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Differential optimal dopamine levels for set-shifting and working memory in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is an important model for the role of dopamine in supporting human cognition. However, despite the uniformity of midbrain dopamine depletion only some patients experience cognitive impairment. The neurocognitive mechanisms of this heterogeneity remain unclear. A genetic polymorphism in the catechol *O*-methyltransferase (COMT) enzyme, predominantly thought to exert its cognitive effect through acting on prefrontal cortex (PFC) dopamine transmission, provides us with an experimental window onto dopamine's role in cognitive performance in PD. In a large cohort of PD patients ($n=372$), we examined the association between COMT genotype and two tasks known to implicate prefrontal dopamine (spatial working memory and attentional set-shifting) and on a task less sensitive to prefrontal dopamine (paired associates learning). Consistent with the known neuroanatomical locus of its effects, differences between the COMT genotype groups were observed on dopamine-dependant tasks, but not the paired associates learning task. However, COMT genotype had differential effects on the two prefrontal dopamine tasks. Putative prefrontal dopamine levels influenced spatial working memory in an 'Inverted-U'-shaped fashion, whereas a linear, dose-dependant pattern was observed for attentional set-shifting. Cumulatively, these results revise our understanding of when COMT genotype modulates cognitive functioning in PD patients by showing that the behavioural consequences of genetic variation vary according to task demands, presumably because set-shifting and working memory have different optimal dopamine levels.

1. Introduction

Motor deficits are the most conspicuous symptom of Parkinson's disease (PD). However, cognitive deficits are now recognised as a core feature of the disease (Cools, 2006; Dagher and Robbins, 2009; Postuma et al., 2012). Despite the relative uniformity of midbrain dopamine depletion, PD patients vary greatly in the extent to which they display cognitive abnormalities (Lewis et al., 2005; Monchi et al., 2012; Owen, 2004). While some PD patients display a pattern of cognitive symptoms sufficient to constitute clinical dementia, a separate cohort of patients displays more circumscribed deficits on tests of working memory, attention and planning (Kehagia et al., 2013). The prevalence of cognitive deficits in PD patients also increases with disease duration, with up ~80% of patients displaying deficits at some point in the disease (Healy et al., 2008). Deficits on executive tasks are thought to result from disturbed fronto-striatal processing in a dopamine-dependant manner (Cools et al., 2002; Dagher et al., 2001; Owen et al., 1998; Sawamoto et al., 2008). Again, however, not all patients display deficits on tasks associated with fronto-striatal processing (Lewis et al., 2003a, 2003b, 2005). Elucidating the neurochemical mechanisms of cognitive dysfunction in PD is essential for understanding and ultimately ameliorating these deficits. Genetic differences in dopaminergic processing in the prefrontal cortex (PFC) provide us with a non-invasive experimental window on the role of PFC dopamine in cognitive dysfunction in PD. The activity of the catechol *O*-methyltransferase (COMT) enzyme plays an important role in modulating cortical and limbic dopamine transmission, particularly in PFC, but has little impact on dorsal striatal dopamine or cortical noradrenaline transmission (Tunbridge et al., 2004; Yavich et al., 2007), presumably due to the existence of alternative mechanisms of inactivating striatal dopamine, e.g., dopamine reuptake transporter (DAT), and noradrenaline, i.e. the noradrenaline transporter (NET). A single nucleotide polymorphism in

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the gene that codes for the COMT enzyme, val158met, has been found to alter the thermolability of this enzyme, thus influencing PFC dopamine levels (Chen et al., 2004). Given that Val allele load is thought to affect COMT activity in a linear manner, Met homozygotes, relative to Val homozygotes, likely have increased levels of active dopamine in the PFC, whilst heterozygotes are thought to be intermediate.

In line with this, the val158met polymorphism has been found to affect several dopamine-sensitive processes such as working memory and attentional set-formation, with Met homozygotes outperforming Val homozygotes on behavioural and/or neural measures (Barnett et al., 2007; Collins and Frank, 2012; Egan et al., 2001; Papenberg et al., 2013). Moreover, the COMT polymorphism has been shown to account for individual variability in the response to pharmacological manipulations that alter dopamine (Apud et al., 2007; Farrell et al., 2012; Kelm and Boettiger, 2013; Mattay et al., 2003). In the context of PD, the val158met polymorphism has emerged as a key determinant of cognitive performance (Foltynie et al., 2004; Hoogland et al., 2010; Nombela et al., 2014; Williams-Gray et al., 2009, 2008, 2007). Interestingly, however, in contrast to healthy Val homozygotes, PD Val homozygotes have been found to outperform PD Met homozygotes on tests of planning and attentional set-shifting while displaying concomitant increases in fronto-parietal activity during the performance of these tasks (Williams-Gray et al., 2008, 2007). These effects of COMT in PD are diametrically opposed to those seen in healthy volunteers and might reflect compensatory up-regulation of dopamine in the PFC of early PD patients (Bruck et al., 2005; Fallon et al., 2013a; Kaasinen et al., 2001; Rakshi et al., 1999).

An extensive array of human and animal work has demonstrated that there is an 'inverted-U'-shaped function linking working memory performance to the level of PFC dopamine receptor stimulation. Specifically, too little or too much D_1 receptor stimulation has been found to impair working memory performance (Floresco and Phillips, 2001; Phillips et al., 2004; Sawaguchi and Goldman-Rakic, 1991, 1994; Seamans et al., 1998; Vijayraghavan et al., 2007; Williams and Goldman-Rakic, 1995; Zahrt et al., 1997). Thus, the previous effects of COMT on cognition in PD patients may occur due to patients being positioned on the right-hand limb of an 'inverted-U'-shaped function linking dopamine levels with cognitive performance. In support of this model, a recent positron emission tomography (PET) study confirmed that presynaptic dopamine, as indexed by ^{18}F-DOPA uptake, is *higher* in PD Met homozygotes compared with PD Val homozygotes (Wu et al., 2012), eliminating the possibility that impaired performance in PD Met homozygotes is due to increased degeneration of dopaminergic pathways. Furthermore, this study found that COMT genotype significantly altered dopamine levels in cortical and not striatal areas in PD, providing direct support for the idea that COMT genotype exerts its cognitive effects through modulating prefrontal rather than striatal dopamine.

