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Prefrontal Dopamine Levels Determine the Balance between Cognitive Stability and Flexibility

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A key mechanism by which the prefrontal cortex (PFC) supports goal-oriented behaviors is attentional set formation: the formation and maintenance of an attentional bias toward relevant features. It has previously been proposed that a common single nucleotide polymorphism (val158met) in the gene that codes for the catechol O-methyltransferase (COMT) enzyme may affect an individual's ability to form and maintain an attentional set by modulating PFC dopamine (DA) levels. Here, we present data from a functional magnetic resonance imaging study that investigated the effect of this polymorphism on the tendency for older adults to display set-like behavior, and we compare these results to preexisting data from Parkinson's Disease (PD) patients. Our results demonstrate that putatively different levels of PFC DA predict both attentional set formation and right dorsolateral PFC (DLPFC) activation. More specifically, while for PD patients, val homozygotes showed heightened DLPFC activation and increased set-like behavior, for healthy older adults, the opposite pattern of results was observed. This interaction between COMT genotype and PD accords well with previous studies that have shown an excess of DA in the PFC in early PD patients and, furthermore, supports the hypothesis that there is an inverted-U shaped functional relationship between PFC DA levels and attentional set formation.

Keywords: COMT, dopamine, Parkinson's disease, prefrontal cortex, set-formation

Introduction

Efficient goal-directed behavior necessitates the ability to selectively focus on those features that are most relevant to the current task while ignoring other, perhaps more salient, or previously relevant features. A demarcation between relevant and irrelevant features can be achieved through the formation of a top-down attentional set. Individuals need to be able to form and maintain, but also to adapt their attentional set according to changes in their internal state (goals) or the environment. Numerous neuropsychological studies that have assessed the ability to shift attentional set have implicated the prefrontal cortex (PFC), particularly the lateral PFC, as playing a crucial role in supporting set-like behavior (Dias et al. 1996; Demakis 2003).

Dopamine (DA) is known to play a prominent role in modulating processes within the PFC, and, consequently, is well placed to modulate set-like behavior (Seamans and Yang 2004). In support of this view, experimental depletions of PFC DA have been found to impair attentional set formation in nonhuman primates (Roberts et al. 1994; Crofts et al. 2001). In humans, genetically induced differences in DA levels may provide an experimental window into the effects of DA on PFC function. For example, inactivation of DA in the PFC is particularly dependent on the catechol O-methyltransferase (COMT) enzyme due to the relative absence of DA transporters (Tunbridge et al. 2004; Yavich et al. 2007). A common single-nucleotide polymorphism of valine for methionine at codon 158 leads to a 40% change in the activity of this enzyme (Chen et al. 2004), with the highest enzyme activity in valine homozygotes and the lowest in methionine homozygotes. Consistent with the findings from the nonhuman primate literature on the role of DA in attentional set shifting, the val158met polymorphism has been shown to modulate measures of set-like behavior in schizophrenic and PD patients (Egan et al. 2001; Williams-Gray et al. 2008). Specifically, PD val homozygotes, who putatively have lower PFC DA levels than PD met homozygotes, showed more evidence of attentional set formation and greater activity in right frontoparietal areas. Williams-Gray et al. (2008) argued that these results represent the right-hand limb of an inverted-U shape function between PFC DA levels and attentional set formation. This result was argued to occur due to the greater capacity of val homozygotes to attenuate the dopaminergic (DAergic) overdosing of the PFC. Ostensibly, the notion that PD patients have excess PFC DA may seem counterintuitive given that this disease is characterized by dramatic reductions in striatal DA. However, although it is perhaps an oversimplification of the multidimensional manner in which these 2 systems interact, prefrontal and striatal DA levels have been found to have an antagonistic relationship with each other, particularly in pathological circumstances (Carter and Pycock 1980; Kolachana et al. 1995; Iwano et al. 1997; Bertolino et al. 1999, 2000). Thus, a reduction in striatal DA levels may produce a corresponding increase in PFC DA levels. This hypothesis has been supported by a series of Positron Emission tomography (PET) studies, using 6-[^{18}F]-L-dopa (FDOPA), which have reported that there appears to be excess levels of PFC DA in early, but not late, PD patients (Rakshi et al. 1999), even in those patients who have yet to initiate DA replacement therapy (Kaasinen et al. 2001; Bruck et al. 2005), though the validity of these findings has been disputed (Cropley et al. 2008).

The interpretation of these previous results (Williams-Gray et al. 2008) is complicated further by the absence of an age-matched control group. It was proposed that the enhanced set formation and increased cortical activations in PD val homozygotes relative to PD met homozygotes represented a reversal of the normative direction of the results, whereby met homozygotes would be expected to show increased

set-like behavior and neural activation compared with val homozygotes. However, this pattern of results cannot be assumed. Indeed, the superior performance of val homozygotes with concomitant increases in cortical activation, relative to met homozygotes, has been reported in the case of fluid reasoning in healthy controls (Bishop et al. 2008), suggesting that performance and neural activation differences between different COMT genotype groups may be task dependent. In addition, it is possible that the effect that the val158met polymorphism had on this task may be unique to this group due to coexisting neuropathology.

This study sought to test this inverted-U shape hypothesis more fully by providing data for the other limb of the inverted-U shaped function. Specifically, age-related reductions in PFC DA levels in healthy older adults should push this group toward the left-hand limb of the inverted-U shaped function (Kumakura et al. 2005; Ota et al. 2006), with the impact of these reductions being modulated by participants' COMT genotype. Thus, older adults were predicted to display exactly the opposite relationship between genotype and set-like behavior as PD patients, with healthy met homozygotes (high DA) displaying greater attentional set formation and increased frontoparietal activity than val homozygotes (low DA; Fig. 1).

Materials and Methods

Participants

Fifty-two healthy older Caucasian adults were recruited to take part in this study. Participants were screened for Parkinsonism and were administered the Mini-Mental State Examination (MMSE), Beck Depression Inventory (BDI) and the National Adult Reading Test (NART). These data are presented in Table 1. Data from 29 PD patients described in Williams-Gray et al. (2008) were also included in the analysis. Genotype data for healthy volunteers and PD patients were extracted using standard protocols (see Williams-Gray et al. 2007).

