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Dissociable Genetic Influences on Continuous Performance Task Indices

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Dissociable Genetic Influences on Continuous Performance Task Indices

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Abstract

Dissociable Genetic Influences on Continuous Performance Task Indices
By Yunsoo Park

Attention-deficit/hyperactivity disorder (ADHD) is a complex, heritable childhood disorder with unclear etiology. Numerous dopaminergic candidate genes, including *COMT* and *DAT1,* have been examined for association with ADHD, but have yielded inconclusive findings. Instead of manifest diagnoses or symptoms, using endophenotypes may provide stronger, more replicable results. Deficits in executive functions (EFs) have been proposed as putative endophenotypes for ADHD, given that individuals with ADHD are impaired on various neurocognitive measures, including the Continuous Performance Task (CPT), a widely-used measure of sustained attention and impulsivity. Distinct indices of CPT performance (i.e., omission and commission errors, sensitivity, and response bias) have shown associations with *COMT* and *DAT1*, but there have been no studies examining genetic influences on the trajectories of these indices over time (i.e., across blocks). In this study we investigated the association between AX-CPT indices (considering overall performance and performance across blocks) and the *COMT* val$^{108/158}$met polymorphism and the *DAT1* 40 bp 3' UTR VNTR polymorphism in a clinically-referred sample of children (N = 332). We found a marginally significant association between *COMT* and commission errors and sensitivity, a marginally significant association between *DAT1* and response bias, and a significant association between *DAT1* and commission errors. We found no significant genotype differences in CPT indices across blocks. Our findings provide support for the influence of *COMT* and *DAT1* on distinct CPT indices, but do not suggest effects of either gene in performance across blocks. Further research is needed to elucidate genetic influences on CPT performance, particularly regarding trajectories across time.

Dissociable Genetic Influences on Continuous Performance Task Indices

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Table of Contents

General Introduction 1

Method 6

Participants 6

Genotyping 7

Measures 8

Procedures 9

Quality Control Analyses 9

Data analyses 9

Results 11

Discussion 14

References 20

Tables 37

Figures 40

List of Tables and Figures

Tables

Association Analyses of *COMT* with the Overall Summary CPT Indices 37

Association Analyses of *DAT1* with the Overall Summary CPT Indices 38

Univariate Omnibus Analyses for CPT Indices Across Blocks 39

Figures

Association between residualized omission errors and *COMT* and *DAT1* 40

Association between residualized commission errors and *COMT* and *DAT1* 41

Association between residualized *d'* and *COMT* and *DAT1* 42

Association between residualized lnß and *COMT* and *DAT1* 43

Dissociable Genetic Influences on Continuous Performance Task Indices

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent childhood disorders, and is characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsivity (American Psychiatric Association, 2000). There is evidence for substantial genetic influence on the disorder, with heritability estimates ranging from 0.6 to 0.9 (Waldman & Rhee, 2002), but molecular genetic studies have yielded largely inconsistent findings in identifying susceptibility genes for ADHD (Gizer, Ficks, & Waldman, 2009). Instead of relying on manifest diagnoses or symptoms, using endophenotypes may produce stronger, more replicable results, and provide greater support for the association between ADHD and specific genetic loci. Endophenotypes are intermediate phenotypes that represent heritable phenotypic constructs and are hypothesized to be more strongly and directly influenced by genes than the disorder of interest (Gottesman & Gould, 2003; Waldman, 2005; Walters & Owen, 2007). Numerous molecular genetic studies have demonstrated that impairment in executive functions (EFs), or cognitive mechanisms that enable goal-directed behavior (Welsh & Pennington, 1988), correlate with the presence of ADHD and exhibit evidence of heritability and association with specific genes (e.g. Doyle et al., 2005; Doyle et al., 2008; Durston, de Zeeuw, & Staal, 2009; Rommelse et al., 2008). Accordingly, deficits in EFs have been proposed as potentially valid and useful endophenotypes for ADHD (Doyle et al., 2005), and laboratory tasks intended to measure specific EF domains have been increasingly proposed as assessment tools for impairments in ADHD (Barkley, 1991).

The Continuous Performance Task (CPT) is one of the most widely used laboratory tasks that measure EF constructs believed to be associated with core symptom dimensions of ADHD (Barkley, 1991; DuPaul, Anastopoulous, Shelton, Guevremont, & Metevia, 1992; Klee & Garfinkel, 1983; Meents, 1989). Specifically, the CPT is hypothesized to assess sustained attention and impulsivity, with scores significantly correlating with other commonly accepted psychometric measures and ratings of sustained attention and impulsivity (e.g., Barkley, 1991; Davies & Parasuraman, 1982; Gizer & Waldman, in press; Gordon, 1979; Greenberg & Waldman, 1993; Halperin et al., 1993; Klee & Garfinkel, 1983; Nuechterlein, 1991; Solanto, Etefia, & Marks, 2004; Van Leeuwen et al., 1995). Continuous Performance Tasks require the participant to attend to a series of changing stimuli presented in rapid succession and to respond to a specified target while withholding response to non-targets. Traditionally, commission errors on the CPT are believed to index impulsivity or deficits in inhibition (Dougherty, Bjork, Marsh, & Moeller, 2000), and omission errors are believed to index inattention (Riccio, Reynolds, & Lowe, 2001). It has been proposed that signal detection (SDT) indices might be more sensitive to variations in CPT performance than traditional indices (Lam & Beale, 1991). Signal detection indices have been increasingly used in analyzing CPT performance to quantify and distinguish sensitivity (*d'*), or the degree to which targets are successfully discriminated from nontargets, from response bias (β), or the tendency to over- or under-respond (Davies & Parasuraman, 1981; McNicol, 1972; Parasuraman, 1979; Swets, 1973). The *d'* index reflects attentional and sensory capacity (Davies & Parasuraman, 1982; Swets, Tanner, & Birdsall, 1961), while β measures response style, where a tendency to over-respond (i.e., lower β) indicates an impulsive, risk-taking

response style and a tendency to under-respond (i.e., higher β) suggests a cautious response style (Keilp, Sackeim, & Mann, 2005; McGee, Clark, & Symons, 2000; Rutschmann, Cornblatt, & Erlenmeyer-Kimling, 1977).

Omission and commission errors and SDT indices on the CPT have shown consistently strong relations with multiple ADHD symptom domains (Epstein et al., 2003). CPT performance in children with ADHD has typically been characterized by increased omission and commission errors, and lower *d'* (e.g., see Losier, McGrath, & Klein, 1996), but with more mixed findings regarding β (e.g., lower, no difference, or higher in Nuechterlein, 1983; Losier et al., 1996; Epstein et al., 2003, respectively). Children with ADHD have also been shown to exhibit more shifts in performance states (e.g., distracted, impulsive, and random response states) on the CPT, suggesting less stability in performance (Teicher et al., 2004). Similar types of performance decrements during the task (i.e., decline in *d'* and β) have been reported in control and ADHD children (van der Meere & Sergeant, 1988), but there is also evidence that controls may actually exhibit an increase in β over time (Conners, Epstein, Angold, & Klaric, 2003; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988) or no significant decline in *d'* over time (Cornblatt et al., 1988). It is evident that further research is needed to understand variations in CPT performance in children, as well as factors that may influence deficits in performance.

