

Catechol-O-Methyltransferase (COMT) Val¹⁵⁸Met Genotype is Associated with BOLD Response as a Function of Task Characteristic

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The catechol-O-methyltransferase (COMT) val¹⁵⁸met single nucleotide polymorphism (rs4680) has been shown to be associated with brain activation during a number of neurocognitive and emotional tasks. The present study evaluated genotypic associations with brain function during measurement of cognitive stability (prosaccades) and plasticity (antisaccades). A total of 36 healthy volunteers were genotyped for rs4680 and underwent functional magnetic resonance imaging (fMRI) at 1.5 T. Individuals with at least one val¹⁵⁸ allele (val¹⁵⁸ carriers, $N = 24$) showed lower blood oxygen level-dependent (BOLD) response in ventromedial and dorsomedial prefrontal cortex during antisaccades compared to val¹⁵⁸ noncarriers, whereas met¹⁵⁸ homozygotes ($N = 12$) showed lower BOLD response in a cluster in the posterior cingulate and precuneus during prosaccades compared to val¹⁵⁸ carriers. These findings suggest that associations of COMT val¹⁵⁸met genotype with brain function may be mediated by task characteristics. The findings may be compatible with a hypothesis on the role of COMT val¹⁵⁸met genotype in tonic and phasic dopamine levels in brain and differential effects on cognitive measures of stability (eg prosaccades) and plasticity (eg antisaccades).

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INTRODUCTION

Behavioral genetic studies have demonstrated that there is a significant genetic contribution to most aspects of cognition, behavior, and its disorders (McGuffin *et al*, 2001). Recent studies have begun to delineate specific molecular genetic causes and the neural mechanisms through which these genes may act. In human subjects, this research has progressed rapidly through the combination of genotyping and *in vivo* brain imaging methods, such as functional magnetic resonance imaging (fMRI) (Hariri and Weinberger, 2003; Heinz and Smolka, 2006; Meyer-Lindenberg and Weinberger, 2006; Mitterschiffthaler *et al*, 2006).

The present study addresses associations with brain function of the catechol-O-methyltransferase (COMT) gene,

a widely studied candidate gene for cognition, brain function, and psychiatric disorder (Craddock *et al*, 2006). The COMT enzyme is involved in the catabolism of the catecholamine neurotransmitters dopamine, adrenalin, and noradrenalin. COMT is widely expressed in human brain tissue, but plays a major role in dopamine breakdown in frontal cortex (Hong *et al*, 1998; Lloyd *et al*, 1975). The COMT gene (located in 22q11.1–q11.2) contains a G to A missense mutation, resulting in a substitution of methionine (met) for valine (val) at codon 158 of the membrane-bound isoform of the protein (reference sequence identification code rs4680). This allelic variation (val¹⁵⁸ met) is a functional polymorphism: the met¹⁵⁸ allele has about one-third to one-fourth of the activity of the val¹⁵⁸ allele, resulting in less efficient catecholamine catabolism (Lachman *et al*, 1996; Lotta *et al*, 1995; Weinshilboum *et al*, 1999).

Some human studies have shown that the val¹⁵⁸ allele is associated with worse performance in executive function and working memory (Egan *et al*, 2001; Joobar *et al*, 2002), although the overall effect may be small (Flint and Munafò, 2007) and may be seen only in healthy but not schizophrenic individuals (Barnett *et al*, 2007). The val¹⁵⁸

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allele has also been shown to be associated with inefficient (ie increased) frontal activation (Blasi *et al*, 2005; Egan *et al*, 2001) as well as greater signal-to-noise ratio (Winterer *et al*, 2006).

Bilder *et al* (2004) recently argued that the met¹⁵⁸ allele is linked to increased tonic and reduced phasic dopamine levels in subcortical regions but increased dopamine levels in cortex. The val¹⁵⁸ allele is thought to show the opposite pattern, that is, increased phasic and decreased tonic dopamine transmission subcortically and decreased cortical dopamine concentrations. These effects on dopamine transmission are thought to be reflected at behavioral and cognitive levels, with high tonic dopamine activity (met¹⁵⁸) relating to better performance on tasks measuring cognitive stability, while higher phasic dopamine turnover (val¹⁵⁸) may relate to better performance on tasks of cognitive plasticity (Nolan *et al*, 2004). Measures of stability are defined as those involving the representation of task set and continuous, sustained attention, whereas measures of plasticity are thought to include the adaptive responding to shifts in the current plans, dealing with deviations and errors, and mediating reward incentives (Bilder *et al*, 2004).

The present study employed prosaccade and antisaccade tasks to test the associations of the COMT val¹⁵⁸met polymorphism with measures of brain function in healthy humans. A prosaccade is a rapid eye movement that coincides with a shift of attention (Deubel and Schneider, 1996; Hoffman and Subramaniam, 1995). The antisaccade task is a measure of the ability to suppress an unwanted reflexive response (a saccade toward the peripheral target) in favor of a volitional response (an antisaccade in the opposite direction) (see for review Hutton and Ettinger, 2006). While both tasks involve representation of task set and sustained attention, antisaccades additionally involve the inhibition of inappropriate responses and the monitoring and correction of errors. Prosaccades may thus best be understood in terms of stability, whereas antisaccades may represent a measure of plasticity. We adopted a previously employed approach (Flint and Munafò, 2007; Meyer-Lindenberg *et al*, 2005; Winterer *et al*, 2006) and compared val¹⁵⁸ allele carriers (ie val¹⁵⁸ homozygotes and val¹⁵⁸met heterozygotes) to val¹⁵⁸ noncarriers (ie met¹⁵⁸ homozygotes).

While the performance of saccadic tasks engages well-known dorsal fronto-parieto-striato-thalamic networks, gene effects may also be found in deactivation areas, that is, brain regions that show lower blood oxygenation level-dependent (BOLD) response during an active task relative to a low-demand control condition (Raichle *et al*, 2001). It has been shown that a network of medial frontal (including dorsomedial and ventromedial prefrontal cortex) and medial (posterior cingulate and precuneus) as well as lateral parietal areas is more strongly activated during rest (Mazoyer *et al*, 2001) or low-demand baseline tasks (Gilbert *et al*, 2006) relative to complex, higher-level tasks. While the precise function of this deactivation network is unclear, it has been suggested that it mediates stimulus-independent thought processes such as mind wandering (Mason *et al*, 2007) or stimulus-oriented processes such as enhanced attention to the external environment (Gilbert *et al*, 2007).