Previous work has demonstrated that different tasks have distinct optimal dopamine levels, even in healthy subjects (Clatworthy et al., 2009; Cools and D'Esposito, 2011; Floresco, 2013; Mehta et al., 2004). For example, attentional set-shifting was impaired, while (certain forms of) spatial working memory improved with dopamine receptor blockade in healthy volunteers (Mehta et al., 2004). Based on this prior work, we examined the prediction that the COMT polymorphism in PD has dissociable effects on the distinct cognitive functions of attentional set-shifting and spatial working memory, both strongly associated with frontal dopamine (Crofts et al., 2001; Mehta et al., 2000; Owen et al., 1993; Robbins and Roberts, 2007; Roberts et al., 1994; Sawaguchi and Goldman-Rakic, 1991, 1994; Vijayraghavan et al., 2007; Williams and Goldman-Rakic, 1995). To test this hypothesis, we examined the effect of the val158met polymorphism on these two tasks in a large cohort of PD patients who had participated in the ParkFit study (van Nimwegen et al., 2013).

Finally, previous studies have found that COMT genotype's effects on cognitive function are more prominent for tasks that require the PFC (Williams-Gray et al., 2009). To examine this hypothesis, we also examined performance on the paired associates learning (PAL). Performance on this task depends more readily on posterior cortical regions and medial temporal lobe areas, and, furthermore, is thought to be relatively insensitive to dopamine manipulations in healthy people and PD patients (Dennis et al., 2010; Fallon et al., 2013a, 2013b; Gould et al., 2006a, 2006b; Owen et al., 1993; Sahakian et al., 1988), but there are other results (Bertolino et al., 2006; Harmer et al., 2001; Laatikainen et al., 2013). Thus, given the predominantly weak relationship between PAL performance and dopamine, we predicted that PAL performance would be relatively less sensitive to COMT genotype in PD patients.

2. Methods

2.1. Participants

The PD patients who participated in this study were all enroled in the Parkfit study, a randomized controlled study on the effect of a behavioural change programme on physical activity in PD patients (van Nimwegen et al., 2013). The Parkfit study was ethically approved (CMO Regio Arnhem-Nijmegen) and is a registered clinical trial (nr NCT 00 748 488).

Inclusion criteria for the study were: PD, as defined by UK Brain Bank criteria (Gibb and Lees, 1988), aged between 40 and 75, sedentary lifestyle (defined as less than 3 periods of vigorous exercise lasting more than 60 min a week or less than 3 periods of moderate exercise lasting less than 150 min a week) and a Hoehn and Yahr score <3. Exclusion criteria were: Mini mental state examination score (MMSE) <24, unable to complete Dutch questionnaires, a co-morbidity affecting daily life, institutionalized care and deep brain surgery.

592 PD patients completed the cognitive measures at baseline. A sample of 372 patients was selected from the larger group (on the basis of having attempted the cognitive tests and willingness to give blood) to be genotyped for the val158met polymorphism (see Table 1 for demographics). Cognitive data were available for 362 genotyped patients (Table 1). Computation of equivalent L-dopa dose was done according to a standard algorithm: regular levodopa dose $\times 1$ + slow release levodopa $\times 0.75$ + bromocriptine $\times 10$ + apomorphine $\times 10$ + ropinirole $\times 20$ + pergolide $\times 100$ + pramipexole $\times 100$ + [regular levodopa dose + (slow release levodopa $\times 0.75$)] $\times 0.2$ if entacapone is taken (Esselink et al., 2004). All assessments were made whilst patients were on their medication.

Table 1
Demographic and clinical variables for each COMT genotype group.

	Met/Met	Val/Met	Val/Val	*p* value
N	108	184	80	
Gender (M/F)[a]	73/35	127/57	48/32	$p=.35$
NART IQ	102 (20)	103 (18)	103 (18)	$p=.98$
Age	64 (8)	64 (8)	65.0 (7)	$p=.78$
MMSE[b]	28 (2)	29 (1)	28 (2)	$p=.111$
UPDRS (motor)	31(11)	33(12)	31 (9)	$p=.58$
H and Y (Stage = 1:1.5:2:2.5:3)[b]	3:2:84:11:7	4:7:137:24:9	2:3:61:11:3	$p=.98$
Disease duration (Yrs)	5 (4)	6 (5)	6 (5)	$p=.47$
Equivalent L-dopa dose	480 (415)	496 (371)	509 (399)	$p=.88$

[b] Chi-squared test was used to assess statistical significance.
[a] Non-parametric test (Kruskal–Wallis Test).

2.2. . Genotyping

Blood samples were extracted using venipuncture and DNA was extracted using standard protocols. Analyses were performed at the Department of Human Genetics in the Radboud university medical centre in Nijmegen. A Taqman-based analysis was used to identify the rs4680 polymorphism in the COMT gene. COMT genotyping was performed in a volume of 10 μL which contained 10 ng of DNA. 5 μL of ABgene Mastermix (2_, ABgene Ltd), 0.125 μL of TaqMan assay (TaqMan assay: C_25746809_50, reporter1, VIC-A-allele; Applied Biosystems), and 3.875 μL of water were also added. Amplification was performed on a 7500 Fast Real-Time PCR (Applied Biosystems), starting with 15 min at 95 °C, followed by 50 cycles of 15 s at 95 °C and 1 min at 60 °C. As controls, 5–10% duplicates and at least 3–4% blanks were used in each genotyping plate. Genotypes were scored using manufacturer-supplied (Applied Biosystems) algorithms and software.

2.2.1. Tests

All these tasks can be viewed and in some cases performed on the following website ⟨http://www.cambridgecognition.com/tests/⟩.

