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COMT Polymorphisms and Anxiety-Related Personality Traits

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High neuroticism and low extraversion are characteristic of anxiety-prone individuals. A functional variant in the catechol-*O*-methyltransferase (COMT) gene, the Val158Met ('val/met') polymorphism, has been associated in some prior studies with several phenotypes, including neuroticism. We tested the hypothesis that the val158met polymorphism would be associated with both high neuroticism and low extraversion, making it a plausible candidate locus for anxiety susceptibility. To determine whether val158met is responsible for these effects, we also evaluated the association with haplotypes that included two other SNPs within the COMT gene. We collected a sample of 497 undergraduate college students who were phenotyped on a personality inventory (the NEO-Personality Inventory-Raised (NEO-PI-R)). Subjects were genotyped for three COMT polymorphisms: the well-studied nonsynonymous SNP rs4680 that generates a valine-to-methionine substitution (val158met), rs737865 (near exon #1), and rs165599 (also functional, near the 3′-UTR). Together, these three SNPs define a haplotype that is associated with reduced COMT expression in human brain. Logistic regression analyses were used to examine the effects of individual SNPs on extraversion and neuroticism scores. Score tests for association between these traits (quantitatively and dichotomously considered) and haplotypes were also conducted. We evaluated potential for population stratification artifact by genotyping a set of 36 unlinked highly polymorphic markers previously demonstrated to distinguish sufficiently ancestry of major American populations. Two of the SNPs (rs4680 ('val/met') and rs737865) were significantly associated with (low) extraversion and, less consistently, with (high) neuroticism, with effects confined to women. A significant association between COMT haplotype and (low) extraversion and (high) neuroticism was also observed. Formal testing showed that population structure did not explain the findings. These data suggest that involvement of the COMT locus in susceptibility to anxiety-related traits (ie low extraversion and high neuroticism) is unlikely to be wholly accounted for by the well-studied rs4680 ('val/met') polymorphism. Other functional variants may exist that contribute to this relationship. Possible sex-specific effects remain to be further studied and explained. *Neuropsychopharmacology* (2005) **30,** 2092–2102. doi:10.1038/sj.npp.1300787; published online 8 June 2005

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INTRODUCTION

Neuroticism is viewed as a risk factor (or personality template) for mood and anxiety disorders (Andrews *et al*, 2002; Hirschfeld *et al*, 1989; Kendler *et al*, 2002). Moreover, particularly in the case of major depression, there is evidence that neuroticism interacts with psychosocial stress to yield psychopathology (Kendler *et al*, 2003, 2004). As such, elucidating the genetics of personality traits such as neuroticism may contribute to a better understanding of the etiology of these disorders (Bienvenu and Stein, 2003; Fullerton *et al*, 2003; Reif and Lesch, 2003; Van Gestel and Van Broeckhoven, 2003).

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Numerous studies have evaluated possible associations between candidate genes and neuroticism (and other anxiety-related traits). Most frequently studied in this regard has been the serotonin transporter promoter polymorphism (5-HTTLPR). Two recent meta-analyses (that included a substantially overlapping set of studies) found evidence of an association between 5-HTTLPR and neuroticism, although less so with other anxiety-related constructs (eg harm avoidance) (Schinka *et al*, 2004; Sen *et al*, 2004a). Other genes tested for an association with anxiety-related traits have included monoamine oxidase type A (Eley *et al*, 2003; Jorm *et al*, 2000), cytochrome *P*450 2D6 isoenzyme (Roberts *et al*, 2004), GABA-A receptor alpha-6 subunit (Sen *et al*, 2004b) and, in a number of studies, catechol-*O*-methyltransferase (COMT) (Eley *et al*, 2003; Enoch *et al*, 2003; Henderson *et al*, 2000).

Henderson and colleagues, in a community sample of 2237 Caucasians, found no association between a common COMT polymorphism (rs165688, also known as rs4680, and variously referred to in the literature as val/met or val108met or val158met) and either neuroticism or anxiety

or depressive symptoms (Henderson *et al*, 2000). In a sample of community subjects selected for either high or low on neuroticism, Eley *et al* (2003) found weak evidence for association with COMT val158met genotype, when females and males were considered separately. Another recent study of 101 patients with phobic disorders and 202 age-, sex-, and ethnicity-matched control subjects failed to find an association with val158met and phobic disorders (Samochowiec *et al*, 2004). In a sample of 1234 female nurses, McGrath and colleagues found an association of val158met genotype with phobic anxiety as measured by the Crown–Crisp experimental index, wherein homozygosity for the val allele was associated with a doubling of odds of having high phobic anxiety, compared to met homozygosity (McGrath *et al*, 2004).

When looking at patients with panic disorder, four of five association studies (one of which also provided evidence of linkage; Hamilton *et al*, 2002) have implicated COMT as a probable risk locus (Domschke *et al*, 2004; Hamilton *et al*, 2002; Ohara *et al*, 1998; Woo *et al*, 2002, 2004). Thus, the bulk of the published data implicate the COMT gene or a nearby region as a susceptibility locus for panic disorder and other anxiety-related traits, although the specific site(s) within the gene that confer this susceptibility, and the apparent sex-specific effects (in some studies), remain to be established.

