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COMT *val*^{158}*met* Genotype Affects Recruitment of Neural Mechanisms Supporting Fluid Intelligence

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Fluid intelligence (g_f) influences performance across many cognitive domains. It is affected by both genetic and environmental factors. Tasks tapping g_f activate a network of brain regions including the lateral prefrontal cortex (LPFC), the presupplementary motor area/anterior cingulate cortex (pre-SMA/ACC), and the intraparietal sulcus (IPS). In line with the "intermediate phenotype" approach, we assessed effects of a polymorphism (*val*^{158}*met*) in the catechol-O-methyltransferase (COMT) gene on activity within this network and on actual task performance during spatial and verbal g_f tasks. COMT regulates catecholaminergic signaling in prefrontal cortex. The *val*^{158} allele is associated with higher COMT activity than the *met*^{158} allele. Twenty-two volunteers genotyped for the COMT *val*^{158}*met* polymorphism completed high and low g_f versions of spatial and verbal problem-solving tasks. Our results showed a positive effect of COMT *val* allele load upon the blood oxygen level–dependent response in LPFC, pre-SMA/ACC, and IPS during high g_f versus low g_f task performance in both spatial and verbal domains. These results indicate an influence of the COMT *val*^{158}*met* polymorphism upon the neural circuitry supporting g_f. The behavioral effects of *val* allele load differed inside and outside the scanner, consistent with contextual modulation of the relation between COMT *val*^{158}*met* genotype and g_f task performance.

Keywords: COMT, fMRI, *g*, genotype, intelligence, prefrontal cortex

Introduction

Fluid intelligence (g_f) is a major dimension of individual differences in cognitive function. Commonly measured by tests of reasoning and novel problem solving (Cattell 1971), g_f is conceptually distinct from crystallized intelligence (g_c), which represents acquired knowledge and skill, and highly related to the psychometrically defined construct "*g*" (Spearman 1927), the primary or "general" cognitive factor underlying the observation that the same individuals tend to do well across many different cognitive tasks. A strong predictor of achievement in educational and other domains, at a mechanistic level, g_f has been linked to processes ranging from cognitive flexibility and strategy development to manipulation of stored mental representations and attentional control, in particular, the inhibition of interference (Kane et al. 2005).

There has been much interest in the extent to which genetic factors influence g_f. Heritability studies suggest that g_f is strongly influenced by genetic as well as environmental factors, with genetic influences accounting for 40% or more of the variance in g_f scores (Gray and Thompson 2004). Despite its high heritability, attempts to identify specific genetic contributions to g_f have made relatively little progress. Advances in functional genomics and neuroimaging now enable us to adopt an "intermediate phenotype" approach, examining genetic contributions to variability not in behavior itself but in the underlying neural mechanisms. It has been argued that genetic influences may be clearer at the neurophysiological level as measured by the blood oxygen level–dependent (BOLD) signal in functional magnetic resonance imaging (fMRI) than at the level of behavior. The former is held to be closer to the neurobiological effects of the gene and less susceptible to the sources of noise that can influence behavioral performance, increasing the likelihood of detecting the effects of single genetic polymorphisms (Hariri and Weinberger 2003; Goldberg and Weinberger 2004). In addition to increasing sensitivity to gene effects, this intermediate phenotype approach has the potential to provide new insights into the neurochemical mechanisms that support g_f, and may open a pathway to investigating how environmental factors also modulate the operation of these mechanisms.

During performance of tasks with high g_f loadings, conspicuous activity is seen in the lateral prefrontal cortex (LPFC) (Prabhakaran et al. 1997; Duncan et al. 2000). Given this, a *val*^{158}*met* polymorphism in the catechol-O-methyltransferase (COMT) gene is a striking candidate for influencing g_f-related neural function. COMT metabolizes released dopamine (DA). It is thought to be particularly critical to regulating DA signaling in the prefrontal cortex due to the scarcity of DA transporter in this region (Sesack et al. 1998). The COMT *val*^{158} allele is associated with higher enzymatic activity than the less stable *met* allele, with heterozygous individuals showing intermediate enzyme activity (Lotta et al. 1995; Weinshilboum et al. 1999; Chen et al. 2004). Though a number of other single nucleotide polymorphisms (SNPs) in the COMT gene have also been identified (Bray et al. 2003; Chen et al. 2004), the *val*^{158}*met* polymorphism is the only one to have been reliably shown to impact significantly upon COMT activity across both postmortem human dorsolateral prefrontal tissue samples and lymphoblast cultures (Chen et al. 2004). Haplotype analyses conducted within the context of these studies have also reported no effects on COMT activity other than those attributable to the *val*^{158}*met* polymorphism (Chen et al. 2004). Although recent findings suggest that it may be premature to rule out more complex effects of genetic variation in COMT upon human LPFC function (Meyer-Lindenberg et al. 2006; Tunbridge et al. 2006), the *val*^{158}*met* polymorphism is the strongest single candidate variant in the COMT gene for modulating LPFC function, providing a focus for genomic imaging studies where sample sizes may not easily allow for haplotype analyses.

In line with this, a number of neuroimaging studies have examined the impact of the COMT *val*^{158}*met* polymorphism

upon LPFC activity, reporting that the number of *val* alleles possessed correlates positively with LPFC activity during performance of cognitive tasks including measures of working memory (WM), encoding, and retrieval (Egan et al. 2001; Bertolino, Blasi, et al. 2006, Bertolino, Rubino, et al. 2006; Schott et al. 2006). In contrast to the consistency of these results, findings from investigations of the impact of the COMT $val^{158}met$ polymorphism upon behavioral indices of cognition have been more variable (Egan et al. 2001; Bilder et al. 2004; Diamond et al. 2004; Nolan et al. 2004; Tunbridge et al. 2006; Barnett et al. 2007). It is possible that both state factors, such as the stressfulness of the current environment and the nature of the task performed might influence whether a *met* or *val* behavioral performance advantage is observed (Bilder et al. 2004; Tunbridge et al. 2006). Alternatively, the variability in behavioral results could simply reflect difficulty in reliably detecting effects of single genetic polymorphisms at the behavioral level of analysis.

