Opposite Effects of Catechol-O-Methyltransferase Val158Met on Cortical Function in Healthy Subjects and Patients with Schizophrenia

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Background: Catechol-O-methyltransferase (COMT) is essential for dopamine metabolism in the brain, and normal variation in the COMT Val158Met polymorphism can influence regional brain function during cognitive tasks. How this is affected when central dopamine function is perturbed is unclear. We addressed this by comparing the effects of COMT Val158Met genotype on cortical activation during a task of executive functions in healthy and schizophrenic subjects.

Methods: We studied 90 subjects comprising 48 healthy volunteers (15 Met158/Met158, 20 Val158/Met158, and 13 Val158/Val158) and 42 patients with DSM-IV schizophrenia (13 Met158/Met158, 17 Val158/Met158, and 12 Val158/Val158). Subjects were studied with functional magnetic resonance imaging while performing a verbal fluency task, with performance recorded online. Main effects of genotype and diagnosis and their interaction on cortical activation and functional connectivity were assessed using SPM5.

Results: In the right peri-Sylvian cortex, the Met158 allele of the COMT Val158Met polymorphism was associated with greater activation than the Val158 allele in control subjects; the converse applied in patients (Z = 4.3; false discovery rate p = .04). There was also a strong trend for a group × genotype interaction on functional connectivity between this right peri-Sylvian region and the left anterior insula/operculum (Z = 3.4; p < .001, uncorrected). These findings were independent of between-group differences in task performance, medication, demographic factors, or IQ.

Conclusions: Frontotemporal function during verbal generation is modulated by variation in COMT genotype. This effect is altered in schizophrenia, which may reflect the perturbation of central dopamine function associated with the disorder.

Key Words: Catechol-O-methyltransferase, cerebral cortex, cognitive symptoms, dopamine, imaging, schizophrenia

Catechol-O-methyltransferase (COMT) is an enzyme that catalyzes the O-methylation of extracellular dopamine in the brain (1). It is mainly expressed in its membrane-bound (MB-COMT) form in postsynaptic neurons (2) throughout the brain and at higher levels in the frontal and temporal cortices than in subcortical regions (2,3). Dopamine is removed from central synapses by the dopamine transporter, but because this is less prominent in cortical than subcortical areas, COMT has a relatively greater influence on synaptic dopamine levels in the former than in the latter (4–6).

The enzymatic activity of COMT is altered by a guanine (G) to adenine (A) single nucleotide polymorphism (SNP) change (known as Val158Met or rs4680) in the molecular sequence of the gene. This translates into a valine (Val) to methionine (Met) amino acid change in codon 158 that causes a three- to fourfold decrease in its molecular thermostability. The alleles appear to be codominant as the heterozygote genotype (Val158/Met158) is associated with an intermediate level of COMT activity (1,7).

Within the healthy population, variation in the Val158Met polymorphism is associated with significant differences in the performance of cognitive tasks (8–11) and in cortical activation during execution of these tasks, as measured using functional neuroimaging (9,12–16). This is thought to reflect variation in COMT activity, altering the level of locally available dopamine and thus influencing the “efficiency” of cortical function (17–19). The effect of variation in COMT genotype on activation may depend on the local level of afferent dopaminergic activity. For example, it is altered following experimental administration of amphetamine, which increases synaptic dopamine release (20,21). Schizophrenia is associated with abnormalities in dopaminergic input to the cerebral cortex (22–25) and to the striatum (26–28). The effect of variation in COMT genotype on cortical activation in schizophrenia patients may therefore differ from that in healthy individuals.

The first aim of this study was to determine the influence of COMT Val158Met polymorphism on cortical function during a verbal fluency (VF) task in healthy volunteers. We then sought to compare the effect of COMT Val158Met genotype on activation in healthy volunteers and patients with schizophrenia, using functional magnetic resonance imaging (fMRI). The size of our experimental groups was higher than that of previous studies that successfully detected significant effects of COMT (9,13,14). We studied activation during a VF paradigm, a classical test of executive functions that normally engages the frontal, cingulate, and temporal cortices (29–32). Schizophrenia patients show a robust impairment of VF performance, and execution of the task is generally associated with abnormal activation of the frontal, cognitive symptoms, dopamine, imaging, schizophrenia

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cingulate, and temporal cortex relative to control subjects. Studies that do not control for performance have shown prefrontal hypoactivation in schizophrenia, whereas others report no difference in activation (29–31,33,34).