Neuroimaging evidence has shown that the dorsolateral prefrontal cortex (DLPFC) underlies distinct CPT performance indices, including commission errors, *d'*, and β (Brooks et al., 2006; Häger et al., 1998; Sax et al., 1999; Volz et al., 1999). The DLPFC projects primarily to the basal ganglia, specifically the caudate nucleus

(Alexander, DeLong, & Strick, 1986), and while the caudate nucleus has also been shown to be activated during CPT performance (Häger et al., 1998; Volz et al., 1999; Wu et al., 1991), there are fewer empirical studies examining the role of this structure in distinct CPT indices. Abnormalities in these prefrontal and striatal regions have been found consistently in individuals with ADHD, including abnormalities in size and symmetry, as well as decreased activity (e.g., Castellanos et al., 1996; Lou, Henriksen, Bruhn, Borner, & Nielsen, 1989). These regions are both modulated by dopamine, a neurotransmitter that is essential in regulating attention (e.g., Montague, Dayan, & Sejnowski, 1996; Schultz, 1997). Accordingly, numerous dopaminergic genes have been investigated in candidate gene studies of ADHD, including the dopamine transporter gene (*DAT1*) and the catechol-*O*-methyltransferase gene (*COMT*). Both genes encode proteins involved in terminating the action of dopamine in the brain, but are expressed in dissociable neural regions. *COMT* is predominantly expressed in the DLPFC, with sparse expression in the striatum (Matsumoto et al., 2003a, b), whereas *DAT1* is abundantly expressed in the striatum and midbrain, with minimal expression in prefrontal regions (Ciliax et al., 1999; Lewis et al., 2001; Morón, Brockington, Wise, Rocha, & Hope, 2002; Schott et al., 2006; Sesack, Hawrylak, Matus, Guido, & Levey, 1998).

COMT contains a widely-studied functional single nucleotide polymorphism (SNP) at codon 108/158 ($val^{108/158}met$) that codes for the substitution of valine (val) by methionine (met) (Lachman et al., 1996). Individuals with two copies of the met allele exhibit a three- to four-fold reduction in COMT enzyme activity than individuals with two copies of the val allele, with heterozygotes showing intermediate enzyme function (Chen et al., 2004; Lachman et al., 1996). The most well studied *DAT1* polymorphism is

a variable number of tandem repeats (VNTR) sequence in the 3' untranslated region (UTR) (Vandenbergh et al., 1992). As this VNTR is not in the coding region of the gene, it does not influence the protein sequence, but may affect the translational efficiency, and thus how much protein is ultimately expressed. The most common alleles are the 10- (480-bp) and 9- (440-bp) repeats (Doucette-Stamm, Blakeley, Tian, Mockus, & Mao, 1995). Subjects homozygous for the 10-repeat allele have shown significantly lower dopamine transporter binding than carriers of the 9-repeat allele (Jacobsen et al., 2000). The val allele of the *COMT* $val^{108/158}$*met* polymorphism (e.g., Egan et al., 2001; Eisenberg et al., 1999) and the 10-repeat allele of the *DAT1* VNTR (e.g., Cook et al. 1995) have been considered as risk alleles for ADHD. Association studies between these candidate genes and ADHD have yielded inconclusive results (e.g., Waldman & Gizer, 2006), and a recent meta-analysis suggested a significant but modest association for *DAT1*, but not *COMT* (Gizer, Ficks, & Waldman, 2009).

CPT performance appears to be influenced by genetic factors, as studies have shown that omission and commission errors, and *d'* (Gizer, 2008; Cornblatt et al., 1988), but not response bias (Cornblatt et al., 1988), are heritable. Both *COMT* and *DAT1* have been shown to be associated with performance on tasks that measure attention, including the CPT. *COMT* has been shown to be associated with CPT commission errors and *d'* (Caldú et al., 2007; Eisenberg et al., 1999; Liao et al., 2009), and *DAT1* with commission errors, *d'*, and impulsive response style (i.e., lower β) (Caldú et al., 2007; Gizer & Waldman, in press; Loo et al., 2003). In addition, it has been proposed that *COMT* may be related to stability in CPT performance, potentially by maintaining active representations in prefrontal regions (Stefanis et al., 2005). Nonetheless, there is limited

research investigating genetic factors that influence distinct CPT performance indices in children, as well as dynamic trajectories of these indices during the course of the task. Patterns of changes in specific indices across the task may not be captured by the overall summary indices, and may also be underlied by different genetic factors.

The current investigation had two aims. The first aim was to test the association between AX-CPT performance indices (i.e., omission and commission errors, *d'*, β) and the *COMT* $val^{108/158}met$ polymorphism and the *DAT1* 40-bp repeat VNTR. We hypothesized that *COMT* would be associated with commission errors and *d'*, and that *DAT1* would be associated with commission errors, *d'*, and β. The second aim was to test the association between the trajectory of each of the AX-CPT performance indices over time and *COMT* and *DAT1*. We hypothesized that *COMT* would show association with performance trajectories for all indices.

Method

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

Participants

Participants included a clinically-referred sample of children and their siblings (*N*= 332) from 200 families, with a mean age of 12.1 (*SD* = 3.3) years. The sample included 176 boys (53%) and 156 (47%) girls, with an ethnic composition of 86.4% Caucasian, 5.7% African-American, 0.6% Hispanic, and 7.3% Asian or mixed ethnicity. 135 children met diagnosis for ADHD, which included 65 (19.6%) Predominantly

Inattentive type, 13 (3.9%) Predominantly Hyperactive-Impulsive type, and 57 (17.2%) Combined type.

Participants 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. 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.

Genotyping

DNA collection, extraction, and amplification were performed by use of previously published procedures (Vandenbergh et al. 1992). Buccal cells were collected in 30 ml of 4% sucrose mouthwash swished vigorously in the mouth for 1 min and then were delivered on ice within 48 h to the laboratory. Cells were pelleted at 2,000 *g* for 10 min, the DNA was immediately extracted with a QIAmp Tissue kit (Qiagen) by use of the manufacturer's protocols for crude-cell lysates, and the samples were preserved in TE (10 mM Tris Hcl, 1 mM ethylenediaminetetraacetic acid [EDTA]). 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) as well as in the labs of the Psychiatric Neurodevelopmental Genetics Unit at Massachusetts General Hospital and at the Broad Institute of Harvard and MIT. The 40-bp repeat VNTR in the 3' UTR of *DAT1* was genotyped by PCR, using primers described by Vandenbergh and colleagues (1992). A minimum of two investigators independently determined genotypes

by examining pictures of ultraviolet-illuminated stained gels. A random 5% of the sample was then rescored to confirm the accuracy of genotype determination.