Given these considerations, we were interested in investigating the impact of the COMT $val^{158}met$ polymorphism upon g_f task performance and associated neural activity. In particular, we were interested in whether, as proponents of the intermediate phenotype approach have argued (Hariri and Weinberger 2003; Goldberg and Weinberger 2004), the effects of single genetic variants such as the COMT $val^{158}met$ polymorphism might be more apparent upon g_f-related neural activity than upon g_f task performance. A number of studies have suggested that performance of tasks with high g_f loadings does not activate LPFC alone but recruits a circumscribed cortical circuit including LPFC, presupplementary motor area/anterior cingulate cortex (pre-SMA/ACC), and the intraparietal sulcus (IPS) (Prabhakaran et al. 1997; Esposito et al. 1999; Gray et al. 2003). Consequently, we aimed to address the following questions: 1) whether COMT $val^{158}met$ genotype modulates LPFC activity during g_f-related task performance, with COMT *val* allele load being associated with increased LPFC activation, 2) whether COMT $val^{158}met$ genotype selectively influences LPFC recruitment or modulates activity throughout the extended g_f cortical network, 3) whether COMT $val^{158}met$ genotype modulation of g_f-related neural activity is similar across different domains of processing (spatial and verbal), in keeping with COMT v$al^{158}met$ genotype impacting upon a single common mechanism underlying both verbal and spatial forms of g_f, and 4) whether COMT $val^{158}met$ genotype modulates g_f-related neural activity more robustly than g_f-related task performance.

Materials and Methods

fMRI Study

Participants and Procedure

Twenty-two participants (10 males and 12 females, all Caucasian of European descent, all right-handed, age 19–39 years) completed verbal and spatial problem-solving tasks while both behavioral and fMRI data were collected. Details of participant sex and age are given by COMT $val^{158}met$ genotype in Supplementary Table S1. The 3 COMT $val^{158}met$ genotype groups did not differ significantly on these characteristics (P values >0.1). Informed written consent was obtained from all volunteers, and the study was approved by the Cambridgeshire Local Research Ethics committee and performed in compliance with their guidelines. The standard Cambridge exclusion criteria for fMRI studies were followed (no metal and no history of neurological disease or head injury). In addition, all individuals with current or past history of inpatient psychiatric care, those currently on medication for anxiety, depression or sleeping problems, and those on any other form of medication that might influence neurotransmitter function were excluded. All participants completed a standard test of g_f, the Cattell Culture Fair, Scale 2 Form B, in a separate behavioral testing session, conducted in a quiet environment at either the Department of Experimental Psychology, Cambridge University or the Medical Research Council (MRC) Cognition and Brain Sciences Unit, Cambridge.

Task Design

The verbal and spatial problem-solving tasks were taken from Duncan et al. (2000). In both tasks, each item consisted of 4 display elements—either drawings (spatial task) or letter sets (verbal task), see Figure 1. Participants were instructed to identify the "odd one out"—the element that in some sense differed from the others. In each task, items were split into high g_f and low g_f blocks, which lasted for 33 s (3 s for the block type to be specified and 30 s for completion of trials).

Items in the high g_f spatial blocks were adapted with permission from a standard nonverbal test of g_f, Cattell Culture Fair, Scale 2 Form A and Scale 3 (Institute for Personality and Ability Testing 1973). Display elements were 4 panels, each containing one or more shapes, symbols, or drawings. One panel differed in some respect from the others; extensive problem solving was required to identify this panel because the difference could concern any property, often abstract and/or complex. In the example shown in Figure 1*A*, the relevant property is symmetry; the mismatching panel is the 3rd in the row. In the low g_f spatial blocks, in contrast, there was minimal problem solving. In each display, the 4 panels each contained a single geometrical shape, 3 of which were physically identical, whereas the 4th differed in visually obvious features, such as shape, texture, size or orientation.

Materials for the high g_f verbal blocks were adapted with permission from a standard letter-based problem-solving task, Letter Sets from the Educational Testing Service (ETS) kit of factor-referenced tests (Ekstrom et al. 1976). The high g_f loading of the original test was established by analysis of a large preexisting data set (Wothke et al. 1991). Display elements were 4 sets of 4 letters each. One set differed in some respect from the others; again, the task required extensive problem solving because a variety of alphabetic and other rules could distinguish the mismatching letter set in any given test item. In the example given in Figure 1*B*, the mismatching set is the 3rd, whose letters are equally spaced in the alphabet. In the low g_f verbal blocks, the task was simply to find the one set in each display whose letters were not in strict alphabetical order.

