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Putative cortical dopamine levels affect cortical recruitment during planning

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ABSTRACT

Planning, the decomposition of an ultimate goal into a number of sub-goals is critically dependent upon fronto-striatal dopamine (DA) levels. Here, we examined the extent to which the val158met polymorphism in the catechol *O*-methyltransferase (COMT) gene, which is thought to primarily alter cortical DA levels, affects performance and fronto-parietal activity during a planning task (Tower of London). COMT genotype was found to modulate activity in the left superior posterior parietal cortex (SPC) during planning, relative to subtracting, trials. Specifically, left SPC blood oxygenation level-dependent (BOLD) response was reduced in groups with putatively low or high cortical DA levels (COMT homozygotes) relative to those with intermediate cortical DA levels (COMT heterozygotes). These set of results are argued to occur either due to differences in neuronal processing in planning (and perhaps subtracting) caused by the COMT genotype and/or the cognitively heterogeneous nature of the TOL, which allows different cognitive strategies to be used whilst producing indistinguishable behavioural performance in healthy adults. The implications of this result for our understanding of COMT's effect on cognition in health and disease are discussed.

1. Introduction

Many of the most sought after goals in the world are not immediately attainable. Accordingly, we have had to evolve and develop a capacity to formulate and execute a series of sub-goals whose completion will allow us to achieve our ultimate goal. These behavioural requirements are neatly captured within the Tower of London (TOL) planning task and its cognates (Shallice, 1982). This task has been used extensively to examine the necessary neuroanatomical and neurochemical substrates of planning. Efficient performance on this task has been found to depend upon the integrity of a fronto-striato-parietal network (Carlin et al., 2000; Cazalis et al., 2003; Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009; Kaller, Rahm, Spreer, Weiller, & Unterrainer, 2011; Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Shallice, 1982; van den Heuvel et al., 2003). Furthermore, adequate dopaminerergic tone in these areas is also necessary for efficient planning performance. Specifically, pharmacological manipulations and disease states thought to reduce fronto-striatal dopamine (DA) levels have been associated with reduced planning performance (Cools, Stefanova, Barker, Robbins, & Owen, 2002; Lange et al., 1992; Owen et al., 1992; Reeves et al., 2005), whereas increasing DA (and other catecholamines) has been found to improve planning performance (Elliott et al., 1997).

A well-known phenomenon in psychopharmacology is the existence of an inverted-U shape function between DA levels and performance. This phenomenon has been well demonstrated in the case of working memory, where both excess and deficient DAergic stimulation can impair performance (Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007). Therefore, to the extent that planning depends on cortical functioning, excess cortical DA levels should also impair planning performance. However, there is a dearth of pharmacological substances that can selectively, and safely, modulate cortical DA levels without also affecting striatal DA levels. This makes it difficult to parse out the effects of striatal and cortical DA levels in influencing planning performance. One approach to addressing this problem is to study the effects of genetic polymorphisms that putatively alter cortical DA levels.

The catechol *O*-methyltransferase (COMT) enzyme is thought to have a relatively selective role in regulating cortical DA levels, given that pharmacological or genetic inhibition of this enzyme has been found to have little effect on striatal DA or cortical noradrenaline levels (Tunbridge, Burnet, Sodhi, & Harrison, 2004; Yavich, Forsberg, Karayiorgou, Gogos, & Mannisto, 2007). A single

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nucleotide polymorphism (SNP), which involves the substitution of valine for methionine at amino acid 158 in membrane bound-COMT (val158met), the dominant form of the enzyme expressed in the brain, plays a key role in determining the enzyme's activity. Val homozygotes show 40% higher COMT activity compared to Met homozygotes, and thus putatively have lower cortical (PFC) DA levels, whereas heterozygotes are thought to have intermediate levels (Chen et al., 2004). In addition, COMT genotype has also been found to modulate the level of D_1 receptors throughout the cortex (Slifstein et al., 2008). Thus, the val158met COMT polymorphism provides us with an experimental window into the effects that putative differences in cortical, or at least non-striatal, DA levels, within their normal physiological range, have on cognition in-vivo. In line with this, several studies have reported that Met homozygotes tend to outperform Val homozygotes on tests of working memory and attention, a difference thought to relate to their putatively higher levels of cortical DA (Bertolino et al., 2006; Egan et al., 2001; Meyer-Lindenberg et al., 2006). Moreover, COMT genotype has been found to be an important predictor of planning performance and its concomitant BOLD signal in fronto-parietal areas in patients with Parkinson's disease (PD: (Foltynie et al., 2004; Hoogland et al., 2010; Williams-Gray et al., 2009; Williams-Gray, Hampshire, Barker, & Owen, 2008; Williams-Gray, Hampshire, Robbins, Owen, & Barker, 2007). More specifically, PD Val homozygotes have been found to outperform PD Met homozygotes. The directionality of this result was explained in terms of the hypothetical DAergic overdosing that is thought to occur in the frontal cortex in early PD in compensation for striatal DA depletion (Bruck, Aalto, Nurmi, Bergman, & Rinne, 2005; Kaasinen et al., 2001; Rakshi et al., 1999), and is supported by the recent finding of increased presynaptic DA in frontal regions in PD Met homozygotes relative to PD Val homozygotes (Wu et al., 2012). However, at present, it is unclear whether the effect of the val158met polymorphism on planning performance is unique to PD patients or is also present within healthy older adults free of parkinsonism. Recently, we reported that the COMT val158met polymorphism modulated attentional performance in healthy older adults in the opposite direction to that observed in PD patients (Fallon, Williams-Gray, Barker, Owen, & Hampshire, 2012). Thus, the COMT val158met polymorphism has differential effects on cognition according to disease status. However, whether the COMT val158met polymorphism modulates planning performance and its neural correlates in a healthly age-matched control group (compared to the PD patients) has yet to be investigated. A recent study in younger adults (mean age=43) found no evidence that COMT genotype modulates behavioural performance or the BOLD response during planning (Stokes, Rhodes, Grasby, & Mehta, 2011). However, DA levels are not static across the lifespan (Backman, Nyberg, Lindenberger, Li, & Farde, 2006; Diamond, 2007; Kaasinen & Rinne, 2002), an effect that is paralleled by the non-linear manner in which COMT modulates cognitive function in different age groups, with the relative performance of each COMT val158met genotype group changing with increasing age (Dumontheil et al., 2011; Harris et al., 2005; Smith & Boettiger, 2012). Thus, it is possible that effects may be present within older adults that are not present in younger adults. Furthermore, consistent with the idea that there is a non-linear relationship between DA levels and behaviour, there may also be a non-linear relationship between COMT activity, as determined by the val158-met polymorphism, and behaviour. Indeed, such a relationship has been reported in the case of verbal IQ (Harris et al., 2005). Therefore, this study sought to evaluate whether there is a linear or non-linear relationship between putative DA levels (COMT genotype) and planning performance, and its neural correlates as measured by functional magnetic resonance imaging, in a group of healthy older adults.