The COMT gene (MIM 116790) has been widely speculated (and in some cases, shown) to be associated with a variety of neuropsychiatric disorders and putative endophenotypes beyond panic disorder. It has been extensively studied as a candidate gene for schizophrenia, with some replicated evidence of the involvement of the val/met (rs4680) variant in the etiology of this syndrome (Glatt *et al*, 2003). (COMT also maps in the usual deletion region for velocardiofacial syndrome, which is itself associated with increased risk for schizophrenia; Pulver *et al*, 1994.) The COMT val allele is associated with less efficient prefrontal cognition in persons with schizophrenia (Goldberg *et al*, 2003), presumably through its established effects to increase prefrontal dopamine catabolism that are thought to contribute to an optimization or 'fine-tuning' of dopamine signaling, particularly under conditions of high dopamine load (Akil *et al*, 2003; Bilder *et al*, 2004; Seamans *et al*, 2001a, b; Winterer and Goldman, 2003). Although functional analysis of genetic variation in COMT suggests that rs4680 val activity is the predominant factor determining COMT activity in the prefrontal cortex (Chen *et al*, 2004a), other variants in the COMT gene have also been recently associated with schizophrenia. In particular, the rs165599 SNP (located near the 3′ -UTR of the gene) has been strongly associated with schizophrenia, especially in women, in a large case–control study (Shifman *et al*, 2002). Those investigators also found that a haplotype consisting of rs165599–rs4680–rs737865 was very strongly associated with schizophrenia in their sample. In Irish families with a high density of schizophrenia, a different haplotype, composed of the same three markers but having only the 'val' allele in common, was recently reported to be preferentially transmitted to affected subjects (Chen *et al*, 2004b). These observations are of particular interest because this haplotype is associated with reduced COMT expression in human brain (Bray *et al*, 2003).

We therefore extended our investigation of the COMT gene and its relationship to neuroticism to include the three SNPs that comprise this haplotype (Figure 1). We also extended this area of inquiry by looking at another personality trait, extraversion. Although neuroticism has been studied much more extensively in relation to anxiety (and COMT), it could be argued that extraversion is of equal (or greater) relevance than neuroticism to certain anxiety disorders (eg agoraphobia and social phobia) (Bienvenu and Stein, 2003). Extraversion is defined as having high levels of sociability and preference for large groups and gatherings. Costa and McCrae (1992) describe individuals with high levels of extraversion as being assertive, active, talkative, upbeat, energetic, and optimistic. Persons with social phobia or agoraphobia tend to be very low in extraversion (Bienvenu *et al*, 2001), a trait that is at least as heritable as neuroticism (Jang *et al*, 1996, 1998). We have recently shown an influence of a variant in the beta-1-adrenergic receptor gene on extraversion in a sample that overlaps substantially with the sample described herein (Stein *et al*, 2004).

Population subdivision is thought to be a major potential confound for case–control association studies (Freedman *et al*, 2004). We therefore used the method of Pritchard and Rosenberg (1999) to evaluate the potential for spurious association in our study sample that would result from population stratification (Figure 1).

METHODS

Sample and Procedure

Participants ($N = 497$) were recruited from among undergraduate psychology students at San Diego State University (SDSU) who had, in a group testing session (at which some questionnaires were completed and demographic information, including self-reported race/ethnicity, was provided), indicated their willingness to be contacted by research investigators to participate in future psychological experiments. They each came for a scheduled appointment at which a blood sample (60 ml) was drawn for genetic studies and the subjects completed questionnaires and/or computerized tasks. Subjects gave informed, written consent to participate in this part of the study, which was approved by the Human Research Protection Programs at both SDSU and UCSD. Subjects received $25 for providing the blood sample. Sociodemographic characteristics of the subjects are shown in Table 1.

Questionnaires

NEO-Personality Inventory-Revised (NEO-PI-R) is a widely used, 240-item (plus three validity items) self-report

Figure 1 Relative locations of SNPs studied (not to scale).

Table 1 Sociodemographic Characteristics of Study Subjects ($N = 497$)

Variable	Distribution
Age (years) (mean (SD))	18.9 (2.2)
Sex (*n*) (male/female)	154/343 (31.0%/69.0%)
Race/ethnicity	
African American	21 (4.2%)
Asian American	33 (6.6%)
Hispanic American/Latino	99 (19.9%)
Native American	2 (0.4%)
Filipino American	55 (11.1%)
European American	246 (49.5%)
Other or missing	41 (8.2%)

measure of personality, grouped into five major domains: neuroticism (N), extraversion (E), openness to experience (O), conscientiousness (C), and agreeableness (A) (Costa and McCrae, 1992). Each of the five domains also has six, lower-level facets. Some subjects completed a shorter (60-item) version of the NEO, the NEO-Five Factor Inventory (NEO-FFI) (Costa and McCrae, 1992), which provides domain scores (expressed as T scores) that are highly correlated (Pearson's $r > 0.90$ for each of the five domains) with those obtained from the full instrument, but for which more detailed facet-level scores cannot be obtained. T scores were calculated directly from college-age, sex-specific norms (Robert R McCrae PhD, personal communication, November 14, 2001). As noted above, we limited our analyses to the two most widely studied NEO domains, E and N, which also are likely to be most informative with regard to our understanding of genetic influences on anxiety-related traits (Bienvenu and Stein, 2003; Stein and Bienvenu, 2004).