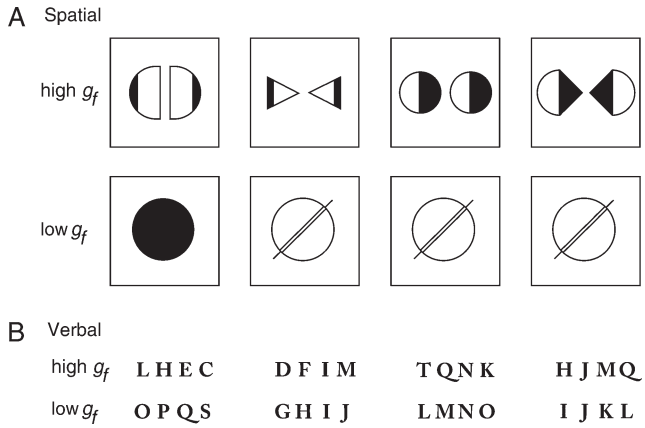


Figure 1. Example test items for each task. Each item consisted of 4 display elements (drawings or letter sets), and the task was to identify the element that in some sense mismatched or differed from the others. Materials for the high g_f tasks were adapted with permission from a standard nonverbal test of g_f, Cattell Culture Fair, Scale 2 Form A and Scale 3 (Institute for Personality and Ability Testing 1973) and a standard letter-based problem-solving task, Letter Sets from the ETS kit of factor-referenced tests (Ekstrom et al. 1976). The high g_f loading of these tasks was previously established (Wothke et al. 1991; Duncan et al. 2000). The low g_f items were structurally similar but with a minimal problem-solving component. Participants were asked to select the only nonidentical item for the low g_f spatial task and to select the string not in alphabetic order for the low g_f verbal task.

For both tasks, the position of the mismatching element was indicated by pressing the corresponding key on a 4-choice keyboard, operated with middle and index fingers of the 2 hands. The screen cleared when a response was made, and a new test item was presented immediately. Participants were instructed not to guess but to continue thinking about each problem until they were confident of their answer or until the block terminated. With this constraint, participants were asked to complete as many items as possible during each block. These arrangements ensured that participants worked continuously, despite long solution times for high g_f items but much shorter times for low g_f items.

The spatial task comprised 4 high g_f and 4 low g_f blocks. The verbal task comprised 5 high g_f and 5 low g_f blocks. Prior to each task, participants were given full instructions and practice items from both the high g_f and low g_f conditions. Stimuli were projected onto a translucent screen positioned behind the head of the participant visible via an angled mirror within the scanner coil. The visual angle subtended by the 4 stimuli presented on each trial was approximately 12°.

Image Acquisition

BOLD contrast functional images were acquired with echo-planar T_2^*-weighted (EPI) imaging using a 3-T Bruker Medspec scanner based at the Wolfson Brain Imaging Centre, Addenbrooke's Hospital, Cambridge, UK. Image volumes were acquired in 23 interleaved 5-mm-thick axial oblique slices giving whole-brain coverage with an in-plane resolution of 3.75 × 3.75 mm (repetition time = 1,200 ms; echo time = 30 ms, flip angle = 67.5°). For each participant, data for the spatial task were acquired in a single scanning run of 4 min and data for the verbal task in a single scanning run of 5 min. The first 11 volumes of each run were discarded to allow for T_1 equilibration effects.

Image Analysis

SPM software was used (http://www.fil.ion.ucl.ac.uk/spm). Standard preprocessing was conducted comprising slice-timing correction, realignment, undistortion (Cusack et al. 2003), and skull-stripped normalization of each participant's EPI data to the Montreal Neurological Institute's MNI/ICBM template. Images were resampled into this space with 3-mm isotropic voxels and smoothed with a Gaussian kernel of 10-mm full-width at half-maximum. Blocks were modeled with step functions of 33-s duration, convolved with the canonical hemodynamic response function to form regressors. A high-pass filter of 75 s was used to remove low-frequency noise. A voxelwise random effects analysis was used to analyze data at a group level. Across-participant whole-brain analyses were conducted separately for the spatial and verbal problem-solving tasks. Neural regions showing increased activity during performance of high g_f versus low g_f conditions were reported if activity passed a whole-brain false-detection rate (fdr) threshold of $P < 0.05$ (Genovese et al. 2002).

Our key analyses examined the effect of COMT *val*^{158}*met* genotype upon high g_f – low g_f task-related activity across a network of cortical regions previously implicated in high g_f task performance (Prabhakaran et al. 1997; Esposito et al. 1999; Duncan et al. 2000; Gray et al. 2003; Haier and Jung 2007). This network includes bilateral dorsal and ventral regions of LPFC, the former corresponding to the dorsal LPFC (DLPFC) region focused upon in genomic imaging studies of WM (Egan et al. 2001; Bertolino, Blasi, et al. 2006), the latter being centered on the frontal operculum/anterior insula (FO/AI). It also encompasses bilateral regions of parietal cortex centered on the IPS and a cortical region extending from the anterior cingulate cortex (ACC) to the presupplementary motor area (pre-SMA). Regions of interest (ROIs) for these regions were derived from a meta-analysis of brain areas coactivated across tasks posing diverse cognitive demands (Duncan and Owen 2000; Duncan 2006). The cortical activation foci from the studies reviewed in those papers were transposed onto 1 hemisphere, smoothed (15-mm Gaussian kernel), and added. The resulting sum map was thresholded to show regions of maximum clustering. This produced peaks in DLPFC ±42, 24, 24; FO/AI ±36, 18, 0; IPS ±36, −54, 39; pre-SMA 0, 21, 45; and ACC 0, 30, 21. It should be noted that the ACC and pre-SMA clusters were not clearly distinct. Our ROIs comprised 10-mm radius spheres centered on these peak coordinates.

The ROIs described above were used to examine the influence of COMT *val*^{158}*met* genotype upon g_f-related neural activity. Specifically, a regressor was created to represent the number of COMT *val* alleles possessed (0: *met*/*met*, 1: *val*/*met*, and 2: *val*/*val*). This effectively divided up the volunteer sample into 3 groups, according to COMT *val* allele load. Two sets of between-group correlational analyses were conducted. First, in line with the analytic approach adopted in previous studies (e.g., Smolka et al. 2005), neural activity during high g_f versus low g_f task performance was regressed against the number of COMT *val* alleles possessed. This analysis was conducted on a voxelwise basis within each ROI, with small volume corrections for multiple comparisons being applied (Worsley et al. 1996). A linear regressor was used, given evidence that *val*/*met* heterozygotes show COMT activity that is intermediate between that of *met*/*met* and *val*/*val* homozygotes. This enabled us to test, for each voxel within our ROIs, whether the magnitude of the BOLD response associated with high g_f – low g_f performance varied as a function of the number of *val* alleles possessed.

