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A Gene–Brain–Cognition Pathway: Prefrontal Activity Mediates the Effect of *COMT* on Cognitive Control and IQ

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A core thesis of cognitive neurogenetic research is that genetic effects on cognitive ability are mediated by specific neural functions, however, demonstrating neural mediation has proved elusive. Pairwise relationships between genetic variation and brain function have yielded heterogeneous findings to date. This heterogeneity indicates that a multiple mediator modeling approach may be useful to account for complex relationships involving function at multiple brain regions. This is relevant not only for characterizing healthy cognition but for modeling the complex neural pathways by which disease-related genetic effects are transmitted to disordered cognitive phenotypes in psychiatric illness. Here, in 160 genotyped functional magnetic resonance imaging participants, we used a multiple mediator model to test a gene–brain–cognition pathway by which activity in 4 prefrontal brain regions mediates the effects of *catechol-O-methyltransferase* (*COMT*) gene on cognitive control and IQ. Results provide evidence for gene–brain–cognition mediation and help delineate a pathway by which gene expression contributes to intelligence.

Keywords: cognitive control, cognitive neurogenetics, *COMT*, fMRI, IQ

Introduction

New research has taken root at the intersection of cognitive neuroscience and behavioral genetics (Goldberg and Weinberger 2004; Hariri and Holmes 2006; Meyer-Lindenberg and Weinberger 2006; Green et al. 2008). Central hypotheses of this cognitive neurogenetic research predict that effects of specific genes on specific cognitive phenotypes are mediated by specific brain functions (Goldberg and Weinberger 2004; Green et al. 2008). However, to our knowledge, neural mediation has not yet been demonstrated for any significant effect of a gene on a cognitive phenotype. Pairwise relationships between genetic variation and brain function have yielded largely heterogeneous findings to date (Winterer and Weinberger 2004; Baker et al. 2005; Bertolino et al. 2006; Winterer et al. 2006; Tan et al. 2007; Bishop et al. 2008; Green et al. 2008; Congdon et al. 2009; Mier et al. 2010; Krach et al. 2010; Stokes et al. 2011). These heterogeneous findings (a specific set of such findings is considered below) indicate that a multiple mediator modeling approach may be better suited to account for complex relationships involving function at multiple brain regions. To achieve the goal of testing mediation, it is important to establish 1) which brain structures/areas produce a cognitive function and 2) which genes have specific effects on those brain regions. Psychological phenotypes related to intelligence, including cognitive control (CC) and IQ, show strong genetic influence (Posner and Rothbart 2007; Butcher et al. 2008) and are reliably associated with specific prefrontal brain regions (Desimone and Duncan 1995; Smith and Jonides 1998; Duncan et al. 2000; Kane and Engle 2002). These phenotypes are disordered in schizophrenia (Egan et al. 2001; Diaz-Asper et al. 2008), and plausible molecular genetic mechanisms link activity in these prefrontal regions to variation at a functional polymorphism in the *catechol-O-methyltransferase* (*COMT*) gene (Egan et al. 2001; Goldman et al. 2009).

Variation at the Val158Met polymorphism of the dopamine-related *COMT* gene has been the target of much interest in the cognitive neurogenetics of higher-level cognition. The *COMT* gene encodes the COMT enzyme, which catabolically terminates the activity of dopamine in all dopaminergic synapses. In prefrontal cortex (PFC), COMT enzymatic activity is thought to be particularly important for determining dopamine availability because the dopamine reuptake transporter protein, which is a primary determinant of dopamine availability elsewhere in the brain, shows relatively sparse expression in PFC (Pozzi et al. 1994; Lewis et al. 2001; Matsumoto et al. 2003). Dopaminergic neuronal activity in PFC is a known biological substrate for intelligence-related phenotypes, including CC (Luciana et al. 1992; Braver and Cohen 2000; Kane and Engle 2002). *COMT* variation correlates with prefrontal activation during executive cognition (Mier et al. 2010) and with CC performance and IQ, though behavioral effect sizes are generally small (Posner and Rothbart 2007; Barnett et al. 2008). Well-validated measures of CC and IQ make these cognitive phenotypes suitable targets for cognitive neurogenetic investigation (Wechsler 1999; Bush and Shin 2006; Posner and Rothbart 2007).

