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Influence of the *COMT val*$^{108/158}$*met* polymorphism on Continuous Performance Task Indices

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Abstract

The Continuous Performance Task (CPT) is a widely-used measure of sustained attention and impulsivity. Deficits in CPT performance have been found in several psychiatric disorders, such as Attention-Deficit/hyperactivity disorder (ADHD) and schizophrenia. Molecular genetic studies of CPT performance are currently limited and have generally revealed inconsistent findings. The current study tested the associations of the *COMT* val$^{108/158}$met polymorphism with AX-CPT indices (i.e., omission and commission errors, d', and lnβ), as well as the variability of these indices across blocks, in a sample of clinic-referred and non-referred children (N = 380). We found significant associations between *COMT* and variability in the Signal Detection Theory (SDT) indices d' and lnβ across blocks, as well as a statistical trend for association between *COMT* and commission errors. Higher externalizing psychopathology was associated with general impairment on AX-CPT performance, and for some indices (i.e., d' variability and lnβ variability) the effect of *COMT* was stronger at higher levels of psychopathology. Our findings support the role of *COMT* in components of CPT performance and highlight the potential utility of using SDT indices, particularly in relation to variability in performance. Moreover, our results suggest that for some indices the effect of *COMT* is stronger at higher levels of externalizing psychopathology. Our study yields some preliminary insights regarding the neurobiology of CPT performance, which may elucidate the mechanisms by which specific genes confer risk for various cognitive deficits, as well as relevant disorders characterized by these deficits.

Keywords

COMT; Dopamine; Continuous Performance Task; CPT; Endophenotype; ADHD

1. Introduction

The continuous performance task (CPT) is one of the most widely used neuropsychological measures hypothesized to assess sustained attention and impulsivity (e.g., Davies & Parasuraman, 1982). In a CPT, participants view a continuous presentation of changing

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stimuli and must make a response, usually a button press, to a specified target. Distinct indices are collected to analyze different aspects of CPT performance, which have implications for the underlying cognitive mechanisms. Traditionally, commission errors (i.e., responses to non-targets) are posited to index impulsivity or deficits in inhibition, and omission errors (i.e., failures to respond to target stimuli) are believed to index inattention (Riccio, Reynolds, & Lowe, 2001). Signal Detection Theory (SDT) indices have also been increasingly used to quantify and distinguish sensitivity (d') from response bias (lnβ) (McNicol, 1972). The d' index measures the degree to which targets are successfully discriminated from nontargets and reflects attentional capacity (Swets, Tanner, & Birdsall, 1961). The lnβ index measures response style, where a tendency to over-respond (i.e., lower lnβ) indicates an impulsive, risk-taking response style and a tendency to under-respond (i.e., higher lnβ) suggests a cautious response style (Keilp, Sackeim, & Mann, 2005).

There are various versions of the CPT that differ in the type of stimuli used (e.g., numbers, letters, sounds), signal probability (e.g., proportion of target to non-target stimuli), and event rate (e.g., duration of stimulus presentation). The AX-CPT (Cohen, Barch, Carter, & Servan-Schreiber, 1999; Halperin et al., 1988; Servan-Schreiber, Cohen, & Steingard, 1996), a modified version of the classic CPT (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956), requires participants to respond to the target letter 'X', but only if it immediately follows the letter 'A' (the cue). In addition to measuring components of sustained attention and impulsivity (e.g., Davies & Parasuraman, 1982), the AX-CPT differs from simpler versions in that it also indexes components of working memory, a set of cognitive processes involved in actively maintaining and manipulating relevant information to guide goal-directed behaviors (Braver & Cohen, 2000; O'Reilly, Braver, & Cohen, 1999; van den Bosch, Rombouts, & van Asma, 1996). In particular, the AX-CPT measures context processing, a specific component in the domain of working memory that is involved in the active representation and maintenance of context information (provided by the cue stimulus 'A'), which refers to prior task-relevant information that is internally represented in such a form that it can be used to mediate appropriate behavioral responses (Braver & Cohen, 2000; Cohen et al., 1999; Servan-Schreiber et al., 1996).

Deficits in CPT performance have been reported in various complex psychiatric disorders, including Attention-Deficit/Hyperactivity Disorder (ADHD) (e.g., Losier, McGrath, & Klein, 1996) and schizophrenia (e.g., Nuechterlein & Dawson, 1984). The dorsolateral prefrontal cortex (dlPFC) has been shown to play a critical role in CPT performance (e.g., Brooks et al., 2006; Sax et al., 1999). Specifically, computational models and neuroimaging studies of AX-CPTs implicate the dlPFC in the active maintenance and regulation of context information in working memory (Barch et al., 1997; Barch et al., 2001; Braver, Barch, & Cohen, 1999; Braver & Cohen, 2000; Cohen et al., 1997; Cohen & Servan-Schreiber, 1992; Servan-Schreiber et al., 1996). Interestingly, structural and functional abnormalities in this region have been consistently found in disorders such as ADHD (e.g., Konrad & Eickhoff, 2010) and schizophrenia (e.g., Breier et al., 1992), both of which are characterized by deficits in CPT performance. For example, altered prefrontal dopaminergic neurotransmission has been implicated in the pathophysiology of ADHD (Castellanos, 1997; Davids, Zhang, Tarazi, & Baldessarini, 2003), as well as impairment in various cognitive

functions such as CPT performance (Braver et al., 1999; Gasparini, Fabrizio, Bonifati, & Meco, 1997), although the exact underlying neurobiological mechanisms are still unclear. As CPT performance has also been shown to be heritable (e.g., Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988), genes involved in regulating prefrontal function, such as the catechol-O-methyltransferase gene (*COMT*), represent promising candidates for understanding deficits in CPT performance and elucidating the etiology of relevant disorders.