Because variation in COMT Val158Met genotype has previously been found to modulate cortical activation during other cognitive tasks (9,12–16), we first tested the hypothesis that the COMT Val158Met genotype would significantly influence cortical activation during the VF task. We then tested the hypothesis that the effect of COMT Val158Met genotype on activation in these regions would significantly differ in patients with schizophrenia compared with healthy subjects, reflecting the perturbation of central dopamine function associated with the disorder.

Methods and Materials

Sample

Ninety subjects, all native English speakers, participated. Patients (n = 42) had established schizophrenia as defined by DSM-IV criteria, and healthy volunteers (n = 48) had no history of mental illness. For subject recruitment details, see Supplement 1. All subjects, 90% of whom were Caucasian, were genotyped for the rs4680 single nucleotide polymorphism, which encodes the Val158Met polymorphism (details in Supplement 1, Table 1). There were no significant differences (p < .05) between the patient and control groups in age, ethnicity, or handedness, but patients had a lower mean IQ, fewer years of education, and a higher proportion of men (Table 1). Between the genotype subgroups, either within diagnostic categories or across the whole sample, there were no significant differences (p < .05) for any of the demographic (Table 1), psychopathological, or medication variables (Supplement 2).

VF Task and Image Acquisition

The task and image acquisition was performed as previously described in Fu et al. (32) (see Supplement 1 for details). Briefly, during a “generation” condition, subjects were visually presented with a series of letters and were required to articulate overtly a word beginning with the presented letter. This was contrasted with a “repetition” condition in which subjects were presented with the word “rest” and were required to say “rest” out loud. Task difficulty was manipulated by presenting separate sets of “easy” and “hard” letters (32). Task performance analysis was performed with SPSS software (Supplement 1).

Neuroimaging Analysis

Analysis was performed using SPM5 software (http://www.fil.ion.ucl.ac.uk/spm) (35), running under Matlab 6.5 (Mathworks, Sherbon, Massachusetts). For data preprocessing, see Supplement 1. First, the statistical analysis of regional responses was performed in a subject-specific fashion by convolving a stick function encoding the onset of each sort of trial. To minimize performance confounds, we modeled correct and incorrect trials separately using an event-related model. This resulted in four experimental conditions: 1) easy generation, 2) hard generation, 3) repetition, and 4) incorrect responses. To remove low-frequency drifts, data were high-pass filtered using a set of discrete cosine basis functions with a cutoff period of 128 sec. The parameter estimates were calculated for all brain voxels using the general linear model, and contrast images for “easy generation > repetition” and “hard generation > repetition” were computed in a subject-specific fashion. Second, the subject-specific contrast images were entered into a full-factorial analysis of variance to permit inferences at the population level (36).
allowed us to characterize the impact of the experimental task on brain activation in “easy” and “hard” separately within each experimental group (i.e., Met158/Met158 control subjects; Val158/Met158 control subjects; Val158/Val158 control subjects; Met158/Met158 patients; Val158/Met158 patients; Val158/Val158 patients), to test for the main effect of diagnostic group, the main effect of genotype, and their interaction. The t images for each contrast at the second level were transformed into statistical parametric maps of the Z statistic. We first contrasted the homozygote groups (Met158/Met158 against Val158/Val158). When we found a significant difference between them, we formally assessed whether heterozygotes (Val158/Met158) had an intermediate level of activation by using a linear regression test with SPSS software (Supplement 1).

Unless otherwise indicated, we report and discuss findings that are significant at cluster size greater than 20 voxels and after voxelwise false discovery rate (FDR) correction for multiple comparisons at $p < .05$ across the whole brain. For completeness, we also report but do not interpret trends at uncorrected $p < .001$. To confirm that demographic and medication variables did not bias our analyses, we performed additional analyses using them as covariates of no interest.

Results

Task Performance

As expected, task difficulty (hard vs. easy) had a significant effect on the number of correct responses ($t = -8.22; p < .0001$). Irrespective of genotype, patients generated significantly ($p < .05$) fewer correct responses than control subjects on both versions individually or combined ($p = .001$; Supplement 3). In healthy volunteers, there was no significant difference ($p < .05$) in performance between Met158/Met158 and Val158/Val158 genotypes. However, within patients, the Val158 allele was associated with poorer performance, in the opposite direction to controls, on the hard version of the task ($F = 4.2; p = .05$) and when versions were combined ($F = 4.6; p = .06$) (data not shown). Within the patient sample including heterozygotes, there was a trend for a linear correlation between the number of Val158 alleles and the number of errors during the hard version ($R^2 = .09; B = 1.72; t = 3.7; p = .06$), and this was significant for combined versions ($R^2 = .09; B = 3.03; t = 2.7; p = .05$) (data not shown). Furthermore, there was a significant genotype × diagnostic group interaction on performance during the easy, hard, and combined versions of the task ($p = .02, p = .04$, and $p = .01$, respectively; Supplement 5).