COMT Met/Met homozygotes seem to approximate optimal dopamine availability, that is, the peak of the characteristic inverted U-shaped function describing the effect of dopamine dosage on cognitive performance (Cools and Robbins 2004; Meyer-Lindenberg et al. 2005). In contrast, lower baseline dopamine availability in *COMT* Val allele carriers appears to be a disadvantage for CC function, putatively due in part to diminished signal-to-noise ratio in PFC (Mattay et al. 2003; Meyer-Lindenberg et al. 2005; Apud et al. 2007). Treatments that increase dopamine availability in PFC improve executive function in *COMT* Val/Val homozygotes (Mattay et al. 2003; Meyer-Lindenberg et al. 2005; Apud et al. 2007). These treatments also influence the level of neural activity in prefrontal regions associated with intelligence-related executive function, including CC (Apud et al. 2007; Bush et al. 2008).

Several investigations have found decreased neural activation associated with the *COMT* Met allele (Winterer and Weinberger 2004; Bertolino et al. 2006; Tan et al. 2007; Bishop et al. 2008),

including evidence that number of Met alleles (load) is associated with decreased blood oxygen level–dependent (BOLD) response in prefrontal regions during a 2-back working memory task (Bertolino et al. 2006). However, several other reports indicate increased neural activity associated with the Met allele (Baker et al. 2005; Winterer et al. 2006; Congdon et al. 2009; Krach et al. 2010; Stokes et al. 2011), including increased prefrontal activation in Met homozygotes compared with Val carriers during a visual oddball task. The heterogeneity of cognitive neurogenetic findings owes to the complexity of genetic expression. For *COMT* in particular, there is evidence that pleiotropic effects on prefrontal function contribute to heterogeneous neural responses within PFC (Mier et al. 2010). This heterogeneity indicates that a multiple mediation approach may be best equipped to explain the effect of *COMT* on prefrontal cognition by integrating nonuniform activation in multiple prefrontal regions.

Here, we tested *COMT* Met effects on cognition using a multiple mediator model equipped to account for complex associations with brain function in separate a priori prefrontal regions. Specifically, we tested the hypothesis that 4 prefrontal regions implicated in CC mediate the relationship between *COMT* Met allele load and behavioral measures of CC and IQ.

Materials and Methods

Participants and Tasks

Participants were 160 healthy right-handed native English speakers (131 males, mean age = 22.1 years) recruited from the Yale University and New Haven communities and providing informed consent prior to participation in behavioral and functional magnetic resonance imaging (fMRI) sessions as well as consent for genomic DNA to be collected from saliva samples. The procedure was approved by the Yale University School of Medicine Human Investigation Committee.

Tasks

Participants performed the Multi-Source Interference Task (MSIT; Fig. 1) during event-related fMRI. On each MSIT trial, participants pressed 1 of 3 buttons to indicate which of 3 concurrently presented digits differed numerically from the other 2. On Incongruent trials, attentional conflict was elicited by the presence of incorrect number choices that differed from the 2 other numbers with respect to position and size. MSIT was selected because it is a well-validated measure of CC phenotype, reliably recruits a predictable set of executive function-related brain regions, including in PFC, for a priori regional hypotheses (Bush et al. 2003; Bush and Shin 2006), and because the strength of neural recruitment during this task is influenced by changes in dopaminergic function with methylphenidate treatment (Bush et al. 2008). The demonstrated consistency of MSIT in recruiting the same brain regions across individuals (Bush et al. 2003; Bush and Shin 2006) was particularly important for the mediation analysis we used in this study because we defined each individual's regions of interest (ROIs) based on overlap with static anatomical atlas-defined regions. Thus, it was a priority to minimize individual variation with respect to the regions that were recruited for the task. CC has been identified as a key substrate of intelligence, both cognitively and biologically (Kane and Engle 2002), so brain activity supporting CC is likely to also support IQ performance. Outside the scanner, participants were administered the Wechsler Adult Scale of Intelligence (WASI) abbreviated full-scale IQ measure (Wechsler 1999) comprising 4 subtests (Vocabulary, Similarities, Block Design, and Matrix Reasoning).

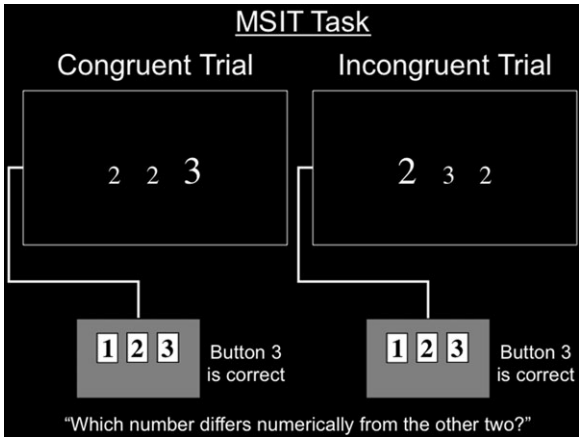

Figure 1. Example MSIT Congruent and Incongruent trials.