Genotype Analysis

DNA was extracted from frozen whole blood using standard methods. Subjects were genotyped for three COMT polymorphisms: (1) the well-studied rs4680 polymorphism that produces a valine→methionine (val/met) substitution at codon 158 in the membrane-bound form of the COMT transcript; (2) rs737865, located in the first intron; and (3) rs165599, located near the 3′-UTR. Genotypes for rs4680 and rs165599 were obtained using PCR-RFLP techniques. Primers for rs4680 were 5′-agc cct ccg tgc tgc tgg agc tgg-3′ and 5′-cat gcc ctc cct gcc cac agc cgg-3′; the polymorphism was recognized with *Nla*III digestion. Primers for rs165599 were 5′-gaa gga gat gct tcc act ctg t-3′ and 5′-aca ttc aaa gct ccc ctt gac-3′; the polymorphism was recognized with *Msp*I digestion. Restriction enzymes were purchased from New England Biolabs (Beverly, MA, USA). Gels were double-scored and double-entered. In all, 8% of genotypes were repeated at random as quality checks, with complete concordance. Genotypes for rs737865 were obtained using the ABI Taqman system as an 'assay-by-design' with primers (f) 5′-ggc ttg gag ggt cac ttt aaa caa t-3′ and (r) 5′-ccc tgc taa cag acc tgc ttt t-3′, and reporter sequences cac aaa aac ccc tgg ctg (vic) and aca caa aaa tcc ctg gct g (fam). Post-PCR fluorescence detection was accomplished with an ABI 7900 instrument. All Taqman genotypes were repeated in duplicate.

Ancestry-Informative Marker Panel

In all, 36 STR markers were used; selection and evaluation of these markers is described in detail elsewhere (Yang *et al*, 2005). First, we used the AmpFLSTR Identifiler PCR Amplification Kit (Applied Biosystems (ABI), Foster City, CA), marker details available at http://www.appliedbiosystems.com/catalog/myab/StoreCatalog/products/CategoryDetails.jsp?hierarchyID=101&category1st=111763&category2nd=111778&category3rd=111962, which provides data from a set of 15 loci frequently used in forensic applications. Second, we selected 21 markers known to have high δ (calculated as the sum over all alleles of the absolute value of allele frequency difference between two populations divided by 2) between European Americans and African Americans, and in some cases Hispanic and Asian populations (Smith *et al*, 2001). Markers included were D1S196, D1S2628, D2S162, D2S319, D5S407, D5S410, D6S1610, D7S640, D7S657, D8S272, D8S1827, D9S175, D10S197, D10S1786, D11S935, D12S352, D14S68, D15S1002, D16S3017, D17S799, and D22S274. All STR markers were analyzed on an ABI PRISM 3100 semiautomated capillary fluorescence sequencer. Data were scored using Genemapper (ABI). The average missing data rate for ancestry-informative markers was 10%.

Data Analysis

Most calculations, including linear regression analyses, were made using the biostatistical analysis program STATA (Version 8.2) (StataCorp, 2003). Between-group (ie, sex, ethnicity) differences in means are tested using Student's *t*-test; 95% confidence intervals (CIS) for the differences between groups are also provided. Deviation from the genotype counts predicted by Hardy–Weinberg (HW) equilibrium expectations was tested with the installed user-written STATA package 'sg110' available at http://www.stata.com/stb/stb48. The value of D', a standardized measure of linkage disequilibrium (LD) (Lewontin 1988), was computed. Allele frequencies were compared between the two largest ethnic groups in our sample (ie European American (EA) and Hispanic) using χ^2 analysis.

Robust regression analyses were used to predict scores on the questionnaire measures using genotype as the independent variable. Power to detect a quantitative trait locus accounting for 2% of the phenotypic variance, given the sample size and frequency for the biallelic marker, was over 90% (Purcell *et al*, 2003). Analysis of variance was also used to compare questionnaire scores by genotype, in order to demonstrate the existence of dose–response relationships. Odds ratios, on an allelic basis (Sasieni, 1997), were calculated to demonstrate the association between particular polymorphisms and extraversion scores (dichotomized into appropriate groupings); these tests were conducted with the installed user-written STATA package 'genassoc'

written by David Clayton and available at http://www-gene.cimr.cam.ac.uk/clayton/software/stata. Analyses stratified by sex are also reported, but stratification by self-reported race/ethnicity was not possible owing to the substantially reduced power for such analyses (eg sample size for Hispanics ranges from 86 to 99 for various analyses).

We used the haplo.score package (version 1.0.2, dated September 13, 2002; available at http://www.mayo.edu/statgen). This software computes score statistics (which test the null hypothesis of no association of the trait with the genotype) to evaluate associations between ambiguous (reconstructed) haplotypes and traits (including quantitative traits) in unrelated subjects, and can consider the effects of nongenetic covariates (Schaid *et al*, 2002). The method is particularly useful when there may be more than one functional variant at the locus (as for COMT). An additional advantage is that speed of computation allows for empirical evaluation of statistical significance by means of simulation.