2.2.2. Spatial working memory (SWM)

This task is fully described elsewhere (Owen et al., 1990). Briefly, participants were presented with an array of boxes at different spatial locations on the screen. Participants were told that on each trial there was one token "hidden" among the boxes, and that they had to search through the boxes (by touching the screen) to try this token. They were instructed that if they found a token in one of the boxes on a any given trial, then a token would never again appear in that box on subsequent trials (until all the tokens had been found). Thus, optimal performance in this task is characterized by never searching in the same box twice. Errors were divided into within-search errors, e.g., searching the same box *within* a trial, and between-search errors, e.g., searching within a box where a token had been found on a previous trial. Difficulty of the task was manipulated by varying the number of boxes in the array; there could be four, six or eight boxes in the array. Our main outcome measures were the number of within-search errors and the number of between-search errors. Between-search and within search errors were both analysed using mixed ANOVAs with repeated measures on load (4, 6 or 8 box problems) and COMT as a between subject variable. Finally, where appropriate, supplementary trend analyses examined whether COMT had a linear or non-linear effect on errors on the appropriate metric.

2.2.3. Intradimensional/Extradimensional (ID/ED) set-shifting task (Downes et al., 1989)

In short, initial stages of the task required participants to form a bias (attentional set) in responding to one set of perceptual features in the environment and to ignore other features in the environment. In later stages of the experiment, participants had to shift their attentional set, i.e., attend to the previously irrelevant perceptual dimension and ignore the previously relevant perceptual dimension, e.g., from attending to shapes to lines. This was achieved by requiring participants to make a series of visual discriminations across nine stages, in which different task elements were serially introduced. Participants advanced to the next stage when they reached a criterion of six consecutive correct responses.

For the task, participants were presented with four rectangular boxes (centre-left, centre-right, top and bottom). Test stimuli only appeared in two of these boxes. The nature of the test stimuli varied according to the stage of the task. In the first, simple discrimination (SD), stage, participants were presented with two stimulus exemplars (polygon shapes) presented within two (of the four) windows on the screen. The same set of exemplars was used for the first five stages of the experiment. Selecting one of these exemplars led to the presentation of positive feedback, whilst selecting the other led to the presentation of negative feedback. At this stage, participants had to make discriminations on the basis of shape; thus shape was the relevant dimension. This stage measures the ability to learn to choose between two exemplars based on positive and negative feedback. In the second simple discrimination reversal (SDR) stage, the association between the stimulus exemplars and the feedback was reversed, e.g. the previously rewarded stimulus led to negative feedback and vice versa. This stage indexes the ability to overcome the previous reinforcement history associated with the two stimuli. Next, in the third, compound distraction (C_D) stage, a second stimulus dimension (lines) was introduced and participants had to continue to discriminate between different stimuli based on shape whilst ignoring the irrelevant dimension (lines). The exemplars of the irrelevant dimension (lines) did not overlap with the exemplars of the relevant dimension (shapes). Thus, this phase measures the ability to continue responding in the face of non-overlapping irrelevant stimuli. In the fourth, compound discrimination (CD) stage, participants had to maintain the previous discrimination, but now the irrelevant information (lines) was superimposed onto the shapes (CD). As such, this stage measures the ability to maintain responding in the presence of overlapping, irrelevant stimuli. In the fifth, compound discrimination reversal (CDR), stage the contingencies reversed for the shape dimension, so that the previously rewarded shape became punished and the previously punished shape became rewarded. Here, it is possible to assess the ability to overcome the previous reinforcement history of the stimuli in the presence of distracting information. In the sixth, intradimensional set-shifting (IDS), stage, a new set of exemplars (2 shapes and 2 lines) was displayed. This stage required participants to continue to select exemplars from the previously relevant dimension shape, while ignoring the line dimension. Importantly, this stage measures the ability to maintain and generalise a previous attentional set, i.e., response to shapes, and apply it to a new set of exemplars. In the seventh intradimensional reversal (IDS) stage, the previous discrimination had to be reversed to the other exemplar in the relevant dimension (IDR). Again, this stage indexes the strength of an attentional set (bias) towards the relevant information. In the eighth stage of the task, another new set of exemplars was introduced (EDS stage). This time, however, participants had to shift responding to the previously irrelevant dimension and ignore the previously relevant dimension. This crucial phase of the experiment assays the ability of participants to shift (overcome) their previous attentional set (bias to responding to shapes), which can be considered a hallmark of adaptive behaviour and is analogous to the perseveration metric obtained via the Wisconsin Card Sorting Test (WCST; (Grant and Berg, 1948). In the final stage, participants had to perform a reversal, i.e., shift to the other exemplar within the currently relevant dimension (EDR stage). Again, this phase can be though to index the ability shift attentional set.

In all participants, we examined the effect of COMT genotype on the number of participants passing all 9 stages of the task (analysed using a chi-square test) and total number of errors (using one-way ANOVA). Within the sub-sample of PD patients who completed all nine stages of the ID/ED task, we examined the effect of COMT genotype on extradimensional set-shifting (average errors on EDS and EDR stages). Supplementary analyses examined whether COMT had a linear or non-linear effect on extradimensional errors.

We also sought to examine the selectivity of COMT genotype's effect on extradimensional shifting. Animal and patient work has

confirmed that the extradimensional stages of the test are sensitive to a putatively hypodopaminergic state in the frontal cortex (Crofts et al., 2001; Diaz-Asper et al., 2008; Jazbec et al., 2007). Thus, we compared the effects of COMT on extradimensional set-shifting (which requires high cognitive flexibility) with other stages of the task that require high cognitive stability, namely stage 3 (C_D stage), stage 7 (IDS phase) and stage 8 (IDR)).