Measures

The A-X CPT was programmed according to the parameters outlined by Halperin and colleagues (1988). Stimuli consisted of 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. 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 and response criterion were calculated for analyses according to McNicol (1972). Sensitivity is typically measured with the *d'* index, which depends on both the hit rate, *H* (i.e., proportion of responses to targets), and the false alarm rate, *F* (i.e., proportion of responses to nontargets), such that *d'* increases when either *H* increases or *F* decreases. The *d'* index was calculated by subtracting the standardized *H* from the standardized *F*: $d' = z(H) - z(F)$. Response bias is often quantified with β, which is based on a likelihood ratio of changes in *H* and *F*. Because β is an asymmetrical measure (i.e., much narrower range of values for a *yes* bias compared to the *no* bias), the natural logarithm of β (lnβ) is often analyzed instead, such that a negative lnβ indicates a more liberal response criterion (i.e., bias toward the *yes* response), and a positive lnβ indicates a more conservative criterion (i.e., bias toward the *no* response). The lnβ index was computed by squaring the

standardized *H*, subtracting the square of the standardized *F*, and dividing the result by –2: $\ln\beta = -0.5 \times [\, z(H)^2 - z(F)^2 \,]$.

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 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.

Quality Control Analyses

Reliability of genotyping was assessed by examining the concordance of genotypes across the different platforms. For *COMT*, there was acceptable genotyping concordance across the three platforms, ranging from 82 – 92% (ϕ_c = .74 – .88, $p = 7.28 \times 10^{-58} - 2.52 \times 10^{-86}$). For *DAT1*, there was also acceptable genotyping concordance between the two platforms at 96% (ϕ_c = .83, $p = 1.08 \times 10^{-34}$). Departure from Hardy-Weinberg equilibrium (HWE) was also used to evaluate genotyping reliability. The genotype frequencies for our sample were as follows for *COMT*: met/met, 26%; val/met, 47%; and val/val, 27%. These genotypic frequencies were consistent with HWE (p = .295). The genotype frequencies were as follows for *DAT1*: 9/9, 8%; 9/10, 42%; and 10/10, 50%. The genotypic frequencies were also consistent with HWE (p = .300).

Data Analyses

Relations between the overall summary CPT indices and *COMT* and *DAT1* were examined 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 (e.g., negative binomial), 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, 1986; Zeger, Liang, & Albert, 1988). Given the distributions of the outcome variables examined (i.e., the 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's χ^2 statistic that was used in hypothesis testing and converted into the effect size index R^2 (i.e., proportion of the variance accounted for) using the formula χ^2 / N, where N = the number of children included in the analysis (Rosenthal, 1991). In our analyses, we controlled for sex, age, and ethnicity. Non-linear terms for age (i.e., age^2) and the interactions of the age terms with sex (i.e., sex × age, [sex × age]^2) also were included as covariates. Participants' *COMT* and *DAT1* genotypes were entered and treated as factors with three levels, corresponding to the three genotypes at each marker.

Performance across blocks for each CPT index was examined using General Linear Model (GLM) repeated measures analyses using the CPT indices for each block as within-subject factors and *COMT*, *DAT1*, and sex as between-subject factors. Age, ethnicity, non-linear terms for age (i.e., age^2), and the interactions of the age terms with sex (i.e., sex × age, [sex × age]^2) were also included as covariates. Participants' *COMT* and *DAT1* genotypes were entered as treated as factors with three levels, corresponding to the three genotypes at each marker. The GLM repeated measures analyses generate a partial eta-squared (η_p^2) as an effect size coefficient associated with each factor, which is the ratio of variance accounted for by an effect and that effect plus its associated error variance. For all indices, block effects and their interactions were examined using

univariate, rather than multivariate, models, due to the violation of multivariate normality and the assumption of the homogeneity of variance-covariance matrices ($p < .05$) (Stevens, 1992). In cases in which the sphericity assumption was violated, the Greenhouse-Geisser adjustment was used.

Results

Tests of Association between the Overall Summary CPT Indices and *COMT* and *DAT1*

Tables 1 and 2 summarize the results from the association analyses between the overall summary CPT indices and *COMT* and *DAT1*.

There were no significant differences in omission errors across *COMT* or *DAT1* genotypes (all p's > .05; see Figure 1). There were significant effects of covariates on omission errors, including age (for *COMT*: Wald's $\chi^2 = 108.11$, $p = .001$, $R^2 = 33\%$; for *DAT1*: Wald's $\chi^2 = 102.78$, $p = .001$, $R^2 = 31\%$) and age^2 (for *COMT*: Wald's $\chi^2 = 5.74$, $p = .017$, $R^2 = 2\%$; for *DAT1*: Wald's $\chi^2 = 6.27$, $p = .012$, $R^2 = 2\%$).

There was a marginally significant difference in commission errors across *COMT* genotypes (Wald's $\chi^2 = 3.61$, $p = .057$, $R^2 = 1\%$), 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) (Figure 2). There was also a significant linear trend in commission errors across *DAT1* genotypes (Wald's $\chi^2 = 10.16$, $p = .001$, $R^2 = 3\%$), such that the presence of a 10-repeat allele was associated with increased commission errors, and individuals with at least one 10-repeat allele (i.e., the 9/10 and 10/10 genotypes) made more commission errors than those with no 10-repeat allele (i.e., the 9/9 genotype) (Wald's $\chi^2 = 9.64$, $p = .002$, $R^2 = 3\%$) (Figure

2). There were also significant effects of covariates on commission errors, including sex (for *COMT*: Wald's $\chi^2 = 11.56$, $p = .001$, $R^2 = 3\%$; for *DAT1*: Wald's $\chi^2 = 11.34$, $p = .001$, $R^2 = 3\%$), age (for *COMT*: Wald's $\chi^2 = 122.92$, $p = .001$, $R^2 = 37\%$; for *DAT1*: Wald's $\chi^2 = 108.28$, $p = .001$, $R^2 = 33\%$), and sex × age (for *COMT*: Wald's $\chi^2 = 3.93$, $p = .047$, $R^2 = 1\%$; for *DAT1*: Wald's $\chi^2 = 3.74$, $p = .053$, $R^2 = 1\%$).

There was a marginally significant difference in *d'* across *COMT* genotypes (Wald's $\chi^2 = 3.60$, $p = .058$, $R^2 = 1\%$), such that individuals with two valine alleles (i.e., the val/val genotype) tended to have lower *d'* compared to those with at least one methionine allele (i.e., the val/met and met/met genotypes) (Figure 3). There were no significant differences in *d'* across *DAT1* genotypes (all p's > .05) (Figure 3). There were also significant effects of covariates on *d'*, including sex (for *COMT*: Wald's $\chi^2 = 4.98$, $p = .026$, $R^2 = 2\%$; for *DAT1*: Wald's $\chi^2 = 5.05$, $p = .025$, $R^2 = 2\%$), age (for *COMT*: Wald's $\chi^2 = 79.38$, $p = 4.879\times10^{-19}$, $R^2 = 24\%$; for *DAT1*: Wald's $\chi^2 = 79.76$, $p = 4.337\times10^{-19}$, $R^2 = 24\%$), and age^2 (for *COMT*: Wald's $\chi^2 = 31.74$, $p = 1.768\times10^{-8}$, $R^2 = 10\%$; for *DAT1*: Wald's $\chi^2 = 31.57$, $p = 1.922\times10^{-8}$, $R^2 = 10\%$).