COMT is predominantly expressed in the dlPFC, and COMT enzymatic activity is especially important for regulating dopamine levels in this region due to sparse expression of the dopamine transporter protein, which is a primary determinant of dopamine reuptake in most dopaminergic neurons (Matsumoto et al., 2003a, b; Sesack, Hawrylak, Matus, Guido, & Levey, 1998). *COMT* contains a widely-studied single nucleotide polymorphism (SNP) (*val*$^{108/158}$*met*) that codes for the substitution of valine (val) by methionine (met) (Lachman et al., 1996). This specific marker is highly functional, with the enzymatic activity of the val allele being three to four times higher than that of the met allele (Chen et al., 2004; Lachman et al., 1996). Accordingly, the val allele is associated with increased dopamine catabolism (Lachman et al., 1996), and the consequent lower dopamine availability in val allele carriers appears to be related to decreased efficiency in dlPFC activity, which may contribute to impairment in prefrontally-mediated cognitive functions (e.g., Meyer-Lindenberg et al., 2005) and relevant disorders such as ADHD (Eisenberg et al., 1999). Nonetheless, a recent meta-analysis suggests that there is no association between this polymorphism in *COMT* and ADHD (Gizer, Ficks, & Waldman, 2009) and the few studies thus far that have specifically examined the association between *COMT* and cognitive functions in ADHD populations have also been inconclusive (Bellgrove et al., 2005; Matthews et al., 2012; Mills et al., 2004; Taerk et al., 2004). This warrants further investigation for a better understanding of the pathophysiological mechanisms (e.g., the nature of abnormalities in prefrontal dopamine neurotransmission) underlying specific cognitive deficits in relevant disorders such as ADHD (e.g., Faraone & Biederman, 2002; Kirley et al., 2002).

There is limited research investigating the influence of *COMT val*$^{108/158}$*met* polymorphism on CPT performance and thus far, the findings have been mixed (Caldú et al., 2007; Eisenberg et al., 1999; Liao et al., 2009; MacDonald, Carter, Flory, Ferrell, & Manuck, 2007; Mills et al., 2004). Importantly, the exact nature of the role of *COMT* in cognitive function is unclear with regard to specificity. For example, there is evidence that *COMT* is related to cognitive stability that reflects the maintenance of representations in working memory in CPT performance (Stefanis et al., 2005) and that accordingly, *COMT* may be more closely associated with a specific context processing deficit measured by modified versions of AX-CPTs, rather than a more generalized cognitive deficit (MacDonald et al., 2007). These specific cognitive functions likely depend considerably on efficient prefrontal dopaminergic signaling (MacDonald et al., 2007; Seamans & Yang, 2004; Stefanis et al., 2005) and thus AX-CPT performance indices that more precisely capture these functions may be particularly informative for elucidating the role of *COMT* in cognition and relevant disorders. For instance, proficient context processing is largely reflected in the d' index (Cohen et al., 1999) and cognitive stability can be indexed by the variability in performance

across blocks of the task (Stefanis et al., 2005). Relatedly, recent evidence suggests that in children with ADHD, *COMT* specifically influences these aforementioned cognitive processes, but not other aspects of cognitive performance (e.g., updating of information) (Matthews et al., 2012), which may also suggest that the effect of *COMT* on these processes may be stronger in such disorders that are characterized by dysfunctional prefrontal dopamine neurotransmission compared to controls (del Campo, Chamberlain, Sahakian, & Robbins, 2011; Solanto, 2002; Swanson et al., 2007). Nonetheless, the role of *COMT* in specific components of CPT performance, particularly as it relates to performance across blocks of the task, remains elusive. For instance, while variability in response time (RT) has been shown to be associated with *COMT* (Stefanis et al., 2005), the stability of other indices across the task is unknown. Moreover, the role of *COMT* in cognitive processes in children is especially unclear and given the prolonged structural and functional changes that occur in prefrontal regions throughout childhood and adolescence (Casey, Giedd, & Thomas, 2000), *COMT* may differentially influence cognitive functions underlying CPT performance throughout development.

In the current study we tested the association between AX-CPT performance indices (i.e., omission and commission errors, d', lnβ) and the *COMT* $val^{108/158}met$ polymorphism in children. We hypothesized that *COMT* would be associated with these performance indices, with the SDT indices (i.e., d', lnβ) showing the strongest associations. We also tested the association between *COMT* and the AX-CPT performances indices across blocks (i.e., the variability of each of the AX-CPT performance indices). We hypothesized that *COMT* would be associated with the variability of these indices across blocks, with d' variability and lnβ variability showing the strongest associations. Further, we examined the effect of externalizing psychopathology (i.e., as operationalized in this study by clinic-referred status for disruptive disorders such as ADHD) on AX-CPT performance indices and whether the effects of *COMT* on AX-CPT indices were moderated by differing levels of externalizing psychopathology. We hypothesized that the effects of *COMT* would be stronger in children with higher levels of externalizing psychopathology.

2. Method

All assessment procedures were approved by the Emory University Institutional Review Board. Parents read and signed an informed consent form prior to study participation, and verbal assent was obtained from the children.

2.1. Participants

Participants included a clinic-referred sample of children and their siblings (N = 224) from 138 families and a twin sample (N = 156) from 83 families, with a mean age of 12.2 (SD = 3.2) years. Additional sample characteristics are provided in Table 1. Participants in the clinic-referred sample were recruited through the Center for Learning and Attention Deficit Disorders (CLADD) at the Emory University School of Medicine and the Emory University Psychological Center in Atlanta, Georgia. Both clinics specialize in the assessment and treatment of childhood learning disabilities and externalizing disorders. The clinic-referred participants consisted of probands and their siblings, where probands refer to members of a family who brought the family to the attention of researchers because they were clinically-

referred for assessment of criteria for an externalizing disorder (e.g., Attention-Deficit/Hyperactivity Disorder, Conduct Disorder, Oppositional Defiant Disorder). Participants in the twin sample were drawn from the Georgia Twin Registry, a sample of twins from the general population of Georgia and recruited through state birth records. Children diagnosed with autism, traumatic brain injury, or neurological conditions (e.g., epilepsy) were excluded, as were children with IQs < 75. Other diagnoses remained confidential and did not influence inclusion in the study.

2.2. Genotyping

DNA collection, extraction, and amplification were performed by use of previously published procedures (Gizer & Waldman, 2012). The *val*$^{108/158}$*met* polymorphism of *COMT* was genotyped along with 23 other SNPs in *COMT* on the Sequenom iPlex genotyping platform by the company (i.e., Sequenom) and at the Broad Institute of Harvard and MIT. Genotypes were called using the Sequenom iPlex chemistries and the MassARRAY system (Sequenom Inc., San Diego, CA, USA).

2.3. The A-X Continuous Performance Task (AX-CPT)

The AX-CPT was programmed according to the parameters outlined by Halperin and colleagues (1988). Stimuli comprised 11 letters, presented for 200 ms each, with an interstimulus interval of 1500 ms. Participants were to respond (i.e., press the space bar) whenever the target sequence “A-X” (i.e., an A followed by an X) appeared. There were 40 target trials distributed across 400 trials during the 12-minute test, which was divided into 4 blocks. Subjects underwent a brief practice session prior to the test.