2.2.4. . Paired-associates learning (PAL) test

This task is also fully described elsewhere (Sahakian et al., 1988). Participants were presented with 6 boxes in 6 different spatial locations on the screen, each containing an abstract shape. The test contained two phases: a study phase and a test phase. In the study phase participants were shown the contents of each of the 6 boxes. Participants had to remember which abstract shape appeared in which box. In the recall phase participants were presented with an object in the centre of the screen and then they had to touch the box where an object previously appeared. Participants had to correctly match all the objects to their respective box in order to advance to the next stage. If participants were unsuccessful in matching all of the objects then they were shown the study phase again. Participants completed two 1, 2 and 3 box problems and one 6 box problem. As in Fallon et al. (2013b) the main dependant variables on this task were the number of people completing the 6-box stage and the number of errors at the 6-box stage. The former was analysed using a chi-squared test and the latter using a one-way ANOVA.

2.2.5. Analysis

Data were analysed using IBM SPSS statistics version 21.0 (IBM SPSS for Windows, version 21.0). Data for each outcome measure were screened for outliers using box and whisker plots and outliers (1.5 interquartile range (IQR) of the upper quartile; (Tukey, 1977)). Where the assumption of sphericity was violated (as indicated by a significant Mauchly test), then the degrees of freedom were modified using the Greenhouse–Geisser correction method. In addition, where indicated, the whole data set (with outliers) was analysed using robust regression in MATLAB (MATLAB and Statistics Toolbox Release 2012b, The MathWorks, Inc., Natick, Massachusetts, United States), a method robust in the presence of outliers. Following significant ($p < 0.05$) between-subject results post-hoc comparisons were performed using Tukey's honestly significant difference.

We also sought to distinguish between the effects of COMT on the two PFC dopamine tasks (ID/ED and SWM). To this end, we performed a mixed ANOVA on z-scored ($Z = \frac{(\chi - \mu)}{\sigma}$) errors on the ID/ED task (extradimensional stages) and total errors on the SWM task (in the sub-set of participants who passed all nine stages of the ID/ED task).

To examine the confounding effect of age, equivalent L-dopa dose, disease duration and UPDRS motor sub-score, we performed each analysis again (separately) with each covariate added to the design. Covariates were always mean-centred. Gender was analysed in a separate analysis by adding it as a between-subject factor.

3. Results

The distribution of participants between the genotype groups did not differ significantly from that expected from the Hardy–Weinberg theorem ($\chi(1)=0.11$, $p=0.74$). There was no difference between the COMT genotype groups in terms of age, NART IQ, MMSE score, H and Y score, disease duration, UPDRS motor sub-score, equivalent L-dopa dose or gender distribution (Table 1). In general there was no evidence that the use of a particular medication was more prevalent in one COMT group compared to another (Supplementary Table 1). However, there was a significant difference between the groups in terms of the use of peripheral COMT inhibitors (entacapone; Fisher's exact text, $p=0.040$), with only 8/69 patients in the Val/Val grouping taking COMT inhibitors, compared with 25/106 and 41/179 for the Met/Met and Val/Met groups respectively.

3.1. Spatial working memory

Genotype differences in between-search errors were examined using a mixed ANOVA with difficulty (4 boxes, 6 boxes and 8 boxes) as a within-subject factor and COMT genotype as a between-subject variable. COMT genotype group had a significant main effect (irrespective of difficulty) on the number of between-search errors ($F(2,359)=4.72$, $p=0.009$). Pairwise (corrected) comparisons revealed that this was due to the Val/Met group making fewer errors than the Met/Met group ($t(359)=2.74$, $p=0.018$) and a trend compared with the Val/Val group ($t(359)=2.22$, $p=0.068$). There was no difference between the Met/Met and the Val/Val group ($t(359)=0.21$, $p=0.97$). Trend analysis of the total number of between-search errors revealed that there was no significant linear effect of COMT ($t(359)=0.21$, $p=0.831$), but there was a significant quadratic, non-linear effect of COMT genotype ($t(359)=3.00$, $p=0.003$). Thus, spatial working memory was influenced by COMT, and therefore putative prefrontal dopamine, in a non-linear, 'Inverted-U'-shaped manner (Fig. 1a).

Correcting for non-sphericity, there was also a significant main effect of difficulty ($F(1.6, 581.68)=1221.45$, $p < 0.001$). Participants made more errors on 8 box problems than on 6 ($t(358)=29.0$, $p < 0.001$) and 4 ($t(358)=41.55$, $p < 0.001$)) box problems, and more errors on 6 box problems than on 4 box problems ($t(358)=26.00$, $p < 0.001$)). There was a trend towards a significant interaction between COMT genotype and difficulty ($F(3.2, 581.68)=2.26$, $p=0.06$).

The significant effect of COMT genotype group on between-search errors did not alter when age, equivalent L-dopa dose, disease duration and UPDRS motor sub-score were included separately as covariates in supplementary analyses. With regards to gender, there was a main effect of gender ($F(1,356)=4.48$, $p=0.035$), with men making fewer errors than women. However, there was no significant interaction between gender and COMT ($F(2,356)=0.283$, $p=0.75$). The disparity in the use of peripheral COMT inhibitors between the genotype groups could be responsible for generating the group differences in between-search errors. However, removing patients who were taking peripheral COMT inhibitors from the analysis did not alter the statistical significance of the results; there was still a significant difference between the COMT genotype groups in the number of between search errors ($F(2,285)=4.85$, $p=0.008$).

Genotype differences in within-search errors were examined using the same model as that used for between-search errors. There was no significant main effect of COMT genotype group ($F(2,359)=1.30$, $p=0.27$) and no interaction between COMT and difficulty ($F(2.87,516.60)=0.21$, $p=0.88$). There was a main effect of difficulty ($F(1.4,516.6)=68.31$, $p < 0.001$). Again, this was due to more errors on more difficult problems (8 vs. 6, $t(358)=7.82$, $p < 0.001$; 8 vs. 4, $t(358)=9.47$, $p < 0.001$; 6 vs. 4, $t(364)=3.90$, $p < 0.001$).

