre-existing position on the curve.

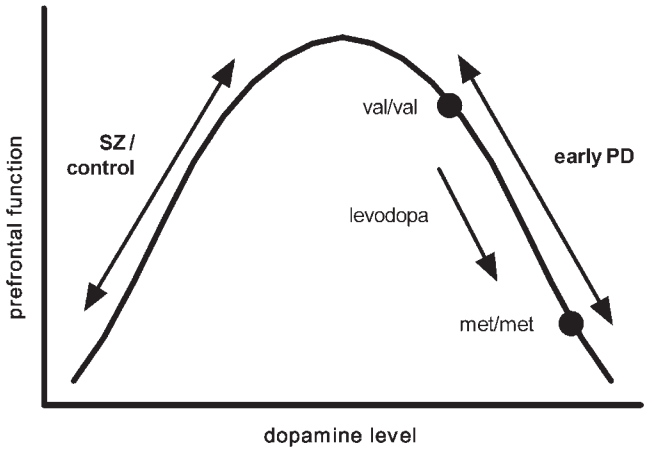

Fig. 7 Hypothesized inverted U-shaped relationship between prefrontal function and dopamine levels. Position on the curve is likely to be determined by factors influencing baseline prefrontal dopamine level including pathology [e.g. PD, schizophrenia (SZ)] and COMT genotype. Our data support the suggestion that patients with early PD operate on the right-hand arm of the curve, with those homozygous for val nearer the peak and those homozygous for met nearer the base. Hence exogenous levodopa might be expected to produce a greater negative effect on prefrontal function in val/val than met/met PD patients.

Indeed, we observed a greater detrimental effect of exogenous dopamine in PD val homozygotes who are expected to be nearer the peak of the curve than in PD met homozygotes who are already near the base of the curve, suggesting a floor effect in the latter group (Fig. 7).

The underlying neural mechanism of the inverse relationship between dopamine levels and executive performance in early PD is uncertain, although a 'dopamine overload hypothesis' has been proposed. Specifically, in the presence of high 'tonic' dopamine levels in the PFC in early disease, further elevation in prefrontal dopamine may have detrimental functional consequences due to a down-regulation of the neural response to 'phasic' dopamine, i.e. a reduced SNR (Grace, 1993). It has been proposed that tonic dopaminergic transmission reflects the activation of extra-synaptic D1 receptors, whilst post-synaptic D2 activation mediates phasic dopamine signalling (Cohen *et al.*, 2002), thus a reduced SNR in the 'dopamine overload' state may reflect a supra-optimal D1/D2 activation ratio. As the disease advances, there is a reduction in prefrontal dopamine storage (Brooks and Piccini, 2006) presumably due to the loss of mesocortical dopaminergic projections. The 'dopamine overload' effect is therefore likely to disappear, such that increases in prefrontal dopamine and the D1/D2 activation ratio are beneficial rather than detrimental in terms of executive performance.

Irrespective of the underlying neural mechanisms, it seems that the effects of dopamine on cognitive performance must be interpreted in light of an individual's pre-existing position on a U-shaped curve, which is likely to be influenced by pathology within the dopaminergic system

(such as schizophrenia or PD) as well as COMT genotype. Dopaminergic activity in the PFC also declines with advancing age (Kaasinen and Rinne, 2002) and with disease duration in PD (Brooks and Piccini, 2006), further complicating the issue. In addition, it has been suggested that the optimal range of dopamine signalling (i.e. position of the peak of the curve) varies as a function of the nature of the task in question (Williams and Castner, 2006), which would be in keeping with the reported observation that the COMT polymorphism has differential effects according to task demand. Specifically, Nolan and colleagues have demonstrated that in healthy controls, met alleles improve performance on tasks requiring cognitive stability, whilst impairing performance on tasks dependent on cognitive flexibility (Nolan *et al*., 2004). As might be expected, we observed an opposite pattern in our PD patients, with met alleles impairing ability to form an attentional set (reflecting cognitive stability) whilst having a tendency to improve ability to shift from one stimulus dimension to another (reflecting cognitive flexibility; see Fig. 2).