On the basis of Bilder's hypothesis, it may be expected that val¹⁵⁸ carriers would show better performance on antisaccades than met¹⁵⁸ homozygotes, which may be manifested at a neural level as either less (more efficient) activation in task-related areas or larger deactivations of fronto-parietal deactivation areas; the inverse pattern was expected for prosaccades. These assumptions are based on fMRI evidence showing that greater deactivations are associated with better performance on a trial-by-trial basis (Polli *et al*, 2005; Weissman *et al*, 2006) as well as in analyses of interindividual differences (Harrison *et al*, 2007); conversely, it has been found that lesser (ie more efficient) BOLD response in areas activated by a task is associated with better performance (Blasi *et al*, 2005; Rypma and D'Esposito, 1999).

MATERIALS AND METHODS

Participants

We recruited right-handed (Oldfield, 1971) healthy volunteers from the university staff and students. All participants were Caucasian and free of current or past psychiatric illness and of a family history of psychosis in first-degree relatives. Parental socioeconomic status (SES) was measured separately for father and mother on a 4-point scale (The Stationary Office, 2000) of standard occupational classifications (1 being the lowest, 4 being the highest). All participants provided written informed consent and the study had ethical approval.

DNA Extraction and Genotyping

Deoxyribonucleic acid (DNA) was obtained from venal blood or buccal swabs using established procedures (Freeman *et al*, 2003). COMT val¹⁵⁸met (rs4680) genotype was determined by a TaqMan Drug Metabolising Genotyping assay (Applied Biosystems, Assay ID C_25746809_50) following the manufacturer's instructions. Endpoint analysis was performed on an ABI7900 DNA analyzer and genotypes called with the SDS package with a probability greater than 95%. To improve genotyping reliability, many samples of similar DNA quality and concentration were genotyped at the same time.

fMRI Data Acquisition

Scanning was performed on a 1.5T GE Signa Advantage MRI scanner. Participants wore headphones to reduce the impact of scanner noise. Head movements were minimized using foam padding and a forehead band. A localizer scan for placing the volume of interest and a high-resolution structural scan for image co-registration were first acquired.

T2-weighted MR echo-planar images of the whole brain showing the BOLD response were collected. A quadrature headcoil was used for radiofrequency transmission and reception. Images were aligned parallel to the intercommisural plane (AC-PC line). Image parameters were as follows: repetition time (TR) = 2 s, echo time (TE) = 40 ms, field of view (FOV) = 24 cm, flip angle = 80° and in-plane resolution = 3.75 × 3.75 mm, yielding 22 axial slices of slice thickness 5 mm with 0.5 mm inter-slice gap. A total of 240

images were acquired in one continuous run with a total scanning time per subject of 8 min. Four 2-s scans of dummy data acquisition were performed before each run to allow for the establishment of steady-state longitudinal magnetization; these scans were not used in the analysis.

Task Design and Stimuli

A block-design was employed, consisting of five blocks of antisaccades, five blocks of prosaccades, and five blocks of fixation presented in the same quasi-random order for each participant. Each block lasted 30 s. There were 10 trials in each saccade block. Each trial consisted of a central target and a peripheral target. Target presentations were quasi-random (1100–1900 ms) and were timed such that each trial lasted 3 s. In antisaccade trials, the central target was red, and in prosaccade trials, it was green following previous procedures (eg Connolly *et al*, 2002). The peripheral target ($\pm 8^\circ$) was always black and the background was gray. Equal numbers of right and left targets were used in each block. Participants were instructed to look at the mirror image location of the peripheral target on antisaccade trials and to look at the peripheral target on prosaccade trials. Fixation blocks consisted of a 30 s black central target. On fixation trials, participants were instructed to simply keep their eyes on the central target. There was a 2 s instruction screen before each block, reminding participants of the task (antisaccade: 'Look Away'; prosaccade: 'Follow the Dot'; fixation: 'Center'). All participants were practiced on the task prior to the fMRI scan.

Oculomotor Data Acquisition and Analysis

Horizontal movements of the left eye were recorded using an MRI-compatible infrared oculographic limbus tracker (MR-Eyetracker, CRS Ltd, Rochester, UK). The MR-Eyetracker uses fiber optic cables for guiding infrared light between the hardware in the control room and an eyepiece fixed to the head coil and placed beneath the participant's left eye. The system has a minimum spatial resolution of 0.2° and a horizontal range of $\pm 20^\circ$. Signals were digitized using 12-bit analog-to-digital converter (Data Translation DT9802) and sampled at 500 Hz. A three-point calibration ($\pm 8^\circ$, 0°) was performed before the scan.

Saccades were identified using Eyemap (AMTech GmbH) using minimum latency (100 ms) and amplitude (1°) criteria. Prosaccade and antisaccade latencies were calculated. Additionally, the percentage of reflexive errors on the antisaccade task (saccades to the peripheral target) and the percentage of corrections (antisaccade following a reflexive error) were calculated.

fMRI Data Analysis

Analysis was carried out using Statistical Parametric Mapping 2 (SPM2) software (<http://www.fil.ion.ucl.ac.uk/spm/>) implemented in Matlab 6. Preprocessing consisted of three steps. First, motion correction was carried out by realigning each subject's images along the first image in the time series. Second, images were transformed into standard space using affine registration and nonlinear

transformations and the Montreal Neurological Institute template in SPM2. Third, images were spatially smoothed with an 8 mm Gaussian full-width at half-maximum (FWHM) filter.