3.2. Attentional set-shifting

3.2. .1 General performance

There was no significant effect of COMT genotype group on the likelihood of passing all 9 stages of the ID/ED task, $\chi(2)=0.574$,

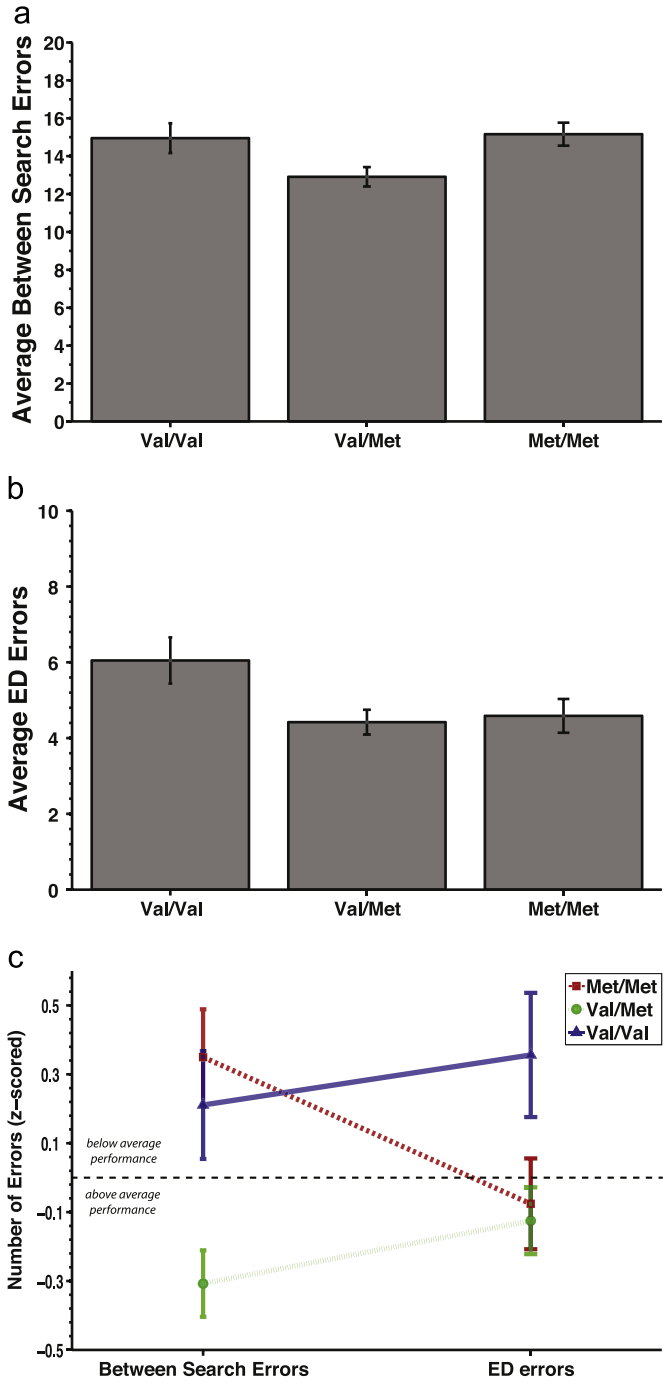

Fig. 1. (A) Between-search errors on the spatial working memory task for PD patients as a function of COMT genotype Error bars refer to the standard error of the mean (SEM). (B) Total errors (extradimensional and intradimensional) on the ID/ED task. Error bars refer to the standard error of the mean (SEM). (C) Total errors (extradimensional and intradimensional) on the ID/ED task and between-search errors on the spatial working memory (SWM) task. Both variables have been z-scored (see method section). Error bars refer to the standard error of the mean (SEM).

$p=0.751$. In the participants who passed all nine stages (Met/Met=53 (49.1%); Val/Met=90 (48.9%); Val/Val=43 (53.8%)) there was no significant effect of COMT on the total number of errors collapsed across the nine different stages of the task, $F(2,181)=0.690$, $p=0.503$. Data on the effect of COMT on the other stages of the ID/ED task are presented in the supplementary materials (Supplemental Fig. 1).

3.2. .2 Set-shifting

From subsequent stage-wise analyses of error rates, four participants (1 Met/Met, 2 Val/Met, 1 Val/Val) were removed due to having an extreme number of extradimensional errors (see below for supplementary analyses where these outliers were included). A significant main effect of COMT genotype on extradimensional shifts, $F(2,179)=3.60$, $p=0.029$, was observed (Fig. 1b). Post-hoc comparisons, corrected for multiple comparisons (Tukey HSD), revealed this was due to the Val/Val group making more errors than Val/Met ($t(179)=2.60$, $p=0.027$) and a trend towards more errors than Met/Met ($t(179)=2.11$, $p=0.090$). However, there was no significant difference between the Val/Met and Met/Met group ($t(179)=0.28$, $p=0.956$).

Supplemental analyses examined the selectivity of this effect of COMT by comparing mean errors on stages requiring set-shifting (EDS and EDR) with stages requiring set-formation and set-maintenance (C_D, IDS and IDR). This revealed a significant interaction between COMT and shifting type ($F(2,179)=3.12$, $p=0.046$), due to COMT genotype group affecting extradimensional shifting (as above) but not performance on trials requiring high set-formation and -maintenance ($F(2,179)=0.430$, $p=0.651$).

As with the SWM data, significant effects of COMT genotype on extradimensional shifting remained significant when age, equivalent L-dopa dose, disease duration and UPDRS motor subscore were included as covariates in supplementary analyses. There was no significant main effect of gender or interaction between gender and COMT on extradimensional shift errors ($Fs<1$). Again, as above, we also examined the effect of COMT genotype after removing patients who were taking COMT inhibitors. Again, the effect of COMT genotype on extradimensional shift errors remained significant even after excluding those patients who were taking COMT inhibitors ($F(2,145)=5.72$, $p=0.004$). Thus our results are not influenced by the differential use of (peripheral) COMT inhibitors amongst the COMT genotype groups.