We have speculated that the underactivation that we observed within the frontoparietal network in PD met homozygotes reflects impaired prefrontal function. Other studies have similarly reported a decrease in prefrontal BOLD response in association with impaired executive performance in both schizophrenics (Callicott and Weinberger, 1999) and patients with PD (Lewis *et al*., 2003b; Williams-Gray *et al*., 2007b). However, some authors have observed reductions in BOLD response in association with stable or improved behavioural performance on working memory tasks, and thus argue that such changes might reflect an increase in cortical efficiency (Egan *et al*., 2001; Mattay *et al*., 2003; Blasi *et al*., 2005). Callicott and colleagues attempted to specifically investigate this conundrum by exploring fMRI activation in controls and schizophrenic patients divided into subgroups according to performance ability on the N-back working memory task. Their data suggest that prefrontal circuitry is underrecruited in patients whose task performance is poor, whereas those that perform well alter their neural recruitment pattern through compensatory overactivation of other prefrontal areas (Callicott *et al*., 2003). In a further recent study employing an attentional shifting task, Monchi and colleagues reported areas of both increased and decreased PFC activation in PD patients versus controls in association with impaired performance. Decreased activation was reported during those components of the task requiring caudate activation, whereas increased activation was reported when the caudate was not involved. The authors suggest that directionality of the change in BOLD response might reflect whether the cognitive process is dependent on corticostriatal or mesocortical networks (Monchi *et al*., 2007). Hence the relationship between BOLD activation and behavioural performance might vary according to both behavioural ability of the subjects and task demand.

In this study, we have focused principally on the effects of COMT genotype and dopaminergic medication on frontoparietal activity, given that firstly, the task generated significant BOLD activation exclusively within this cortical network, and secondly the dopamine-regulating influence of COMT appears to be confined to cortical areas (Karoum *et al*., 1994; Gogos *et al*., 1998; Mazei *et al*., 2002) due to low numbers of dopamine transporters there (Lewis *et al*., 2001). However, it is possible that COMT also exerts some of its effects on set-shifting performance in PD through subcortical mechanisms, despite our observation that genotype had no effect on caudate activation during the task. Recent evidence from a multimodal imaging study suggests that COMT genotype influences the interaction between prefrontal activation during a working memory task and midbrain dopamine synthesis, with a negative correlation in met homozygotes but a positive correlation in val carriers. Hence COMT may be involved in a mesocortical tuning mechanism which aims to maintain prefrontal dopamine at an optimum level for cognitive performance (Meyer-Lindenberg *et al*., 2005).

A final point for consideration is the use of equivalent levodopa dose as a quantitative measure of total dopaminergic medication. This measure is open to criticism as it may not accurately reflect frontal dopaminergic stimulation in individuals with different COMT genotypes, given that levodopa is subject to the metabolic effects of COMT whereas dopamine agonists are not. However, a recent study exploring the impact of the COMT polymorphism on levodopa pharmacokinetic-pharmacodynamic response patterns failed to identify any differences between genetic subgroups (Contin *et al*., 2005). Furthermore, it is clearly necessary to account quantitatively for the impact of dopamine agonists in some way, thus we feel that the calculated equivalent levodopa dose provides the best achievable estimate of overall dopaminergic stimulation.

In summary, we have demonstrated that a single functional polymorphism within the COMT gene alters the strategy adopted during an attentional shifting task in PD patients through altering activation in frontoparietal networks. Furthermore, the effect of dopaminergic medication on both performance and cortical activation is influenced by COMT genotype, as predicted by the inverted U hypothesis relating dopamine levels to prefrontal function. This work therefore reveals for the first time that attentional control in PD is crucially dependent on genetically determined and pharmacological variations in dopamine within frontoparietal networks, and clarifies the reasons underlying heterogeneity of executive function in PD. Furthermore, this study highlights the risk of medication-induced cognitive dysfunction in certain genotypic groups of patients, which may ultimately have implications for clinical practice.

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