Data were analyzed with a general linear model in SPM2, involving two steps. First, single-subject maps were obtained for prosaccade > fixation and antisaccade > prosaccade. Fixation was used as low-level comparison condition for prosaccades to study brain activation in relation to saccadic eye movements, as carried out previously (McDowell *et al*, 2002; Sweeney *et al*, 1996). The prosaccade task was used as a comparison (or baseline) task for the antisaccade task (as described previously, eg McDowell *et al*, 2002; O'Driscoll *et al*, 1995; Sweeney *et al*, 1996), as in this part of the experiment, we aimed to study brain activation specific to the cognitive components involving antisaccade task performance. As described before (Hutton and Ettinger, 2006; Reuter and Kathmann, 2004), these processes include response inhibition, complex sensorimotor transformations, and volitional (as opposed to reflexive) response generation. Prosaccades share with antisaccades the recruitment of basic saccadic processes but lack these complex cognitive demands (Sweeney *et al*, 1996). Additionally, as argued elsewhere (Gilbert *et al*, 2006), simple reflexive motor tasks (such as prosaccades) can be considered useful low-demand baseline tasks in fMRI experiments and represent appropriate comparison conditions for more complex tasks.

Single subject maps were then combined at the group level in a random effects analysis to produce statistical parametric maps (SPMs) of group activation. A one-sample *t*-test was carried out to investigate activation during prosaccade > fixation and antisaccade > prosaccade. The threshold for significance was set at $p < 0.05$ (corrected cluster level).

To investigate effects of val¹⁵⁸met genotype on BOLD response, val¹⁵⁸ homozygotes and val¹⁵⁸met heterozygotes were combined into a group of val¹⁵⁸ allele carriers and compared to val¹⁵⁸ allele noncarriers. This was done in order to obtain sufficient group sizes for analysis of between-group effects as implemented previously (Flint and Munafò, 2007; Meyer-Lindenberg *et al*, 2005; Winterer *et al*, 2006). Two-sample *t*-tests, unbiased without anatomical restraints, were carried out to compare BOLD response between val¹⁵⁸ carriers and val¹⁵⁸ noncarriers. The threshold for significance was set at $p < 0.05$ (corrected) at the cluster level with a height threshold of $p < 0.001$ at the voxel level. We also applied small volume corrections (SVC; consisting of a sphere with radius = 10 mm) to clusters differing between val¹⁵⁸ carriers and noncarriers at $p < 0.05$ (uncorrected).

MNI coordinates of identified areas given in SPM2 were converted to Talairach coordinates (Talairach and Tournoux, 1988) using a nonlinear transformation algorithm (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>; Brett *et al*, 2002). Macroanatomical localization of the peak voxel in each cluster and corresponding Brodmann area (BA) was identified on the basis of the stereotaxic atlas by Talairach and Tournoux (1988). The functional labels frontal and supplementary eye fields were chosen on the basis of previous literature (Grosbras *et al*, 2005).

Table 1 Demographic and Oculomotor Variables by Group

	Val ¹⁵⁸ Carriers (N = 24)	Val ¹⁵⁸ noncarriers (N = 12)	Statistical analysis
Age (years)	26.51 (5.86)	26.17 (4.49)	$t = 0.85$, $df = 34$, $p = 0.38$
Sex (% male)	66.67	33.33	$\chi^2 = 3.60$, $p = 0.06$
Education (years)	17.96 (2.56)	18.17 (2.44)	$t = -0.23$, $df = 34$, $p = 0.82$
Ethnicity (% Caucasian)	100	100	—
Handedness (% right-handed)	100	100	—
Paternal SES (median, range)	4 (1–4)	4 (3–4)	$Z = -0.36$, $p = 0.72$
Maternal SES (median, range)	4 (1–4)	4 (2–4)	$Z = -0.73$, $p = 0.47$
Prosaccade latency (ms)	206.07 (28.60)	208.92 (21.68)	$t = -0.29$, $df = 32$, $p = 0.77$; $d = -0.11$
Antisaccade latency (ms)	281.83 (37.47)	266.37 (46.03)	$t = 1.05$, $df = 32$, $p = 0.30$; $d = 0.38$
Antisaccade error rate (%)	10.24 (10.90)	11.96 (10.02)	$t = -0.44$, $df = 32$, $p = 0.66$; $d = -0.16$
Antisaccade correction rate (%)	99.28 (3.48)	95.33 (22.67)	$t = 0.83$, $df = 31$, $p = 0.41$; $d = 0.30$

Data indicate means (SD) unless indicated otherwise. SES = socioeconomic status; d = effect size (Cohen, 1988).

Table 2 BOLD Response during Prosaccades in the Combined Group

Macroanatomical label	Hemisphere	Functional label	Brodmann area	Stereotaxic coordinates			
				x	y	z	Z
Superior frontal gyrus	R/L ^a	SEF	6	0	1	57	6.79
Precentral gyrus	R	FEF	6	48	-1	52	6.11
Cuneus	L	—	18	-12	-87	8	5.99
Precentral gyrus	L	FEF	6	-30	-6	44	5.77
Cuneus	R	—	17	14	-75	13	5.44
Intraparietal sulcus	R	—	7	20	-61	56	5.41
Intraparietal sulcus	L	—	7	-14	-69	59	4.82

Abbreviations: FEF, frontal eye field; SEF, supplementary eye field.

The table shows the results of the contrast prosaccade > fixation in the combined group ($N = 36$). Significance is thresholded at $p < 0.05$ (corrected cluster level). Stereotaxic coordinates are based on Talairach and Tournoux (1988) and are given for the peak voxel in the cluster.

^aActivation extends across midline.

RESULTS

Genotype, Demographic, and Oculomotor Variables

Thirty-six participants completed the study. There were 6 val¹⁵⁸ homozygotes, 18 val¹⁵⁸met heterozygotes, and 12 met¹⁵⁸ homozygotes. The genotype distribution did not deviate significantly from Hardy-Weinberg equilibrium ($p = 0.98$). Descriptive statistics of demographic and oculomotor variables are summarized in Table 1. Val¹⁵⁸ carriers ($N = 24$) did not significantly differ from val¹⁵⁸ noncarriers ($N = 12$) in demographic variables or oculomotor performance.

Activations and Deactivations during Prosaccades and Antisaccades

Table 2 and Figure 1 show the network of brain activation during prosaccades compared to fixation (prosaccade > fixation). This contrast shows activation bilaterally in the frontal eye fields, the supplementary eye field (one cluster in the superior frontal gyri of both hemispheres), bilaterally in the intraparietal sulcus (including the parietal eye fields),

and in occipital cortex. The cluster in the occipital cortex extended bilaterally into the cerebellum. This network replicates the well-established cortical areas supporting prosaccades (Grosbras *et al*, 2005).