Trend analysis revealed a significant linear effect of COMT genotype on extradimensional shifting ($t(179)=2.11$, $p=0.036$), but only a trend for a significant quadratic effect of COMT on extradimensional shifting ($t(179)=1.80$, $p=0.07$). When outliers were included in the analysis the result remained significant using robust regression (linear effect of COMT: $beta=0.72$, $t(186)=1.97$, $p=0.049$, quadratic effect of COMT: $beta=0.87$, $t(186)=1.66$, $p=0.09$). Thus, COMT genotype group affected ID/ED performance in a linear manner.

Analysing SWM performance (between-search errors) in the subset of patients who passed all nine stages of the ID/ED task revealed that there was still a significant main effect of COMT ($F(2,179)=9.01$, $p=0.0002$) and a significant interaction, between COMT genotype and load, $F(3.25, 291.22)=3.61$, $p=0.006$ (Supplemental Fig. 2). Thus, the non-linear effect of COMT genotype on spatial working memory was present also within the small sample of participant who completed all ID/ED stages.

3.3. Set-shifting vs. Spatial working memoty

In addition, we examined, within this subgroup, whether the effect of COMT genotype had dissociable effects on SWM and extradimensional shifting. Importantly, there was a significant interaction between COMT genotype and task type ($F(2,159)=5.96$, $p=0.003$), indicating that COMT genotype had differential effects on the two tasks (Fig. 1c). This interaction was driven by a significant interaction between task and genotype when comparing Met/Met with Val/Met ($F(1,138)=8.05$, $p=0.005$) and a significant interaction between task and genotype when comparing Met/Met with Val/Val ($F(1,92)=4.76$ $p=0.032$). However, there was no significant task by genotype interaction when comparing Val/Met with Val/Val ($F(1,128)=0.027$, $p=0.871$). Simple main effects

analysis confirmed that these significant interactions were due to Met/Met patients making relatively more errors on the SWM task than the ID/ED task ($t(179)=2.50$, $p=0.013$). However, there were no significant difference in relative task performance for Val/Met $t(179)=1.31$, $p=0.16$) or Val/Val patients $t(179)=0.76$, $p=0.44$).

3.4. Paired Associate Learning

There was no significant association between COMT genotype and the likelihood of passing the most difficult 6-box stage (Met/Met 29 (27%), Val/Met 105 (18%), Val/Val 18 (23%): $\chi(2)=2.83$, $p=0.243$). Of those participants who passed the six-shape stage, there was no significant effect of COMT on the number of errors at this stage ($F(2,278)=0.203$, $p=0.816$).

4. Discussion

The present study shows that performance of PD patients on tasks sensitive to frontal dopamine is influenced by their COMT-val158met genotype. In contrast, no such relationship was found for paired associates learning. Critically, COMT genotype had dissociable effects on attentional set-shifting and spatial working memory, implying that optimal performance on these two tasks is associated with, respectively, relatively high and low levels of dopamine (Fig. 2).

The putative activity of the COMT enzyme (as indexed by COMT genotype group) affected spatial working memory performance in a non-linear manner. PD heterozygotes showed superior working memory performance (in terms of between-search errors) to PD Met homozygotes and PD Val homozygotes. This suggests that PD patients with putatively intermediate PFC dopamine levels performed better on the spatial working memory task than those groups who putatively have lower or higher levels of PFC dopamine. Therefore, these results reveal an 'inverted-U' shaped function between PFC dopamine levels and working memory performance, with PD COMT heterozygotes positioned at the apex and PD Val homozygotes and PD Met homozygotes on, respectively, the left- and right-hand limb of the 'inverted-U' shaped function. Thus, impaired spatial working memory in PD Val homozygotes might arise from deficient levels of PFC dopamine receptor stimulation, whereas impaired spatial working memory in PD Met homozygotes might reflect an excess level of dopamine receptor stimulation (Fig. 2).

In contrast to the SWM results, COMT genotype influenced performance on the set-shifting task in a relatively linear manner, with putatively lower dopamine levels being associated with lower cognitive flexibility (more extradimensional errors).

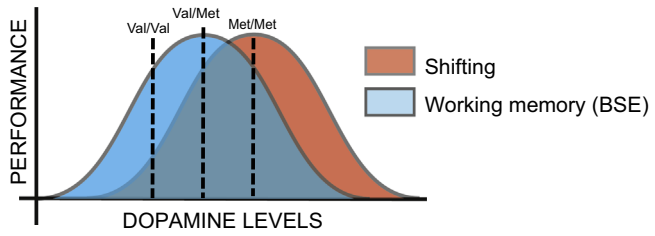

Fig. 2. Hypothetical explanation of the differential effect of COMT genotype on extradimensional shifting and spatial working memory. COMT heterozygotes exhibited optimal spatial working memory (decreased between-search errors [BSE]) due to optimal levels of dopamine. PD Val homozygotes are hypothesised to have poor spatial working memory because of deficient levels of dopamine, whereas PD Met homozygotes are hypothesised to have impaired SWM because of excess levels of dopamine. In contrast, the relationship between dopamine levels and extradimensional shifting is hypothesised to result from a separate, rightward-shifting inverted-U response function.