In addition, confirmatory analyses of the influence of COMT *val*^{158}*met* genotype upon neural activation during high g_f – low g_f task performance were conducted using the MARSBAR ROI toolbox for SPM99 (Brett et al. 2002). This enables the researcher to extract and average the activation associated with a given contrast across all voxels within an ROI. Using this method, the correlation between the number of COMT *val* alleles possessed by each individual (0–2) and their high g_f – low g_f neural activity was calculated for each ROI for both the spatial and verbal tasks.

DNA Isolation and Genotyping Analyses

All volunteers gave informed consent for a buccal swab to be obtained using a buccal brush. DNA was isolated using the MasterAMP Buccal Swab DNA Extraction Kit (Epicentre Technologies, Madison, WI). This provides yields of 0.5 to 3 μg of DNA from each buccal sample. Polymerase chain reaction (PCR) restriction fragment length polymorphism analysis with horizontal gel electrophoresis was used to determine COMT *val*^{158}*met* genotype (following Daniels et al. 1996; Egan et al. 2001; Bertolino et al. 2004; Bertolino, Blasi, et al. 2006; Schott et al. 2006) Taq polymerase, PCR buffer, and deoxyribonucleotide triphosphates were obtained from Qiagen (www.qiagen.com) and used at recommended concentrations for a 20-ul PCR. A "touchdown" PCR cycling regimen and the addition of dimethyl sulfoxide (10% final v:v) was used in order to optimize the hybridization stringency. Forward: 5′-ACTGTGGCTACTCAGCTGTG-3′ and reverse 5′-CCTTTTTCCAGGTCTGACAA-3′ primers were used. PCR conditions were as follows: 94 °C for 3 min initial heating, then 12 cycles of 94 °C for 30 s, 58 °C for 45 s, and 72 °C for 30 s and then 28 cycles of 94 °C for 30 s, 50 °C for 45 s, and 72 °C for 30 s. This was followed by restriction digestion with *Nla*III. Gel electrophoresis in Metaphor agarose followed by staining in ethidium bromide was used to resolve and visualize DNA fragments. See Supplementary Materials for further details.

Additional Behavioral Study

A total of 146 volunteers (63 males, 83 females; mean age = 25.9 years, all Caucasian of European descent) came into either the Department of Experimental Psychology at Cambridge University or the MRC Cognition and Brain Sciences Unit, Cambridge, for a 1-h behavioral testing session. Informed written consent was obtained from all volunteers and the study was approved by the Cambridgeshire Local Research Ethics committee and performed in compliance with their guidelines. During the behavioral session, participants completed the Cattell Culture Fair, Scale 2 Form B. It was administered in a quiet environment, according to the manual guidelines. In addition, participants completed a number of questionnaires and a medical screening form (for past neurological injury, medication, and psychiatric history) and provided a buccal swab for DNA analysis (as described under DNA Isolation and Genotyping Analyses above). Participant sex and age are given by COMT *val*^{158}*met* genotype in Supplementary Table S1. The 3 COMT genotype groups did not differ significantly on these characteristics (*P* values >0.1).

Results

Across Participants: High g_f Conditions Activate LPFC, IPS, and Pre-SMA/ACC

Across participants, whole-brain analyses conducted separately on data from the spatial and verbal tasks revealed significant

increases in activity in LPFC, pre-SMA/ACC, and IPS during high g_f versus low g_f conditions. These results held for both tasks (see Fig. 2). The high g_f versus low g_f subtraction gave extensive bilateral activations in the spatial task and predominantly left lateralized activation in the verbal task, in line with our prior results (Duncan et al. 2000). This subtraction also produced activation in the cerebellum for the spatial task and in the precuneus and orbitofrontal cortex for the verbal task, but no regions outside of the predicted network showed enhanced activity across both high g_f conditions.

COMT val^{158}met Genotype Modulates Activity across the Whole Frontoparietal High g_f Network during Performance of High g_f versus Low g_f Tasks

As predicted, between-group regression analyses showed a significant positive correlation between COMT *val* allele load (number of *val* alleles possessed, 0–2) and high g_f – low g_f neural activity in LPFC. Parallel effects were observed in other regions across the extended high g_f network including pre-SMA, ACC, and IPS (see Fig. 3 and Table 1). The results obtained with the independent measures of g_f-related brain activity from the spatial and verbal tasks were strikingly similar, with right DLPFC, right and left IPS, and pre-SMA showing a significant correlation between *val* allele load and high g_f – low g_f neural activity in both tasks.

In order to confirm these results, additional whole-ROI analyses were conducted using the MARSBAR ROI toolbox for SPM (Brett et al. 2002; see Materials and Methods). In these analyses, activation was averaged across all the voxels in each ROI, the resulting composite value for each ROI being regressed, across volunteers, against the number of COMT *val* alleles possessed (0–2). These analyses also revealed a significant positive relationship between *val* allele load and high g_f – low g_f neural activity in right DLPFC, right and left IPS, and pre-SMA across both tasks, with a similar but weaker pattern in ACC (see Table 2).