The Pritchard and Rosenberg stratification test statistic was computed with STRAT software (Pritchard *et al*, 2000). This test statistic (which is based on summing the χ^2 test statistics for case–control comparisons at each of the unlinked stratification test loci) allows determination of whether cases and controls are appropriately matched; if mismatched, they are potentially subject to stratification error. Since this test can be performed only with binary (not quantitative) phenotypes, we recoded phenotypes to affection or nonaffection using a median split for these analyses. This should be a reasonable approximation, because the phenotypes (ie extraversion and neuroticism) followed a normal distribution (Figure 2).

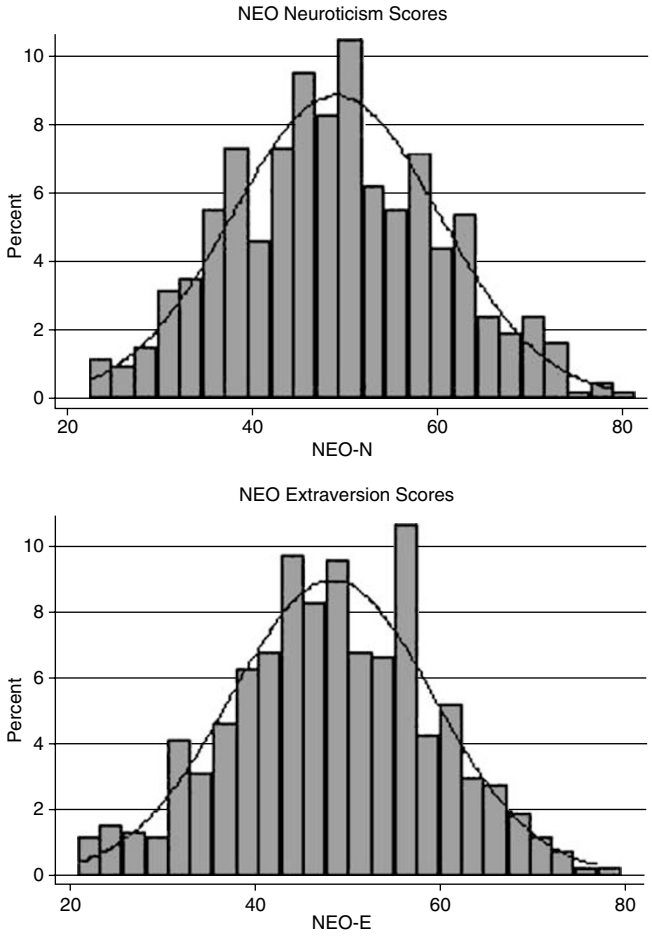

Figure 2 Distribution of NEO neuroticism (NEO-N; top) and extraversion (NEO-E; bottom) *T*-scores ($N = 497$).

RESULTS

Behavioral Measures

Distribution of NEO-E and NEO-N T-scores in the sample is shown in Figure 1. There were no significant differences in NEO-E scores between EA and Hispanic subjects, but EAs had significantly higher NEO-N scores (50.2 SD 11.9 *vs* 47.3 SD 10.5; $t = 2.10$, $df = 343$, $p = 0.04$).

COMT Allele and Genotype Frequencies

There was no deviation from HW equilibrium expectations at any of the three loci for the overall sample. Distributions of the genotypes and alleles for all three loci are shown in Table 2. LD between the three loci was determined separately in EAs and Hispanics. In EAs: for rs165599 and rs4680, Lewontin's $D' = 0.51$; for rs165599 and rs737865, $D' = 0.21$; and for rs4680 and r737865, $D' = 0.73$. In Hispanics: for rs165599 and rs4680, Lewontin's $D' = 0.96$; for rs165599 and rs737865, $D' = 0.05$; and for rs4680 and r737865, $D' = 0.58$.

Ethnic differences. There was no deviation from HW equilibrium expectations for any of the three polymorphic systems in either the EA or Hispanic subgroups. However, there were significant ethnic differences in the allelic distribution of all three systems: rs16559 ($\chi^2 = 11.35$, $df = 1$, $p < 0.0005$), rs4680 ($\chi^2 = 7.09$, $df = 1$, $p = 0.008$), and rs737865 ($\chi^2 = 8.77$, $df = 1$, $p = 0.003$) (Table 2). The EA genotype frequencies for rs165599 are similar to those reported elsewhere for 'Mixed Europeans' (Palmatier *et al*, 2004), for a large control (for breast cancer cases) sample of white Americans (Millikan *et al*, 1998), and for a large control (for schizophrenia cases) sample of Israelis of predominantly European descent (Shifman *et al*, 2002). The EA genotype frequencies for rs737865 in our study show a lower frequency of the rarer homozygous type (G/G) than in another study (Shifman *et al*, 2002); reasons for this difference are unclear. The EA rs4680 genotype frequencies in our study are also similar to those found in these two other studies (Millikan *et al*, 1998; Shifman *et al*, 2002).

Population Stratification Test

Extraversion. The two groups (ie created by split along median extraversion level for all subjects) were not significantly different by self-reported race/ethnicity ($\chi^2 = 2.79$, 5 df, $p = 0.73$). $N = 441$ subjects with complete data; $\sum\chi^2 = 245.8$ (284 df), $p =$ NS. Thus, by this test, use of this entire sample with the extraversion phenotype should not be subject to stratification artifact.