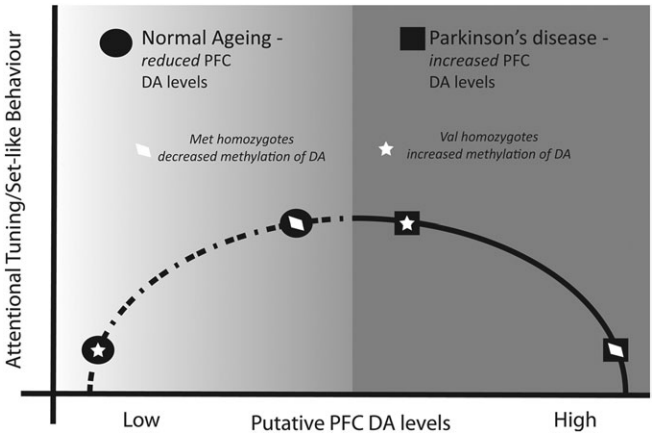

Figure 1. A graphical illustration of the predicted nonlinear effect COMT val158met genotype and PD will have on attentional functioning.

Table 1
The demographics of healthy older adults and PD patients according to COMT genotype

	Healthy met/met	Healthy val/met	Healthy val/val	PD met/met	PD val/val
Age	63.6 (6.6)	66.2 (7.4)	63.5 (6.9)	64.0 (9.4)	64.8 (10.4)
MMSE	29.5 (.62)	29.2 (.77)	29.5 (.60)	28.8 (0.7)	28.8 (0.7)
NART IQ	120.7 (5.7)	123.7 (2.5)	120.8 (6.0)	114.5 (6.6)	114.2 (6.9)
BDI	4.4 (3.4)	3.2 (3.0)	3.9 (2.7)	6.5 (4.8)	7.3 (4.0)
Gender (M:F)	7:10	8:7	8:12	8:5	10:6
N	17	15	20	13	16

Note: M, male; F, female.

One-way analyses of variance (ANOVAs) revealed that there were no significant differences between the 3 COMT genotype groups (met homozygotes, val/met heterozygotes, and val homozygotes) in terms of age: $F < 1$, $P > 0.05$, BDI score $F < 1$, $P > 0.05$, MMSE score $F_{2,51} = 1.4$, $P > 0.05$, and NART IQ score $F_{2,51} = 1.8$, $P > 0.05$. A chi-squared test between gender and genotype found no differences in the gender ratios between the genotype groups: $\chi^2 = 1.3$, $P > 0.05$. In the PD sample, there were 13 met homozygotes and 15 val homozygotes. They were matched in terms of BDI, MMSE, and NART, Unified PD Rating Scale, and equivalent levodopa dose (for more details, see Williams-Gray et al. 2008).

Patients and healthy older adults were matched for age: $F_{1,61} > 1$, $P > 0.05$. However, there was a significant difference between patient and control scores on the MMSE: $F_{1,61} = 12.82$, $P < 0.05$; BDI: $F_{1,61} = 11.57$, $P < 0.05$; and NART: $F_{1,61} = 18.8$, $P > 0.05$, with PD patients having lower scores than healthy older adults on all 3 measures.

Design

The task required participants to learn, via trial and error, which stimulus, of the 4 presented on the screen, was designated as the target image. The 4 stimuli were drawn from 2 object dimensions: faces and buildings. The 4 stimuli appeared as 2 compound stimuli on the left- and right-hand side of the screen. Each stimulus consisted of a face and a building superimposed on top of each other (Fig. 2). This task is described in full in Hampshire and Owen (2006). Briefly, however, left button presses selected images on the left-hand side of the screen and right button presses selected images on the right-hand side of the screen. A subtle, but important, feature of this paradigm is that participants are presented with feedback after every 2 trials (responses). Thus, given that over successive trials the face-building combinations reversed, this enables experimenter to discern exactly which image a participant was selecting (attending to) over those 2 trials. Clearly, it is not possible to discern which image (face or house) the participants were attending to after a single response to a compound image.

If participants chose the incorrect image, they had to select a new image, and, in the process, perform either an intradimensional (ID) switch, that is, face to face, or an extradimensional (ED) switch, that is, face to building. It should be noted that these ID and ED switches are not to be confused with the ID or ED "shifts" mentioned below. ID or ED switches refer to changes in participants' attention during the experiment. For example, an ED switch would involve switching attention to a house from a face. ID and ED shifts, however, refer to the changes in the target image that participants are trying to find. For example, an ED shift occurs when the target image changes from a house to a face. Participants had to iterate between each of the 4 stimuli until they selected the target image. (This constitutes the "working out" phase.) Participants also had to make 6 consecutively correct responses to the target image. (This constitutes the "knowing" phase of the experiment.) After reaching criterion, participants were presented with entirely new compound stimuli ("set change"), or there was a change in the reward contingency, that is, another image became the target ("reversal"). If the new target stimulus was drawn from the same category as the previous one, this was termed ID. If it was drawn from the other category, it was termed ED. Thus, trials could be subdivided into 4 types, those in which the participants were required to shift their attention intradimensionally or extradimensionally in the contexts of a change in stimulus set or a reversal of reward contingencies. In keeping with previous nomenclature (e.g., Roberts et al. 1988), these trials shall be referred to as ID shifts (IDS), ID reversals (IDR), ED shifts (EDS), and ED reversals (EDR). Prior to entering the scanner, participants were thoroughly trained on the task.

Empirical Measures of Set Formation and Flexibility

Classically, low error rates on IDS compared with EDS has been seen to be indicative of attentional set formation (Roberts et al. 1988; Downes et al. 1989). Accordingly, the trials to criterion for ID conditions were subtracted from the ED conditions ((EDS + EDR) – (IDS + IDR)).

Although superior performance on IDS compared with EDS trials has been taken as evidence of attentional set formation, the exact nature of