Omission errors (misses, or non-response to the target) and commission errors (responses made to nontargets) were calculated according to procedures described by Halperin and colleagues (1988). Signal detection indices for sensitivity (d') and response bias (lnβ) were calculated for analyses according to McNicol (1972). Intra-individual variability in CPT performance indices was calculated by taking the within-person standard deviation (SD) of each index across the four blocks of the task (Li, Huxhold, & Schmiedek, 2004; MacDonald, Li, & Bäckman, 2009).

2.4. Procedures

All testing was conducted in the subjects’ homes in a quiet room free of distractions using a laptop computer. Parents were instructed to withhold their child’s stimulant medications for the day of testing and compliance was confirmed verbally prior to testing. The time of day of testing varied and was not controlled for.

2.5. Quality Control Analyses

Reliability of genotyping was assessed by examining the concordance of genotypes across the different platforms. There was acceptable genotyping between the two platforms at 91% ($\varphi_c = .86$, $p < .001$). Departure from Hardy-Weinberg equilibrium (HWE) was also used to evaluate genotyping quality. The genotype frequencies for our sample were as follows: met/met, 25%; val/met, 47%; and val/val, 29%, and were consistent with HWE ($p = .295$).

2.6. Data Analyses

We tested for differences in AX-CPT performance (i.e., individual indices and variability of the indices) across the three *COMT* genotypes (i.e., met/met, val/met, and val/val) using Generalized Linear Modeling analyses with generalized estimating equations (GEEs). Generalized Linear Modeling allows for the use of alternative distributions other than the normal distribution to account for non-normality in the outcome variables, while GEE takes into account the nested data structure due to the clustering of children (i.e., multiple siblings) within families (Liang & Zeger, 1986; Zeger, Liang, & Albert, 1988). Given the distributions of the outcome variables examined (i.e., CPT indices), we modeled them using a negative binomial distribution with a log link function to accommodate any overdispersion (i.e., the variance being greater than the mean) (Nelder & Wedderburn, 1972). The Generalized Linear Modeling analyses yield a Wald χ^2 statistic that was used in hypothesis testing and converted into the effect size index R^2 using the formula χ^2/N, where N = the number of children included in the analysis (Rosenthal, 1991). In our analyses, we controlled for ethnicity, sex, age, and age^2 (the non-linear term for age). Ethnicity was coded as a continuous variable, indicating the percentage of European-American ethnicity, for each individual. Age^2 was included to account for potential non-linear (e.g., quadratic) effects of age on the CPT indices (Cohen, Cohen, West, & Aiken, 2003). These covariates were included because they had significant effects on several of the CPT performance indices.

We also conducted these analyses (examining associations between *COMT* and AX-CPT performance indices) including clinical status (i.e., clinic-referred or non-referred subsample) in the model, and included the interaction term between *COMT* and clinical status to examine whether the effects of *COMT* on AX-CPT performance were moderated by clinical status. If interaction effects were present, we proceeded to examine the associations between *COMT* and AX-CPT indices in the non-referred and clinic-referred subsamples separately.

3. Results

3.1. Tests of Association between *COMT* and AX-CPT Indices

Table 2 summarizes the results from the association analyses between *COMT* and the AX-CPT indices. First, for omission errors there were significant effects of covariates, including ethnicity ($p = .029$, $R^2 = 1\%$), age ($p < .001$, $R^2 = 34\%$) and age^2 ($p = .032$, $R^2 = 1\%$). Specifically, omission errors decreased quadratically with increasing age. When the main effect of clinical status was included in the model as a covariate, there was a significant effect of clinical status on omission errors ($p < .001$, $R^2 = 4\%$), such that higher omission errors were found in the clinic-referred subsample.

Second, for commission errors there was a statistical trend for association for the main effect of *COMT* ($p = .100$; see Figure 1), and thus findings from specific genotype contrasts should be interpreted with caution. Nonetheless, there was a significant difference in commission errors across *COMT* genotypes ($p = .038$, $R^2 = 1\%$), such that individuals with two valine alleles (i.e., the val/val genotype) tended to make more commission errors compared to those with at least one methionine allele (i.e., the val/met and met/met genotypes). There

were also significant effects of covariates on commission errors, including sex ($p = .005$, $R^2 = 2\%$) and age ($p < .001$, $R^2 = 25\%$). Specifically, commission errors decreased linearly with increasing age, and higher commission errors were found in males. When the main effect of clinical status was included in the model as a covariate, there was a significant effect of clinical status on commission errors ($p < .001$, $R^2 = 7\%$), such that higher commission errors were found in the clinic-referred subsample.

Third, for d' there were significant effects of covariates, including sex ($p = .020$, $R^2 = 1\%$), age ($p < .001$, $R^2 = 21\%$), and age^2 ($p < .001$, $R^2 = 8\%$). Specifically, d' increased quadratically with increasing age, and higher d' values were found in females. When the main effect of clinical status was included in the model as a covariate, there was a significant effect of clinical status on d' ($p < .001$, $R^2 = 3\%$), such that higher d' values were found in the non-referred subsample. Lastly, for lnβ there was a significant effect of sex ($p = .048$, $R^2 = 1\%$) on lnβ, such that higher lnβ values were found in males.

3.2. Tests of Association between *COMT* and the Variability of CPT Indices Across Blocks

Table 3 summarizes the results from the association analyses between *COMT* and the variability of AX-CPT indices across blocks. First, for omission error variability there was a significant effect of age ($p < .001$, $R^2 = 25\%$), such that omission error variability decreased linearly with increasing age. When the main effect of clinical status was included in the model as a covariate, there was a significant effect of clinical status on omission error variability ($p < .001$, $R^2 = 4\%$), such that higher omission error variability was found in the clinic-referred subsample.

Second, for commission error variability there were significant effects of covariates, including sex ($p = .005$, $R^2 = 2\%$) and age ($p < .001$, $R^2 = 15\%$). Specifically, commission error variability decreased linearly with increasing age and higher commission error variability was found in males. When the main effect of clinical status was included in the model as a covariate, there was a significant effect of clinical status on commission error variability ($p < .001$, $R^2 = 3\%$), such that higher commission error variability was found in the clinic-referred subsample. The *COMT* × clinical status interaction term was significant for commission error variability ($p = .010$, $R^2 = 2\%$). The effects of the *COMT* genotype contrast appeared to go in opposite directions in the clinic-referred and non-referred subsamples (see Figure 2).