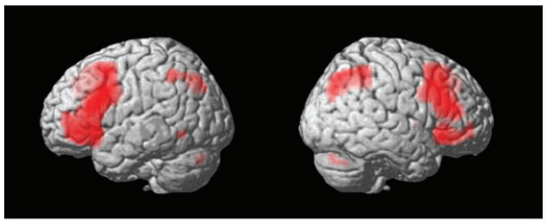
Behavioral Results and Behavior/Brain Regression Analyses

We were interested in whether the relationship between COMT *val^{158}met* genotype and activity across the high g_f network would be linked to differences in g_f-related task performance. As noted in the introduction, proponents of the intermediate phenotype approach have suggested that gene–behavior effects may be less robust and harder to reliably detect than genetic influences upon neural activity. Given this and in the light of null results from previous studies investigating influences of specific genetic markers upon intelligence test scores (Plomin et al. 2001), we did not have strong predictions as to whether we would observe COMT *val^{158}met* genotype effects upon performance of our g_f measures.

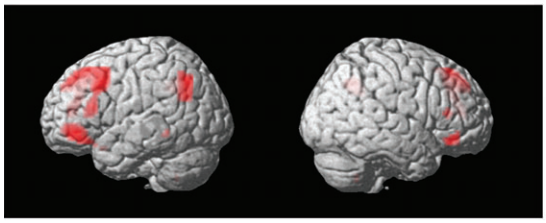
Our behavioral results were as follows. In the scanner, a positive correlation was observed between COMT *val* allele load and performance (number of correct responses) for the spatial high g_f task; $r = 0.47$, $P < 0.03$ 2 tailed, with a non-significant trend in the same direction for the verbal high g_f task; $r = 0.31$, $P = 0.15$ 2 tailed. We conducted additional regression analyses in order to examine the relationship between performance in the spatial and verbal high g_f tasks and task-related neural activity across the entire group of volunteers. These revealed a positive relationship between performance and recruitment of right DLPFC during high versus low g_f conditions of the spatial task, $x, y, z = 42, 24, 27$, $Z = 3.10$, $P = 0.02$ small volume corrected (svc), whereas for the verbal task, there was a trend towards a similar result for left FO/AI, $x, y, z = -36, 27, -3$, $Z = 2.68$, $P = 0.06$ svc. There was no significant relationship between high g_f task performance and activity in any of the other ROIs (P values >0.1).

A

(i) Spatial task



(ii) Verbal task



B

Brain Regions	Co-ordinates	Z score
Spatial task ($P < 0.05$ whole brain fdr corrected)		
Peaks within the a priori ROIs		
Left DLPFC	-48 27 21	6.01
Right DLPFC	48 27 30	5.39
Left FO/AI	-30 21 -6	5.30
Right FO/AI	33 24 -6	5.40
ACC	3 33 30	3.72
Pre SMA	-3 24 45	5.26
Left IPS	-39 -51 48	4.00
Right IPS	33 -63 42	4.22
Additional peaks (for clusters of 20+ voxels)		
Cerebellum	15 -78 -33	4.91
Verbal task ($P < 0.05$ whole brain fdr corrected)		
Peaks within the a priori ROIs		
Left DLPFC	-45 21 33	3.90
ACC	-6 36 24	3.70
Pre SMA	-3 30 48	4.35
Left IPS	-39 -63 39	3.65
Additional peaks (for clusters of 20+ voxels)		
Left OFC	-45 36 -12	5.25
Right OFC	36 36 -15	4.15
Precuneus	-3 -57 39	4.05

Figure 2. Neural activation associated with high g_f versus low g_f task performance. (*A*) Significant activations at a whole-brain fdr threshold of $P < 0.05$, rendered onto the canonical T_1-weighted brain image of SPM99. (i) Spatial high g_f – spatial low g_f. (ii) Verbal high g_f – verbal low g_f. (*B*) Activation peaks. For significant (fdr, $P < 0.05$) clusters of any size that overlap the a priori specified ROIs, the table gives peak voxel within the ROI. For other brain areas, peaks are reported only for clusters of 20 or more significant voxels. OFC: orbitofrontal cortex.