Table 3 and Figure 2 show the network of brain activation during antisaccades compared to prosaccades (antisaccade > prosaccade). This activation network overlaps considerably with that seen for prosaccades, including frontal eye fields, supplementary eye field, intraparietal sulcus, and occipital cortex. Additionally, there is activation bilaterally in the ventrolateral prefrontal cortex. These areas are in agreement with previous neuroimaging studies of antisaccade eye movements (Hutton and Ettinger, 2006; Munoz and Everling, 2004).

Areas of deactivation during prosaccades (fixation > prosaccade) were found in a distributed network of five extensive clusters (Figure 3): (1) posterior cingulate and precuneus; (2) right middle temporal gyrus, inferior parietal lobule, and cerebellum; (3) left postcentral gyrus and superior temporal gyrus; (4) left fusiform gyrus extending into the left cerebellum; and (5) anterior cingulate. These areas lie within previously described networks showing deactivations during the task relative to baseline condition

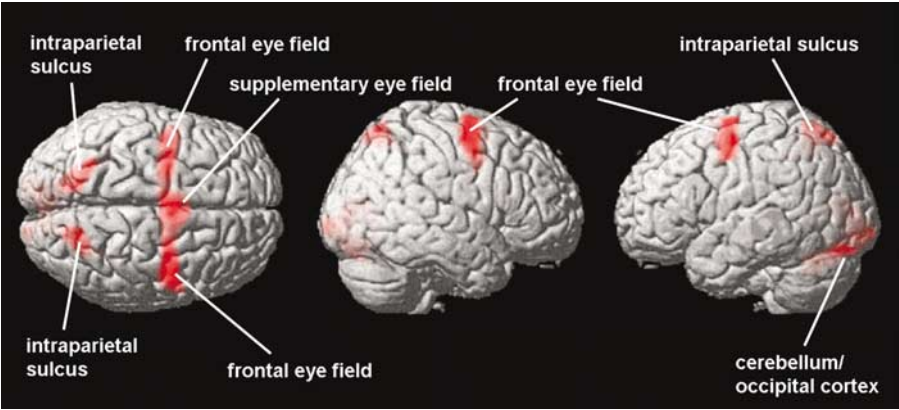


Figure 1 BOLD response during prosaccades in the combined group. The figure shows activations (in red) during prosaccades (relative to fixation) in the combined group ($N=36$). Significance is thresholded at $p<0.05$ (corrected cluster level) ($N=36$).

Table 3 BOLD Response during Antisaccades in the Combined Group

Macroanatomical label	Hemisphere	Functional label	Brodmann area	Stereotaxic coordinates			
				x	y	z	Z
Intraparietal sulcus	R	—	7	14	−65	53	6.92
Cerebellum	L	—	—	−32	−58	−26	6.61
Intraparietal sulcus	L	—	7	−12	−69	51	6.08
Middle frontal gyrus	R	FEF	6	34	−3	48	5.87
Middle frontal gyrus	R	FEF	6	−26	−3	50	5.67
Superior frontal gyrus	R/L ^a	SEF	6	4	7	53	5.63
Inferior frontal gyrus/superior temporal gyrus	R	—	38/47	50	13	−9	4.77
Inferior frontal gyrus/superior temporal gyrus	L	—	22/47	−59	6	−2	3.94
Supramarginal gyrus	R	—	40	57	−33	29	3.51

Abbreviations: FEF, frontal eye field; SEF, supplementary eye field.
The table shows the results of the contrast antisaccade > prosaccade in the combined group ($N=36$). Significance is thresholded at $p<0.05$ (corrected cluster level). Stereotaxic coordinates are based on Talairach and Tournoux (1988) and are given for the peak voxel in the cluster.
^aActivation extends across midline; only right hemisphere is reported.

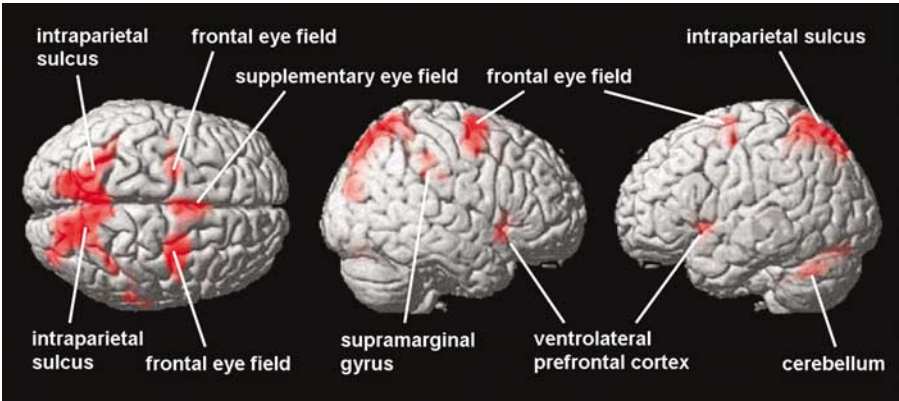


Figure 2 BOLD response during antisaccades in the combined group. The figure shows activations (in red) during antisaccades (relative to prosaccades) in the combined group ($N=36$). Significance is thresholded at $p<0.05$ (corrected cluster level).

(Gusnard *et al*, 2001; Mazoyer *et al*, 2001; McKiernan *et al*, 2003) and overlap with a previous study of deactivations during prosaccades relative to fixation (Sweeney *et al*, 1996).