There were no significant differences in lnβ across *COMT* genotypes (all p's > .05; see Figure 4). There was a marginally significant linear trend in lnβ across *DAT1* genotypes (Wald's $\chi^2 = 3.54$, $p = .060$, $R^2 = 1\%$), such that the presence of a 10-repeat allele was associated with more conservative response biases, and individuals with at least one 10-repeat allele (i.e., the 9/10 and 10/10 genotypes) tended to respond more conservatively than those with no 10-repeat allele (i.e., the 9/9 genotype) (Wald's $\chi^2 = 3.17$, $p = .075$, $R^2 = 1\%$) (Figure 4). There were also significant effects of covariates on lnβ, including sex (for *COMT*: Wald's $\chi^2 = 5.09$, $p = .024$, $R^2 = 2\%$; for *DAT1*: Wald's χ^2

= 5.14, p = .023, R^2 = 2%), sex × age (for *COMT*: Wald's χ^2 = 5.61, p = .018, R^2 = 2%; for *DAT1*: Wald's χ^2 = 5.53, p = .019, R^2 = 2%), and (sex × age)^2 (for *COMT*: Wald's χ^2 = 4.10, p = .043, R^2 = 1%; for *DAT1*: Wald's χ^2 = 4.08, p = .043, R^2 = 1%).

Tests of Association between the CPT Indices Across Blocks and *COMT* and *DAT1*

Table 3 summarizes the results from the univariate omnibus tests of association between the CPT indices across blocks and *COMT* and *DAT1*.

There was a significant difference in omission errors across the blocks (F = 21.37, $p = 4.406\times10^{-12}$, η_p^2 = 6%), with a significant linear trend (F = 44.39, $p = 1.191\times10^{-10}$, η_p^2 = 12%), such that omission errors increased across the blocks. The omission errors across blocks also significantly differed by age (F = 11.97, $p = 4.940\times10^{-7}$, η_p^2 = 4%), by age^2 (F = 3.95, p = .011, η_p^2 = 1%), and by sex × age (F = 3.44, p = .021, η_p^2 = 1%), with significant linear trends for omission errors across blocks by age (F = 25.86, $p = 6.291\times10^{-7}$, η_p^2 = 8%), by age^2 (F = 7.81, p = .006, η_p^2 = 2%), and by sex × age (F = 6.45, p = .012, η_p^2 = 2%). There were no significant interactions between omission errors across the blocks and either gene (all p's > .05).

There was a significant difference in commission errors across the blocks (F = 3.79, p = .012, η_p^2 = 1%), with a significant linear trend (F = 6.59, p = .011, η_p^2 = 2%), such that the commission errors decreased across the blocks. The commission errors across blocks also significantly differed by (sex × age)^2 (F = 3.97, p = .010, η_p^2 = 1%), with a significant linear (F = 5.64, p = .018, η_p^2 = 2%) and quadratic trend (F = 4.95, p = .027, η_p^2 = 2%). There were no significant interactions between commission errors across the blocks and either gene (all p's > .05).

There were no significant differences in *d'* across the blocks (F = 0.11, p = .949, $\eta_p^2 \approx 0\%$). The *d'* index across blocks significantly differed by sex × age (F = 3.10, p = .028, $\eta_p^2 = 1\%$), with a significant linear trend (F = 7.28, p = .007, $\eta_p^2 = 2\%$). There were no significant interactions between *d'* across the blocks and either gene (all p's > .05).

There were no significant differences in lnβ across the blocks (F = 0.23, p = .801, $\eta_p^2 \approx 0\%$). There was a marginally significant interaction between lnβ across the blocks and *COMT* (when *COMT* was entered in the model before *DAT1*: F = 1.99, p = .091, η_p^2 = 1%; when *DAT1* was entered in the model before *COMT*: F = 2.03, p = .085, $\eta_p^2 = 1\%$), with a marginally significant linear (when *COMT* was entered in the model before *DAT1*: F = 2.49, p = .085, $\eta_p^2 = 2\%$; when *DAT1* was entered in the model before *COMT*: F = 2.55, p = .080, $\eta_p^2 = 2\%$) and cubic trend (when *COMT* was entered in the model before *DAT1*: F = 2.49, p = .084, $\eta_p^2 = 2\%$; when *DAT1* was entered in the model before *COMT*: F = 2.57, p = .078, $\eta_p^2 = 2\%$). Upon further inspection of the data, it appeared that there were no clear, distinguishable patterns in lnβ across blocks that differentiated the *COMT* genotypes.

Discussion

In the present study, we investigated the effects of commonly studied markers in *COMT* and *DAT1* on AX-CPT performance indices (i.e., omission and commission errors, sensitivity, and response bias), considering both overall performance and performance across blocks of the task. Our analyses of the overall summary indices revealed a marginally significant association between the *val*$^{108/158}$*met* polymorphism of *COMT* and commission errors and sensitivity (*d'*), consistent with previous findings (Caldú et al., 2007; Eisenberg et al., 1999; Liao et al., 2009). Specifically, children with

two valine (val) alleles tended to exhibit lower *d'* scores and increased commission errors compared to children with at least one methionine (met) allele. We also found a significant association between the 40-bp repeat VNTR of *DAT1* and commission errors, consistent with previous findings that the 10-repeat allele was associated with increased commission errors (Caldú et al., 2007; Loo et al., 2003). In addition we found a marginally significant linear trend between *DAT1* and response bias (lnβ), such that the 10-repeat allele was associated with under-responding (i.e., higher lnβ scores). Contrary to this finding, a previous study suggested that the 10-repeat allele was associated with over-responding (i.e., lower lnβ scores), although in a relatively small sample of children ($N = 27$) compared to our current sample (Loo et al., 2003). Findings for lnβ in children with ADHD compared to controls have also been quite mixed as well (Epstein et al., 2003; Losier et al., 1996; Nuechterlein, 1983), and it has been suggested that a liberal criterion is more likely depending on task parameters (i.e., if the task is difficult and the targets are rare) (van Leeuwen et al., 1998), which warrants further investigation in the literature.

Lastly, our analyses of performance indices across blocks of the CPT revealed a trend for the influence of *COMT* on lnβ, but upon further examination of the data, clear patterns of differences across the genotypes were not observed. It is plausible that response style trajectories during the AX-CPT could reflect patterns of consistency in cognitive performance, consistent with previous research suggesting that *COMT* may be associated with stability in CPT performance (Stefanis et al., 2005). Fluctuations in distinct indices across blocks of a task may capture a more detailed characterization of performance compared to overall summary indices, especially in tasks that measure the

maintenance of some cognitive ability over time (e.g., sustained attention in CPTs). As studies of genetic influences on distinct CPT performance indices are currently limited, particularly for trajectories of indices during the course of the task, further research is needed to elucidate the neurobiology of these component indicators of performance.