Functional Magnetic Resonance Imaging

Scanning was performed on a 3-T Allegra System (Siemens, Erlangen, Germany) to collect whole-brain T_2^*-weighted BOLD functional images (asymmetric spin-echo echo-planar sequence; whole-brain repetition time, TR = 2000 ms; echo time = 25 ms; field of view = 256 mm; flip angle = 80°; matrix = 64 × 64; axial slices 4 mm thick). The functional run comprised 183 sequential whole-brain volumes (32 contiguous slices). Ninety-six task trials were presented for 1750 ms during the functional run, with jittered intertrial intervals, across a range from 250 to 4250 ms in steps of 2000 ms (1 TR). The scanning run began with an unanalyzed fixation period equal to 3 TRs, which allowed the scanner to reach steady state.

fMRI data processing was carried out using FEAT (fMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The following prestatistics processing was applied: motion correction using MCFLIRT (Jenkinson et al. 2002); spatial smoothing using a Gaussian kernel of full-width at half-maximum 5 mm; grand-mean intensity normalization of the entire 4D data set by a single multiplicative factor; high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s). ICA-based exploratory data analysis was carried out using MELODIC (Beckmann and Smith 2004), in order to investigate the possible presence of unexpected artifacts or activation. Registration to high-resolution structural and, subsequently, standard space images was carried out using FLIRT (Jenkinson and Smith 2001; Jenkinson et al. 2002). Higher level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 and stage 2 with automatic outlier detection (Beckmann et al. 2003; Woolrich et al. 2004; Woolrich 2008). Z (Gaussianized T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a minimum (corrected) cluster significance threshold of $P = 0.01$ (Worsley 2001).

Genotyping

DNA from each participant was genotyped for the $COMT^{Val158Met}$ single nucleotide polymorphism (SNP). Saliva collection kits [Oragene DNA, Kanata, Ontario, Canada] were used to extract genomic DNA with yields of 10–50 μg of DNA from each sample. Following genomic DNA extraction and quantification via UV absorption at 260 nm, polymerase chain reaction (PCR) restriction fragment length polymorphism analysis with horizontal gel electrophoresis was used to determine $COMT^{Val158mMet}$ genotype following published methods (Daniels et al. 1996; Egan et al. 2001; Bertolino et al. 2004, 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-μL PCR. A "touchdown" PCR cycling regimen and the addition of dimethyl sulfoxide (10% final v:v) were 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 2-h restriction digestion with NlaIII (NEB). Gel electrophoresis for 6 h at 50 V in 4% Metaphor

agarose followed by staining in ethidium bromide was used to resolve and visualize the 169 bp (G or Valine allele) fragment from the 122 + 47 bp (A or Methionine allele) fragments. Genotype frequencies in our sample were 45 Val/Val, 76 Val/Met, and 39 Met/Met, in Hardy–Weinberg equilibrium with population frequencies for the population generally and for Caucasians of European descent (our sample was 92% Caucasian).

Mediation Models

Mediation modeling was done in AMOS 16 (SPSS Inc., Chicago, IL), a structural equation modeling add-on to the SPSS statistical software. Inputs were genotype data, fMRI data extracted from FSL, and behavioral performance data from all participants. Bias-corrected bootstrapping 95% confidence intervals were calculated over 500 bootstrap samples. Covariances were explicitly modeled between each mediator ROI such that the shared variance was partialled out (rather than double counted) in calculating the indirect effect of *COMT* Met on MSIT and IQ. The unique (unshared) variance of each mediator ROI was used to calculate individual path coefficients. This was done to ensure that each ROI's contribution to the mediation was not driven by covariance/colinearity with other ROI(s). The independent variable in the mediation model was Methionine (Met) allele-load at the $COMT^{Val158Met}$ SNP. Four prefrontal brain regions that are involved in CC and rely on COMT enzymatic dopamine clearance were selected a priori as mediators in the pathway. Anterior cingulate cortex (ACC), superior frontal gyrus (SFG), medial frontal gyrus (MFG), and inferior frontal gyrus (IFG) were selected because Bush and colleagues (Bush et al. 2003; Bush and Shin 2006) have reported these as areas of reliable PFC recruitment for CC during the MSIT.