Third, for d' variability there was a significant main effect of *COMT* ($p = .046$, $R^2 = 2\%$), such that children with two methionine alleles (i.e., the met/met genotype) showed less variability in sensitivity (d') compared to children with at least one valine allele (i.e., the val/met and val/val genotypes) ($p = .014$, $R^2 = 2\%$; see Figure 3). There were also significant effects of covariates on d' variability, including ethnicity ($p = .011$, $R^2 = 2\%$), sex ($p = .010$, $R^2 = 2\%$), and age ($p < .001$, $R^2 = 41\%$). Specifically, d' variability decreased linearly with increasing age and higher d' variability was found in males. When the main effect of clinical status was included in the model as a covariate, there was a significant effect of clinical status on d' variability ($p < .001$, $R^2 = 8\%$), such that higher d' variability was found in the clinic-referred subsample. The *COMT* × clinical status interaction term was significant for d' variability ($p = .007$, $R^2 = 3\%$). Follow-up analyses showed a non-

significant association for the main effect of *COMT* on *d′* variability in the non-referred subsample ($p = .165$), but a significant effect in the clinic-referred subsample ($p = .001$, $R^2 = 6\%$) (see Figure 2). Findings from the subsequent specific genotype contrasts in the clinic-referred subsample was significant ($p < .001$, $R^2 = 6\%$), such that children with two methionine alleles (i.e., the met/met genotype) showed less variability in sensitivity (*d′*) compared to children with at least one valine allele (i.e., the val/met and val/val genotypes).

Lastly, for lnβ variability there was a significant main effect of *COMT* ($p = .009$, $R^2 = 2\%$), such that children with two valine alleles (i.e., the val/val genotype) showed greater variability in response bias (lnβ) compared to children with at least one methionine allele (i.e., the val/met and met/met genotypes) ($p = .002$, $R^2 = 2\%$; see Figure 3). There were also significant effects of covariates on lnβ variability, including ethnicity ($p = .010$, $R^2 = 2\%$), sex ($p = .005$, $R^2 = 2\%$), age ($p < .001$, $R^2 = 30\%$), and age^2 ($p = .004$, $R^2 = 2\%$). Specifically, lnβ variability decreased quadratically with increasing age, and higher lnβ variability was found in males. When the main effect of clinical status was included in the model as a covariate, the association between *COMT* and lnβ variability became less significant ($p = .013$, $R^2 = 2\%$), as well as the findings from the specific genotype contrasts ($p = .005$, $R^2 = 2\%$) (see Figure 3). There was a significant effect of clinical status on lnβ variability ($p < .001$, $R^2 = 10\%$), such that higher lnβ variability was found in the clinic-referred subsample. The *COMT* × clinical status interaction term was significant for lnβ variability ($p = .018$, $R^2 = 2\%$). Follow-up analyses showed a non-significant association for the main effect of *COMT* on lnβ variability in the non-referred subsample ($p = .366$), but a significant effect in the clinic-referred subsample ($p = .009$, $R^2 = 4\%$) (see Figure 2). Findings from the subsequent specific genotype contrasts in the clinic-referred subsample was significant ($p = .003$, $R^2 = 4\%$), such that children with two valine alleles (i.e., the val/val genotype) showed greater variability in response bias (lnβ) compared to children with at least one methionine allele (i.e., the val/met and met/met genotypes).

4. Discussion

In the present study, we investigated the effects of the *COMT val$^{108/158}$met* polymorphism on AX-CPT performance indices. Our analyses revealed a significant association between *COMT* and variability in the Signal Detection Theory (SDT) indices, *d′* and lnβ, across blocks, which represents a novel finding in the literature. Further, we found an overall trend for *COMT* to be associated with commission errors, consistent with previous studies (i.e., Caldú et al., 2007; Eisenberg et al., 1999), and specific contrast analyses revealed a significant difference between the val/val genotype and methionine carriers (i.e., the val/met and met/met genotypes). It is important to mention that the previous studies by Caldú and colleagues (2007) and Eisenberg and colleagues (1999) specifically found an effect of the *COMT* val allele (comparing met/met homozygotes to val carriers) on commission errors, whereas our study found a significant effect when comparing val/val homozygotes to met carriers. This difference may reflect the use of different CPT task versions, and/or specific cognitive mechanisms measured within tasks, that may have differential sensitivity to dopamine levels in the prefrontal cortex (Landi et al., 2013; Stokes, Rhodes, Grasby, & Mehta, 2011; Tan et al., 2007). Accordingly there is evidence that val/val homozygosity (compared to met carriers) is associated with a specific context processing deficit, as

measured by a modified AX-CPT (MacDonald et al., 2007), and a recent meta-analysis of neural substrates associated with *COMT* (Mier, Kirsh, & Meyer-Lindenberg, 2010) found that performance on cognitive tasks that primarily measure attention and working memory was better in met allele carriers, while performance on emotional processing tasks was better for val allele carriers, suggesting differential effects of the *COMT* val/met alleles on different aspects of task performance (Landi et al., 2013; Mier et al., 2010). In addition, differences in sample characteristics across studies (e.g., age, psychiatric diagnostic status) may also affect dopamine signaling, which in turn may influence how variations in *COMT* affects aspects of cognition. In particular, Caldú and colleagues (2007) studied undergraduate adults whereas Eisenberg and colleagues (1999) recruited children (probands) diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD). Tonic and phasic levels of dopamine in prefrontal regions change across age, which likely impact differential effects of *COMT* on cognitive performance throughout development (Mechelli et al., 2009; Wahlstron, White, & Luciana, 2010). Further, abnormal dopaminergic signaling has also been suggested in ADHD (del Campo, Chamberlain, Sahakian, & Robbins, 2011; Solanto, 2002; Swanson et al., 2007), which may also contribute to differences in the effects of the *COMT* polymorphism on prefrontally-mediated cognition (Bellgrove et al., 2005; Diamond, Briand, Fossella, & Gehlbach, 2004). Thus, as variations in *COMT* genotype may be influenced by task parameters, age, and various psychiatric conditions, future research should aim to more comprehensively explore potential sources of differences in dopaminergic signaling and its implications for *COMT*'s effects on cognition.