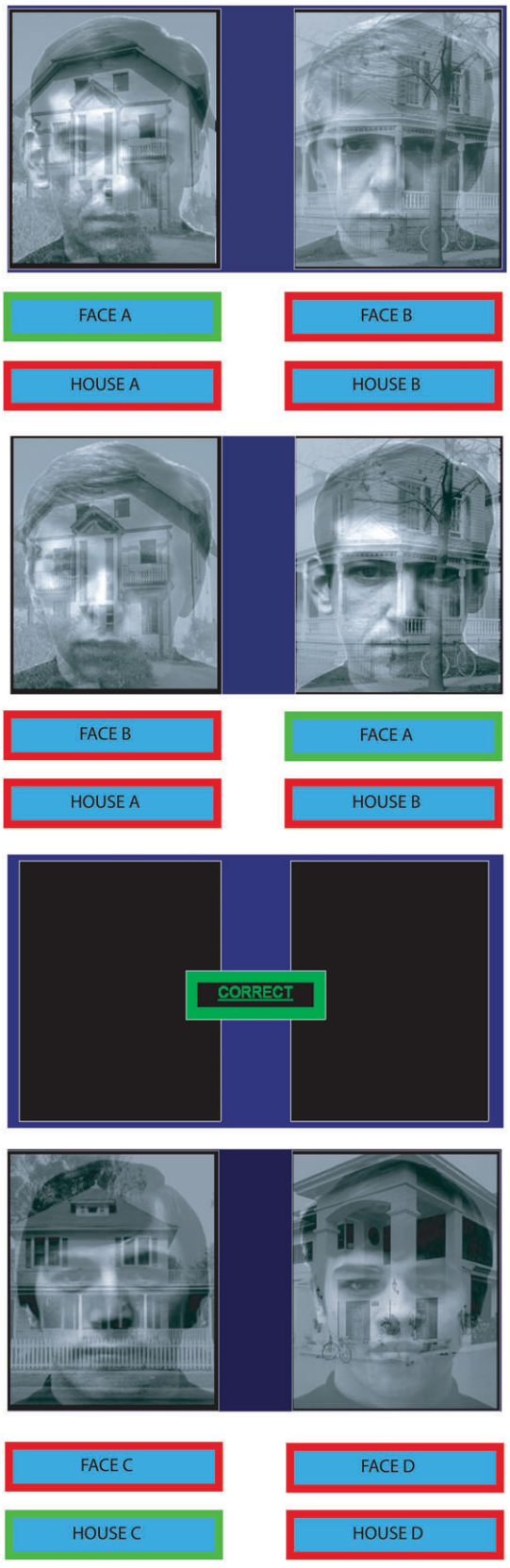

Figure 2. An illustration of the task. Participants have to select either a house or a face until they find the correct answer. To select an image on the left or right, participants have to press the left or right button, respectively. In this example, the participant has to make 2 consecutive left responses in order to find the target (Face A). Participants are informed about the correct target by the presentation of feedback. After making 6 consecutively correct responses, the target will change (see text for details on the experimental manipulations).

this behavioral difference has not previously been explored in detail. More specifically, when searching for the target amongst the 4 objects, there may be an enduring attentional bias to select an image from the previously relevant dimension. Alternatively, within a given search, the individual may tend to eliminate all objects from one category before trying the other. The level of attentional bias was quantified by taking the proportion of total shift trials in which participants chose to select an object from the previous target's dimension. By contrast, the level of dimensionally structured searches was quantified by taking the proportion of times that participants eliminated all objects from one dimension before trying the other. These measures were arcsine transformed (2 arcsine square-root (x)) to conform to parametric assumptions (Howell 1997).

Overall level of performance was assessed by taking the average number of errors for each of the 4 conditions. The level of perseveration toward individual images was also calculated. As in previous studies (Hampshire et al. 2008), perseverative errors were divided into 2 classes. These were consecutive perseverative errors, where the individual selected the same nontarget object immediately after receiving negative feedback, and nonconsecutive perseverative errors, where the participant chose a different object after receiving negative feedback, but then went back and retried the eliminated object.

Data Acquisition

Participants were scanned at the Medical Research Council Cognition and Brain Sciences Unit, Cambridge, using a 3 Tesla Siemens TIM Trio MRI scanner. 880 T_2-weighted echo-planar images depicting blood oxygenation level–dependent (BOLD) signal were acquired for each of the two 16-min runs (time repetition = 1.1 s), with the first 18 scans being discarded. Each image consisted of 21 slices of 4 mm thickness with a 1-mm interslice gap, with an in-plane resolution of 3.2 × 3.2 mm, and slices were angled away from the orbits. Stimuli were on 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 approximately 1°.

Preprocessing

Functional magnetic resonance imaging (fMRI) data were analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, University College London, UK). Preprocessing was implemented using an automated analysis script (http://imaging.mrc-cbu.cam.ac.uk/imaging/AutomaticAnalysisRecipes). Data were first corrected for slice timing errors, realigned to correct for movements, co-registered to the structural Magnetization-prepared rapid gradient echo image, normalized to a standard template (Montreal Neurological Institute) and then smoothed using an 8-mm full-width at half-maximum Gaussian kernel.

fMRI Modelling

The BOLD response was modeled to the onset times and durations of a number of events. Four of these involved the participant switching their focus of attention, namely: "ID switches" and "ED switches" while participants searched for the target; switching attention to a novel object following a change in stimulus set ("set change"); switching attention away from a previous target to a previous nontarget following a change in reward contingency ("reversal"); responding to a target that was known to be correct, as positive feedback had been received ("known correct"); and, finally, positive and negative feedback events. All onsets were taken from the time the stimuli appeared on the screen. For nonfeedback 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 (500 ms).

Given the previous observation (Williams-Gray et al. 2008), that COMT genotype modulated the activity of regions recruited during the working out phase of the task relative to baseline, the main focus of this

study was concerned with ascertaining whether comparable genotype effects were present in healthy older adults. Therefore, the same 3-step analysis procedure that was performed in Williams-Gray et al. (2008) was also performed here. First, brain regions that were involved in the working out phase of the task were identified by collapsing across healthy and PD homozygotes (thereby excluding healthy val/met heterozygotes). This involved contrasting all events that occurred while participants were actively working out the target (ID switches, ED switches, set changes, and reversals) with "known correct" events. Second, 5-mm radius regions of interest (ROIs) were defined at peak activation coordinates within each cluster. Finally, using the contrast of all events while working out the target (ID switches, ED switches, set changes, reversals, and responses with positive and negative feedback) versus baseline, we extracted ROI data using the Marseille Boîte A Region d'Intérét (Marsbar) toolbox. This data was examined for cross-group effects in SPSS version 12 (Chicago, USA) using repeated measures ANOVA.

Results

Six people were unable to provide complete data sets due to technical difficulties leaving 15 healthy met homozygotes, 13 healthy val/met heterozygotes, and 18 healthy val homozygotes. There were 16 PD val homozygotes and 13 PD met homozygotes. The results from healthy heterozygotes were not included in any of the subsequent statistical analyses as Williams-Gray et al. (2008) did not include heterozygotes in their analyses. However, the results for the heterozygotes are presented on the graphs for illustrative purposes.

Behavioral Results

A two-way ANOVA revealed, as predicted, that there was an interaction between disease and genotype on a measure of set-like behavior, mean responses made on EDS/EDR minus IDS/IDR blocks ($F_{1,58}$ = 9.81, P < 0.01). There were no significant main effects of disease or genotype on performance (Fs < 1). Simple main effects analysis revealed that healthy met homozygotes showed greater set-like behavior (significantly more trials to complete EDS than IDS blocks) than val homozygotes, $F_{1,58}$ = 4.97, P < 0.05, while for PD patients, val homozygotes showed greater set-like behavior than met homozygotes, $F_{1,58}$ = 4.84, P < 0.05 (see Fig. 3).