Neuroticism. The two groups (ie created by split along median neuroticism level for all subjects) were not

Table 2 Allele and Genotype Distribution of the COMT Receptor Polymorphisms

	Allele frequency (%)		Genotype frequency (%)		
Variant	**G**	**A**	**G/G**	**A/G**	**A/A**
rs737865					
Total sample ($N=473$)	252 (0.266)	694 (0.734)	28 (0.059)	196 (0.414)	249 (0.526)
European American only ($N=232$)	145 (0.313)	319 (0.688)	16 (0.069)	113 (0.487)	103 (0.444)
Hispanic only ($N=93$)	36 (0.194)	150 (0.806)	1 (0.018)	34 (0.366)	58 (0.624)
	val (G)	**met (A)**	**val/val**	**val/met**	**met/met**
rs4680 ('val/met')					
Total sample ($N=497$)	591 (0.595)	403 (0.405)	185 (0.372)	221 (0.445)	91 (0.183)
European American only ($N=246$)	254 (0.516)	238 (0.484)	66 (0.268)	122 (0.496)	58 (0.236)
Hispanic only ($N=99$)	125 (0.631)	73 (0.369)	43 (0.434)	39 (0.394)	17 (0.172)
	G	**A**	**G/G**	**A/G**	**A/A**
rs165599					
Total sample ($N=461$)	372 (0.404)	550 (0.597)	81 (0.176)	210 (0.456)	170 (0.369)
European American only ($N=225$)	152 (0.338)	298 (0.662)	25 (0.111)	102 (0.453)	98 (0.436)
Hispanic only ($N=86$)	84 (0.488)	88 (0.512)	22 (0.256)	40 (0.465)	24 (0.279)

significantly different by self-reported race/ethnicity ($\chi^2=5.99$, 5 df, $p=0.31$). $N=441$ subjects with complete data; $\Sigma\chi^2$ 265.6 (284 df), $p=$ ns. Thus, by this test, use of this entire sample with the neuroticism phenotype should not be subject to stratification artifact.

Association of Individual COMT Polymorphisms with Extraversion and Neuroticism

rs4680 (val/met).

Extraversion: For rs4680 (*val/met*), presence of a *met* allele was associated with a higher odds of having low extraversion (ie being in the lower half of extraversion scores in this sample), although this failed to reach statistical significance (OR = 1.24, 95% CI 0.96–1.59; $\chi^2=2.68$, df = 1, $p=0.10$). When considering genotype, being homozygous for the *met* allele was associated with a significantly higher odds of having low extraversion (OR = 1.71, 95% CI 1.05–2.82; $\chi^2=5.23$, df = 2, $p=0.02$). Mean NEO-E scores were 45.4 (SD 11.0) in *met* homozygotes compared to 48.3 (SD 11.4) in *val* hetero or homozygotes (t = 2.28, df = 495, $p=0.02$).

When only women were considered, being homozygous for the *met* allele of rs4680 was associated with a significantly higher odds of having low extraversion (OR = 2.66, 95% CI 1.40–5.20; $\chi^2=10.42$, df = 1, $p=0.001$); when only men were considered, there was no significant association noted ($\chi^2=0.27$, df = 1, $p=0.6$). Mean NEO-E scores were 43.2 (SD 10.6) in female *met* homozygotes compared to 47.9 (SD 11.8) in *val* hetero- or homozygotes (t = 2.88, df = 341, $p=0.004$); there were no differences when only men were considered (t = 0.156, df = 152, $p=0.9$).

Neuroticism: Being homozygous for the *met* allele was associated with a nonsignificantly higher odds of having high neuroticism, that is, being in the top half of the distribution of neuroticism in this sample (OR = 0.70, 95% CI = 0.43–1.14; $\chi^2=2.34$, df = 1, $p=0.13$), although this was statistically significant (and marginally so) in women only (OR = 0.57, 95% CI 0.31–1.05; $\chi^2=3.79$, df = 1, $p=0.05$). Mean NEO-N score in female *met* homozygotes was 52.4 (SD 11.5) compared to 48.2 (SD 11.5) in *val* hetero- or homozygotes (t = 2.54, df = 341, $p=0.01$).

rs737865.

Extraversion: For rs737865, when considering men and women together, neither presence of an *A* allele (OR = 1.23, 95% CI 0.92–1.63; $\chi^2=1.99$, df = 1, $p=0.16$) nor, when considering genotype, being homozygous for the *A* allele (OR = 1.26, 95% CI 0.87–1.84; $\chi^2=1.60$, df = 2, $p=0.21$), was associated with a significantly higher odds of having low extraversion.

However, when only women were considered, being homozygous for the *A* allele of rs737865 was associated with a marginally significantly higher odds of having low extraversion (OR = 1.53, 95% CI 0.97–2.42; $\chi^2=3.77$, df = 1, $p=0.052$). Mean NEO-E scores were 45.5 (SD 12.2) in *A* homozygotes compared to 48.7 (SD 10.8) in *G* hetero- or homozygotes (t = 2.62, df = 332, $p=0.0093$); there were no significant differences when only men were considered (t = 0.83, df = 140, $p=0.41$).

Neuroticism: There were no significant associations between rs737865 and neuroticism at either the allelic or genotypic level.

rs165599. For rs165599, there were no significant associations with extraversion or neuroticism at either the allelic or genotypic level.