Neuroimaging Data

Main Effect of Task. In both control subjects and patients, word generation (irrespective of task demand or genotype) was associated with activation in a distributed network that included the bilateral inferior frontal (gyrus and operculum), insular and cingulate cortices, the caudate and thalamus, as well as the left middle frontal, superior temporal, and inferior parietal cortices (Supplements 4 and 5). Conversely, repetition was associated with activation in the precuneus, rostral anterior cingulate gyrus, and occipital cortex.

Main Effect of Diagnostic Group. Activation in the left frontal operculum, inferior frontal gyrus, and anterior insula was greater in patients than in control subjects (uncorrected $p < .001$; Figure 1; Supplement 5). There were no areas that were more activated in control subjects than patients at this threshold.

Main Effect of COMT Val158Met Genotype. In both diagnostic groups, the Met158/Met158 genotype was associated with greater activation than the Val158/Val158 in the dorsal part of the left anterior cingulate gyrus (8 30 20) at an uncorrected level ($Z = 3.5; p < .001$; Figure 1). There was a negative linear effect of Val158 load in this region, with activation greatest for Met158/Met158 followed by Val158/Met158 and then Val158/Val158 ($R^2 = .07; B = -.49; t = -3.59; p = .00004$). There were no areas that were more activated in Val158/Val158 than Met158/Met158 subjects across both groups at this threshold (uncorrected $p < .001$).

Group × Genotype Interaction

There was a significant group × genotype interaction in a right peri-Sylvian region that comprised the adjacent parts of the frontal operculum/anterior insula, the middle temporal gyrus, and the parietal operculum, in both task versions combined (Table 2, Figure 2). At these loci, in healthy volunteers, the...
Met158/Met158 genotype was associated with greater activation than its Val158/Val158 counterpart, whereas in patients, the opposite occurred (voxelwise FDR correction for multiple comparisons across the brain \( p = .04 \); Figure 2).

Furthermore, there was also a significant linear effect of genotype \( (p < .05) \) in all three areas, with a negative correlation between the number of Val158 alleles and activation in healthy volunteers but a positive correlation in patients (Supplement 6). A multivariate general linear model analysis revealed that the COMT \( \times \) group interaction accounted for 13\% of interindividual variance on activation in the right frontal operculum \( (R^2 = .13; p = .0002) \), 11\% in the parietal operculum \( (R^2 = .11; p = .001) \), and 10\% in the middle temporal gyrus \( (R^2 = .10; p = .005) \).

**Functional Connectivity**

To establish putative disconnections that were responsible for the regional responses described earlier showing a group \( \times \) phenotype interaction, we used the region of peak activation (right frontal operculum/anterior insula) as a reference (or seed region) in an analysis of group-specific effects on its functional connectivity. To do this, we used exactly the same between-subject modeling as for the analysis of the activation effects but with contrasts that reflected coupling (as opposed to activations). The within-subject contrasts of functional connectivity were constructed by using the activity in the reference region as an explanatory variable or regressor (Supplement 1).

The results revealed a trend for a main effect of diagnostic group on the functional connectivity of the right frontal opercular region: in patients, activity in this area was more strongly coupled to that in the head of the caudate nucleus bilaterally than in healthy volunteers \( (p < .01, \) uncorrected). However this difference was no longer present after covarying for dose and duration of treatment with antipsychotics.