Our findings provide support for a potential double genetic dissociation between *COMT* and *DAT1*, which has previously been suggested in the literature. *COMT* is primarily expressed in the dorsolateral prefrontal cortex (DLPFC), with minimal expression in the striatum (Matsumoto et al., 2003a, b), while *DAT1* is abundantly expressed in the striatum and midbrain, with minimal expression in frontal cortical regions (Ciliax et al., 1999; Lewis et al., 2001; Morón et al., 2002; Schott et al., 2006; Sesack et al., 1998). In addition to this neuroanatomical dissociation, these two circuits may reflect overlapping yet unique aspects of executive functioning and decision-making mechanisms, which would also suggest a functional dissociation. This has been characterized in various models of attention that implicate prefrontal regions in top-down control and maintenance of relevant information, and the basal ganglia in bottom-up arousal mechanisms and inhibition of irrelevant behaviors (e.g., Halperin & Schulz, 2006; Johnson et al., 2007; O'Connell et al., 2008). Specifically for AX-CPTs, computational models of prefrontal and subcortical (e.g., midbrain, basal ganglia) interactions have been proposed, implicating prefrontal regions in the active maintenance of context information (i.e., the 'A' that is presented before the 'X'), and subcortical regions in the flexible and selective updating of representations (Braver & Cohen, 2000; Frank, Loughry, & O'Reilly, 2001). Proficiency in using context information in the AX-CPT can be reflected in the *d'* index (Cohen, Barch, Carter, & Servan-Schreiber, 1999),

for which the DLPFC plays a critical role (Braver & Cohen, 2000, 2001; Braver, Cohen, & Barch, 2002). *COMT* has been shown to be related to prefrontal cognition, specifically top-down, goal-directed maintenance of information (Egan et al., 2001), consistent with our findings showing a marginal association between *COMT* and *d'*. In contrast, *DAT1* has been implicated in inhibitory control processes (Cornish et al., 2005), which could reflect aspects of impulsivity (Logan, Schachar, & Tannock, 1997). Our study suggested associations between *DAT1* and response bias and commission errors, indices which have been shown to be associated with impulsivity (Brooks et al., 2006; Keilp et al., 2005; McGee et al., 2000).

Our study also has implications for individual differences in personality traits associated with certain CPT indices. For example, both *COMT* and *DAT1* have been shown to influence impulsivity (Paloyelis, Asherson, Mehta, Faraone, & Kuntsi, 2010), a key component of ADHD (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001), as well as risk-taking (Kreek, Nielsen, Butelman, & LaForge, 2005). As discussed, CPT commission errors likely reflect deficits in inhibitory control that manifests as increased impulsivity (Brooks et al., 2006), and a more liberal response style on the CPT has also been associated with impulsivity as well as risk-taking (Keilp et al., 2005; McGee et al., 2000). Our results suggest associations with commission errors for both *COMT* and *DAT1*, albeit to a greater degree for *DAT1*, which may indicate some overlapping genetic influences. Nonetheless, a novel and interesting finding in the present study is the preliminary evidence for the dissociable effects of *COMT* and *DAT1* on specific signal detection (SDT) indices (i.e., *d'* and lnβ). This lends support to the utility of SDT indices over traditional omission and commission errors, and suggests that the SDT indices may

allow for a more effective method of characterizing accuracy and error in decision-making processes.

Although the present findings have important implications for genetic influences on CPT performance, as well as molecular genetic studies of ADHD, several limitations should be noted. Since single polymorphisms exert very weak main effects, there is a need for replication in larger samples of children in order to provide sufficient statistical power (Lohmueller, Pearce, Pike, Lander, & Hirschhorn, 2003). Further research should also explore other genes that are highly expressed in neural regions or pathways that are associated with specific CPT performance indices. For example, β has been shown to be significantly associated with parietal cortical activity (Loo et al., 2009), and accordingly, future studies may investigate the effects of genes that are widely expressed in the parietal cortex, such as the Cadherin-6 gene (*CDH6*) (Suzuki, Inoue, Kimura, Tanaka, & Takeichi, 1997) or the ephrin-A5 gene (*EFNA5*) (Mackarehtschian, Lau, Caras, & McConnell, 1999). In addition, given that other psychiatric disorders such as schizophrenia have also been shown to involve impairment in attentional processes that are influenced by *COMT* (e.g., Neuhaus et al., 2009), questions remain about the specificity of the CPT in discriminating ADHD from other psychiatric disorders (e.g., Barkely, DuPaul, & McMurray, 1990; Koriath, Gualtieri, Van Bourgondien, Quade, & Werry, 1985), although there is evidence that the CPT is able to differentiate between subtypes of ADHD (e.g. Egeland, Johansen, & Ueland, 2009). Furthermore, as numerous versions of the CPT exist, it is important to investigate the generalizability of our findings to other CPT variations. Differences in CPT task parameters may influence discrete aspects of performance by placing different demands on certain cognitive abilities

(Solanto et al., 2004), resulting in conflicting findings in the literature regarding CPT performance, as has been noted in comparisons of β between children with ADHD and controls (van Leeuwen et al., 1998). In addition, while our study examined four indices frequently used to analyze CPT performance, other indices that also provide valid measures of specific constructs, such as the Halperin error indices (Halperin et al., 1988), may be informative for understanding genetic factors involved in distinct underlying cognitive mechanisms (e.g., Gizer & Waldman, in press).

In conclusion, our results provide support for the effects of *COMT* and *DAT1* on distinct AX-CPT summary indices, in addition to having somewhat overlapping genetic effects. Further, our findings suggest that additional research is needed to investigate genetic influences on the trajectories of specific indices across the task. The implication of a double genetic dissociation in SDT indices but overlapping effects for commission errors represents a novel contribution to the psychopathology literature that warrants further investigation, particularly in children. Further studies are needed to replicate our findings in other samples, and also to investigate other genes that may be involved in AX-CPT performance. As the neurobiology of AX-CPT performance indices becomes better understood, research could potentially elucidate the underlying mechanisms by which these candidate genes confer risk for ADHD. Future research should aim to evaluate the validity and utility of AX-CPT performance indices as putative endophenotypes for ADHD (e.g., Waldman, 2005).

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Table 1

Association Analyses of COMT with the Overall Summary CPT Indices

	Omission errors				Commission errors				*d'*				lnβ			
Predictor	Wald's χ^2	df	*p*	R^2	Wald's χ^2	df	*p*	R^2	Wald's χ^2	df	*p*	R^2	Wald's χ^2	df	*p*	R^2
Sex	1.06	1	.304	0%	11.56	1	.001**	3%	4.98	1	.026**	2%	5.09	1	.024**	2%
Age	108.11	1	.001**	33%	122.92	1	.001**	37%	79.38	1	4.879×10^{-19}**	24%	0.12	1	.735	0%
Age^2	5.74	1	.017**	2%	1.37	1	.243	0%	31.74	1	1.768×10^{-8}**	10%	0.23	1	.632	0%
Sex × Age	0.30	1	.583	0%	3.93	1	.047**	1%	2.15	1	.143	1%	5.61	1	.018**	2%
$(Sex \times Age)^2$	0.03	1	.855	0%	0.41	1	.521	0%	0.23	1	.628	0%	4.10	1	.043**	1%
COMT	2.86	2	.239	1%	5.89	2	.053*	2%	3.57	2	.168	1%	2.63	2	.268	1%
COMT val/val vs. val/met & met/met combined	1.15	1	.283	0%	3.61	1	.057*	1%	3.60	1	.058*	1%	0.20	1	.651	0%
COMT val/met vs. met/met	2.25	1	.134	1%	.001	1	.979	0%	0.12	1	.735	0%	1.27	1	.260	0%

* $p < .10$. ** $p < .05$.