Lateral PFC, inclusive of regions of the 3 selected frontal gyri, was a broad area of *a* priori interest because activity in this area has been reported to vary as a function of *COMT* Met allele load (Bertolino et al. 2006). Lateral PFC and ACC were also areas of interest because they have been widely implicated in supporting intelligence (Duncan et al. 2000; Gray et al. 2003). We focused on PFC because the virtual absence of functional dopamine transporters in PFC makes COMT activity a decisive factor in dopamine availability within this region (Pozzi et al. 1994; Lewis et al. 2001; Matsumoto et al. 2003). Studies of *COMT* knockout mice (Gogos et al. 1998) as well as pharmacological manipulations employing COMT inhibitors show regionally specific prefrontal effects on dopamine levels (Tunbridge et al. 2004) and on cognitive performance in animal models (Khromova et al. 1997; Liljequist et al. 1997) and in humans (Gasparini et al. 1997; Apud et al. 2007). Regions were defined anatomically using the Harvard–Oxford Cortical Structural Atlas in FSL. The anatomical regions were then masked by group-level activations for the MSIT Incongruent > Congruent contrast to produce the ROIs. In the path model, each region is represented by activity averaged across that ROI for each subject. The dependent variables were MSIT Incongruent minus Congruent response time (RT) and WASI estimated full-scale IQ. We modeled the mediated relationships between *COMT* Met allele load and MSIT (i.e., the indirect path from *COMT* Met allele load to MSIT performance via activation in our ROIs). The model also included the unmediated relationship (direct path) from *COMT* Met to MSIT. We then used the same model to predict out of scanner IQ (substituting IQ for MSIT in the model).

Results

Behavioral

The Met allele was significantly related to cognitive performance. This relationship held for RTs on the MSIT performed during fMRI ($r = 0.18$, $P < 0.01$) and for the IQ test performed outside the scanner ($r = 0.24$, $P < 0.01$). RT differences for Incongruent minus Congruent trials, reflecting the efficiency of CC processes to resolve executive conflict, showed significant inverse correlation with Met allele load ($r = -0.18$, $P = 0.01$; average RT difference for Val/Val = 353 ms, Val/Met = 337 ms, and Met/Met = 293 ms). RT is the primary measure of MSIT performance (Bush et al. 2003) because accuracy is typically near ceiling, as it was in the present study (average response accuracy for Val/Val = 93.49%, Val/Met = 95.63%, and Met/Met = 95.61%), however, we observed a positive correlation between Met allele load and accuracy ($r = 0.13$, $P = 0.04$). This was driven by a difference in accuracy between Val/Val homozygotes and Met allele carriers, which approached significance ($P = 0.06$). IQ was significantly correlated with Met allele load ($r = 0.24$, $P < 0.01$; average IQ for Val/Val = 123, Val/Met = 124, and Met/Met = 131). IQ was inversely correlated with MSIT Incongruent minus Congruent RT differences ($r = -0.25$, $P < 0.001$), indicating that subjects who resolved conflict more efficiently on MSIT also had higher IQ on average.

Functional Magnetic Resonance Imaging

CC in the MSIT task was assayed by the MSIT Incongruent > Congruent contrast. This contrast revealed recruitment of brain regions previously linked to executive function (Table 1), including within our ROIs in ACC, SFG, MFG, and IFG.

This finding was consistent with our prediction based on the prior reports of Bush et al. (Bush et al. 2003; Bush and Shin 2006). Whole-brain parametric analysis for Met allele load revealed extensive activation increases (Table 2), including in ACC and MFG, as well as activation decreases (Table 3), including in SFG and IFG. The ROIs we investigated were selected a priori because they are reliably recruited for CC during MSIT (Bush and Shin 2006; Bush et al. 2008) and located in prefrontal cortical regions where COMT enzymatic activity determines dopamine availability (Lewis et al. 2001). Variation in neural function within these regions is thus a plausible consequence of *COMT* variation.