Our study also found that the clinic-referred subsample with higher levels of externalizing psychopathology tended to show general impairment in AX-CPT performance. Further, for d' variability and lnβ variability, *COMT* had a significant effect in the clinic-referred subsample but not in the non-referred subsample, whereas for commission error variability the effects of *COMT* went in the opposite direction in the two subsamples. These findings suggest that the effects of *COMT* on several CPT performance indices differ by levels of externalizing psychopathology, and that for some AX-CPT indices, particularly the variability indices across blocks, the effect of *COMT* was stronger at higher levels of externalizing psychopathology. This may suggest that dopaminergic genes, such as *COMT*, that are crucially involved in regulating prefrontal dopamine levels may be especially important for cognitive functions in disorders such as ADHD that are characterized by dysfunction in prefrontal dopaminergic signaling (del Campo, Chamberlain, Sahakian, & Robbins, 2011; Solanto, 2002; Swanson et al., 2007). Specifically, prefrontal dopaminergic hypo-function has been implicated in the pathophysiology of ADHD (e.g., Krause, Dresel, Krause, la Fougere, & Ackenheil, 2003) and due to lower prefrontal dopamine levels, cognitive performance in individuals with ADHD may be more strongly influenced by the increased dopamine catabolism associated with the val allele of *COMT* (Lachman et al., 1996) compared to that in controls. Nonetheless, the exact nature of the abnormalities in prefrontal dopamine neurotransmission in ADHD is still unclear and debated (e.g., Bellgrove et al., 2005) and further research is needed to examine the nature of the relation between ADHD and prefrontal function (e.g., differential activation patterns) and the relevant role of *COMT* in the context of various cognitive impairments (Congdon & Canli, 2005). For instance, there is some recent evidence that in children with ADHD, the val allele

of *COMT* may have a stronger effect on specific cognitive functions that depend more crucially on prefrontal dopamine function, such as the stable maintenance of representations in working memory, and that this may represent an important mechanism by which *COMT* confers susceptibility to ADHD (Matthews et al., 2012). Although these the current findings regarding stronger effects of *COMT* at higher levels of externalizing psychopathology are interesting, it is important to note that these are novel, exploratory results and need to be replicated in independent datasets in future studies.

Our results yield some preliminary insights regarding the precise function of *COMT* in distinct components of CPT performance. These effects, particularly on the variability of SDT indices across blocks, may be specific to *COMT* compared to other candidate genes in the dopaminergic system. For example, supplementary results from the current sample indicated no significant association between the dopamine transporter gene (*DAT1*) and variability of AX-CPT performance indices across blocks (*p*-values ranged from .481 to .861, $R^2 \approx 0\%$), supporting the specificity of *COMT*'s influence on cognitive stability, or the active maintenance of representations in working memory (Stefanis et al., 2005). Interestingly, while *COMT* was not associated with lnβ, results from our sample indicated a significant but modest effect of *DAT1* on lnβ ($p = .037$, $R^2 = 1\%$), which has also been found in a previous study (Loo et al., 2003). In addition, similar to *COMT*, *DAT1* was not significantly associated with omission errors ($p = .555$, $R^2 \approx 0\%$) or d' ($p = .692$, $R^2 \approx 0\%$). Nonetheless, there also is some evidence of similar effects on AX-CPT performance of *COMT* and *DAT1*. In particular, findings from the current sample showed a significant association between *DAT1* and commission errors ($p = .014$, $R^2 = 2\%$), albeit to a greater degree compared to *COMT* ($p = .100$, $R^2 = 1\%$). The association between *DAT1* and commission errors has also been supported in the previous literature (Caldú et al., 2007; Gizer & Waldman, 2012; Loo et al., 2003). While in need of replication, our results provide some support for the unique effects of *COMT* and *DAT1* on distinct AX-CPT performance indices, in addition to having some common effects, and thus have important implications for the neurobiological mechanisms underlying CPT performance.

Although both *DAT1* and *COMT* are involved in terminating the action of dopamine in the brain, they are predominantly expressed in different regions. Specifically, *COMT* is primarily expressed in the dlPFC with minimal expression in subcortical regions (Matsumoto et al., 2003a, b), whereas *DAT1* is abundantly expressed in subcortical areas (e.g., striatum and midbrain), with minimal expression in frontal cortical regions (e.g., Ciliax et al., 1999; Sesack et al., 1998). These brain regions form components of separate, but interdependent neural circuits that underlie different elements of cognitive and affective control involved in the pathophysiology of disorders such as ADHD (Alexander, Crutcher, DeLong, 1991; Nigg & Casey, 2005). Thus, in addition to this neuroanatomical dissociation, these two neural pathways may also underlie distinct cognitive mechanisms, also suggesting a functional dissociation. For AX-CPTs in particular, computational models of prefrontal and subcortical interactions have been proposed, implicating prefrontal regions in the active maintenance of context information (provided by the cue stimulus 'A' before the 'X') and subcortical regions in the flexible and selective updating of representations (Braver & Cohen, 2000). Accordingly, *COMT* has been shown to be related to prefrontal cortical

underpinnings of attention and working memory (e.g., Egan et al., 2001), as well as cognitive stability (e.g., Stefanis et al., 2005), consistent with our findings of associations between *COMT* and variability in performance (i.e., SDT indices across blocks). In contrast, *DAT1* has been implicated in inhibitory control processes (Cornish et al., 2005) that more strongly reflect aspects of impulsivity (Logan, Schachar, & Tannock, 1997). Consistent with this, supplementary results from our sample suggest associations between *DAT1* and lnβ and commission errors, indices which have been shown to reflect impulsivity (e.g., Brooks et al., 2006; Gizer & Waldman, 2012; Keilp, Sackeim, & Mann, 2005). Thus, findings from our sample provide preliminary evidence for dissociable effects of *COMT* and *DAT1* on AX-CPT performance and their corresponding underlying neural mechanisms, which warrants further investigation in the literature.