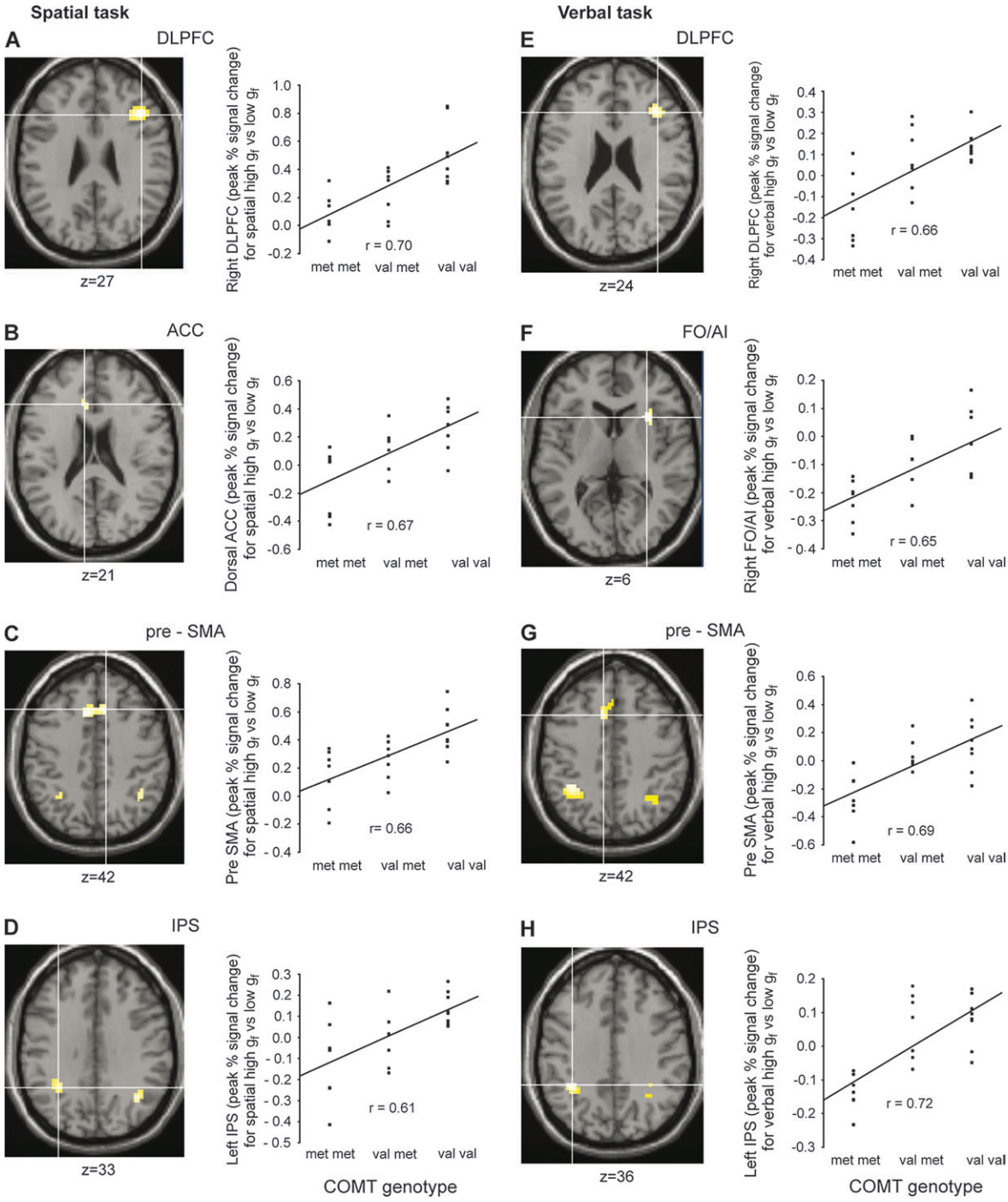


Figure 3. Correlation between number of COMT *val* alleles possessed (0: *met*/*met*, 1: *val*/*met*, and 2: *val*/*val*) and activation for high g_f versus low g_f conditions for the spatial problem-solving task (*A*: right DLPFC, *B*: dorsal ACC, *C*: pre-SMA, and *D*: left IPS) and the verbal problem-solving task (*E*: right DLPFC, *F*: right FO/AI, *G*: pre-SMA, and *H*: left IPS). Left: Activations thresholded at $P < 0.05$ svc are overlaid on the canonical T_1 SPM99 brain. Right: Individual BOLD responses were extracted from the voxel with the highest *Z* value inside the ROI and plotted against number of COMT *val* alleles possessed.

Notably, with high g_f task performance entered as a covariate, all the reported associations between COMT $val^{158}met$ genotype and regional fMRI activity remained significant (see Table 1). However, entering high g_f versus low g_f right DLPFC activity as a covariate for the spatial task and high g_f versus low g_f left FO/AI activity for the verbal task removed any relationship between COMT $val^{158}met$ genotype and high g_f task performance; $r(19) = 0.19$, $P > 0.4$; $r(19) = 0.11$, $P > 0.5$, respectively.

Effect of COMT $val^{158}met$ Genotype on High g_f Task Performance Outside the Scanner

As mentioned above, previous studies have found no significant effect of COMT $val^{158}met$ genotype on behavioral performance

Table 1
Voxelwise correlational analyses of the effect of COMT *val*^{158}*met* genotype upon high g_f − low g_f neural activity

Brain regions	Coordinates[a]	*Z* score	*P*[b]	*r*[c]	r_p[d]
Spatial task					
Right DLPFC	42, 24, 27	3.62	$P < 0.005$	0.70	0.60
ACC	−9, 27, 21	3.43	$P < 0.01$	0.67	0.65
Pre-SMA	9, 24, 42	3.32	$P < 0.02$	0.66	0.59
Left IPS	−33, −51, 33	3.04	$P < 0.05$	0.61	0.54
Right IPS	39, −60, 33	3.27	$P < 0.02$	0.65	0.63
Verbal task					
Left DLPFC	−36, 24, 18	2.70	$P = 0.065$	0.56	0.52
Right DLPFC	39, 27, 24	3.37	$P < 0.02$	0.66	0.64
Left FO/AI	−27, 15, 3	2.96	$P < 0.05$	0.60	0.55
Right FO/AI	30, 18, 6	3.28	$P < 0.02$	0.65	0.69
Pre-SMA	−9, 18, 42	3.52	$P < 0.01$	0.69	0.37
Left IPS	−36, −45, 36	3.77	$P < 0.005$	0.72	0.69
Right IPS	36, −57, 48	3.10	$P < 0.05$	0.62	0.59

Note: The number of COMT *val* alleles possessed (0–2) was correlated against high g_f − low g_f neural activity on a voxel by voxel basis within each ROI.
[a]Correlation peak coordinates. Peaks are reported for each ROI where one or more voxels showed a significant or near significant ($P < 0.1$) correlation between number of COMT *val* alleles possessed and high g_f − low g_f neural activity after small volume correction for multiple comparisons.
[b]*P* value after small volume correction.
[c]Correlation at peak voxel.
[d]Partial correlation at peak voxel after controlling for high g_f behavioral performance (all reported partial correlations are significant at least at $P < 0.05$ uncorrected).