Areas of deactivation during antisaccades (prosaccade > antisaccade) were observed in three large clusters (Figure 3): (1) in an extended bilateral fronto-parieto-temporal region including medial frontal gyrus, anterior cingulate, superior

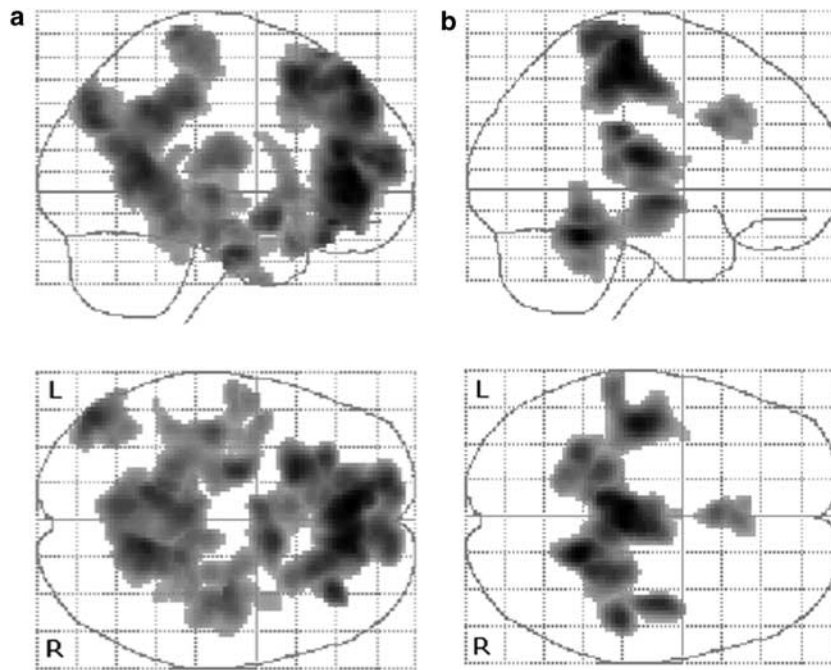


Figure 3 Deactivations during pro- and antisaccades in the combined group. The figure shows clusters of deactivation (shaded in gray) in the combined group ($N = 36$). (a) Deactivations during antisaccades (relative to prosaccades). (b) Deactivations during prosaccades (relative to fixation). Significance is thresholded at $p < 0.05$ (corrected cluster level).

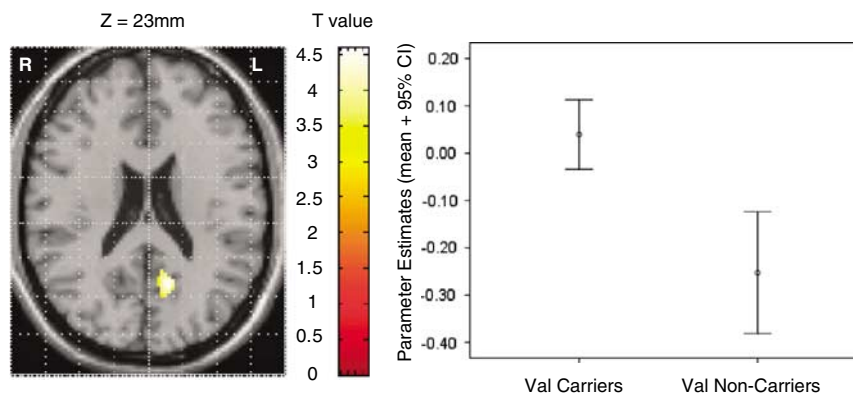


Figure 4 Differences in BOLD response during prosaccades between Val¹⁵⁸ carriers ($N = 24$) and Val¹⁵⁸ noncarriers ($N = 12$) during prosaccades imposed on a single subject's T1-weighted scan. The graph on the right shows the parameter estimates (mean + 95% confidence intervals) for the peak voxel in the cluster ($x = -12$, $y = -57$, $z = 23$). The parameter estimates equate to percent change in the global mean BOLD signal.

frontal gyrus, orbitofrontal cortex, the medial aspects of middle frontal and inferior frontal gyrus, posterior cingulate gyrus, precuneus, and middle temporal gyrus; (2) in the left angular gyrus; and (3) in the right postcentral gyrus and superior temporal gyrus. This network overlaps with previous findings of deactivations in ventromedial and orbital frontal areas during antisaccades relative to prosaccades (Sweeney *et al*, 1996) and deactivations in precuneus, posterior cingulate, and angular gyrus during cue-instructed, volitional saccades relative to prosaccades (Mort *et al*, 2003). The network is also similar to areas reported during a simple reaction time baseline task relative to more complex tasks by Gilbert *et al* (2006).

Effects of COMT Val¹⁵⁸Met Genotype on BOLD during Prosaccades

The two-sample *t*-test for the comparison of val¹⁵⁸ carriers and noncarriers showed one discrete cluster (cluster size = 167 voxels). Val¹⁵⁸ carriers showed greater activation levels than noncarriers in the medial parietal cortex (Figure 4) in BA23/31, including precuneus and posterior cingulate ($x = -12$, $y = -57$, $z = 23$). The difference was significant at the cluster level ($p = 0.02$ uncorrected; $p = 0.002$ corrected with SVC). The mean parameter estimate for the combined group was -0.06 ($SD = 0.23$) (Figures 4 and 5).