Impaired performance by Val homozygotes, particularly on extradimensional trials, is consistent with data from studies employing the classic Wisconsin Card Sorting Test (Grant and Berg, 1948). For example, COMT genotype has been shown to impact perseveration – the ability to shift attention away from one perceptual dimension to another (Egan et al., 2001). An increased number of perseverative errors on the WCST has usually been associated with reduced PFC integrity and lower dopamine levels (Demakis, 2003; Milner, 1963; Weinberger, et al., 2001). Moreover, there also appears to be an 'inverted-U' shaped function between the levels of D_1 receptor stimulation in the PFC and perseverative errors, with very high or very low levels of D_1 density being associated with increased errors (Takahashi et al., 2008). COMT genotype has also been found to modulate perseverative errors; individuals carrying the Val allele showed more perseverative errors than Met homozygotes (Egan et al., 2001), an impairment that was ameliorated by boosting catecholamine levels with amphetamine (Mattay et al., 2003). The finding of impaired WCST performance in healthy Val carriers is consistent with the impairment seen by the PD Val/Val seen here. Thus, on the basis of these findings, increased errors on extradimensional shifting in PD Val homozygotes is likely to have occurred due to deficient levels of dopamine in the PFC (Fig. 2). In contrast, the linear reduction in extradimensional errors with decreasing COMT activity (leading to higher dopamine levels) likely resulted from these groups having dopamine levels closer the task-specific optimum (Fig. 2).

The ID/ED task was designed to decompose the cognitive requirements of the WCST into their constituent elements. We found a specific effect of COMT genotype on trials requiring high cognitive flexibility (extradimensional shifting trials), while leaving unaltered performance on earlier set-formation and -maintenance stages of the task. The type of cognitive flexibility needed to perform extradimensional shifts has been found to be sensitive to the integrity of the lateral PFC and to lead to increased blood oxygenated level dependant (BOLD) signal in these regions using fMRI (Dias et al., 1996; Hampshire and Owen, 2006, Williams-Gray et al., 2008). Furthermore, anatomically circumscribed depletions of PFC dopamine levels have been found to lead to *reduced* extradimensional errors in non-human primates (Crofts et al., 2001; Robbins and Roberts, 2007; Roberts et al., 1994). Variations in the activity of COMT have also been found to have specific effects on attentional set-shifting. In rats, administration of tolcapone (COMT inhibitor) was found to improve extradimensional shifting (Tunbridge et al., 2004). Microdialysis measurements found that while tolcapone modulated the level of induced dopamine release in the medial PFC, there was no such effect on noradrenaline. Thus, increased cortical dopamine levels were found to be associated with enhanced extradimensional shifting, which is in exact agreement with this study's findings. Similarly, in humans, tolcapone administration was found to improve intradimensional shifting in Val homozygotes but to impair intradimensional shifting in Met homozygotes (Apud et al., 2007). It has been proposed that PFC dopamine is important for attentional set formation (Robbins and Roberts, 2007), i.e, that PFC dopamine is important for building up a bias towards relevant information, resulting in privileged access to information from the task-relevant category but in impaired access to information from outside the relevant category. Behaviourally, on the ID/ED task, reduced attentional set-formation should materialise as reduced errors on the early stages of the task prior to the extradimensional shift trials during which the attentional set is being acquired and maintained. However, we found no effect of COMT genotype on performance at these earlier stages that require high attentional stability. This is in contrast to previous work, where reduced attentional tuning towards the relevant dimension was associated with a relatively enhanced ability to shift attention (Williams-Gray et al., 2008; Fallon et al., 2013a,

2013b).

One possibility is that this discrepancy reflects reduced sensitivity of the ID/ED task, employed in the current study, to effects on attentional stability. Conversely, the task used in the previous studies (Hampshire and Owen, 2006) is likely more sensitive to attentional set-formation and -maintenance, because participants had to perform multiple shifts. Thus in the previous version of the task participants had to form and break attentional set on numerous occasions, allowing repeated assessment of set formation and shifting performance. In the present study, participants had to acquire one attention set and shift set only once and may therefore lack the sensitivity to uncover subtle differences in the set formation period.

Cumulatively, the results from this study reveal that the effects of COMT genotype in PD patients depend on the cognitive phenotype of interest. The ID/ED and SWM tasks have previously been found to respond differentially to pharmacological manipulations. In rats, set-shifting and working memory performance responded to dopaminergic receptor stimulation in dissociable ways (Floresco, 2013), with attentional set-shifting being more sensitive to the balance between D1 and D2 receptor stimulation than working memory. More directly, however, using the exact same tasks as used here, the administration of sulpiride, a D2 receptor antagonist to healthy volunteers, significantly improved performance on SWM but impaired performance on the ID/ED task (Mehta et al., 2004). Therefore, the results of this study suggest that distinct cognitive deficits in PD arise from a departure from a task-specific optimal level of dopaminergic stimulation (Fig. 2). This conclusion is generally consistent with a variety of other findings showing that, due to spatiotemporal progression of dopamine depletion in PD, there is an uneven pattern of performance on cognitive tasks in PD patients, with some tasks benefitting from L-dopa administration whilst others are impaired (Cools et al., 2001; Duthoo et al., 2013; Fern-Pollak et al., 2004; Lewis et al., 2005; Moustafa et al., 2008; Rowe et al., 2008; Shohamy et al., 2006; Shook et al., 2005; Swainson et al., 2006). Therefore, given that different tasks have different optimal levels of dopamine, it seems unlikely that a specific COMT genotype would be associated with superior cognitive performance across all tasks and all psychological states. Heterozygocity for the COMT enzyme (which leads putatively to intermediate dopamine levels) may represent an optimal compromise between either have low dopamine levels (Val homozygotes) or too much dopamine (Met homozygotes) (Fallon et al., 2013b).

In contrast to the ID/ED and SWM task, no association was found between COMT genotype and performance on the PAL task. The lack of a behavioural effect of COMT genotype on PAL performance is consistent with previous findings (Dennis et al., 2010; Fallon et al., 2013a, 2013b). A relationship between COMT genotype on PAL performance could have been anticipated on the basis that the COMT enzyme also affects dopamine levels in the hippocampus (Laatikainen et al., 2013), a region that is critical for normal performance on the PAL (Owen et al., 1995). However, performance on the PAL has been found to be relatively insensitive to changes in dopamine levels in both healthy older adults and controls (Owen et al., 1993). Neuroimaging may help resolve this discrepancy; activation of medial temporal lobe structures has been found to vary according COMT genotype groups during face-scene pairing tasks (Dennis et al., 2010). Thus, it is possible that while there is no effect of COMT genotype on performance of the PAL task, the neural mechanisms recruited to perform this task may vary according to COMT genotype (Fallon et al., 2013b). Future studies should seek to evaluate this question.