Our findings further lend support to the potential utility of using the SDT indices, and in particular, highlight the specific role of *COMT* in the variability of SDT indices across the task, which may provide further insights regarding the core cognitive deficits in relevant psychiatric disorders such as ADHD. In particular, given that genetic associations with specific diagnoses (e.g., ADHD) have often failed to replicate and have shown small effect sizes (e.g., Faraone et al., 2005; Gizer et al., 2009), valid intermediate phenotypes (i.e., endophenotypes) may be helpful in identifying susceptibility loci for disorders by more directly assessing the biological mechanisms hypothesized to underlie those disorders (Doyle et al., 2005; Gottesman & Gould, 2003; Waldman, 2005). Accordingly, there is evidence that CPT indices may represent useful endophenotypes for ADHD (Doyle et al., 2005; Gizer & Waldman, 2012; Waldman, 2005), consistent with our findings. Our results go beyond previous findings to suggest that the SDT indices, particularly in relation to cross-block variability in performance, may represent especially useful endophenotypes for molecular genetic studies. Thus our large sample consisting of children spanning a range of psychopathology allows for increased statistical power (Lohmueller, Pearce, Pike, Lander, & Hirschhorn, 2003) to 1) detect the effects of *COMT* on the putative endophenotype measures (i.e., AX-CPT indices) and 2) to examine how these effects vary as a function of clinical status, such that these effects tend to be stronger at higher levels of externalizing psychopathology for several indices. Given that there has been a lack of support for association between *COMT* and ADHD (Gizer et al., 2009), utilizing such putative endophenotypes may be especially informative for elucidating the underlying neurobiological pathways by which specific genes confer risk for ADHD.

Although the present findings have important implications for the role of *COMT* on CPT performance and relevant disorders, our study has several limitations. Given the novelty of our results, they need to be replicated in independent samples. Moreover we did not control for multiple testing in the current study. It has been proposed that adjustments for multiple comparisons may not be strictly required for exploratory methods, as in the current investigation, that primarily aim to identify preliminary evidence to inform future research, as such adjustments may potentially dismiss important relations by decreasing statistical power (Bender & Lange, 2001; Cohen, 1994; Cole, 1979, 1993; Michels & Rosner, 1996; Poole, 1991; Rothman, 1990; Savitz & Olshan, 1995). Exploratory methods with flexible statistical approaches have been proposed as a good tool for understanding and gaining

preliminary information from the data, instead of relying solely on strict criterion for significance testing (Cohen, 1994). In addition, the current investigation focused on omnibus tests of association, which diminishes the multiple testing problem as it involves fewer overall tests being conducted (Cohen, Cohen, West, & Aiken, 2003). Nonetheless, it is critical for these findings to be rigorously tested for replication in other independent datasets (Bender & Lange, 2001; Cohen, 1994).

Further, while our sample was relatively large compared to other genetic association studies of neurocognitive measures, larger samples are needed for sufficient statistical power (Lohmueller et al., 2003), especially for tests of multiple genetic markers. In addition, given that differences in CPT task parameters may differentially influence aspects of cognitive performance (Solanto, Etefia, & Marks, 2004), it is important to investigate the generalizability of our findings to other versions of CPTs and to explore other potentially valid performance indices (Halperin et al., 1988). In particular, previous research indicates that *COMT* may be more closely linked to versions of the AX-CPT in which certain parameters are modified to more specifically capture aspects of context processing (MacDonald et al., 2007). This suggests that *COMT* may play a more specific role in context processing deficits, rather than a more generalized deficit within the broader cognitive domain (e.g., working memory). Thus focusing on more specific functions like context processing may be advantageous for finding associations of cognitive deficits with specific genes and further assist in the understanding of the neurobiology of relevant psychiatric disorders (MacDonald et al., 2007). Future research should also explore other genes that influence the neurobiological pathways associated with CPT performance, such as *DAT1* discussed above, for a more comprehensive understanding of distinct components of AX-CPT performance.

In conclusion, our results provide support for the influence of *COMT* on specific AX-CPT performance indices in children, which has been investigated only rarely in the extant literature, especially the variability of SDT indices, d' and lnβ, across the task. Our study also suggests that the effects of *COMT* on specific AX-CPT performance indices differ by levels of externalizing psychopathology. As the neurobiology of the component indicators of AX-CPT performance indices becomes better understood, these findings will potentially allow for a more comprehensive conceptualization of relevant disorders that are characterized by specific deficits in CPT performance.

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Highlights

- *COMT* was associated with variability in d' and lnβ across blocks of the AX-CPT.
- *COMT* showed a statistical trend for association with commission errors.
- Higher externalizing psychopathology was associated with impaired CPT performance.
- Some indices were more strongly related to *COMT* at higher levels of psychopathology.
- CPT indices may represent useful endophenotypes for relevant disorders (e.g., ADHD).