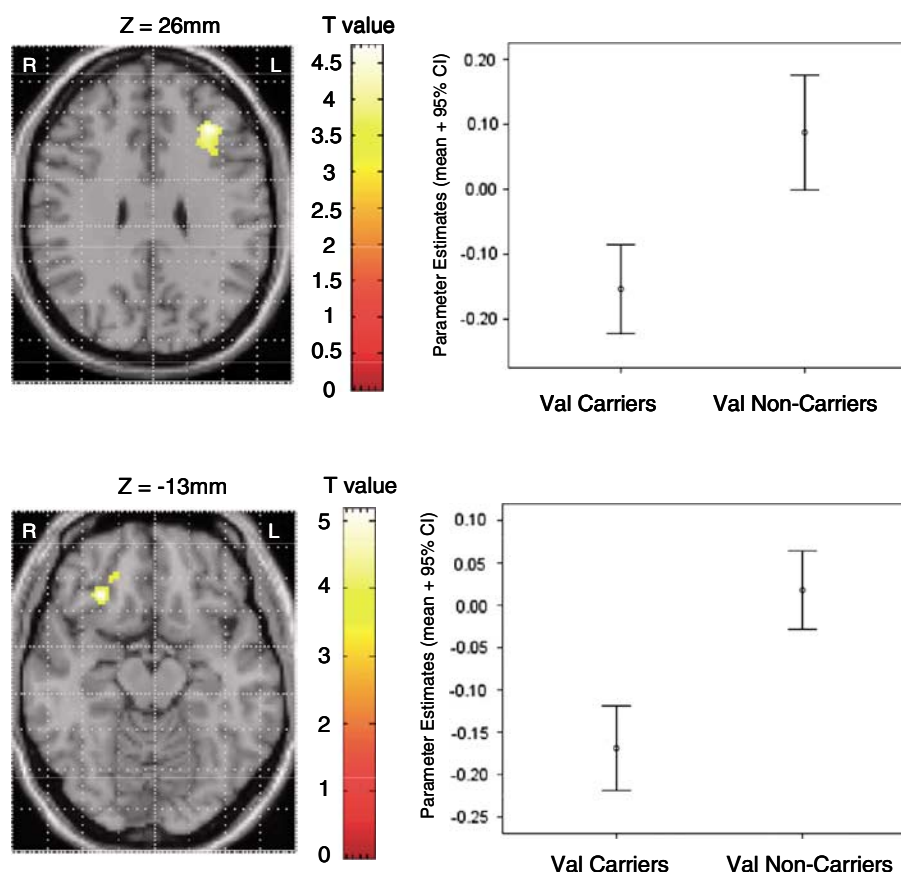


Figure 5 Differences in BOLD response during antisaccades between Val¹⁵⁸ carriers and Val¹⁵⁸ noncarriers. The axial brain images on the left display the differences in activation between val¹⁵⁸ carriers ($N = 24$) and val¹⁵⁸ noncarriers ($N = 12$) during antisaccades imposed on a single subject's T1-weighted scan. The charts on the right show the parameter estimates (mean + 95% confidence intervals) for the peak voxel in each cluster (upper panel: $x = -32$, $y = 30$, $z = 26$; lower panel: $x = 30$, $y = 28$, $z = -13$). The parameter estimates equate to percent change in the global mean BOLD signal.

Further inspection of the data of the subgroups within the val¹⁵⁸ allele carriers (ie val¹⁵⁸ homozygotes vs val¹⁵⁸met heterozygotes) showed that the two groups of val¹⁵⁸ carriers showed similar mean parameter estimates (val¹⁵⁸ homozygotes: 0.002; val¹⁵⁸met heterozygotes: 0.05) when compared to met¹⁵⁸ homozygotes. Met¹⁵⁸ homozygotes, however, differed clearly from the two val¹⁵⁸ carrier groups (Figure 4). Additionally, given the smaller sample size of the val¹⁵⁸ homozygotes, the 95% confidence intervals for β coefficients in this group were larger than in the val¹⁵⁸met heterozygotes (val¹⁵⁸ homozygotes: -0.23 to 0.24 ; val¹⁵⁸met heterozygotes: 0.05 to -0.03); 95% confidence intervals in the val¹⁵⁸ group were also larger than in the met¹⁵⁸ homozygotes (see Figures 4 and 5). These data support the strategy of combining val¹⁵⁸ homozygotes and val¹⁵⁸met heterozygotes and comparing these to met¹⁵⁸ homozygotes (Flint and Munafò, 2007; Winterer et al, 2006).

Effects of COMT Val¹⁵⁸Met Genotype on BOLD during Antisaccades

The two-sample t -tests for the comparison of val¹⁵⁸ carriers and val¹⁵⁸ noncarriers showed two clusters (Figure 5). In both clusters, val¹⁵⁸ noncarriers showed greater activation levels than val¹⁵⁸ carriers. The clusters focused on the medial aspect of the ventral prefrontal cortex in BA47

($x = 30$, $y = 28$, $z = -13$; cluster size = 146 voxels) and the medial aspect of the dorsal prefrontal cortex in BA9 ($x = -32$, $y = 30$, $z = 26$; cluster size = 215 voxels). The differences were significant at the cluster level for BA47 ($p = 0.03$ uncorrected; $p = 0.003$ corrected with SVC) and BA9 ($p = 0.01$ uncorrected; $p = 0.002$ corrected with SVC). The mean parameter estimates for these areas in the combined group were -0.11 (SD = 0.14) for BA47 and -0.07 (SD = 0.19) for BA9.

Further inspection of the data of the subgroups within the val¹⁵⁸ allele carriers showed that the two subgroups (val¹⁵⁸ homozygotes and val¹⁵⁸met heterozygotes) showed similar mean parameter estimates for BA47 (val¹⁵⁸ homozygotes: -0.14 ; val¹⁵⁸met heterozygotes: -0.19) and BA9 (val¹⁵⁸ homozygotes: -0.09 ; val¹⁵⁸met heterozygotes: -0.17) when compared to met¹⁵⁸ homozygotes. Met¹⁵⁸ homozygotes, however, differed clearly from the two val¹⁵⁸ carrier groups (Figure 5). Additionally, given the smaller sample size of the val¹⁵⁸ homozygotes, the 95% confidence intervals for β coefficients in this group were larger than in the val¹⁵⁸met heterozygotes for BA47 (val¹⁵⁸ homozygotes: -0.24 to -0.04 ; val¹⁵⁸met heterozygotes: -0.24 to -0.12) and BA9 (val¹⁵⁸ homozygotes: -0.24 to 0.05 ; val¹⁵⁸met heterozygotes: -0.26 to -0.09); 95% confidence intervals in the val¹⁵⁸ homozygote group were also larger than in the met¹⁵⁸ homozygotes (Figure 5). As for prosaccades, these data

agree with the strategy of combining val¹⁵⁸ homozygotes and val¹⁵⁸met heterozygotes and comparing these to met¹⁵⁸ homozygotes.

Interaction between Area, Task, and Group

Given that different, regionally specific group differences emerged for the two different contrasts, we aimed to explore whether this pattern could be confirmed by a significant group-by-task-by-area interaction. Parameter estimates from the peak voxel within each cluster were entered into repeated measures ANOVA with group (val¹⁵⁸ carriers, val¹⁵⁸ noncarriers) as between-group factor and task (antisaccade, prosaccade) and area (BA9, BA47, BA23/31) as within-subjects factor. As predicted, there was a significant interaction ($F(2,68) = 23.71, p < 0.001$). This interaction indicated that val¹⁵⁸ carriers showed lower activations than val¹⁵⁸ noncarriers in frontal areas only during antisaccades, while val¹⁵⁸ noncarriers showed lower activations than val¹⁵⁸ noncarriers in BA23/31 only during prosaccades.