Table 2

Association Analyses of DAT1 with the Overall Summary CPT Indices

	Omission errors				Commission errors				*d'*				lnβ			
Predictor	Wald's χ^2	df	*p*	R^2	Wald's χ^2	df	*p*	R^2	Wald's χ^2	df	*p*	R^2	Wald's χ^2	df	*p*	R^2
Sex	0.87	1	.351	0%	11.34	1	.001**	3%	5.05	1	.025**	2%	5.14	1	.023**	2%
Age	102.78	1	.001**	31%	108.28	1	.001**	33%	79.76	1	4.337×10^{-19}**	24%	0.11	1	.745	0%
Age^2	6.27	1	.012**	2%	0.33	1	.566	0%	31.57	1	1.922×10^{-8}**	10%	0.23	1	.633	0%
Sex × Age	0.15	1	.696	0%	3.74	1	.053*	1%	2.09	1	.149	1%	5.53	1	.019**	2%
$(Sex \times Age)^2$	0.04	1	.849	0%	0.06	1	.810	0%	0.28	1	.596	0%	4.08	1	.043**	1%
DAT1	0.79	2	.675	0%	9.07	2	.011**	3%	0.78	2	.677	0%	3.49	2	.175	1%
DAT1 9/9 vs. 9/10 & 10/10 combined	0.09	1	.763	0%	9.64	1	.002**	3%	0.50	1	.481	0%	3.17	1	.075*	1%
DAT1 9/10 vs. 10/10	0.51	1	.476	0%	1.53	1	.217	0%	0.44	1	.506	0%	1.62	1	.204	0%

* $p < .10$. ** $p < .05$.

Table 3

Univariate Omnibus Analyses for CPT Indices Across Blocks

	Omission errors			Commission errors			*d'*			lnβ		
	F	*p*	η_p^2	F	*p*	η_p^2	F	*p*	η_p^2	F	*p*	η_p^2
Block	21.37	4.406×10^{-12}**	6%	3.79	.012**	1%	0.11	.949	0%	0.23	.801	0%
Linear	44.39	1.191×10^{-10}**	12%	6.59	.011**	2%	0.04	.841	0%	0.39	.533	0%
Quadratic	1.09	.298	0%	3.59	.059*	1%	0.19	.664	0%	0.30	.582	0%
Cubic	3.43	.065*	1%	0.04	.848	0%	0.13	.724	0%	0.01	.919	0%
Sex × block	0.19	.880	0%	1.05	.367	0%	0.62	.596	0%	0.42	.669	0%
Age × block	11.97	4.940×10^{-7}**	4%	1.10	.345	0%	1.56	.199	1%	0.36	.709	0%
Linear	25.86	6.291×10^{-7}**	8%	2.89	.090*	1%	3.18	.076*	1%	0.67	.415	0%
Quadratic	0.25	.618	0%	0.14	.706	0%	0.39	.531	0%	0.19	.664	0%
Cubic	0.40	.529	0%	0.03	.866	0%	0.50	.480	0%	0.29	.590	0%
Age^2 × block	3.95	.011**	1%	1.17	.320	0%	0.18	.903	0%	1.01	.366	0%
Linear	7.81	.006**	2%	3.08	.080*	1%	0.03	.873	0%	0.13	.715	0%
Quadratic	0.24	.628	0%	0.04	.841	0%	0.03	.858	0%	1.58	.210	1%
Cubic	1.40	.237	0%	0.18	.670	0%	0.61	.437	0%	1.09	.298	0%
(Sex × Age) × block	3.44	.021**	1%	1.56	.201	1%	3.10	.028**	1%	0.81	.451	0%
Linear	6.45	.012**	2%	4.31	.039**	1%	7.28	.007**	2%	2.84	.093*	1%
Quadratic	1.34	.249	0%	0.02	.898	0%	0.32	.575	0%	0.01	.934	0%
Cubic	0.27	.604	0%	1.86×10^{-3}	.966	0%	0.07	.794	0%	3.18×10^{-3}	.955	0%
$(Sex \times Age)^2$ × block	1.03	.375	0%	3.97	.010**	1%	1.58	.195	1%	0.32	.739	0%
Linear	0.76	.383	0%	5.64	.018**	2%	2.46	.118	1%	0.44	.509	0%
Quadratic	0.43	.512	0%	4.95	.027**	2%	0.77	.382	0%	0.47	.495	0%
Cubic	2.43	.120	1%	1.16×10^{-5}	.997	0%	1.21	.273	0%	0.02	.895	0%
COMT × block	1.23/1.26[a]	.292/.279[a]	1%	0.87/0.85[a]	.513/.526[a]	1%	0.89/0.90[a]	.501/.491[a]	1%	1.99/2.03[a]	.091*/.085*[a]	1%
Linear	1.98/2.01[a]	.140/.136[a]	1%	0.54/0.50[a]	.584/.607[a]	0%	0.15/0.17[a]	.865/.847[a]	0%	2.49/2.55[a]	.085*/.080*[a]	2%
Quadratic	0.10/0.11[a]	.904/.896[a]	0%	1.57/1.54[a]	.210/.216[a]	1%	1.86/1.84[a]	.157/.161[a]	1%	1.24/1.23[a]	.292/.294[a]	1%
Cubic	1.34/1.38[a]	.265/.254[a]	1%	0.24/0.27[a]	.786/.766[a]	0%	0.84/0.89[a]	.433/.415[a]	0-1%	2.49/2.57[a]	.084*/.078*[a]	2%
DAT1 × block	0.43/0.46[b]	.836/.817[b]	0%	0.34/0.33[b]	.904/.914[b]	0%	0.72/0.73[b]	.632/.621[b]	0-1%	0.32/0.36[b]	.871/.844[b]	0%

* $p < .10$. ** $p < .05$.

a: *DAT1* is entered in the model before *COMT*, b: *COMT* is entered in the model before *DAT1*