Table 2
ROI-composite correlational analyses of the effect of COMT *val*^{158}*met* genotype upon high g_f − low g_f neural activity

Neural ROI (region, ROI centre point)[a]	*Z* score	Significance (*P*)
Spatial task		
Left DLPFC (−42, 24, 24)	0.94	$P > 0.1$
Right DLPFC (42, 24, 24)	3.11	$P < 0.001$[b]
Left FO/AI (−36, 18, 0)	0.97	$P > 0.1$
Right FO/AI (36, 18, 0)	0.88	$P > 0.1$
ACC (0, 30, 21)	2.22	$P < 0.02$
Pre-SMA (0, 21, 45)	2.66	$P < 0.005$[c]
Left IPS (−36, −54, 39)	2.68	$P < 0.005$[c]
Right IPS (36, −54, 39)	2.69	$P < 0.005$[c]
Verbal task		
Left DLPFC (−42, 24, 24)	2.46	$P < 0.01$
Right DLPFC (42, 24, 24)	2.60	$P < 0.005$[c]
Left FO/AI (−36, 18, 0)	2.31	$P < 0.01$
Right FO/AI (36, 18, 0)	2.75	$P < 0.003$[c]
ACC (0, 30, 21)	1.39	$P = 0.08$
Pre-SMA (0, 21, 45)	2.65	$P < 0.005$[c]
Left IPS (−36, −54, 39)	2.83	$P < 0.005$[c]
Right IPS (36, −54, 39)	2.75	$P < 0.005$[c]

Note: For each ROI, the number of COMT *val* alleles possessed (0–2) was correlated against high g_f − low g_f neural activity using a composite measure of activation extracted from and averaged across all voxels within the ROI.
[a]All ROIs were 10-mm radius spheres.
[b]Significant at $P < 0.01$ when corrected for number of ROIs examined.
[c]Significant at $P < 0.05$ when corrected for number of ROIs examined.

of other standardized tests of intelligence such as the Wechsler Intelligence Scale for Children—Revised (Plomin et al. 2001). While these measures arguably have greater g_c loadings than the measures used in the current study, we were interested in whether the behavioral effect we observed for the spatial g_f task performed within the scanner would be replicated with a parallel measure administered outside of the scanner environment.

All participants in the fMRI study were additionally asked to complete scale 2B of Cattell Culture Fair (Institute for Personality and Ability Testing 1973) as part of a separate behavioral testing session. In contrast to the results obtained with the spatial high g_f task in the scanner, no significant association was observed between COMT *val* allele load and scale 2B performance outside of the scanner environment, $r(22) = 0.10$, $P > 0.1$. We confirmed this result with a larger sample of 146 volunteers who also completed scale 2B of Cattell Culture Fair outside the fMRI environment (see Materials and Methods and Supplementary Table S1). Here again, we found no significant association between COMT *val* allele load and scale 2B scores, $r(145) = -0.11$, $P > 0.1$.

Discussion

Across participants, whole-brain analyses conducted separately on data from the spatial and verbal g_f tasks revealed significant increases in activity in LPFC, pre-SMA/ACC, and IPS during high g_f versus low g_f conditions. No other neural regions showed enhanced activity across both high g_f conditions. This supports the contention that a fairly constrained network of regions including LPFC, pre-SMA/ACC, and IPS comprises the neural substrate that supports g_f. This falls in line with findings by Prabhakaran et al. (1997), Esposito et al. (1999), and Gray et al. (2003) and extends the results from our earlier PET study (Duncan et al. 2000), which primarily indicated a role for LPFC.

Regression analyses showed a significant positive correlation between COMT *val* allele load and high g_f – low g_f neural activity in LPFC, pre-SMA/ACC, and IPS. This held for both verbal and spatial measures of g_f. It is of note that COMT *val*^{158}*met* genotype modulated activity associated with high g_f versus low g_f task performance across the whole frontoparietal extended high g_f network and not just in LPFC. There are a number of potential explanations for this finding. First, the COMT *val*^{158}*met* polymorphism may have a direct impact on DA metabolism in all the regions concerned. LPFC, ACC, and IPS all receive dopaminergic projections (Bentivoglio and Morelli 2005). Furthermore, in addition to the established influence of the COMT *val*^{158}*met* polymorphism upon LPFC function (Winterer and Goldman 2003), recent studies have also reported COMT *val*^{158}*met* genotype modulation of ACC and IPS function (Blasi et al. 2005; Bertolino, Blasi, et al. 2006; Williams-Gray et al. 2007). Second, it is possible that the COMT *val*^{158}*met* polymorphism affects activity in one or more regions of the high g_f network through its influence upon

metabolism of norepinephrine (Mannisto and Kaakkola 1999, though see Tunbridge et al. 2006); the ascending catecholamine neuromodulatory systems operating both separately and conjointly to influence cortical function (Robbins and Everitt 1995). Finally, an alternative account would be that modulation of LPFC function by COMT *val*^{158}*met* genotype in turn up- or downregulates activation in other key regions, accounting for the association between COMT *val*^{158}*met* genotype and activation in these additional areas.

Another question of interest concerns the relationship of the current findings to previous reports of COMT *val*^{158}*met* genotype modulation of prefrontal activity during tasks tapping executive function, in particular, WM as assessed by the "*n*-back" task (Egan et al. 2001; Bertolino, Blasi, et al. 2006). Here, work on the relationship between g_f and WM is particularly pertinent (Ackerman et al. 2005; Kane et al. 2005). The observation of relatively low zero-order correlations between performance on WM tasks and tests of g_f (Engle et al. 1999; Ackerman et al. 2005) has led to a relative consensus that WM capacity is not isomorphic with *g* or g_f (Kane et al. 2005; Birney et al. 2006; Heitz et al. 2006). Latent variable analyses of short-term memory tasks (which primarily involve temporary storage of information) and WM tasks (which involve online manipulation as well as temporary storage of information, e.g., the *n*-back task) have suggested that it is the WM residual (the component not shared with short-term memory tasks) which loads strongly onto g_f (Engle et al. 1999, though see Colom et al. 2006). This has been taken as evidence that the component of WM variance explained by g_f is related to the executive or attentional aspects of WM (Engle et al. 1999; Gray et al. 2003). Given this, an interesting prediction for future work is that no significant effect of COMT *val*^{158}*met* genotype on *n*-back–related LPFC activity will be observed after controlling for this attentional or executive component. More generally, continued application of the latent variable approach to tests of g_f, attentional control, WM, and other cognitive processes, combined with analysis of genomic imaging data from multiple tests of higher order cognition, should enable us to achieve a clearer picture of the component processes central to g_f and their individual or collective modulation by both the COMT *val*^{158}*met* SNP and other functional genetic polymorphisms.

