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# Association of the Catechol-*O*-Methyltransferase (COMT) Val158Met Polymorphism and Anxiety-Related Traits: A Meta-Analysis

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## Abstract

**Objectives—**The main goals of this study were: (i) to examine genotypic association of the COMT val158met polymorphism with anxiety-related traits via a meta-analysis; (ii) to examine sex and ethnicity as moderators of the association, and (iii) to evaluate whether the association differed by particular anxiety traits.

**Methods—**Association studies of the COMT val18met polymorphism and anxiety traits were identified from the PubMed or PsycInfo databases, conference abstracts and listserv postings. Exclusion criteria were: (a) pediatric samples, (b) exclusively clinical samples, and (c) samples selected for a non-anxiety phenotype. Standardized mean differences in anxiety between genotypes were aggregated to produce mean effect sizes across all available samples, and for subgroups stratified by sex and ethnicity (Caucasians vs. Asians). Construct-specific analysis was conducted to evaluate the association of COMT with neuroticism, harm avoidance, and behavioral inhibition.

**Results—**Twenty seven eligible studies (*N*=15,979) with available data were identified. Overall findings indicate sex-specific and ethnic-specific effects: Val homozygotes had higher neuroticism than Met homozygotes in studies of Caucasian males ( $\overline{ES}=0.13$, 95%CI: 0.02 – 0.25, $p = 0.03$), and higher harm avoidance in studies of Asian males ( $\overline{ES}=0.43$, 95%CI: 0.14 – 0.72, $p = 0.004$). No significant associations were found in women and effect sizes were diminished when studies were aggregated across ethnicity or anxiety traits.

**Conclusions:** This meta-analysis provides evidence for sex and ethnicity differences in the association of the COMT val158met polymorphism with anxiety traits. Our findings contribute to current knowledge on the relation between prefrontal dopaminergic transmission and anxiety.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

**Keywords**

Catechol-*O*-methyltransferase; COMT; anxiety; neuroticism; harm avoidance; meta-analysis; genetic association studies

## INTRODUCTION

Catechol-O-methyltransferase (COMT) is an enzyme that plays a key role in inactivating catecholamine neurotransmitters (dopamine, epinephrine, norepinephrine), their metabolites, catechol estrogens and catechol drugs via methylation. In humans, the gene coding for COMT is located on chromosome 22, between bands q11.1 and q11.2 (Grossman *et al.*, 1992). COMT mRNA transcripts encode two isoforms: soluble cytoplasmic (S-) and membrane-bound (MB-) COMT. The latter represents 70% of the total COMT polypeptides in the human brain (Tenhunen *et al.*, 1994) and has a 10-fold higher affinity for dopamine and norepinephrine than S-COMT; therefore, MB-COMT is more effective in metabolizing catecholamines (Lotta *et al.*, 1995; Roth, 1992) and highly relevant for the study of psychiatric and cognitive phenotypes.

Regulation of COMT enzyme activity depends in part on a COMT gene polymorphism involving a change in amino acid from valine (GTG, or Val) to methionine (ATG, or Met) at codon 108 of S-COMT or codon 158 at MB-COMT (Lachman *et al.*, 1996). Val homozygotes have higher COMT enzyme activity than Met homozygotes (Chen *et al.*, 2004), with heterozygotes demonstrating intermediate activity (Weinshilboum *et al.*, 1999). The role of COMT on dopamine catabolism in the prefrontal cortex (PFC) provides the basis for its association with cognitive and emotional processes. Across COMT val158met genotypes, Met/Met is linked to the lowest level of COMT enzyme activity and yields the highest level of extracellular dopamine in the PFC. It is thought of as being positioned at the peak of the putative inverted-U shaped curve of PFC function and dopamine transmission. Higher COMT activity of Val-carriers result in lower levels of PFC dopamine and prefrontal function at baseline, thus Val-carriers are placed on the up slope of the inverted U, with Val/Val at the leftmost position (Goldman-Rakic *et al.*, 2000; Tunbridge *et al.*, 2006).