Haplotype Analyses

Extraversion. Score tests using haplo.score (Schaid *et al*, 2002) revealed a consistent association between extraversion as a dichotomous trait (split along the median for this sample, as described above) or as a quantitative trait and one or more of the haplotypes (dichotomous trait global score statistic = 16.38, df = 7, $p = 0.02$; quantitative trait global score statistic = 13.27, df = 7, $p = 0.07$; a rare haplotype with estimated frequency <0.005 was excluded from the analyses). Haplotype-specific scores are as shown in Tables 3a and 3b. In both the dichotomous (Table 3a) and quantitative trait (Table 3b) analyses, two of the haplotypes (rs737865 '*A*'–rs4680 '*val*'–rs16599'*A*' and rs737865 '*G*'–rs4680 '*met*'–rs16599 '*A*') were associated with higher NEO-E scores, whereas a third haplotype (rs737865 '*A*'–rs4680 '*met*'–rs16599'*A*') was associated with lower NEO-E scores. When rerun separately for women and men, the same three haplotypes emerged as being significantly associated with extraversion *in women only* (absolute value of haplotype scores ranged from 2.06 to 2.45, all *p*-values <0.05) (Tables 3a and 3b).

Neuroticism. Score tests revealed an association between neuroticism as a dichotomous trait (split along the median for this sample, as described above) (Table 4a) or as a quantitative trait (*in women only*) (Table 4b) and one or more of the haplotypes (dichotomous trait global score statistic = 13.55, df = 7, $p = 0.056$ and simulated $p = 0.03$; quantitative trait global score statistic *in women only* = 11.89, df = 7, $p = 0.10$; a rare haplotype with frequency <0.005 was excluded from the analyses). In the dichotomous trait analysis (in the entire sample and in women only), a different haplotype (rs737865 '*G*'–rs4680 '*met*'–rs16599'*A*') was associated with higher neuroticism (haplotype score = 2.87 in the entire sample and 2.82 in women only, both $p < 0.005$) (Table 4a). In the quantitative trait analyses *in women only*, the same three 3-SNP haplotypes that showed an association with extraversion were implicated (haplotype scores ranging from 1.6 to 2.0, with *p*-values ranging from 0.04 to 0.10) (Table 4b).

DISCUSSION

Studying normative personality has relevance for the understanding of the genetic basis of disordered personality (Jang and Livesley, 1999). In this study, we found that polymorphisms of the COMT gene were associated with variation in two traits that are over- and underexpressed, respectively, in anxiety (and some mood) disorders: neuroticism and extraversion (Bienvenu and Stein, 2003; Stein and Bienvenu, 2004). One of the polymorphisms, rs4680 (often referred to in the literature as 'va108met'), thought to be functional on the basis of its effects on catecholamine metabolism in animal studies (Matsumoto *et al*, 2003) and its dose–response relationship to executive function in humans (Goldberg *et al*, 2003), has been the most widely studied. In many studies over the past half-decade, variation in val158met has been associated with a variety of personality traits such as harm avoidance (Enoch

Table 3a Haplotype-Specific Scores for Extraversion as a Dichotomous Trait (Median Split)

	rs737865	val158met	rs165599	Frequency	Score	*p*	Sim. *p*
I. Entire sample (N = 452)[a]							
[1]	A	A	A	0.315	1.80	0.071	0.07
[2]	A	G	G	0.239	0.61	0.54	0.54
[3]	A	A	G	0.058	1.10	0.270	0.25
[4]	G	G	G	0.106	−0.21	0.83	0.80
[5]	G	G	A	0.129	−1.17	0.24	0.25
[6]	G	A	A	0.027	−2.17	0.030	0.03
[7]	A	G	A	0.123	−2.32	0.02	0.02
II. Women only (N = 347)[b]							
[1]	A	A	A	0.305	2.06	0.04	0.04
[2]	A	G	G	0.263	0.80	0.43	0.43
[3]	A	A	G	0.055	1.70	0.09	0.09
[4]	G	G	G	0.086	−0.50	0.62	0.63
[5]	G	G	A	0.139	−1.91	0.06	0.04
[6]	G	A	A	0.040	−2.45	0.01	0.02
[7]	A	G	A	0.108	−2.26	0.02	0.03

[a]Global statistic = 16.4, df = 7, $p = 0.02$ (simulated $p = 0.02$).
[b]Global statistic = 20.5, df = 7, $p = 0.005$ (simulated $p = 0.002$).

Table 3b Haplotype-Specific Scores for Extraversion as a Quantitative Trait

	rs737865	val158met	rs165599	Frequency	Score	*p*	Sim. *p*
I. Entire sample (N = 452)[a]							
[1]	A	A	A	0.315	−2.47	0.02	0.02
[2]	A	G	G	0.239	−0.548	0.58	0.54
[3]	A	A	G	0.058	−0.451	0.65	0.65
[4]	G	G	G	0.106	0.786	0.43	0.42
[5]	G	G	A	0.129	1.68	0.09	0.10
[6]	G	A	A	0.027	1.73	0.08	0.07
[7]	A	G	A	0.123	1.76	0.08	0.08
II. Women only (N = 347)[b]							
[1]	A	A	A	0.305	−2.44	0.02	0.01
[2]	A	G	G	0.263	−0.92	0.36	0.35
[3]	A	A	G	0.055	−1.23	0.22	0.24
[4]	G	G	G	0.086	1.12	0.27	0.27
[5]	G	G	A	0.139	2.47	0.01	0.01
[6]	G	A	A	0.040	1.94	0.05	0.04
[7]	A	G	A	0.108	1.61	0.11	0.13

[a]Global statistic = 13.3, df = 7, $p = 0.07$ (simulated $p = 0.07$).
[b]Global statistic = 16.5, df = 7, $p = 0.02$ (simulated $p = 0.04$).