To examine differences in set-like behavior further, a similar two-way ANOVA on the proportion of trials after a stimulus set change in which participants selected an exemplar from the previously relevant dimension was performed. Again, there was an interaction between disease and genotype, $F_{1,58}$ = 4.84, P < 0.05. Simple main effect analysis revealed a significant difference between healthy adult homozygote groups with met homozygotes showing a greater tendency to maintain an attentional set than val homozygotes, $F_{1,58}$ = 4.50, P = 0.038, but not in patients $F_{1,58}$ = 1.05, P > 0.05 (see Fig. 4). There was no main effect of disease or genotype (Fs < 1).

The participants' overall bias toward selecting faces or buildings was examined at the first response after a reversal or a set change. A two-way ANOVA revealed no face or building bias, and no significant main effects or interactions between face-building bias and disease or genotype (Fs < 1).

The degree of structure within a participants' search for the correct object (the tendency to choose both exemplars from one dimension first) was examined in a two-way ANOVA (Fig. 5). There was a significant interaction between disease and genotype, $F_{1,58}$ = 4.58, P < 0.05. Simple main effects analysis revealed that there was a significant effect of dimensionality for healthy adults according to COMT val158met genotype, $F_{1,58}$ = 5.87, P < 0.05, but not PD patients (F < 1), in that, healthy met homozygotes displayed a significantly greater level of dimensional searching compared with healthy val homozygotes.

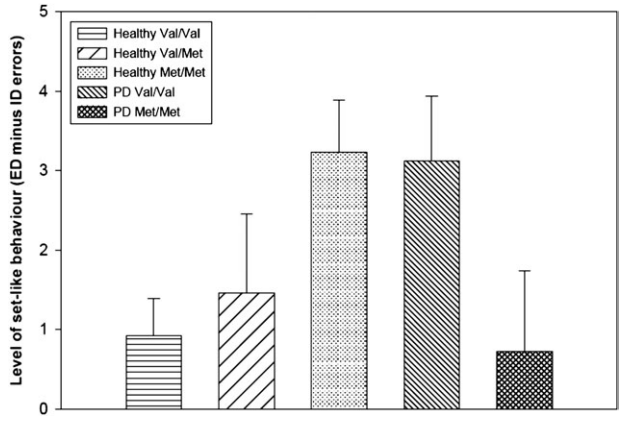

Figure 3. The level of set-like behavior in PD patients and healthy older adults according to COMT genotype. Higher scores mean more set-like behavior. Healthy val158met heterozygotes are shown for comparison. Error bars represent standard error of mean.

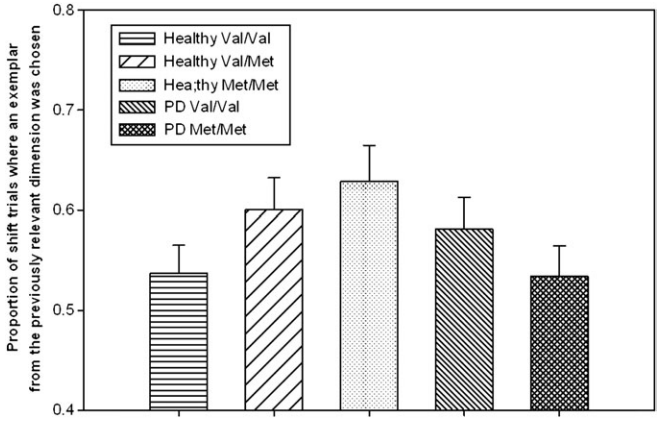

Figure 4. The proportion of total shift trials where participants chose the previously relevant dimension according to COMT genotype. Healthy val158met heterozygotes are shown for comparison. Error bars represent standard error of mean.

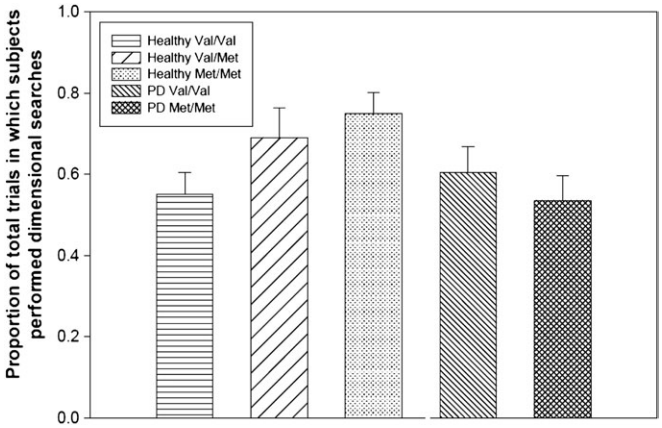

Figure 5. The proportion of total trials that participants performed dimensional search according to COMT val18met genotype. Healthy val158met heterozygotes are shown for comparison. Error bars represent standard error of mean.

A two-way ANOVA found that there was a subthreshold trend toward a significant effect of genotype on the number of total errors, $F_{1,58} = 3.07$, $P = 0.08$, val homozygotes making more errors than met homozygotes. There was no significant effect of disease, $F_{1,58} = 1.34$, $P > 0.05$, and no significant interaction between disease and genotype, $F_{1,58} = 1.99$, $P > 0.05$. The descriptive data can be seen in Supplementary Table S1.

The number of consecutive and non-consecutive perseverative errors were analysed in the same manner (for descriptive data, see Supplementary Table S1). For the former, there was a significant effect of disease, $F_{1,58} = 4.60$, $P < 0.05$, with PD patients making more consecutive perseverative errors than healthy older adults. There was no significant main effect of genotype or interaction between disease and genotype (Fs < 1). The same pattern of results was found for the number of nonconsecutive perseverative errors with a significant main effect of disease, $F_{1,58} = 5.12$, $P < 0.05$. Again, there was no significant main effect of genotype or interaction between genotype and disease (Fs < 1). Therefore, it would appear that irrespective of COMT genotype, PD patients are less efficient in their search, making more consecutive and nonconsecutive perseverative errors than healthy older adults.

Participants' reaction times across 5 different types of response were examined in a mixed 3-way ANOVA. The 5 response types were ID switches, ED switches, first response after a reversal, first response after a set change, and a baseline measure of "Known Correct" reaction times (that is, events where the participant knew the correct answer on the basis of previous positive feedback and was therefore responding with minimal deliberation time). There was a significant main effect of event type on reaction times, $F_{4,232} = 180.71$, $P < 0.05$, with participants being quicker to respond when the target was known compared with when the target was unknown (ID switch, ED switch, reversal, and set change). In addition, there was a main effect of disease on reaction times, $F_{1,58} = 9.34$, $P < 0.05$, with patients displaying prolonged response latencies. There was no main effect of genotype on reaction times, $F_{1,58} = 1.40$, $P > 0.05$, although there was a trend toward a significant interaction between genotype and disease $F_{1,58} = 3.66$, $P = 0.061$. This trend was due to PD met homozygotes tending to show increased response latencies compared with the other 3 groups. None of the other interactions were significant.