Bilder *et al.*'s (2004) extension of the tonic-phasic dopamine hypothesis (Grace, 1991) provides a framework for understanding the effects of COMT val158met on vulnerability to neuropsychiatric disorders. COMT activity has differential effects on dopamine transmission in the PFC and the nucleus accumbens. In the PFC, high COMT activity by the Val allele results in greater dopamine metabolism, weaker postsynaptic D1 receptor-mediated excitation of pyramidal neurons, and lower PFC-accumbens glutamate transmission compared to the low-activity Met allele. In the accumbens, Val-allele is hypothesized to yield less glutamate-stimulated tonic dopamine release into the extrasynaptic space. High COMT activity by Val allele results in lower extracellular (tonic) dopamine in this region, which stimulates higher D2 transmission and is associated with stronger phasic response to external stimuli. The Val-linked, stronger D2 stimulation in subcortical systems facilitate set-switching, updating neural networks with novel information, and inhibiting previously rewarded responses (i.e., allowing extinction of conditioned responses). This has led some to

speculate that the Val allele confers protection from distressing stimuli via rapid disengagement of the cortical circuits from the stimuli. The low-activity COMT Met allele, on the other hand, is linked to sustained D1 activation, which helps maintain stable neural networks by preventing attentional distraction. However, the Met allele is also considered to index risk for psychiatric disorders due to a hypothesized inflexibility in switching set away from negative stimuli (Stein *et al.*, 2006; also see Goldman, 2012; Mier *et al.*, 2010).

Rodent studies using knock-out and transgenic models have linked COMT deficiency with higher anxiety responses, including heightened startle activity, greater pain perception, exaggerated stress-induced hyperthermia, less exploratory behavior, and blunted stress response (e.g., Papaleo *et al.*, 2008). Reports of sex differences are inconsistent, with some studies finding effects of lower COMT on higher anxiety just in females (e.g., Gogos *et al.*, 1998) or just in males (e.g., Papaleo *et al.*, 2008).

Human studies of the COMT val158met polymorphism have provided mixed evidence for an association with anxiety disorders. A meta-analysis of eight case-control studies found that men but not women having the Met allele were at greater risk for obsessive-compulsive disorder (Pooley *et al.*, 2007). In a meta-analysis of COMT and panic disorder (PD) based on six Caucasian and Asian case-control samples, Zintzaras and Sakelaridis (2007) reported no evidence for an association. The association was also non-significant when samples were stratified by sex or by ethnicity. However, using the same set of studies, Domschke *et al.* (2007) further stratified the samples by sex and ethnicity and found that the Val allele was associated with higher risk of PD among Caucasian women, but lower risk in Asian women. There was no evidence of an association between COMT val158met polymorphism and PD in men. A recent study examining the effects of COMT genotype on symptom trajectories in a sample of Caucasian PD patients receiving cognitive-behavioral therapy found that Val-carriers (Val/Val or Val/Met) endorsed more anxiety and depressive symptoms than Met homozygotes at baseline, but also experienced greater symptom improvement (Lonsdorf *et al.*, 2010). These results are consistent with earlier findings linking the Met/Met genotype to difficulties extinguishing conditioned fear (Lonsdorf *et al.*, 2009).

## Anxiety-Related Personality Traits in Genetic Association Studies

Association studies have also investigated the genetic basis for anxiety-related personality traits (abbreviated as “anxiety traits” in this report). Anxiety traits are theoretically informative because of their overlapping genetic and environmental vulnerability with a range of psychiatric diagnoses (Ducci *et al.*, 2007; Fanous *et al.*, 2007; Hettema *et al.*, 2006). Anxiety traits also meet the criteria for endophenotypes for anxiety disorders outlined by Gottesman and Gould (2003): First, Individuals with high scores on neuroticism and harm avoidance have higher risk of anxiety disorders (Khan *et al.*, 2005; Starcevic *et al.*, 1996). Second, these traits are heritable. Studies in populations of Western European ancestry find genetic factors underlie 26% to 51% of individual differences in neuroticism (Jardine *et al.*, 1984; Lake *et al.*, 2000; Pedersen *et al.*, 1988; Viken *et al.*, 1994; Wray *et al.*, 2007), and 32% to 49% of harm avoidance (Heath *et al.*, 1994; Heiman *et al.*, 2003; Stallings et al., 1996). Third, elevations in these traits precede illness and are manifested regardless of whether an illness is “active.” Fourth, genetic correlations between neuroticism

and several anxiety disorders are high (0.67 – 0.82; Hettema *et al.*, 2006), supporting a shared genetic basis. Practical and methodological benefits of focusing on anxiety traits rather than diagnoses include: availability of psychometrically-validated self-reported instruments for anxiety traits, ease of collecting data from large samples, greater statistical power derived from normally distributed traits compared to categorical (diagnostic) entities, and less sampling bias that are sometimes associated with clinical samples.