The finding that of differential performance in PD patients according to COMT genotype could potentially lead to the prospect of tailoring individual patient's dopaminergic medication regime according to their task requirements and COMT genotype status. For example, patients with more active COMT enzyme could be given more, or a different type, of dopaminergic medication. Although the results could provide the rationale for such treatments, there are a number of outstanding questions and limitations to the study that need to be addressed.

Firstly, a clear limitation of the study is the absence of any quantification or manipulation of dopamine levels. Quantification of frontal or striatal dopamine levels would greatly enhance the neural specificity of our findings, i.e., that the results are due to differential dopamine levels in the frontal cortex. Similarly, the absence of any medication manipulation (withdrawal of L-dopa) prevents us from examining the effect of medication. All the patients tested in this study were on their dopaminergic medication, which may have influenced the results here as in previous studies. However, the inclusion of medication dose (equivalent L-dopa) as a covariate in our analysis did not alter the significance of our results. Another potential limitation of this study is the diverse and heterogeneous dopaminergic medication regimes of PD patients. However, our effects of interest are unlikely to reflect these differences as, generally, the groups did not differ in terms of the types of medication they were taking. Moreover, removing those patients taking COMT inhibitors from our analyses did not alter the statistical significance of any of our results. PD patients are frequently prescribed the peripheral COMT inhibitor entacapone in order to boost the efficaciousness of other dopaminergic drugs. Unlike tolcapone, however, entacapone does not cross the blood brain barrier. Therefore, its effect on dopamine methylation in the brain (and cognition) may be more limited. However, given the small numbers of patients taking entacapone in the Val/Val group, we were unable to perform a factorial analysis taking into account COMT genotype and the use of entacapone. Future studies should seek to address this question.

In addition to disruption of dopamine systems, PD is also associated with disruption of noradrenalin transmission (Baloyannis et al., 2006). This noradrenergic dysfunction may also contribute to some of the cognitive deficits seen in PD (Kehagia et al., 2010), although the val158met polymorphism has been repeatedly found not to modulate cortical noradrenaline levels (Laatikainen et al., 2013; Tunbridge et al., 2004). One future avenue of enquiry would be to investigate how the effects of noradrenergic manipulations, such as guanfacine, depend on COMT genotype. This is especially important given that both extradimensional shifting and spatial working memory have been found to be sensitive to noradrenergic manipulations in both animals and humans (Arnsten, 2011; Coull et al., 1995; Lapiz and Morilak, 2006; Middleton et al., 1999).

Another limitation of the study is the sample of PD patients that were tested in this study. The ParkFit study assessed sedentary PD patients. Accordingly, there is the possibility that the sample of PD patients tested in this study may not represent the PD population as a whole. For example, the patients tested in this study may have a more advanced (as measured in terms of disease severity or disease duration) form of the disease. However, it should be noted that none of the demographic or clinical variables were found to modulate the effects of COMT on cognition observed in this study. Thus, it seems unlikely that the results of this study would change when testing a different sample of PD patients.

A final limitation of the study is the absence of a control group of healthy older adults. At present it is unknown whether the effects observed in this study are specific to PD or would also be found in a matched group of healthy older adults. However, a large study ($n=1000+$) found no effect of the val158met polymorphism in healthy adults with an age range between $\sim$25 and 70 on spatial working memory or ID/ED performance (Dennis et al., 2010). Thus, the effects of the COMT val158met polymorphism are likely disease specific. Indeed, this has previously been

demonstrated in the case of planning, where COMT genotype group influenced performance only in PD patients and not in healthy age-matched controls (Fallon et al., 2013b). Thus, COMT genotype group appears to have a greater effect on cognitive function in PD patients compared with controls, possibly reflecting the dopaminergic degeneration that occurs in PD. Given that the supply of dopamine is compromised in PD patients (due to midbrain degeneration), it is likely that enzymatic regulation of PFC dopamine levels has a greater role in determining the levels of dopaminergic stimulation in the PFC.

In summary, this study examined cognitive performance in a large cohort of PD patients according to COMT val158met genotype. Consistent with the known neuroanatomical locus of the COMT enzyme's effects, performance on tasks known to be sensitive to PFC dopamine differed between COMT val158met genotype groups. However, COMT genotype groups showed differential performance on spatial working memory and attentional set-shifting. This difference between COMT genotype groups implies that these two tasks have different optimal levels of dopaminergic stimulation. Thus, the results of this study have revised our understanding of prefrontal dopamine's association with cognitive performance differences in PD; while prefrontal dopamine may be an important arbiter of cognitive functioning in PD patients, it does not affect cognition in a uniform way. The present findings also have implications for models of cognitive control in the normal brain. Several models of cognitive control implicate dopamine as an important determinant of cognitive control (Cohen et al., 2002; Cools and D'Esposito, 2011; Cools and Robbins, 2004; Durstewitz and Seamans, 2008; Hazy et al., 2007). There is large individual variability in the degree to which healthy people exhibit cognitive control and this likely reflects, in part, individual variability in genetically determined dopamine function. However, in the healthy population, associations between individual cognitive differences and variation in the COMT gene are more difficult to isolate than in Parkinson's disease, due to the integrity of the dopamine neurons. In Parkinson's disease, dopamine metabolism is determined to a greater degree by COMT, because of the degeneration of these dopamine neurons and their dopamine transporters, which otherwise provide an alternative metabolic route. As such, in this study, Parkinson's disease served also as a model for isolating effects of the COMT gene that are likely present, but possibly masked in the healthy brain. Our results demonstrate that individual differences in the COMT gene do not have a unitary, monotonic effect on cognitive control. Rather certain functions may be enhanced whereas other functions may either not change or be impaired as a function of such genetic variation.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2015.07.031.

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