DISCUSSION

In this study, we investigated the association between COMT val¹⁵⁸met genotype and brain function. We found that genotype is associated with BOLD response as a function of task characteristic: val¹⁵⁸ allele noncarriers showed lower BOLD response than val¹⁵⁸ carriers in posterior cingulate/precuneus during prosaccades, whereas val¹⁵⁸ allele carriers showed lower BOLD response than noncarriers in dorsomedial and ventromedial prefrontal areas during antisaccades. This pattern of findings suggests that the association between COMT val¹⁵⁸met genotype and BOLD response depends on the type of behavioral probe used to elicit brain function.

Bilder *et al* (2004) postulated that the met¹⁵⁸ allele should be associated with better performance on measures of stability, whereas the val¹⁵⁸ allele should be associated with better performance on tasks involving plasticity or flexibility. Applied to the present tasks, this theory predicts that val¹⁵⁸ noncarriers should show superior prosaccade performance, whereas val¹⁵⁸ carriers should show superior antisaccade performance. As outlined above, both prosaccade and antisaccade tasks involve elements of cognitive stability, such as the representation of task set and sustained attention. Importantly, antisaccades (but not prosaccades) additionally require features of plasticity tasks, such as inhibition of inappropriate responses and monitoring and correction of errors. Directional errors occur on a substantial proportion of trials on antisaccade tasks (Hutton and Ettinger, 2006) but very rarely on prosaccade trials, with the vast majority of subjects not committing any errors. In this and previous studies, directional errors in the antisaccade task are corrected in the vast majority of trials, requiring error monitoring and correction processes (Nieuwenhuis *et al*, 2001; Polli *et al*, 2005). Finally, antisaccade performance is sensitive to monetary reward incentives (Duka and Lupp, 1997; Jazbec *et al*, 2005). Therefore, for the purpose of the present discussion, prosaccade tasks may be considered a measure of stability,

whereas antisaccade tasks may represent a measure of plasticity.

In the present study, there were no gene effects on oculomotor performance (although val¹⁵⁸ carriers showed nonsignificantly better scores on antisaccade error and correction rate), likely in part due to the relatively small number of subjects in this sample and the small magnitude of gene effects on behavior. Our findings are thus compatible with the notions (1) that single-gene effects on behavior require large samples to detect and (2) that functional neuroimaging endophenotypes may be more sensitive at detecting gene effects than behavioral performance measures (Hariri and Weinberger, 2003). Formal power calculation indicated that for the key performance measure of antisaccade errors, 484 subjects per group are needed to achieve 80% power of detecting a significant ($p < 0.05$) effect.

The present data may provide a neurophysiological explanation of the hypothesized (Bilder *et al*, 2004) and observed (Nolan *et al*, 2004) COMT val¹⁵⁸met effects on neurocognitive performance. It can be inferred on the basis of our data that one possible reason for the differential gene effects hypothesized in Bilder *et al* (2004) is the ability to appropriately deactivate brain areas in the medial fronto-parietal network that show greater activations during low-level control tasks compared to active tasks (Gusnard *et al*, 2001; Mazoyer *et al*, 2001; McKiernan *et al*, 2003; Raichle *et al*, 2001). Our data suggest that val¹⁵⁸ carriers appropriately deactivate these areas during antisaccades (a measure of cognitive flexibility), whereas val¹⁵⁸ noncarriers appropriately deactivate these areas during prosaccades (a measure of stability). Our interpretation is compatible with previous observations of relationships between better performance and greater deactivations both at the level of interindividual (Harrison *et al*, 2007) and trial-by-trial differences (Polli *et al*, 2005; Weissman *et al*, 2006) and in pharmacological studies (Hahn *et al*, 2007). Additionally, it has been observed that a number of neuropsychiatric patient groups, such as people with autism (Kennedy *et al*, 2006), fragile X syndrome (Menon *et al*, 2004), Parkinson's disease (Tinaz *et al*, 2006), or dementia (Sauer *et al*, 2006), fail to show (or show lower levels of) the typical pattern of deactivations seen in healthy, normal-performing controls.

While little is known about the role of dopamine in the brain deactivation patterns detected in fMRI, it has been found that individual differences in extraversion, a personality trait mediated by dopamine turnover (Rammsayer, 2004), are associated with levels of activation and deactivation in medial fronto-parietal brain areas (Kumari *et al*, 2004). It is also of interest to acknowledge that in the present study, there were no differences in task-activated brain areas (such as those displayed in Figures 1 and 2). It is unclear why we did not find differences in this network, but our findings suggest that COMT val¹⁵⁸met effects during the particular tasks selected here may be stronger at the level of deactivation than activation areas. Larger samples are needed to address this issue more conclusively.

In this context, it is important to note that the frontal areas found to differ between groups in this study do not correspond to dorsolateral and ventrolateral prefrontal cortices seen during antisaccade activation in this and

previous studies (McDowell *et al*, 2002; Sweeney *et al*, 1996); instead, they are more medial and correspond better to typical deactivation areas (Gusnard *et al*, 2001; Mazoyer *et al*, 2001; McKiernan *et al*, 2003). While the two frontal clusters observed here are not mid-line structures, they are close to peaks described in a meta-analysis (see Table 4 in Mazoyer *et al*, 2001) and shown in an illustrative overview of deactivation areas (see Figure 1 in McKiernan *et al*, 2003). As described in Results, the overall group means at the areas of difference between val¹⁵⁸ carriers and noncarriers were negative. This finding confirms that in the combined group, the areas were deactivated during active task compared to control conditions; however, the overall level of deactivation was weak and the genetic findings suggest that there was significant between-subject variance explained by COMT val¹⁵⁸met genotype.