Table 4a Haplotype-Specific Scores for Neuroticism as a Dichotomous Trait (Median Split)

	rs737865	val158met	rs165599	Frequency	Score	*p*	Sim. *p*
I. Entire sample (N = 452)[a]							
[1]	A	A	A	0.315	−1.19	0.23	0.22
[2]	A	G	G	0.239	0.25	0.81	0.80
[3]	A	A	G	0.058	−0.05	0.96	0.95
[4]	G	G	G	0.106	−0.68	0.49	0.45
[5]	G	G	A	0.129	0.65	0.51	0.56
[6]	G	A	A	0.027	2.87	0.004	0.002
[7]	A	G	A	0.123	0.46	0.65	0.67
	rs737865	**val158met**	**rs4680**	**Frequency**	**Score**	***p***	**Sim. *p***
II. Women only (N = 347)[b]							
[1]	A	A	A	0.305	−1.07	0.28	0.27
[2]	A	G	G	0.263	−0.21	0.83	0.82
[3]	A	A	G	0.055	−0.35	0.73	0.71
[4]	G	G	G	0.086	−0.44	0.66	0.66
[5]	G	G	A	0.139	0.23	0.81	0.8
[6]	G	A	A	0.039	2.82	0.005	0.01
[7]	A	G	A	0.108	1.13	0.26	0.27

[a]Global statistic = 13.5, df = 7, $p = 0.06$ (simulated $p = 0.03$).
[b]Global statistic = 13.2, df = 7, $p = 0.07$ (simulated $p = 0.06$).

et al, 2003), neuroticism (Eley *et al*, 2003) (but not in all studies; Henderson *et al*, 2000), and aggression (Rujescu *et al*, 2003). It has also been strongly associated with one anxiety disorder in particular—panic disorder (Domschke *et al*, 2004; Hamilton *et al*, 2002; Woo *et al*, 2002, 2004)—but not with a mixture of anxiety–phobic disorders in several other studies (Ohara *et al*, 1998; Samochowiec *et al*, 2004) and, according to a recent meta-analysis, not with obsessive–compulsive disorder (Azzam and Mathews, 2003).

Table 4b Haplotype-Specific Scores for Neuroticism as a Quantitative Trait

	rs737865	val158met	rs4680	Frequency	Score	*p*	Sim. *p*
I. Entire sample (N = 452)[a]							
[1]	A	A	A	0.315	1.34	0.18	0.158
[2]	A	G	G	0.239	−0.94	0.35	0.308
[3]	A	A	G	0.058	−0.39	0.70	0.678
[4]	G	G	G	0.106	0.68	0.50	0.492
[5]	G	G	A	0.129	0.72	0.47	0.466
[6]	G	A	A	0.027	−1.59	0.11	0.13
[7]	A	G	A	0.123	−1.23	0.22	0.224
II. Women only (N = 347)[b]							
[1]	A	A	A	0.305	1.96	0.05	0.04
[2]	A	G	G	0.263	−1.11	0.27	0.3
[3]	A	A	G	0.055	0.05	0.96	0.97
[4]	G	G	G	0.086	0.46	0.65	0.63
[5]	G	G	A	0.139	0.57	0.57	0.56
[6]	G	A	A	0.039	−1.63	0.10	0.10
[7]	A	G	A	0.108	−1.76	0.08	0.06

[a]Global statistic = 8.63, df = 7, $p = 0.28$ (simulated $p = 0.29$).
[b]Global statistic = 11.9, df = 7, $p = 0.10$ (simulated $p = 0.12$).

There was therefore ample *a priori* reason to hypothesize that we would find an effect of the val158met polymorphism on neuroticism and extraversion in this study. And although val158met is by far the most widely studied of the COMT polymorphisms, evidence is emerging that other loci either within or near the COMT gene may confer susceptibility to panic disorder (Hamilton *et al*, 2002) and schizophrenia (Palmatier *et al*, 2004; Shifman *et al*, 2002). In the case of schizophrenia, a particular functional (Bray *et al*, 2003) 3-SNP haplotype consisting of the three loci studied here was strongly associated with schizophrenia (Shifman *et al*, 2002). We therefore considered the possibility that this haplotype might be associated with extraversion and neuroticism in our sample. This provided us with the opportunity to test the hypothesis that loci other than (or in addition to) the val158met locus might be associated with these traits.