Figure 1

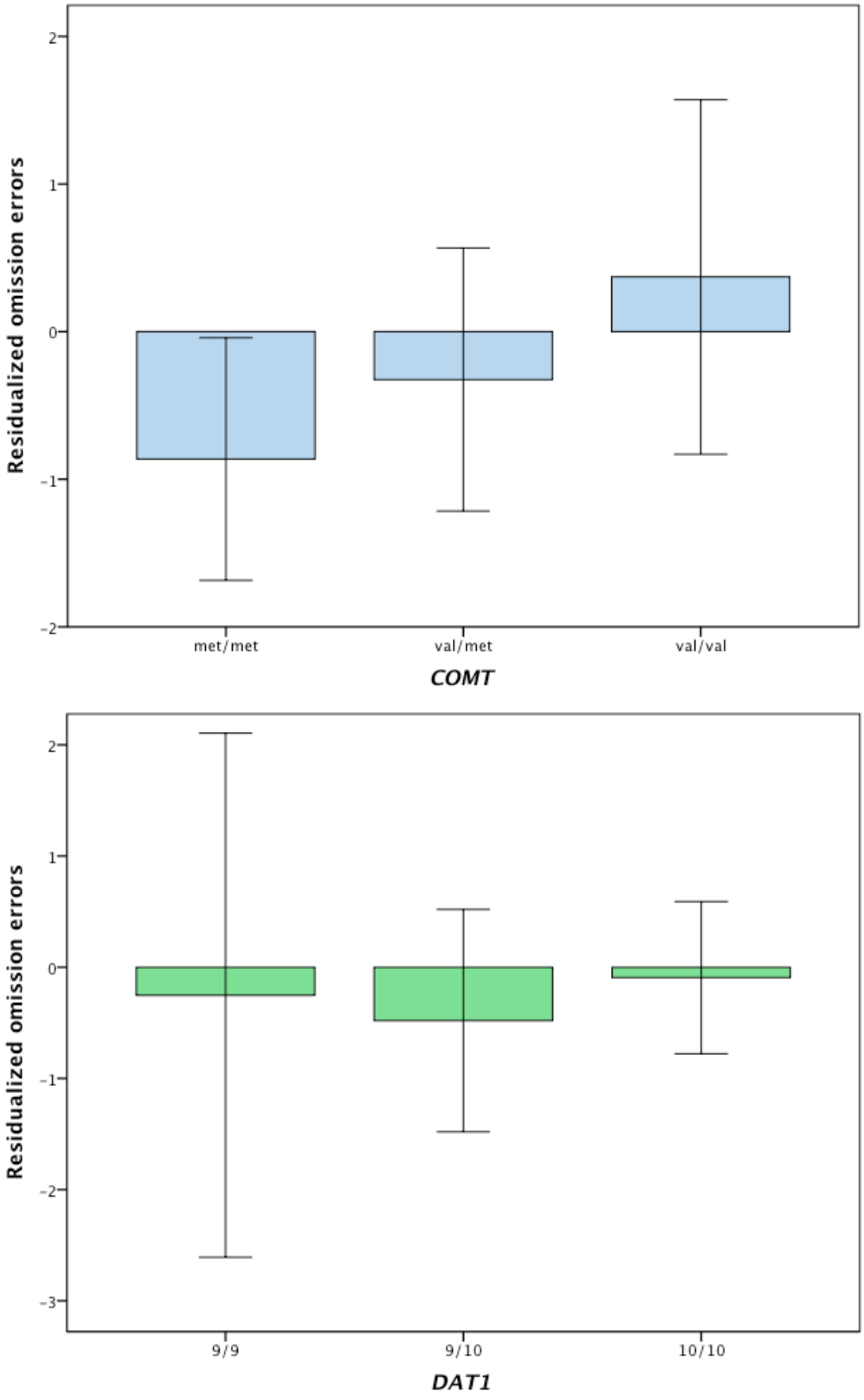

Figure 1. Association between residualized omission errors and *COMT* and *DAT1*.

Figure 2

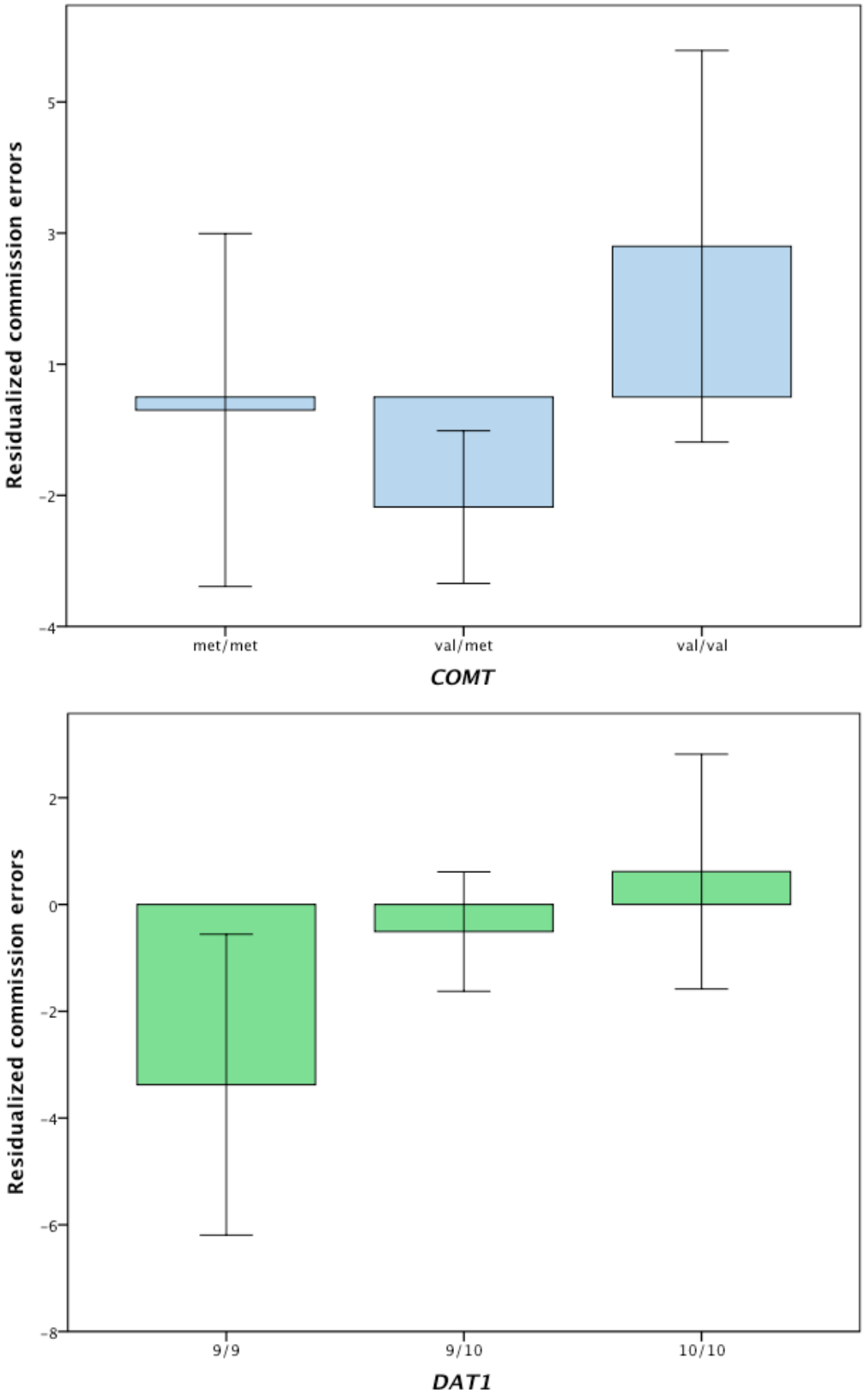

Figure 2. Association between residualized commission errors and *COMT* and *DAT1*.