We constructed a mediation model representing our main hypothesis that *COMT* Met effects on cognition are mediated by activity in the 4 prefrontal ROIs. Path analysis of the mediation model revealed that activity in the 4 prefrontal ROIs for the Incongruent > Congruent contrast significantly mediated the *COMT* Met allele-load effect on MSIT performance (indirect effect = 0.13, $P < 0.01$; Fig. 2; Supplementary Table 1 shows zero-order correlations for modeled variables). To test whether CC-related brain function mediates the effect of *COMT* Met on IQ, we replaced MSIT performance with out of scanner IQ in the model. Path analysis revealed significant mediation by the 4

Table 1
Whole-brain contrast MSIT Incongruent > Congruent

Anatomical region	BA	*Z*-stat	Talairach coordinates			Cluster size
			x	*y*	*z*	Number of voxels
Left superior parietal lobule	40	13.4	−40	−41	46	377
Right superior parietal lobule	40	12.9	42	−44	48	368
Left middle occipital gyrus	37	12	−41	−64	3	543
Left anterior cingulate gyrus	32	12.3	−3	13	38	489
Left MFG	9	11.8	−30	4	52	351
Right IFG	19	11.4	48	−58	−2	369
Right insula	13	12.9	32	22	0	361
Left IFG	6	11.9	−50	4	33	318
Right IFG	9	12.2	50	6	26	372
Left SFG	6	11.8	−13	10	53	151
Right MFG	6	10.5	30	−3	48	137
Right lentiform nucleus	NA	10.1	13	2	2	36

Note: All results cluster thresholded at $Z > 2.3$, cluster $P < 0.0001_{corrected}$. BA, Brodmann area; NA, not applicable.

ROIs in the IQ model (indirect effect = 0.11, $P < 0.01$). This finding supports our main mediation hypothesis and is consistent with the prediction that CC function in PFC supports IQ performance. For both MSIT and IQ, increased Met allele load and better performance were associated with increased activation in 2 of the mediator regions, ACC and MFG (indicated by positive *COMT*-mediator path coefficients), and with decreased activation in the other 2 regions, SFG and IFG (negative *COMT*-mediator path coefficients). Single mediator models constructed for each of the a priori mediator ROIs individually (for both MSIT and IQ), revealed no significant single mediation pathway ($P > 0.1$ for all indirect effects).

Because the possibility of undetected covariates of mediator variables is an important theoretical concern for mediation models (see Supplementary Discussion), we tested for other brain regions in which activity covaried with activity in our 4 mediator ROIs. For each ROI, average BOLD response across all voxels of the ROI over the time course of the MSIT task was included as an experimental variable in the design matrix to identify regions that covaried with the ROI, first at the individual subject level and then at the group level. This allowed us to test for activity outside the 4 a priori mediator regions that was predicted by activity within these 4 regions. Clusters were identified in left caudate and right putamen that covaried with the ACC ROI and clusters in left precentral gyrus and right superior temporal gyrus covaried with the IFG ROI (Supplementary Table 2). We included activity in these identified clusters as mediators in the model to test whether the mediation effect was unique to the a priori mediator ROIs. None of these clusters, when added to the model as an additional mediator, explained any additional variance. When these clusters were substituted for the ROI with which they covaried, less variance was explained by the model and, in each case, the indirect effect was no longer significant. In addition, entering all of these alternative clusters into the MSIT and IQ models simultaneously yielded a nonsignificant indirect effect ($P > 0.1$ for both indirect effects). This evidence indicates that covarying brain function outside our modeled mediator regions does not explain the mediation effect and supports the

Table 2
Activation increases (between subjects) identified by whole-brain parametric analysis of *COMT* Met allele load

Anatomical region	BA	*Z*-stat	Talairach coordinates			Cluster size
			x	*y*	*z*	Number of voxels
Left supramarginal gyrus	40	6.8	−44	−41	43	197
Right supramarginal gyrus	40	6.3	45	−39	43	173
Left MFG	6	5.6	−32	−2	50	158
Right middle occipital gyrus	19	5.4	48	−58	−7	323
Left middle occipital gyrus	37	5.3	−37	−63	8	329
Left cingulate gyrus	32	5.9	−1	14	42	322
Right MFG	6	5.3	30	0	48	95
Right angular gyrus	39	6.2	33	−60	37	88
Left precuneus	7	6.4	−12	−68	48	66

Note: All results cluster thresholded at $Z > 2.3$, cluster $P < 0.0001_{corrected}$. BA, Brodmann area.

Table 3
Activation decreases (between subjects) identified by whole-brain parametric analysis of *COMT* Met allele load

Anatomical region	BA	*Z*-stat	Talairach coordinates			Cluster size
			x	*y*	*z*	Number of voxels
Left IFG	9	7.4	−49	4	33	435
Right posterior superior parietal	7	5.7	29	−53	42	653
Left posterior superior parietal	7	5.7	−30	−53	42	628
Right insula	13	5.3	41	11	2	238
Right IFG	44	5.6	49	7	21	123
Left SFG	6	5.6	−10	8	54	158
Right SFG	6	5.3	24	10	48	95
Right MFG	46	5	49	38	19	59
Left middle occipital gyrus	19	4.5	−36	−81	14	42

Note: All results cluster thresholded at $Z > 2.3$, cluster $P < 0.0001_{corrected}$. BA, Brodmann area.