In analyses on a SNP-by-SNP basis, we found that two of the three loci studied—val158met and rs737865—were associated with variation in extraversion and, somewhat less consistently, neuroticism. When the 3-SNP haplotypes were considered, we found evidence of modest influence of several of the haplotypes on extraversion levels (and to a lesser extent, on neuroticism levels). The haplotype analyses showed that neither variation in val158met nor 737865 alone could explain the relationship with extraversion: SNPs that contained alternate versions of either SNP were noted to influence the trait in ways that would be inconsistent with single-locus effects (eg haplotypes that influenced extraversion in a particular direction could contain either the *val* or the *met* variant of val158met). Thus, these observations using haplotypes (Fallin *et al*, 2001; Martin *et al*, 2000) strongly suggest that the most powerful (if not the sole) influences on extraversion (and, to a lesser extent, neuroticism) are contributed by loci that either lie between rs737865 and val158met, or lie elsewhere within the COMT gene or nearby genes in linkage disequilibrium with these loci. Similar conclusions have recently been reached in the case of schizophrenia, where it has been recognized that val/met is unlikely to be the disease causing gene (Handoko *et al*, 2004). Resequencing efforts may provide evidence to support this hypothesis.

Of particular interest is our observation that the genetic associations to COMT (when observed from either a single- or multi haplotype perspective) were confined to women. An effect of val158met on harm avoidance in women was also reported to be confined to women (Enoch *et al*, 2003) and, to the extent that the combination of low extraversion and high neuroticism correspond to high harm avoidance, our observations can be considered to be a replication of those results. Furthermore, several studies have found associations of val158met and panic disorder specific to women (Domschke *et al*, 2004; Woo *et al*, 2004). These results also fit well with the fact that most anxiety (and depressive) disorders are more common in women, and are consistent with preclinical data indicating the possibility for sexually dimorphic effects of COMT variants on catecholamine metabolism (Huotari *et al*, 2002). This observation must be interpreted with caution, however, because there were more than twice as many women as men in our sample, so we might have lacked power to detect a signal in men. Replication of our results in larger samples will be required.

Our study has a number of additional limitations and caveats. We chose three markers based on prior knowledge that they generated the most meaningful haplotype information in a previous study (Shifman *et al*, 2002). However, we did not genotype all known COMT SNPs, and

we therefore could have missed true associations with other variants. Although the number included is sufficient to enable us to fairly confidently exclude val158met as a sufficient explanation for the findings, it is insufficient to enable us to further localize influential loci to other DNA sequence variations in COMT or even to other nearby genes that could be in LD with the SNPs (and haplotypes) observed here. This will require more extensive genotyping of multiple COMT polymorphic sites. Other limitations are shared by many other studies that aim to associate complex phenotypes with specific genetic variants: relatively small sample size, uncertain prior odds of association (Sullivan *et al*, 2001), and testing of multiple phenotypes against multiple genetic polymorphisms (Colhoun *et al*, 2003; Hirschhorn *et al*, 2002; Ioannidis *et al*, 2003). Given that our study focused on a single gene and its relationship to these two well-studied personality traits (ie we were not intending to make multiple inferences), some biostatisticians would argue that in this context no adjustments are needed for multiple comparisons (Rothman, 1990; Saritz and Olshan, 1995). However, each of these limitations is sufficiently important that our findings must be considered preliminary until they are more widely replicated.

Also, we studied a racially mixed sample, and in the course of the work demonstrated significant differences in allele distribution for all three variants studied by self-reported race. Even prior to the formal test, we felt that we were at low risk for stratification artifact because extraversion, the phenotype with the strongest and most consistent findings in this study, was not observed to be significantly different among Hispanics and EAs (the two groups large enough to permit comparison), although such differences did appear for neuroticism. However, without a formal test for stratification, it could also have been argued that in the worst case, this could have led to a false positive finding via population stratification (Freedman *et al*, 2004). However, using a set of 36 markers including 21 that were selected specifically for their population-distinguishing characteristics, we tested formally for possible effects of population structure in creating spurious association, and were able to exclude this possibility. Still, even though we have shown previously that the 36 marker set separates out clusters that correspond well to self-reported race/ethnicity in this sample (Stein *et al*, 2004) and in other samples (Yang *et al*, 2005), we cannot exclude the possibility that more subtle heterogeneity exists than can be accounted for with this limited number of markers (Burchard *et al*, 2003). On the other hand, given the extremely high correspondence between self-identified race/ethnicity and genetic clusters and the lack of evidence of substantial subgroups within these clusters (Tang *et al*, 2005), the potential for confounding in these populations—while not eliminated—is certainly mitigated. Furthermore, the fact that our Hispanic subjects—the ethnic group with the greatest within-group genetic differentiation on the basis of current geographic location—were all sampled from the same geographic region (Southern California) also provides some degree of reassurance in this regard (Tang *et al*, 2005).

Our finding that common variants in COMT are associated with variation in common personality traits is not inconsistent with the notion that common genetic variants are likely to influence common diseases (or traits) (Lohmueller *et al*, 2003). The magnitude of effects attributable to the COMT variants studied here was, however, quite small, raising the question of what role, if any, these variants might play as susceptibility factors for psychopathology. Thus, in addition to seeing our work replicated by other research groups in other samples, a next step to confirm the relevance of COMT variants to mental disorders will be to test its importance, through association and linkage studies, to other disorders characterized by extremely low extraversion, for example, generalized social phobia (Jang *et al*, 2001; Stein *et al*, 2001).

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CONFLICT OF INTEREST

None of the authors declare any financial or other form of conflict of interest with the content of this manuscript.

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