Functional Neuroimaging Results

A contrast between BOLD responses during events when participants were actively looking for the correct answer minus events when participants knew the correct answer showed a robust increase in activation throughout the frontoparietal network (Fig. 6). Based upon the whole data set (homozygotes only), 5mm ROIs were created bilaterally in the dorsolateral PFC (DLPFC) (x = ±46, y = 36, and z = 26), ventrolateral/BA 13 PFC (x = ±30, y = 22, and z = −2), and parietal cortex (x = ±34, y = −2, and z = 41). Five millimeter ROIs were created bilaterally in the dorsolateral PFC (DLPFC) (x = ±46, y = 36, and z = 26), ventrolateral/BA 13 PFC (x = ±30, y = 22, and z = −2), and parietal cortex (x = ±34, y = −2, and z = 41), Given that the caudate is a major recipient of DAergic innervation, it is possible that the COMT val158met polymorphism may modulate the activity in this area. Therefore, to examine this possibility, an anatomical caudate ROI was generated using the Automated Anatomical Labeling method (Tzourio-Mazoyer et al. 2002).

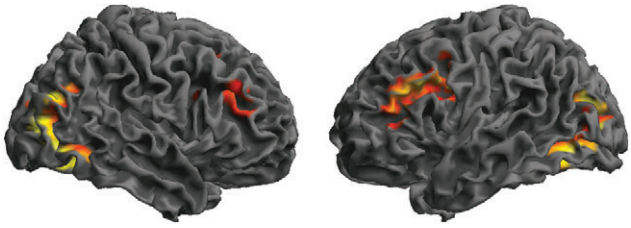

Figure 6. A statistical parametric map of voxels, which are significantly more active for the "working-out" minus "knowing" phase of the experiment, corrected for multiple comparisons (Family Wise Error [FWE] corrected = 0.05).

"Working-Out" Minus Baseline

To examine differences in activity across each ROI according to COMT genotype and disease, a mixed ANOVA was performed with repeated measures of ROI (left parietal, right parietal, left ventrolateral PFC (VLPFC), right VLPFC, left DLPFC, right DLPFC (RDLPFC), and caudate) and between participant factors of disease and genotype. There was a significant main effect of ROI, $F_{6,348} = 37.69$, $P < 0.05$. However, there was no significant main effect of disease, $F_{1,58} = 2.14$, $P > 0.05$, COMT genotype ($F < 1$), or interaction between COMT genotype and disease, $F_{1,58} = 1.34$, $P > 0.05$. There was a significant three-way interaction between ROI, disease, and COMT genotype, $F_{1,348} = 2.76$, $P < 0.05$. No other interactions were significant. To examine the three-way interaction further, a series of between-subjects ANOVA was performed for each ROI. The results of these ANOVAs are displayed in Table 2. As can be seen from the table, there was a significant interaction between disease and genotype for activity in the RDLPFC, but not for any of the other ROIs. The activity in this ROI for each COMT genotype group is displayed in Figure 7.

Discussion

This study examined how putative differences in PFC DA catabolism predict frontal-lobe activity and set-like behavior in PD patients and healthy older adults. Our results confirmed that

Table 2
Activation in each ROI according to disease, genotype, and interaction with genotype for "working-out" minus baseline

ROI	Contrast	*F* value	*P* value	Coordinates		
				x	*y*	*z*
Left parietal	Disease	2.11	>0.05	−32	54	41
	Genotype	0.00	>0.05			
	Disease × genotype	0.00	>0.05			
Right parietal	Disease	0.26	>0.05	32	54	41
	Genotype	0.00	>0.05			
	Disease × genotype	3.23	>0.05			
Left VLPFC	Disease	0.60	>0.05	−30	22	−2
	Genotype	0.00	>0.05			
	Disease × genotype	0.12	>0.05			
Right VLPFC	Disease	0.06	>0.05	30	22	−2
	Genotype	0.09	>0.05			
	Disease × genotype	1.38	>0.05			
Left DLPFC	Disease	0.34	>0.05	−46	36	26
	Genotype	0.05	>0.05			
	Disease × genotype	0.00	>0.05			
Right DLPFC	Disease	5.06	<0.05	46	36	26
	Genotype	0.17	>0.05			
	Disease × genotype	**6.99**	**<0.05**			
Caudate[a]	Disease	1.17	>0.05	+/−15	16	7
	Genotype	0.47	>0.05			
	Disease × genotype	0.00	>0.05			

[a]Denotes that activity for this region was pooled for both left and right regions.

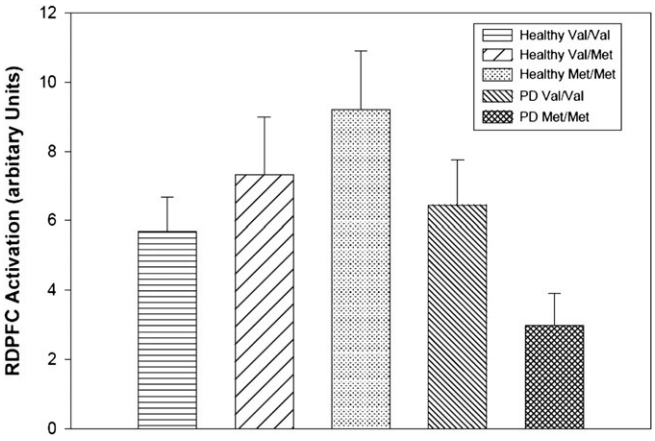

Figure 7. Activation in the RDLPFC according to COMT genotype group for the "working-out" minus baseline contrast.

when older adult and PD COMT val158met genotype groups were ordered according to putative DA levels, right DLPFC activation and the tendency to apply a top-down attentional set followed an inverted-U shape function. These findings accord well with the hypothesis of an inverted-U shaped relationship between PFC DA levels and set-like behavior and support the view that within the PFC, the DLPFC may play a particularly prominent role in attentional set formation. Beyond the clinical implications highlighted by Williams-Gray et al. (2008), these results have theoretical implications regarding how genetic differences that putatively modulate PFC DA level affect attentional control, and, as a corollary of this, the nature of frontal-lobe organization.