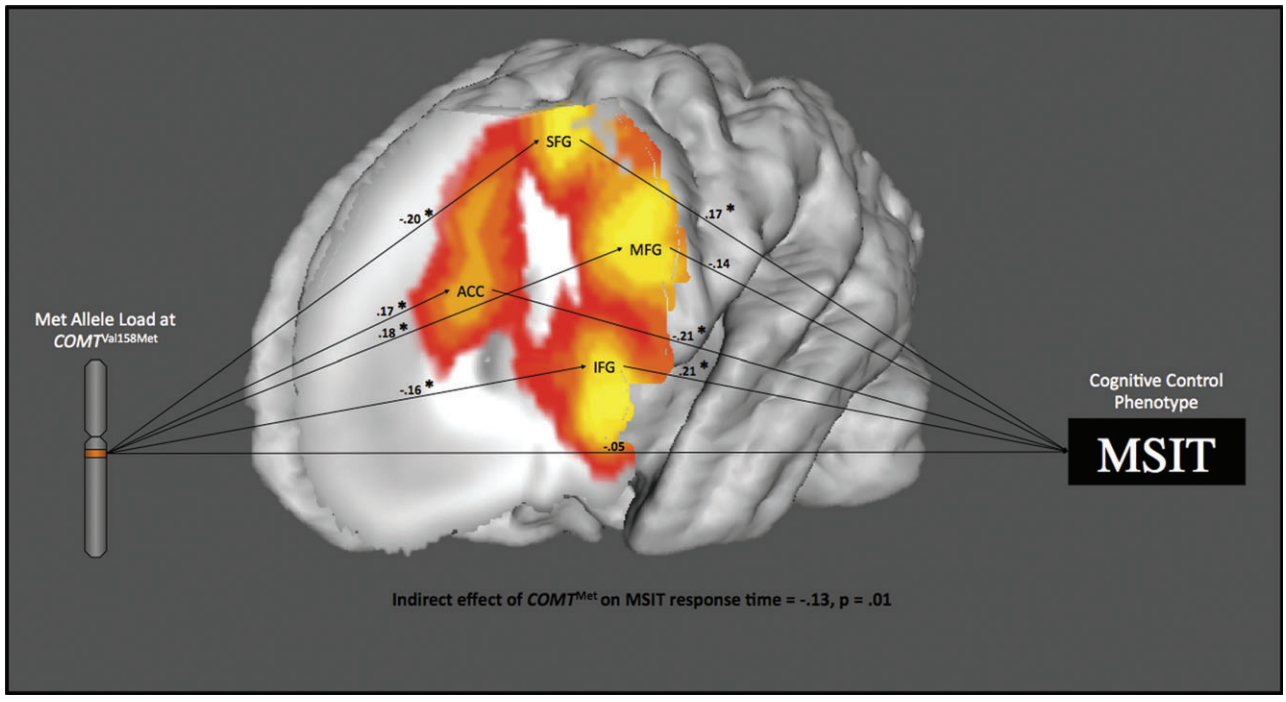

Figure 2. Indirect (via activity in 4 mediator brain regions) and direct paths from *COMT* Met allele load to MSIT RT, with path coefficients indicated.

particular role of the selected ROIs in mediating the effects of *COMT*^{Val158Met} genotype on CC and IQ. Psychophysical interaction analyses, in which the interaction between activity in each ROI and a task vector was included as an experimental variable in the design matrix, did not reveal any additional covaried clusters significant at the $Z > 2.3$, cluster $P < 0.01$ threshold.

Discussion

The finding that activity in prefrontal brain regions mediates the effects of *COMT* Met on CC and IQ represents new evidence for neural mediation of genetic effects on cognitive ability. To our knowledge, 3 studies, each investigating anxiety-related personality traits, have reported analyses to investigate gene–brain–cognition mediation effects. Two of these did not find a significant mediation effect (Buckholtz et al. 2008; Furmark et al. 2008) and one reported mediation of a non-significant gene–phenotype direct effect (Fakra et al. 2009). Each of these studies focused on a single amygdala-related neural variable, whereas no work to our knowledge has tested multiple neural variables via multiple mediation modeling. Additionally, no work has yet tested neural mediation of genetic effects on cognitive ability. The present neural mediation findings help to elucidate a pathway by which gene expression contributes to intelligent cognition, empirically constraining the likely causal pathway through which variation in the *COMT* gene comes to influence CC and IQ in healthy cognition and, putatively, in schizophrenia. Notably, this pathway appears to involve multiple contributing brain regions, some showing greater activation and others less activation related to better performance.