The task-related areas of activation are in good concordance with previous block-design functional neuroimaging studies of reflexive saccades and antisaccades in healthy humans (McDowell *et al*, 2002; O'Driscoll *et al*, 1995; Sweeney *et al*, 1996). Prosaccades and antisaccades share recruitment of dorsal frontal and parietal oculomotor areas. Additionally, antisaccades have been shown to involve ventrolateral prefrontal cortex (Tu *et al*, 2006; Walker *et al*, 1998) and supramarginal gyrus (Chikazoe *et al*, 2007; Matsuda *et al*, 2004). Activation in the dorsolateral prefrontal cortex, an area of overall importance in antisaccade performance (Dyckman *et al*, 2007; Ploner *et al*, 2005), was seen in the present study but did not survive correction for multiple comparisons.

The present study may have implications for psychiatric genetics, in particular with regard to schizophrenia. The COMT val¹⁵⁸met polymorphism has been implicated in a number of neuropsychiatric conditions (Tunbridge *et al*, 2006). It has been widely studied in relation to schizophrenia, although the overall association may be very small (Munafo *et al*, 2005). Given that associations between specific candidate genes and the schizophrenia phenotype appear to be of small effect size, it has been suggested that the study of intermediate phenotypes, or endophenotypes, may be advantageous (Braff *et al*, 2007; Gottesman and Gould, 2003). Endophenotypes are thought to be a more proximal and homogeneous measure of a gene effect than the complex behavioral (or disease) phenotype and may therefore be used profitably in molecular genetic designs, such as linkage and association studies (Braff *et al*, 2007; Gottesman and Gould, 2003). While a large number of previous studies have employed cognitive and neuropsychological endophenotypes, it has recently been suggested that the brain functional response may be a more proximal and neurobiologically plausible intermediate phenotype (Meyer-Lindenberg and Weinberger, 2006).

The present findings may be viewed within this framework, specifically with regard to intermediate phenotypes for schizophrenia. Hariri and Weinberger (2003) outlined three principles that should be considered to facilitate detection of meaningful gene effects on brain function using functional imaging. First, the polymorphism under study should be a well-defined, functional polymorphism with candidate gene status for a certain behavior or disorder. Second, groups (eg allele carriers vs noncarriers) should be matched on important demographic variables to avoid

masking true gene effects on brain function or producing spurious ones. Third, the task used to elicit brain function should be a well-characterized paradigm known to produce robust activation in relevant brain regions.

The present study clearly fulfills these criteria: first, COMT val¹⁵⁸met is one of the most widely studied, functional polymorphisms in psychiatry and cognitive neuroscience, in particular with regard to schizophrenia and frontal lobe function (for reviews on the val¹⁵⁸met polymorphism, see Barnett *et al*, 2007; Bilder *et al*, 2004; Flint and Munafo, 2007; Heinz and Smolka, 2006; Munafo *et al*, 2005; Savitz *et al*, 2006; Tunbridge *et al*, 2006; Winterer and Goldman, 2003). Second, val¹⁵⁸ carriers and noncarriers in this study did not significantly differ in age, gender, ethnicity, handedness, level of education, or parental socioeconomic status. Third, the antisaccade task is a paradigm that has been studied in detail with regard to its status as a candidate endophenotype for schizophrenia. Antisaccade performance is a temporally stable trait marker with significant impairments in schizophrenia (Calkins *et al*, 2003; Curtis *et al*, 2001; Ettinger *et al*, 2003; Gooding *et al*, 2005). The task recruits well-replicated fronto-parietal networks (Muri *et al*, 1998; O'Driscoll *et al*, 1995; Sweeney *et al*, 1996), which are abnormal in schizophrenia patients (McDowell *et al*, 2002; Raemaekers *et al*, 2002) and their relatives (Raemaekers *et al*, 2006). Antisaccade impairments are observed in people at risk for schizophrenia, for example, the unaffected biological relatives of schizophrenia patients (Calkins *et al*, 2004; Clementz *et al*, 1994; Curtis *et al*, 2001; Ettinger *et al*, 2006), individuals at ultra-high risk for schizophrenia (Nieman *et al*, 2007), and people with heightened scores of schizotypal traits (Ettinger *et al*, 2005; O'Driscoll *et al*, 1998; Smyrnis *et al*, 2003).

Given this evidence of antisaccade impairments across the schizophrenia spectrum, it would be of interest to study the relationship between COMT val¹⁵⁸met genotype and BOLD response in people with schizophrenia as well as genetic high-risk populations, such as biological relatives of schizophrenia patients or people with schizotypal personality traits. In this context, it is important to note, however, that the present study of healthy individuals has certain methodological advantages over patient studies. Healthy controls do not display confounds such as pharmacological treatment, acute symptoms, and factors secondary to the disease that might affect performance and/or brain function. Therefore, the study of healthy individuals provides an important model within which to characterize gene effects on brain function.

Limitations

A number of limitations of the present study should be acknowledged. First, while gender distribution did not significantly differ between genotype groups, it should be noted that two-thirds of val¹⁵⁸ allele carriers were male compared to only one-third of val¹⁵⁸ allele noncarriers. The sample sizes prohibited a more detailed analysis of gender or gender-by-genotype effects on brain function; this issue should be considered in future studies.

Second, the attribution of prosaccades and antisaccades to the domains of cognitive stability and plasticity,

respectively, may, to some extent, be confounded by the level of task difficulty. Future research is needed to investigate genetic and brain functional correlates of stability and plasticity measures matched for the level of task difficulty.

Third, the sample size of the present study was small compared to large-scale investigations of genes with small effects (Craddock *et al*, 2006; Wang *et al*, 2005) and the results regarding the COMT effects were observed at the uncorrected level. While the sample size was comparable to some previous fMRI studies of gene effects (Blasi *et al*, 2005; Winterer *et al*, 2006), future research will be needed to test whether the gene-brain associations observed here are reproducible.

CONCLUSIONS

We observed associations between COMT val¹⁵⁸met genotype and BOLD response during prosaccade and antisaccade task performance in the absence of a gene effect at the behavioral level. The findings are compatible with the notion that the val¹⁵⁸ allele is associated with improved brain plasticity performance, while the met¹⁵⁸ allele is associated with improved brain stability performance (Bilder *et al*, 2004). Future research is required to replicate the present findings using larger samples in order to provide further evidence of validity. The present design may also be extended to schizophrenia patients and those at risk for the illness.

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DISCLOSURE/CONFLICT OF INTEREST

The authors state no conflict of interest.

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