In terms of increasing our understanding of the relationship between DA and attentional control, the results presented here add to those reported previously, by more precisely defining how COMT genotype can affect cognitive function in PD. More specifically, while it was previously proposed that the results of Williams-Gray et al. (2008) arose from an inverted-U shaped function between PFC DA levels and set-like behavior, it could equally have been argued that the results reflected the normative manner in which COMT affects attention and would, therefore, also have been evident in the same direction in age-matched controls. Yet another possibility would have been that the COMT polymorphism's capacity to modulate set-like behavior was quite specific to PD, being dependent on coexisting neuropathology. Both of these interpretations seem unlikely in the context of the current findings, as the COMT genotype had a symmetrical affect on both attention and PFC activity in healthy controls and PD patients. Thus, cumulatively, the results of the 2 studies support the interpretation made by Williams-Gray et al. (2008), who argued that the direction of their results arose due to excess PFC DA in PD patients (Rakshi et al. 1999; Kaasinen et al. 2001; Bruck et al. 2005) pushing them over onto the right-hand limb of an inverted-U shaped function. Subsequent studies have also confirmed the idea that there is excess PFC DA in early PD by demonstrating that the longitudinal progressions of cognitive impairment in PD met homozygotes is nonlinear. For example, whereas planning performance in PD met homozygotes is impaired early in the disease, relative to PD val homozygotes, this pattern reverses as the disease progresses. More precisely, planning performance improves in PD met homozygotes, but not PD val homozygotes (Williams-Gray et al. 2009). Given that planning performance has repeatedly been found to decline with increasing disease duration (Owen et al. 1992), this finding is hard to accommodate within alternative hypotheses which do not involve DA overdosing of the PFC.

Previous studies, using the Wisconsin Card Sorting Task (WCST), have reported that val homozygotes show less cognitive flexibility than met homozygotes (as indexed by the number of perseverative errors) and have demonstrated that this pattern can be reversed by pharmacological manipulation (Egan et al. 2001; Mattay et al. 2003). These results seem to directly contradict those presented here, where healthy val homozygotes displayed greater cognitive flexibility than healthy met homozygotes. The WCST, however, is a cognitively heterogeneous task, as evidenced by the fact that its numerous behavioral subcomponents have dissociable neuroanatomical and neurochemical underpinnings (Dias et al. 1996; Crofts et al. 2001; Clarke et al. 2007; Robbins and Roberts 2007). Moreover, as mentioned in the introduction, the experimental depletion of PFC DA in animals increases cognitive flexibility (reduced set formation; Roberts et al. 1994; Crofts et al. 2001). Furthermore, administering tolcapone, a COMT inhibitor that will increase PFC DA levels, has been found to improve ID shifting in val homozygotes but impair ID shifting in met homozygotes (Apud et al. 2007). Thus, after administering tolcapone, the healthy control group seems to show the same behavioral differences according to COMT genotype as the PD patients in this study. Finally, it would also appear that there is an inconsistent relationship between the val158met polymorphism and perseverative errors on the WCST (Barnett et al. 2007). Thus, it is possible that the capacity of the task applied here to selectively decompose and quantify many of the behavioral subcomponents of executive control may make it more appropriate for directly relating subtle genetic variations to changes in cognitive processes.

Previously, an inverted-U shaped function relating DA levels and behavior has been most robustly demonstrated in the context of spatial working memory (Williams and Goldman-Rakic 1995; Vijayraghavan et al. 2007). It is possible that there is a more general overarching explanation that can account for why PFC DA levels affect both spatial working memory and attentional set formation. A recent computational model has argued that the neurophysiological actions of DA can engender a relationship, whereby DA enhances task-relevant representations through the selective suppression of competing irrelevant representations but at higher doses, suppresses task-relevant representations as well (Durstewitz and Seamans 2008). Thus, task-relevant representations may require optimal levels of DA in order to be stable, with both suboptimal and supraoptimal levels promoting destabilization by competition and inhibition, respectively. In such a model, cognitive stability and cognitive flexibility may be envisaged as being placed at different points along the same DAergic axis.

This explanation could potentially explain the nonlinear modulation of attentional set formation observed in this study, in that, at intermediate DA levels (argued to occur in healthy met homozygotes and PD val homozygotes), there is an optimal level of DA for stabilizing the mental representation of the currently relevant category by suppressing representations from the irrelevant category. This representation of the relevant category would have the effect of biasing attention and choices toward images from the most recently selected category, thus leading to greater errors on EDSs than IDSs. However, if there is either too much, or too little, DA then there will be little differentiation between the representations

of the previously relevant and irrelevant categories and the level of categorical bias would therefore be reduced.

These findings also appear to highlight the hierarchical nature of PFC organization. For example, it has been suggested that more ventral/posterior lateral PFC regions are involved in simple "first-order" executive functions (Petrides 1995) such as the orientation of attention (Corbetta and Shulman 2002) and the effortful control of responses (Hampshire et al. 2010; Verbruggen et al. 2010). By contrast, it has been suggested that more dorsal/anterior PFC regions are involved in higher order executive functions such as the manipulation of items held in working memory (Owen et al. 1999), relational integration in reasoning (Christoff et al. 2001; Badre et al. 2009; Hampshire et al. 2011), and cognitive branching (Koechlin and Hyafil 2007). Furthermore, the dorsal/anterior portion of the right lateral PFC has recently been reported to respond to predefined targets at a more categorical or abstract level in some task contexts (Hampshire et al. 2007). The possibility that the right DLPFC plays a prominent role in processing the abstract rules, dimensions, and the relationships that makeup the overarching task schema may be equally applicable to planning, reasoning, and attentional set formation. Much work is still required to understand the nature of representation and functional specialization within the frontal lobes. However, the fact that the task applied here can behaviorally and functionally fractionate different components of executive control suggests it may provide a unique tool for examining the nature of frontal-lobe specialization by comparing the different behavioral and functional abnormalities present in diverse patient groups. On the same task, older adults, relative to young controls, were found to show decreased activation in the posterior/inferior lateral PFC, the preSMA, and the anterior insula. This pattern of underactivation co-occurred with inefficient search behavior (more nonconsecutive perseverative errors; Hampshire et al. 2008). This measure was unaffected by COMT genotype in this study. By contrast, higher level attentional tuning, which was affected here by COMT genotype, was not significantly affected by normal ageing. Again, this apparent double dissociation across studies supports the idea that dorsal and ventral PFC regions support subtly different cognitive functions.