There were no main effects of genotype on the functional

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**Table 2.** Where Catechol-O-Methyltransferase Val158Met Genotype Had Opposite Effects on Activation and Functional Connectivity in Patients and Control Subjects

<table>
<thead>
<tr>
<th>Regions</th>
<th>Control Subjects</th>
<th>Patients</th>
<th>Genotype ( \times ) Diagnosis Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Met/Met &gt; Val/Val</td>
<td>Val/Val &gt; Met/Met</td>
<td></td>
</tr>
<tr>
<td>R Frontal Operculum/Anterior Insula</td>
<td>46 6 14 (2.0)</td>
<td>40 8 12 (4.0)</td>
<td>40 6 14 (4.3); ( k = 1112 ) (FDRp = .04)</td>
</tr>
<tr>
<td></td>
<td>36 14 0 (3.0)</td>
<td>36 10 10 (3.8)</td>
<td>34 14 6 (4.0); ( k = 1112 ) (FDRp = .04)</td>
</tr>
<tr>
<td>R Parietal Operculum</td>
<td>50 – 20 14 (3.3)</td>
<td>50 – 24 22 (3.2)</td>
<td>50 – 24 18 (4.0); ( k = 1112 ) (FDRp = .04)</td>
</tr>
<tr>
<td>R Middle Temporal Gyrus</td>
<td>54 – 12 – 6 (3.1)</td>
<td>56 – 10 – 16 (3.3)</td>
<td>54 – 10 – 14 (3.9); ( k = 1112 ) (FDRp = .04)</td>
</tr>
</tbody>
</table>

Inferences were made by comparing the homozygote groups (Met/Met vs. Val/Val) in the hard and easy conditions combined. All inferences at uncorrected \( p < .001 \) for interactive effects are reported (last column), and coordinates are presented in bold when corrected for multiple comparisons (FDRp < .05).

FDR, false discovery rate.

*Presented with foci of maximal significance and associated \( Z \) score (in brackets).
connectivity of the right peri-Sylvian region. However, there was a trend for an interaction between group and genotype on the coupling of activity in the right frontal operculum with that in both the dorsal and ventral parts of the left anterior insula/frontal operculum ($p < .001$, uncorrected). In healthy volunteers, its functional connectivity with these regions was stronger in Met158/Met158 than Val158/Val158 subjects, whereas in patients the converse applied (Table 2). This effect of genotype in each group was linear ($p < .05$), with heterozygotes showing intermediate activation (Supplement 6). The group × genotype interaction accounted for 20% of the variance ($R^2 = .20; p = .002$) in the functional connectivity with the left ventral anterior insula and 12% of that with the left dorsal anterior insula/frontal operculum ($R^2 = .12; p = .06$).

Effects of Potentially Confounding Factors on Activation

Whole-brain regression analyses indicated that activation in the areas where there were significant effects of COMT Val158Met was not related to either the dose or the duration of antipsychotic treatment, even at a liberal statistical threshold ($p = .01$, uncorrected). Additionally, when these medication variables and type of antipsychotic (first or second generation) were entered in the analyses of genotype effects as covariates of no interest, they did not change the loci of maximal significance or the associated $Z$ scores. This was also the case when IQ, years of education, handedness, ethnicity, and sex were entered as covariates. The only finding attributable to an effect of antipsychotic medication was the group difference in functional connectivity between the right frontal operculum and the caudate (described earlier).

Discussion

The network of areas engaged by the VF task was consistent with that reported in previous studies, with both groups showing bilateral activation in the inferior frontal, insular, and cingulate cortex; the caudate and thalamus; as well as in the left middle frontal, superior temporal, and inferior parietal cortex (29–32). Patients and healthy volunteers showed differential activation in the left frontal operculum, anterior insula, and inferior frontal gyrus. Most studies of patients with schizophrenia and control subjects have reported differences in left frontal and insular activation during VF (30,31,33,34,37), but some have not (29,38). This may partly reflect small sample sizes and differences in the degree to which studies controlled for the effects of impaired task performance in schizophrenia. To our knowledge, this study is the largest functional imaging investigation of VF in schizophrenia to date. We used a paced overt paradigm and restricted the analysis to images associated with correct responses, therefore controlling for performance bias. Greater prefrontal activation in patients than control subjects has frequently been reported in studies of working memory tasks in schizophrenia (14,39–41) and has been interpreted as a correlate of impaired prefrontal cortical efficiency secondary to the reduced afferent dopaminergic activity that is thought to be a feature of the disorder (42). The same mechanism could underlie the increased inferior frontal activation that we observed in patients with schizophrenia during a VF task. Indeed, overactivation of the left prefrontal cortex during VF, in relation to increased temporal activation, was one of the original results that led to the functional dysconnectivity hypothesis of schizophrenia (43). In this context, increased frontal activation can be regarded, heuristically, as a compensatory attempt by frontal regions to overcome an impaired or reduced influence over other cortical regions. This reduced influence may be coupled with abnormal central dopaminergic function in schizophrenia (29).