We turn now to consideration of COMT *val*^{158}*met* genotype effects upon g_f-related task performance. Within the scanner, a positive correlation was observed between COMT *val* allele load and performance on the spatial high g_f task, with a trend in the same direction for the verbal high g_f task. Regression analyses revealed that entering high g_f versus low g_f LPFC activity as a covariate eliminated the relationship between COMT *val*^{158}*met* genotype and high g_f task performance. In contrast, with high g_f task performance entered as a covariate, all the reported associations between COMT *val*^{158}*met* genotype and regional fMRI activity remained significant. These findings provide some support for the claim put forward by proponents of the "candidate gene intermediate phenotype" approach that a more direct and robust relationship exists between genetic markers and neural activity than between genetic markers and behavioral performance (Hariri and Weinberger 2003; Goldberg and Weinberger 2004). This suggests that attempts to advance understanding of genetic and environmental influences upon g_f beyond assessment of heritability may be facilitated not only by the consideration of specific genetic markers but also by complementing behavioral indices of performance with consideration of intermediate neural mechanisms.

The positive correlation observed between COMT *val* allele load and the spatial measure of g_f derived from the Cattell Culture Fair for use within the scanner is consistent with the prediction of a *val* advantage on tasks requiring flexible cognition (Bilder et al. 2004). However, it is of note that, outside the scanner, we observed no significant relationship between COMT *val*^{158}*met* genotype and Cattell Culture Fair Scale 2B scores. This is in line with previous studies which have failed to find a replicable effect of single genetic polymorphisms, including the COMT *val*^{158}*met* polymorphism, upon behavioral performance of standardized intelligence tests (e.g., Plomin et al. 2001) though, as mentioned earlier, those studies used less pure indices of g_f. The difference in our behavioral findings inside and outside the scanner might simply reflect the low power of gene-behavior analyses, leading to difficulties in the replication of behavioral results with relatively small sample sizes. Indeed, it has been suggested that sample sizes in the 100s to 1,000s may be needed to reliably detect effects of single genes upon cognitive performance measures, whereas far smaller samples may suffice for detecting effects of the same genes upon neural activation indices (Hariri and Weinberger 2003). An alternative, potentially more interesting possibility is that the scanner environment itself may have a moderating influence. Like ours, other studies have reported differing behavioral effects of the COMT *val*^{158}*met* polymorphism inside and outside the fMRI environment (Egan et al. 2001; Goldberg et al. 2003). It has also been speculated that state or environmental factors impacting on arousal levels may modulate the effect of COMT *val*^{158}*met* genotype upon prefrontal function (Tunbridge et al. 2006). Scanner noise could be one such factor. It has been demonstrated that noise can act similarly to DA D1 agonists in moving subjects along the inverted U–shaped response function that characterizes the relationship between DA D1 receptor stimulation and prefrontal function (Arnsten and Goldman-Rakic 1998). It is conceivable that scanner noise could alter positioning on the D1-PFC response function such that increased DA metabolism associated with the COMT *val* allele optimizes high g_f task performance. Other factors associated with task performance within the scanner—for example partial immobilization leading to mild claustrophobia or "restraint stress" in some individuals—could also contribute to a potential interaction of COMT genotype by context (task performed inside vs. outside the scanner). The possibility that cognitive function in general and indices of g_f in particular may be influenced by aspects of the current environment that alter arousal levels or affective state is receiving renewed attention (Gray et al. 2002; Blair 2006). Together with increasing awareness of the potential impact of immediate environmental context and longer term environmental factors upon gene–brain and gene–behavior associations (Caspi et al. 2003; Canli et al. 2006; Tunbridge et al. 2006), this highlights the need for future work directly addressing these issues.

In summary, our findings indicate that the COMT *val*^{158}*met* polymorphism has a significant influence upon neural activity across a network of cortical regions, including LPFC, pre-SMA/ACC, and IPS, during performance of high g_f versus low g_f tasks. We obtained 2 measures of g_f-related neural activation using tasks from very different domains (1 spatial and 1 verbal). In both cases, the number of the more metabolically active COMT

val alleles possessed significantly predicted the strength of the neural response in right DLPFC, pre-SMA, and bilateral IPS during performance of high g_f versus low g_f items. The strong influence of the COMT $val^{158}met$ polymorphism upon the extended cortical circuitry underlying g_f-related task performance is in line with the suggestion that the effects of single genes may be observed relatively clearly at the neurophysiological level of analysis achieved by fMRI. It also suggests that genetic influences upon catecholamine modulation of this circuitry might account for a significant proportion of individual variability in the neural response to increases in higher cognitive demands across differing domains of processing. These genetic influences are inevitably complex and likely to extend beyond the $val^{158}met$ SNP studied here. Additional studies of other common genetic variants impacting upon catecholamine function, together with larger scale haplotype studies and analysis of imaging data acquired using multiple measures of higher cognitive function, should aid in further clarifying genetic contributions to catecholamine modulation of higher cognitive function.

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Supplementary Material

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

Notes

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