Although the behavioral and neural changes seen in this experiment can be explained by current models of DAergic functioning, it is possible that there is some, as yet, unarticulated effect of variations in the efficiency of this enzyme on noradrenergic functioning. Variations in noradrenergic levels in the PFC are known to affect attentional set-switching tasks (Lapiz and Morilak 2006). Recent evidence has also expanded our conception of the way in which the val158met polymorphism alters functioning across different neuronal circuits. Although the consequences for neuronal activity of the val158met polymorphism would appear to have their origin in the PFC, it has become apparent that other regions are also affected as a consequence of this polymorphism such as the midbrain (Akil et al. 2003; Meyer-Lindenberg et al. 2005) and the parietal cortex (Tan et al. 2007; Williams-Gray et al. 2007). There is, therefore, a pressing need for further PET studies that are capable of obtaining direct estimates of DA levels in subcortical regions, and how these levels differ according to COMT genotype and disease status. Furthermore, given that the validity of FDOPA measurements in cortical areas has been questioned (Cropley et al. 2008), future studies that seek to probe the integrity of PFC DA function in PD, and its genetic modulation, should use appropriate radioligands and methodologies.

In summary, this study has contributed to the known cognitive, neuroanatomical, and neurochemical substrates of attentional set formation and shifting. It has been demonstrated that putative variations in DA levels caused by genetic differences and disease status can modulate attentional set formation and activation in the right DLPFC, according to an inverted-U shaped response function. The regional specificity of the observed findings can be explained due to the physiological actions of COMT, which are thought to prominently affect the PFC, and that the RDLPFC, in particular, seems capable of generalizing its responses from low-level stimulus to the high-level properties that that stimulus contains, that is categorical information. The above findings also seem to fit comfortably within a frame that sees prefrontal DA as the arbitrator between cognitive stability and flexibility.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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Notes

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References

Akil M, Kolachana BS, Rothmond DA, Hyde TM, Weinberger DR, Kleinman JE. 2003. Catechol-O-methyltransferase genotype and dopamine regulation in the human brain. J Neurosci. 23(6):2008–2013.

Apud JA, Mattay V, Chen J, Kolachana BS, Callicott JH, Rasetti R, Alce G, Iudicello JE, Akbar N, Egan MF, et al. 2007. Tolcapone improves cognition and cortical information processing in normal human subjects. Neuropsychopharmacology. 32(5):1011–1020.

Badre D, Hoffman J, Cooney JW, D'Esposito M. 2009. Hierarchical cognitive control deficits following damage to the human frontal lobe. Nat Neurosci. 12(4):515–522.

Barnett JH, Jones PB, Robbins TW, Muller U. 2007. Effects of the catechol-O-methyltransferase Val158Met polymorphism on executive function: a meta-analysis of the Wisconsin Card Sort Test in schizophrenia and healthy controls. Mol Psychiatry. 12(5):502–509.

Bertolino A, Breier A, Callicott JH, Adler C, Mattay VS, Shapiro M, Frank JA, Pickar D, Weinberger DR. 2000. The relationship between dorsolateral prefrontal neuronal N-acetylaspartate and evoked release of striatal dopamine in schizophrenia. Neuropsychopharmacology. 22(2):125–132.

Bertolino A, Knable MB, Saunders RC, Callicott JH, Kolachana B, Mattay VS, Bachevalier J, Frank JA, Egan M, Weinberger DR. 1999. The relationship between dorsolateral prefrontal N-acetylaspartate measures and striatal dopamine activity in schizophrenia. Biol Psychiatry. 45(6):660–667.

Bishop SJ, Fossella J, Croucher CJ, Duncan J. 2008. COMT val158met genotype affects recruitment of neural mechanisms supporting fluid intelligence. Cereb Cortex. 18(9), 2132–2140.