In terms of both task performance and activation, the most significant effects of COMT Val158Met were specific to each group. At the behavioral level, the Val158 allele was associated with poorer task performance in patients, but there was no significant effect in healthy volunteers (although the direction was opposite), and there was a significant interaction between the effects of genotype and group. Studies of other tasks that engage executive functions have also reported worse performance in patients with schizophrenia who carry the Val158 allele (9,10,44,45). Some studies (8–11) and a meta-analysis (46) have found the same effect of COMT Val158Met genotype on performance in healthy volunteers, but other studies of the same tasks have not (45,47). Our data are consistent with a recent meta-analysis of working memory data (48) that found COMT Val158Met effects were significantly different and in opposing directions in patients and control subjects, with, respectively, Met158 and Val158 being associated with better performance. Those behavioral findings were interpreted in terms of an inverted-U curve model, which is discussed further later in the present article.

More important, a significant interaction between the effects of genotype and diagnostic group was also evident at the level of regional activation, even after controlling for their effects on task performance. In the right peri-Sylvian region comprising adjacent parts of the frontal and parietal operculum and the middle temporal gyrus, Val158 had opposite effects on activation in patients and healthy volunteers, being associated with weaker activation (compared with Met158) in healthy volunteers but greater activation in patients. Also in healthy volunteers, the Met158 allele has previously been associated with greater activation in the hippocampus, amygdala, thalamus, and ventrolateral prefrontal cortex during visual affective stimuli (49,50). We cannot exclude the possibility that the greater activation we detected in Met158/Met158 healthy volunteers was related to affective processing, although this is unlikely given that 1) our result was in a different brain region, 2) VF primarily elicits executive processing, 3) this task involved emotionally neutral stimulus (letter cues), and 4) in general, the words generated were emotionally neutral nouns (e.g., table, tree, etc.). This difference between healthy volunteers and patients in the effect of COMT Val158Met genotype is of particular interest in relation to differential frontaltemporal activation in schizophrenia, because it raises the possibility that the distribution of COMT genotypes within samples of patients and healthy volunteers could influence the pattern of group differences. Ideally, group comparisons would control for COMT status (14). This is also the first evidence of a COMT Val58Met effect including temporal and insular areas of the brain, with effects in previous studies limited to the dorsolateral prefrontal and cingulate cortex (9,12–14). Previous studies have reported that Val158 was associated with relatively greater prefrontal activation during working memory tasks in healthy subjects (9,13,34) or attentional control (51). In our study, which involved a VF paradigm, we found that Val158 was associated with greater frontaltemporal activation in patients but the converse in healthy volunteers.

This finding indicates that variants of the same gene may have quite different effects in healthy volunteers and patients with schizophrenia. This has recently been suggested by data from structural neuroimaging studies. Frodl et al. (52) reported that a variant of the serotonin transporter gene was associated with reduced hippocampal volume in patients with depression but not in healthy volunteers. Addington et al. (53) found that a
variant of the Neuregulin1 gene was associated with a pattern of longitudinal volumetric change in patients with childhood onset schizophrenia that appeared to be different from that in healthy volunteers. However, these studies did not formally demonstrate whether the effects of these alleles in patients and healthy volunteers were significantly different. In our study, the pattern of genotype effects not only appeared to be different in each group, there was a significant genotype × group interaction.

Our analysis of the functional connectivity of the right frontal operculum provided some clues as to the basis of the group × genotype interaction in this region. The effect of COMT Val158Met genotype on its functional connectivity with the left anterior insula/frontal operculum was different in the two groups. In patients, coupling between these regions was stronger in Val158/Val158 than the Met158/Met158 subjects, whereas in healthy volunteers, the converse applied. This part of the left frontal lobe normally plays a critical role during VF, and it was in this region that activation during the task was different (p < .001, uncorrected) in patients compared with control subjects. This suggests that the difference in the effect of COMT genotype on right frontal opercular activation in the patients and control subjects may have stemmed from the greater engagement of the left frontal operculum in the patients with schizophrenia, changing its influence on the homologous region in the right hemisphere. Alternatively, the greater left frontal engagement in patients may reflect a need, locally, to activate more to produce the same response in the right homolog, given that coupling between hemispheres is increased during language tasks in schizophrenia (54). This suggests that the influence of the frontal cortex on its targets is somehow compromised by schizophrenia in the context of a genetic dose effect. Both explanatory directions of effect are anatomically plausible and indiscernible in our study because the connections between homologous prefrontal areas in the two hemispheres are especially dense (55,56). Because our functional connectivity findings failed to survive correction for multiple comparisons, they are reported descriptively and, although interesting, need replication.