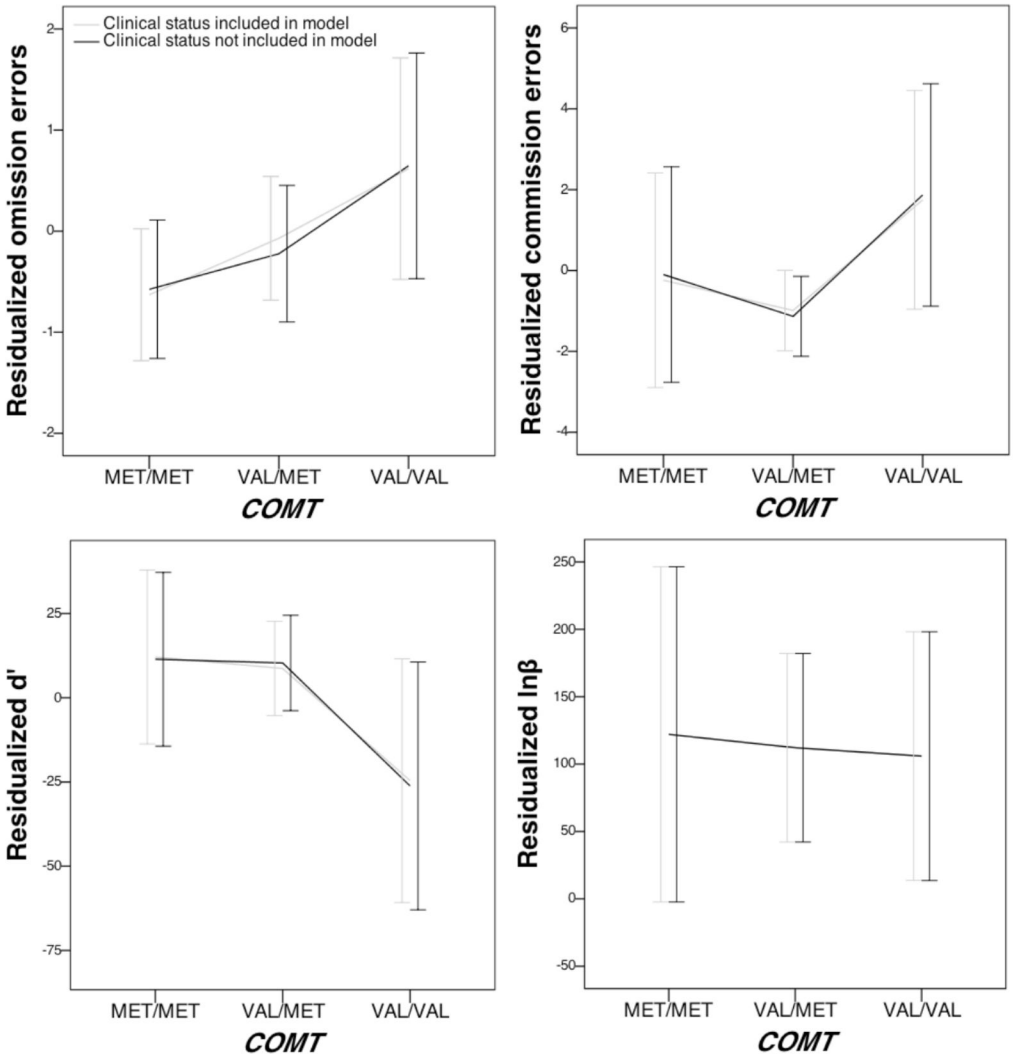

Figure 1.
Association of *COMT* and residualized AX-CPT indices.

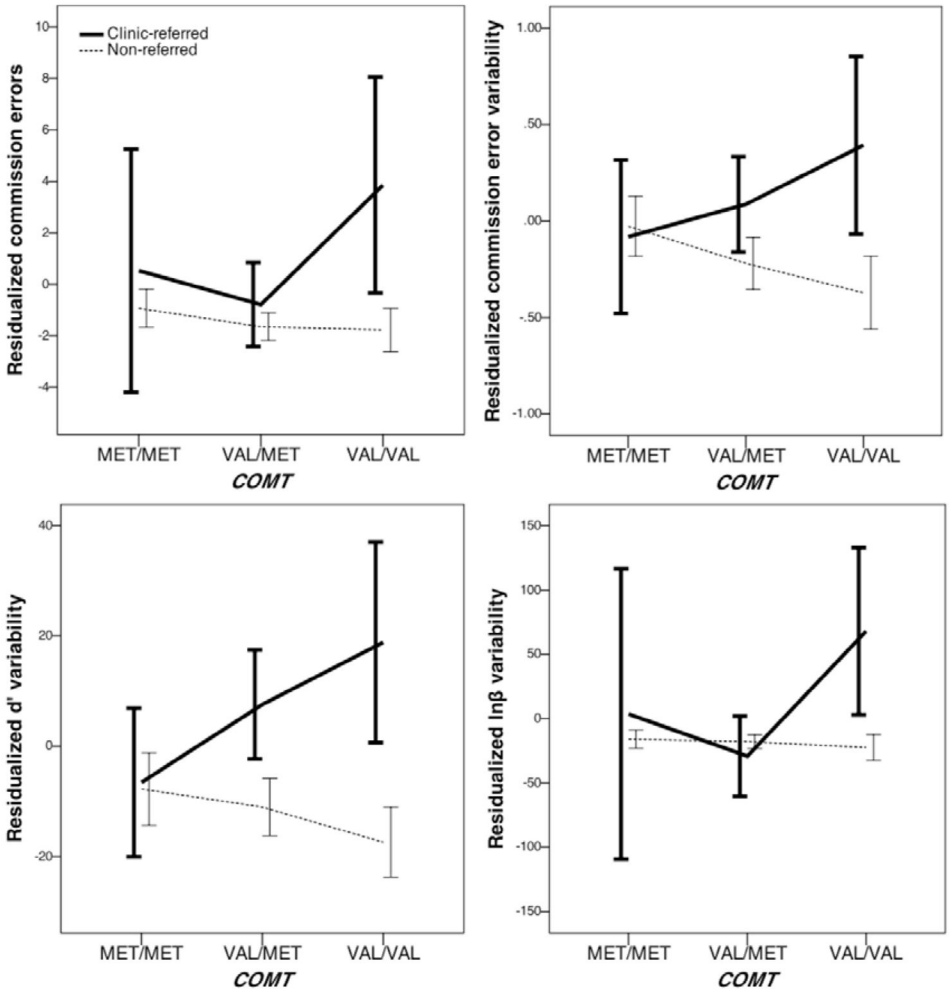

Figure 2.
Association of *COMT* and residualized AX-CPT indices, moderated by clinical status

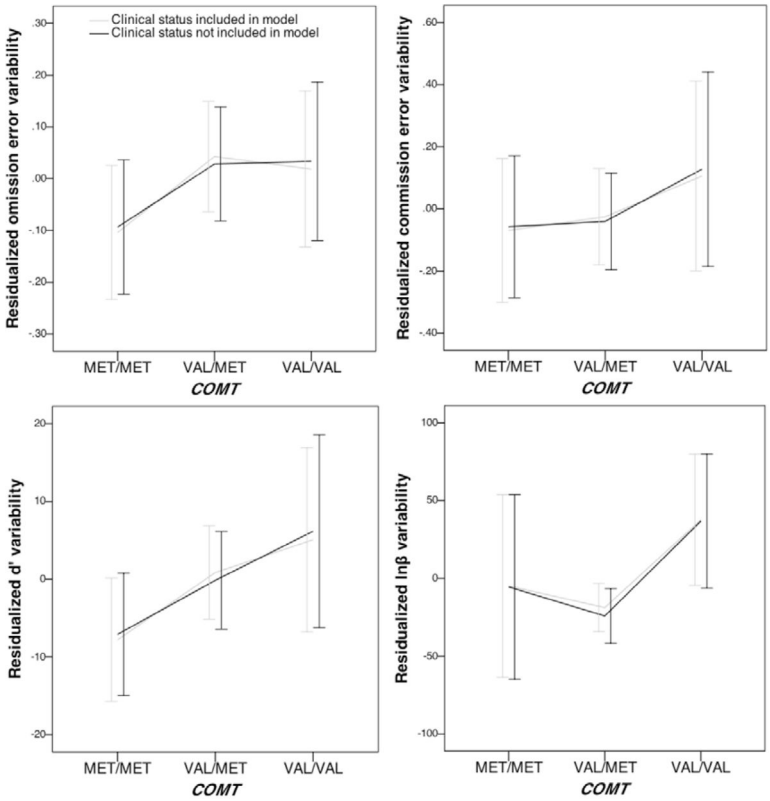

Figure 3.
Association of *COMT* and residualized variability of AX-CPT indices across blocks.