Bruck A, Aalto S, Nurmi E, Bergman J, Rinne JO. 2005. Cortical 6-[18F]fluoro-L-dopa uptake and frontal cognitive functions in early Parkinson's disease. Neurobiol Aging. 26(6):891–898.
Carter CJ, Pycock CJ. 1980. Behavioural and biochemical effects of dopamine and noradrenaline depletion within the medial prefrontal cortex of the rat. Brain Res. 192(1):163–176.
Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, Kolachana BS, Hyde TM, Herman MM, Apud J, et al. 2004. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am J Hum Genet. 75(5):807–821.
Christoff K, Prabhakaran V, Dorfman J, Zhao Z, Kroger JK, Holyoak KJ, Gabrieli JD. 2001. Rostrolateral prefrontal cortex involvement in relational integration during reasoning. Neuroimage. 14(5):1136–1149.
Clarke HF, Walker SC, Dalley JW, Robbins TW, Roberts AC. 2007. Cognitive inflexibility after prefrontal serotonin depletion is behaviorally and neurochemically specific. Cereb Cortex. 17(1):18–27.
Corbetta M, Shulman GL. 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci. 3(3):201–215.
Crofts HS, Dalley JW, Collins P, Van Denderen JC, Everitt BJ, Robbins TW, Roberts AC. 2001. Differential effects of 6-OHDA lesions of the frontal cortex and caudate nucleus on the ability to acquire an attentional set. Cereb Cortex. 11(11):1015–1026.
Cropley VL, Fujita M, Bara-Jimenez W, Brown AK, Zhang XY, Sangare J, Herscovitch P, Pike VW, Hallett M, Nathan PJ, et al. 2008. Pre- and post-synaptic dopamine imaging and its relation with frontostriatal cognitive function in Parkinson disease: pET studies with [11C]NNC 112 and [18F]FDOPA. Psychiatry Res. 163(2):171–182.
Demakis GJ. 2003. A meta-analytic review of the sensitivity of the Wisconsin Card Sorting Test to frontal and lateralized frontal brain damage. Neuropsychology. 17(2):255–264.
Dias R, Robbins TW, Roberts AC. 1996. Dissociation in prefrontal cortex of affective and attentional shifts. Nature. 380(6569):69–72.
Downes JJ, Roberts AC, Sahakian BJ, Evenden JL, Morris RG, Robbins TW. 1989. Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. Neuropsychologia. 27(11–12):1329–1343.
Durstewitz D, Seamans JK. 2008. The dual-state theory of prefrontal cortex dopamine function with relevance to catechol-o-methyltransferase genotypes and schizophrenia. Biol Psychiatry. 64(9):739–749.
Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, et al. 2001. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A. 98(12):6917–6922.
Hampshire A, Chamberlain SR, Monti MM, Duncan J, Owen AM. 2010. The role of the right inferior frontal gyrus: inhibition and attentional control. Neuroimage. 50(3):1313–1319.
Hampshire A, Duncan J, Owen AM. 2007. Selective tuning of the blood oxygenation level-dependent response during simple target detection dissociates human frontoparietal subregions. J Neurosci. 27(23):6219–6223.
Hampshire A, Gruszka A, Fallon SJ, Owen AM. 2008. Inefficiency in self-organized attentional switching in the normal aging population is associated with decreased activity in the ventrolateral prefrontal cortex. J Cogn Neurosci. 20(9):1670–1686.
Hampshire A, Owen AM. 2006. Fractionating attentional control using event-related fMRI. Cereb Cortex. 16(12):1679–1689.
Hampshire A, Thompson R, Duncan J, Owen AM. Lateral prefrontal cortex subregions make dissociable contributions during fluid reasoning. Cereb Cortex. 21(1):1–10.
Howell DC. 1997. Statistical methods for psychology. Belmont (CA): Wadsworth.
Iwano H, Yamamuro Y, Hori K, Yamauchi T, Nomura M. 1997. Effects of discrimination learning on the rat striatal dopaminergic activity: a microdialysis satudy. Neuroreport. 8(5):1095–1098.
Kaasinen V, Nurmi E, Bruck A, Eskola O, Bergman J, Solin O, Rinne JO. 2001. Increased frontal [(18)F]fluorodopa uptake in early Parkinson's disease: sex differences in the prefrontal cortex. Brain. 124(Pt 6): 1125–1130.
Koechlin E, Hyafil A. 2007. Anterior prefrontal function and the limits of human decision-making. Science. 318(5850):594–598.
Kolachana BS, Saunders RC, Weinberger DR. 1995. Augmentation of prefrontal cortical monoaminergic activity inhibits dopamine release in the caudate nucleus: an in vivo neurochemical assessment in the rhesus monkey. Neuroscience. 69(3):859–868.
Kumakura Y, Vernaleken I, Grunder G, Bartenstein P, Gjedde A, Cumming P. 2005. PET studies of net blood-brain clearance of FDOPA to human brain: age-dependent decline of [F-18]fluoro-dopamine storage capacity. J Cereb Blood Flow Metab. 25(7): 807–819.
Lapiz MDS, Morilak DA. 2006. Noradrenergic modulation of cognitive function in rat medial prefrontal cortex as measured by attentional set shifting capability. Neuroscience. 137(3):1039–1049.
Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana B, Callicott JH, Weinberger DR. 2003. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci U S A. 100(10):6186–6191.
Meyer-Lindenberg A, Kohn PD, Kolachana B, Kippenhan S, McInerney-Leo A, Nussbaum R, Weinberger DR, Berman KF. 2005. Midbrain dopamine and prefrontal function in humans: interaction and modulation by COMT genotype. Nat Neurosci. 8(5):594–596.
Ota M, Yasuno F, Ito H, Seki C, Nozaki S, Asada T, Suhara T. 2006. Age-related decline of dopamine synthesis in the living human brain measured by positron emission tomography with L-[beta-C-11]DOPA. Life Sci. 79(8):730–736.
Owen AM, Herrod NJ, Menon DK, Clark JC, Downey SP, Carpenter TA, et al. 1999. Redefining the functional organization of working memory processes within human lateral prefrontal cortex. Eur J Neurosci. 11(2):567–574.
Owen AM, James M, Leigh PN, Summers BA, Marsden CD, Quinn NP, et al. 1992. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. Brain. 115(Pt 6):1727–1751.
Petrides M. 1995. Impairments on nonspatial self-ordered and externally ordered working memory tasks after lesions of the mid-dorsal part of the lateral frontal cortex in the monkey. J Neurosci. 15(1 Pt 1):359–375.
Rakshi JS, Uema T, Ito K, Bailey DL, Morrish PK, Ashburner J, Dagher A, Jenkins IH, Friston KJ, Brooks DJ. 1999. Frontal, midbrain and striatal dopaminergic function in early and advanced Parkinson's disease A 3D [(18)F]dopa-PET study. Brain. 122(Pt 9):1637–1650.
Robbins TW, Roberts AC. 2007. Differential regulation of fronto-executive function by the monoamines and acetylcholine. Cereb Cortex. 17(Suppl 1):i151–i160.
Roberts AC, De Salvia MA, Wilkinson LS, Collins P, Muir JL, Everitt BJ, Robbins TW. 1994. 6-Hydroxydopamine lesions of the prefrontal cortex in monkeys enhance performance on an analog of the Wisconsin card sort test: possible interactions with subcortical dopamine. J Neurosci. 14(5 Pt 1):2531–2544.
Roberts AC, Robbins TW, Everitt BJ. 1988. The effects of intradimensional and extradimensional shifts on visual discrimination learning in humans and non-human primates. Q J Exp Psychol B. 40(4):321–341.
Seamans JK, Yang CR. 2004. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog Neurobiol. 74(1):1–58.
Tan HY, Chen Q, Goldberg TE, Mattay VS, Meyer-Lindenberg A, Weinberger DR, Callicott JH. 2007. Catechol-O-methyltransferase Val158Met modulation of prefrontal-parietal-striatal brain systems during arithmetic and temporal transformations in working memory. J Neurosci. 27(49):13393–13401.
Tunbridge E, Burnet PW, Sodhi MS, Harrison PJ. 2004. Catechol-o-methyltransferase (COMT) and proline dehydrogenase (PRODH) mRNAs in the dorsolateral prefrontal cortex in schizophrenia, bipolar disorder, and major depression. Synapse. 51(2):112–118.
Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage. 15(1):273–289.
Verbruggen F, Aron AR, Stevens MA, Chambers CD. 2010. Theta burst stimulation dissociates attention and action updating in human inferior frontal cortex. Proc Natl Acad Sci U S A. 107(31):13966–13971.

Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten AF. 2007. Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nat Neurosci. 10(3): 376–384.
Williams-Gray CH, Evans JR, Goris A, Foltynie T, Ban M, Robbins TW, Brayne C, Kolachana BS, Weinberger DR, Sawcer SJ, et al. 2009. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain. 132(Pt 11):2958–2969.
Williams-Gray CH, Hampshire A, Barker RA, Owen AM. 2008. Attentional control in Parkinson's disease is dependent on COMT val 158 met genotype. Brain. 131(Pt 2):397–408.
Williams-Gray CH, Hampshire A, Robbins TW, Owen AM, Barker RA. 2007. Catechol O-methyltransferase Val158Met genotype influences frontoparietal activity during planning in patients with Parkinson's disease. J Neurosci. 27(18):4832–4838.
Williams GV, Goldman-Rakic PS. 1995. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. Nature. 376(6541): 572–575.
Yavich L, Forsberg MM, Karayiorgou M, Gogos JA, Mannisto PT. 2007. Site-specific role of catechol-O-methyltransferase in dopamine overflow within prefrontal cortex and dorsal striatum. J Neurosci. 27(38):10196–10209.