The particular brain regions we included as mediators in our model have been reliably indicated in studies of executive function (Duncan et al. 2000; Kane and Engle 2002; Bush et al. 2003; Gray et al. 2003). The pattern of genotype- and performance-related individual differences in activity in these regions may be due to differences in regional physiology. However, it may also be related to differences in the roles these 4 regions play in executive function, as indicated by a recent meta-analysis of functionally dissociable superior, middle, and inferior zones within PFC (Volle et al. 2008).

IFG has been reliably implicated in maintaining pertinent information over the course of complex cognitive tasks and specifically in maintaining task constraints or rules (Brass et al. 2005). Maintaining the specific rules of the MSIT task (e.g., numerical differences matter and other differences between numbers do not) is critical for successful performance and is likely to rely on IFG. Decreased IFG recruitment in Met carriers may be explainable in terms of the dopamine signal-to-noise hypothesis (Winterer and Weinberger 2004; Bertolino et al. 2006; Savitz et al. 2006; Winterer et al. 2006; Apud et al. 2007). This hypothesis posits that the *COMT* Val allele plausibly contributes to a diminished signal-to-noise ratio in PFC and possibly less efficient maintenance of information (e.g., MSIT task constraints) in IFG.

SFG plays a fairly general role in executive function but its involvement appears to be triggered when an individual exerts greater effort for a more demanding executive task (du Boisgueheneuc et al. 2006). ACC and MFG are both broadly implicated in executive function and especially CC, with ACC being particularly important for CC, and MFG being particularly important for mentally manipulating information (e.g., MSIT number stimuli representing different sizes, positions, and numeric values). These regions are reliably recruited for executive function, even at relatively low levels of task complexity (Kerns et al. 2004). The ability to recruit these regions more strongly appears to confer a general advantage for executive function (Gray et al. 2003). Speculatively, this advantage may diminish the demand-triggered recruitment of SFG in individuals for whom a task is less difficult. This interpretation is consistent with the present data and with our prior research demonstrating better executive function associated with increasing ACC and MFG recruitment between individuals (Gray et al. 2003). Nonetheless, the present data do not provide direct evidence to support this interpretation.

Gene–Brain–Cognition Pathways

Cognitive neurogenetics—also frequently called imaging genetics—has typically examined individual pairwise relationships (e.g., gene–brain and gene–cognition relationships) rather than using integrated gene–brain–cognition models to test neural mediation of genetic effects on cognition. This may be due in part to the difficulty of obtaining the large numbers of fMRI participants required to power path analyses. In spite of pragmatic challenges, mediation models have the potential to be more informative than pairwise relationships, not only because they can test neural mediation, but because they can do so in a way that accounts for the complexity of multiple contributing brain regions. As cognitive functions typically involve multiple brain regions, genetic variation is likely to influence multiple brain regions en route to a cognitive phenotype. Characterizing the relative contributions of each area within a single model may help to reconcile heterogeneity among separate pairwise relationships.

In general, mediation models are more rigorous than individual pairwise relationships in that they require at least 3 concurrent relationships between at least 3 variables rather than 1 relationship between 2 variables. They provide a useful framework for directional/causal hypotheses because they conceptually articulate the gene-to-brain-to-cognition pathway. This is usually appropriate because effects generally transmit from genes to brain and cognition rather than vice versa (see Supplementary Discussion).

Recruitment Capacity and/or Efficiency

Heterogeneous associations of prefrontal activation with *COMT* genotype and cognitive performance (Bertolino et al. 2006; Winterer et al. 2006; Green et al. 2008) are situated within a broader paradox in the cognitive neuroscience literature concerning the interpretation of activation differences between subjects (Neubauer and Fink 2009). Some studies of individual differences in executive function have found that increased prefrontal activity (generally interpreted as greater recruitment capacity) is associated with better executive performance (Gray et al. 2003; Osaka et al. 2003; Neubauer et al. 2004; Doppelmayr et al. 2005; Lee et al. 2006). This evidence appears consistent with cognitive aging research that has indicated increased cortical recruitment with advanced age and putatively diminished neural efficiency, including bilateral recruitment for tasks that are more lateralized in younger individuals (Cabeza et al. 2002; Grady et al. 2006). However, a separate set of brain imaging evidence has demonstrated that