2. Method

2.1. Participants

This study conformed to the Helsinki declaration of 1975 and was approved by the local ethics committee (Suffolk Local Research Ethics Committee number 05/Q102/169). All participants gave written informed consent prior to taking part in this study. An initial sample of 80 participants was recruited to take part in this study from a panel of genotyped older adults. The genotype frequencies and demographics of these participants are presented in Supplementary Fig. 1. These participants completed a variety of neuropsychological tests (see below). From this initial sample, 52 participants agreed to take part in the fMRI study. Results from these 52 participants have previously been reported in the case of attentional control (Fallon et al., 2012) and a voxel based morphometry (VBM) study (Rowe et al., 2010). All participants were evaluated with the Mini Mental State Examination (MMSE; (Folstein, Folstein, & McHugh, 1975), Beck Depression Inventory (BDI; Beck, Epstein, Brown, & Steer, 1988) and National Adult Reading Test (NART; Nelson, 1982). Participants were healthy older adults and were selected to be of comparable age ($50 < 80$) to the PD patients tested by Williams-Gray et al. (2007), displaying no evidence of neurological disease on evaluation by a neurologist (CWG), no overt depression (BDI score < 15) and no overt signs of dementia (MMSE > 25). The demographic data for the subjects in the fMRI study are presented in Table 1. DNA was extracted from peripheral blood samples and genotyping for the COMT val158met polymorphism (SNP rs4680) was performed using a Taqman allelic discrimination assay on a 7900HT Sequence Detection System (Applied Biosystems) using standard protocols (see Williams-Gray et al., 2007).

One-way ANOVAs revealed no significant differences between the different COMT genotype groups (in the fMRI study) in terms of age, $F < 1$, $p > 0.05$, BDI score, $F < 1$, $p > 0.05$, MMSE score, $F(2,51) = 1.4$, $p > 0.05$ or 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, $\chi^2 = 1.3$, $p > 0.05$.

2.1.1. Neuropsychological tests

To provide a broader perspective on the effect COMT genotype has on an individual's cognitive phenotype, a larger sample of healthy volunteers performed several tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB). These tests included Pattern Recognition Memory (PRM), Spatial Recognition Memory and Paired Associates Learning (PAL; all tests described in (Sahakian et al., 1988). Finally, a behavioural version of 'one-touch' version of Tower of London (TOL) was also measured (Owen et al., 1995). These tasks have been described extensively elsewhere, therefore only brief descriptions will be given here. In the PRM task, participants viewed series of 12 patterns and had to correctly identify these patterns in a subsequent memory test. Similarly, for the SRM, participants viewed a series of spatial locations that had to be subsequently identified. The main behavioural metric in both tasks was accuracy (% correct). In the PAL, participants were presented with a an array of 6 boxes. Over successive trials, of varying difficulty, participants were shown the 'contents' of each box. Participants had to remember which pattern appeared in which box. The main behavioural measure assessed was the number of participants successively completing the six-shape level (where 6 images had to be paired with 6 locations). The 'one touch' TOL task is identical to the planning task used in the fMRI study (see below for more details) except that, in the behavioural version, there were harder problems (5 move problems). There were 14 experimental trials. Accuracy (% correct) and planning latency served as behavioural output measures.

2.2. fMRI experimental design and procedure

The one-touch Tower of London (TOL) task has been extensively described elsewhere (Owen et al., 1995; Williams-Gray et al., 2007). In this version of the task, there were two alternating conditions: planning and subtracting. In both conditions participants were presented with two arrays of balls at the top and bottom of the screen (see Fig. 1). In the planning condition participants had to mentally rearrange the balls on the bottom half of the display (Start state) so as to match the top half of the display (Goal state). They then indicated the minimum number of

Table 1
Participants demographics according to COMT genotype.

	Met/Met	Val/Met	Val/Val
Age	63.6 (6.6)	66.2 (7.4)	63.5 (6.9)
MMSE	29.5 (.62)	29.2 (.77)	29.5 (.60)
NART IQ	120.7 (5.7)	123.7 (2.5)	120.8 (6.0)
BDI	4.4 (3.4)	3.2 (3.0)	3.9 (2.7)
Gender(M/F)	7:10	8:7	8:12
N	17	15	20