In all the analyses described here, we consistently found that the heterozygous group (Val158/Met158) showed an intermediate level of activation or functional connectivity. This is in line with previous evidence of allelic codominance in the COMT Val158Met locus (1,7,57), which confirms that this polymorphism has a highly relevant effect in modulating COMT’s activity, even though other polymorphisms in the gene may also contribute (58).

Functional MRI cannot directly measure dopamine levels. However, because COMT metabolizes cortical dopamine, differences in the effects of COMT Val158Met genotype on brain activation in patients with schizophrenia and healthy volunteers may plausibly be related to group differences in brain dopaminergic activity. Abnormal dopaminergic function is a fundamental pathophysiologic feature of schizophrenia, with robust in vivo evidence of increased dopamine availability and synaptic release in the striatum (reviewed in 59,60). This striatal dopaminergic overactivity appears to perturb cortical function, as it is correlated with abnormal cortical activation during executive tasks (26), and there is an uncoupling of the normal relationship between striatal dopamine function and executive task performance (61,62). Indirect evidence from in vivo imaging techniques indicates that schizophrenia is associated with reduced dopamine activity in cortical areas (22–25), whereas in healthy subjects, the Val158 COMT allele is associated with reduced cortical dopaminergic tone (63).

Dopaminergic inputs modulate the efficiency of cortical function, mainly through effects on D1 receptors (42,64). This tuning of cortical function can be represented in an inverted-U shaped curve (Figure 3), such that either too little or too much dopaminergic activity impairs cortical function, manifest behaviorally as poorer performance (48) and physiologically as increased activation for a given level of performance (or lower “efficiency”) (42,64). Following this model, because of the putatively lowered cortical dopaminergic tone in schizophrenia, patients lie far to the left of the apex of this curve, such that patients with the Met158/Met158 genotype (who metabolize dopamine less effectively) have dopamine levels closer to the optimum for “efficient” cortical activation than patients with Val158/Val158. Healthy volunteers, whose cortical dopaminergic tone is not reduced, may lie just to the right of the apex of the curve. Healthy volunteers with the Val158/Val158 genotype may thus have a level of cortical dopaminergic activity that is closer to optimum for efficient functioning than healthy volunteers with Met158/Met158 and patients with either genotype (Figure 3). The contrasting effects of COMT genotype on activation in the right peri-Sylvian cortex in patients and healthy volunteers may thus be related to reduced dopamine activity in this region in schizophrenia or in the left frontal operculum/anterior insula, which was differentially activated and differentially coupled to this region in patients and control subjects.

Because all our patients were receiving antipsychotic medication, which has an antagonistic effect on central dopamine receptors, the possibility that this contributed to the group differences in the effect of COMT Val158Met genotype on activation must also be considered. However, there was no difference in the dosage, duration, or type of antipsychotic treatment between the subgroups of patients with different COMT Val158Met genotypes, and activation in the right peri-Sylvian region was not correlated...
with any of these variables. Furthermore, covarying for medication variables had no effect on the group \( \times \) genotype interaction in the right peri-Sylvian region or on the regions functionally connected to it, except for a difference between patients and healthy volunteers in the coupling of activity in the right frontal operculum with that in the caudate nuclei. The latter covaried with the duration of treatment, suggesting that antipsychotic medication alters the functional connectivity between these regions, which is consistent with its prominent effects on striatal D2 receptors (65,66). The potential influence of subjects’ sex is of particular interest because sexually dimorphic effects of \( \text{COMT} \) on dopamine levels, behavior, and susceptibility to schizophrenia has been reported (7,67,68). Nevertheless, introducing sex as well as IQ, handedness, years of education, and ethnicity as covariates of no interest did not alter the results.

In conclusion, these data suggest that the effect of variation in the \( \text{COMT} \) gene on regional brain function during executive processing is different in patients with schizophrenia compared with healthy individuals. The latter may reflect altered dopamine function in schizophrenia, although interactions between \( \text{COMT} \) status and other effects of the disorder or risk factors for the disorder (such as other risk genes) may also contribute.

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Supplementary material cited in this article is available online.

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