Table 1

Sample Characteristics

	Clinic-Referred Sample	Twin Sample	Total
Sample Size			
# of families	138	83	221
Total children	224	156	380
# of probands	135	NA	135
# of siblings	89	53	142
# of controls	NA	103	103
Diagnostic Information			
Probands			
With ADHD	104 (I-43, H-5, C-56)	NA	104 (I-43, H-5, C-56)
With ODD	41	NA	41
With CD	3	NA	3
Siblings			
With ADHD	16 (I-9, H-5, C-2)	34 (I-20, H-5, C-9)	50 (I-29, H-10, C-11)
With ODD	30	0	30
With CD	4	0	4
Demographic Characteristics			
Age*[a]	11.2 (3.3)	13.5 (2.4)	12.2 (3.2)
Gender*[b]	144 M (64%), 80 F	61 M (39%), 95 F	205 M, 175 F
Ethnicity			
Hispanic	2 (1%)	0 (0%)	2
European-American	170 (76%)	134 (86%)	304
African-American*[c]	18 (8%)	4 (3%)	22
Other*[d]	23 (10%)	2 (1%)	25
Missing	11 (5%)	16 (10%)	27

Note. ADHD = Attention-Deficit/Hyperactivity Disorder; ADHD diagnostic subtype information – I = Predominantly Inattentive type, H = Predominantly Hyperactive-Impulsive type, C = Combined type; ODD = Oppositional Defiant Disorder; CD = Conduct Disorder; Gender information – M = Male, F = Female;

* Clinic-referred and twin samples significantly differed;

[a] $t(378) = 7.80$, $p < .001$;

[b] $\chi^2(1, N = 380) = 23.47$, $p < .001$;

[c] $\chi^2(1, N = 380) = 5.03$, $p = .025$;

[d] $\chi^2(1, N = 380) = 8.73$, $p = .003$

Table 2

Association of COMT and AX-CPT Indices

	Omission errors				Commission errors				*d′*				lnβ			
Predictor	**Wald χ^2**	**df**	***p***	***R²***	**Wald χ^2**	**df**	***p***	***R²***	**Wald χ^2**	**df**	***p***	***R²***	**Wald χ^2**	**df**	***p***	***R²***
Ethnicity[a]	4.76	1	.029	1%	2.43	1	.119	0%	2.80	1	.094	1%	1.06	1	.302	0%
Sex	1.28	1	.258	0%	7.93	1	.005	2%	5.39	1	.020	1%	3.90	1	.048	1%
Age	130.13	1	<.001	34%	94.61	1	<.001	25%	81.59	1	<.001	21%	0.04	1	.847	0%
Age^2	4.61	1	.032	1%	1.00	1	.318	0%	31.52	1	<.001	8%	0.18	1	.675	0%
Clinical status	14.08	1	<.001	4%	27.57	1	<.001	7%	13.05	1	<.001	3%	<0.01	1	.954	0%
COMT[b]	2.58	2	.275	1%	4.60	2	.100	1%	3.11	2	.212	1%	1.55	2	.461	0%
COMT val/val vs. val/met & met/met combined[b]	1.89	1	.169	0%	4.32	1	.038	1%	3.10	1	.078	1%	0.02	1	.900	0%
COMT val/met vs. met/met[b]	1.02	1	.313	0%	0.18	1	.670	0%	0.02	1	.886	0%	1.13	1	.288	0%
COMT[c]	2.83	2	.243	1%	3.78	2	.151	1%	2.95	2	.229	1%	1.62	2	.444	0%
COMT val/val vs. val/met & met/met combined[c]	1.34	1	.247	0%	3.15	1	.076	1%	2.92	1	.088	1%	0.02	1	.897	0%
COMT val/met vs. met/met[c]	1.67	1	.196	0%	0.25	1	.618	0%	0.08	1	.783	0%	1.13	1	.287	0%
COMT × Clinical status	0.58	2	.747	0%	4.69	2	.096	1%	3.69	2	.158	1%	1.91	2	.384	1%

Note.

[a] Percentage of European-American ethnicity;

[b] Clinical status not included in model;

[c] Clinical status included in model

Table 3

Association of COMT and Variability of AX-CPT Indices Across Blocks

	Omission error variability				Commission error variability				*d′* variability				lnβ variability			
Predictor	**Wald χ^2**	**df**	***p***	***R²***	**Wald χ^2**	**df**	***p***	***R²***	**Wald χ^2**	**df**	***p***	***R²***	**Wald χ^2**	**df**	***p***	***R²***
Ethnicity[a]	2.26	1	.133	1%	3.44	1	.064	1%	6.44	1	.011	2%	6.59	1	.010	2%
Sex	0.76	1	.385	0%	7.76	1	.005	2%	6.58	1	.010	2%	7.92	1	.005	2%
Age	93.75	1	<.001	25%	55.54	1	<.001	15%	155.97	1	<.001	41%	113.97	1	<.001	30%
Age^2	1.73	1	.188	0%	0.96	1	.328	0%	1.74	1	.188	0%	8.18	1	.004	2%
Clinical status	15.10	1	<.001	4%	13.22	1	<.001	3%	29.44	1	<.001	8%	37.81	1	<.001	10%
COMT[b]	2.13	2	.344	1%	1.48	2	.477	0%	6.16	2	.046	2%	9.48	2	.009	2%
COMT val/val vs. val/met & met/met combined[b]	0.18	1	.669	0%	1.48	1	.224	0%	6.06	1	.014[d]	2%	9.24	1	.002	2%
COMT val/met vs. met/met[b]	2.00	1	.157	1%	0.03	1	.874	0%	0.17	1	.678[e]	0%	0.09	1	.759	0%
COMT[c]	2.65	2	.266	1%	1.00	2	.606	0%	4.46	2	.107	1%	8.66	2	.013	2%
COMT val/val vs. val/met & met/met combine d[c]	0.04	1	.841	0%	0.84	1	.360	0%	3.51	1	.061[d]	1%	7.80	1	.005	2%
COMT val/met vs. met/met[c]	2.47	1	.116	1%	0.04	1	.839	0%	0.01	1	.912[e]	0%	0.18	1	.671	0%
COMT × Clinical status	0.83	2	.660	0%	9.29	2	.010	2%	9.85	2	.007	3%	8.03	1	.018	2%

Note.

[a] Percentage of European-American ethnicity;

[b] Clinical status not included in model;

[c] Clinical status included in model;

[d] *COMT* met/met vs. val/met & val/val combined;

[e] *COMT* val/met vs. val/val.