in at least some instances decreased prefrontal activity (generally interpreted as greater efficiency) leads to better executive performance (Haier et al. 1988; Rypma and D'Esposito 1999; Rypma et al. 2002; Haier et al. 2003). In our participants, regionally distinct increases and decreases in PFC activity were associated with better performance between individuals. Specifically, increasing and decreasing regions of prefrontal activation in the Met allele-load parametric analysis, and the presence of both positive and negative *COMT*-mediator path coefficients, indicate that putatively greater efficiency and putatively higher capacity recruitment occurred during the MSIT task in separate regions tied to performing the task (Bush and Shin 2006).

Reported associations between *COMT* Met and brain activity have been both positive (Baker et al. 2005; Winterer et al. 2006; Congdon et al. 2009; Krach et al. 2010; Stokes et al. 2011) and negative (Winterer and Weinberger 2004; Bertolino et al. 2006; Tan et al. 2007; Bishop et al. 2008), and some studies have found positive and negative associations in separate frontal regions within the same subjects (de Frias et al. 2009; Sambataro et al. 2009). Heterogeneity of associations with *COMT* is consistent with evidence that *COMT* has pleiotropic effects and that both the *COMT* Met and the *COMT* Val alleles may confer advantages for subsets of prefrontal cognition (Mier et al. 2010). Linking intelligence–related phenotypes to specific SNPs is also greatly complicated by the vast polygenicity of intelligence (Davies et al. 2011), and the fact that different subsets of the SNPs that contribute to intelligence may have different affects across individuals. Perhaps most importantly, studies of *COMT* genotype effects on neurocognition have used a variety of tasks and experimental paradigms that require different cognitive operations, which may account for many of the reported differences in regional brain activity.

Additional elements of complexity are also important to consider with respect to heterogeneous *COMT* haplotypes. In particular, several additional loci within the *COMT* gene appear to influence the effect of the Val158Met (rs4680) SNP (Meyer-Lindenberg et al. 2006), including the rs2097603 P2 promoter region SNP and the rs165599 SNP in the 3′ region. Differing *COMT* haplotypes in which the Val158Met SNP occurs result in variations in mRNA secondary structure and subsequent differences in COMT protein translation (Nackley et al. 2006). Although haplotype effects are an important consideration, we focused our investigation on the Val158Met SNP because this is the *COMT* SNP that appears to have the strongest effect (Meyer-Lindenberg et al. 2006) and because this is the SNP that has been, by far, the most widely studied. One of our purposes in this investigation was to apply a multiple mediation analysis to test a central and widely proliferated assumption in the cognitive neurogenetics literature. Nonetheless, a full consideration of the Val158Met SNP must ultimately account for haplotype context, and the influence of other *COMT* SNPs on the neurally mediated indirect effects Val158Met SNP on executive function is an important area for future research. A mediation modeling approach in which additional *COMT* SNPs are tested as moderators may be useful to advance this issue.

Given the complexity of *COMT* genotype and the heterogeneity of associations with brain activity, it is unlikely that any single mechanism explains all *COMT* effects. Strong empirical support has aggregated around the neural efficiency account of cognitive performance and the related dopamine signal-to-noise hypothesis (Winterer and Weinberger 2004; Bertolino et al. 2006; Tan et al. 2007; Bishop et al. 2008). However, a unitary account of the Met allele load producing more efficiency in PFC does not appear sufficient to explain all the data. Much of the activation we observed is consistent with the neural efficiency account (Winterer and Weinberger 2004; Bertolino et al. 2006), including Met-related activation decreases in Brodmann areas 9 and 46 of PFC (Table 3). However, the overall pattern of the data, including Met-related activation increases in Brodmann areas 6 and 32 (Table 2), supports a growing body of evidence that better efficiency and greater recruitment capacity both contribute to prefrontal cognition (Neubauer and Fink 2009). Multiple mediation modeling approaches are likely to be helpful in characterizing complex effects of *COMT* and other candidate genes on brain and cognition.

Conclusion

The data indicate a complex pathway for effects of the *COMT* gene on CC and IQ via regionally distinct prefrontal activation. This result represents proof of concept for neural mediation modeling of a significant genetic effect on cognition and suggests that judicious application of multiple mediator models has informative potential for cognitive neurogenetics.

Supplementary Material

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

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