Figure 3

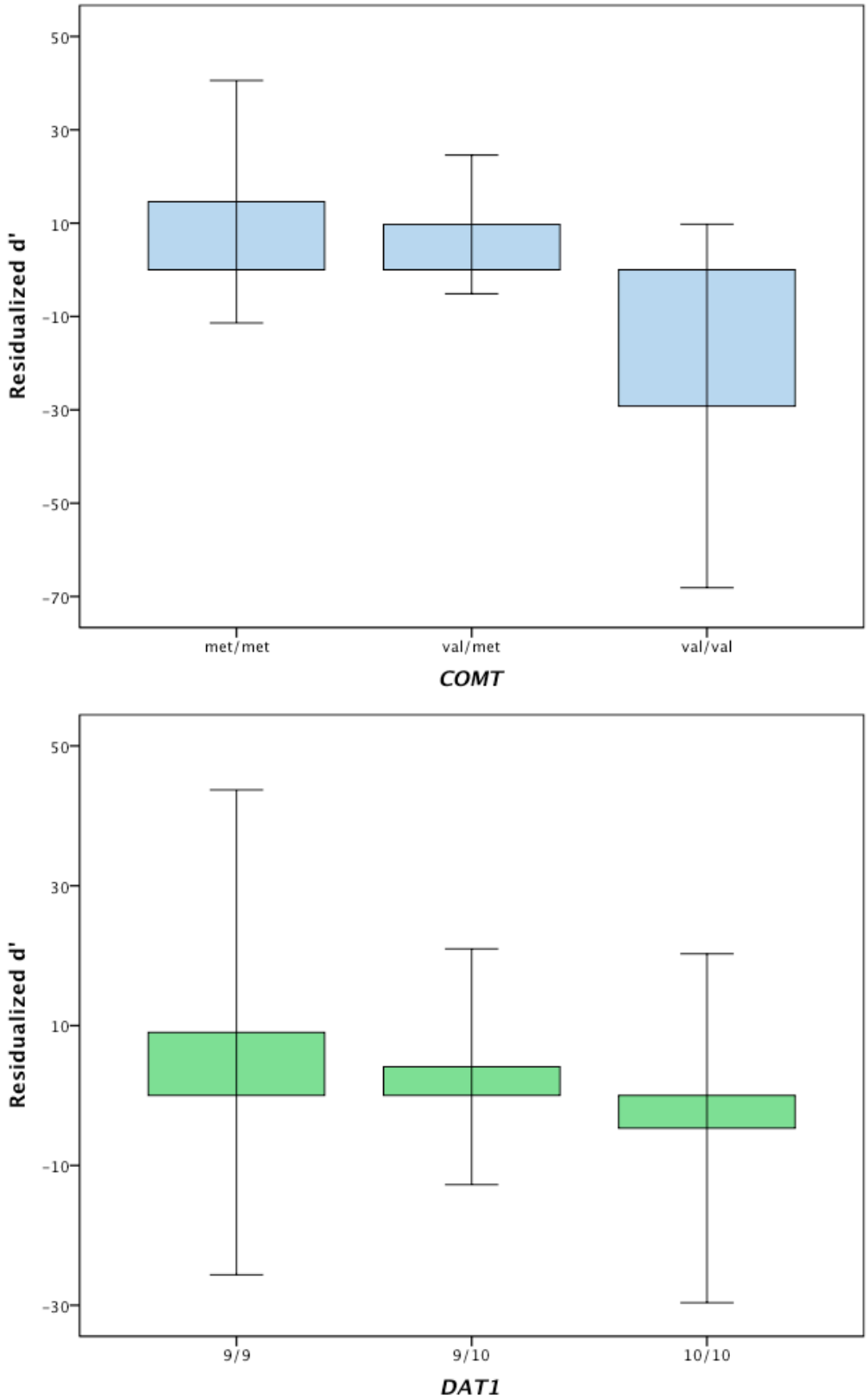

Figure 3. Association between residualized *d'* and *COMT* and *DAT1*.

Figure 4

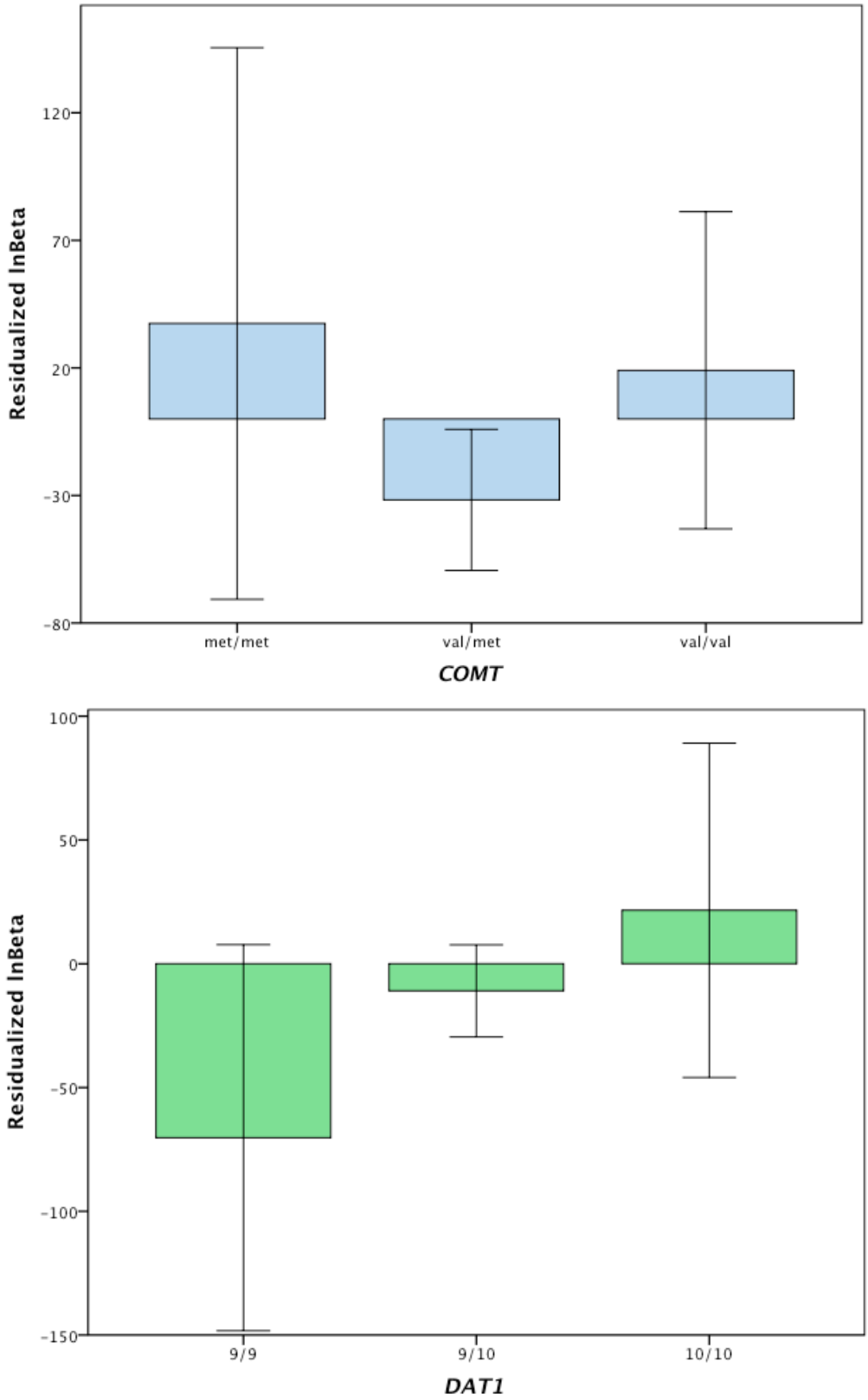

Figure 4. Association between residualized lnß and *COMT* and *DAT1*.