Neuroticism and harm avoidance have been frequently studied as anxiety-related personality traits in candidate gene studies. In the personality literature, neuroticism has been conceptualized under two theoretic models. In Eysenck's personality system, neuroticism reflects a labile autonomic nervous system that triggers frequent, negative emotional distress and expression (Eysenck and Eysenck, 1985). Eysenck neuroticism is indicated by feeling anxious, depressed, moody, irritable, guilty, shy and being interpersonally sensitive. In the NEO system (e.g., NEO-PI; Costa and McCrae, 1985) based on the Five-Factor Model of personality, neuroticism is a somewhat broader construct, with items tapping anxiety, hostility, depression, self-consciousness, impulsiveness and stress vulnerability.

In Cloninger's psychobiological personality model, harm avoidant individuals are characterized as fearful, cautious, insecure, pessimistic, easily tired and sensitive to punishment (Cloninger, 1987). Harm avoidance is theoretically proximal to Gray's behavioral inhibition system (BIS; 1976), which is triggered by novel experience, stimuli associated with aggression, punishment, reward omission or termination, and social interactions. Activation of the BIS results in inhibition of ongoing behaviors and gives rise to anxiety. Anxious individuals are introverted, sensitive to BIS triggers, and respond to them with high degrees of arousal and distress.

## Studies of COMT val158met and Anxiety Traits

Findings from association studies of the COMT val158met polymorphism with anxiety traits are inconsistent. The Val allele has been associated with higher levels of phobic anxiety (McGrath *et al*., 2004), harm avoidance (Kim *et al.*, 2006), negative emotionality (Chen *et al*., 2011), and neuroticism (Hettema *et al*., 2008). Other reports indicate the Met allele is associated with anxiety traits, including neuroticism (Eley *et al*. 2003; Hoth *et al*., 2006) and harm avoidance (Enoch *et al.* 2003, Hashimoto *et al*., 2007; Ishii *et al*., 2007).

Some of the variation in findings may be due to gender composition of the samples, given sex differences in COMT activity (Boudíková *et al*.,1990) and downregulation of COMT gene transcription by estrogen (Xie *et al.*, 1999). Some association studies have been conducted on combined-sex or single-sex samples for which results might not be directly comparable. Among studies reporting results for both sexes, Reuter *et al.* (2006) reported that Val homozygotes had higher behavioral inhibition than Met-carriers in men, but lower behavioral inhibition in women.

Ethnic heterogeneity within and between studies is another challenge in interpreting the existing literature. There are marked population differences in the val158met allele frequency, such that the two alleles are nearly equal in frequency among European populations but Val is more common than Met in Asian populations (Palmatier *et al.*, 1999).

Differences in language and measures used in studies conducted in ethnic populations also make direct comparisons difficult.

A lack of association between COMT val158met and anxiety traits reported in many samples may be due to insufficient power. For example, an 80% power to detect an effect size of 0.3 for the Met/Met vs. Val-carrier contrast requires *N*=340 Caucasians or *N*=884 Asians (accounting for ethnicity-specific genotype frequencies) (Faul *et al.*, 2007). Studies conducted on some Caucasian (Calati *et al*., 2011; Golimbet *et al*, 2007; Reuter and Hennig, 2005) and Asian (Tsai *et al*., 2004; Tochigi *et al*., 2006; Urata *et al*., 2007) samples were likely underpowered.

The inconsistency in this literature motivated us to conduct a meta-analysis to synthesize the results of studies of the genotypic association of the COMT val158met polymorphism with anxiety-related traits. In particular, we test whether evidence for the association differs across sex, ethnicity, and different anxiety-related traits.

## MATERIALS AND METHODS

### Search Strategy

We identified eligible studies by searching the National Library of Medicine's PubMed and PsycInfo databases. Articles from the first date available through December, 2011, were screened. Keywords used in the search included a combination of the terms "COMT" or "Catechol-O-methyltransferase" with "anxiety", "personality", "neuroticism", "behavioral inhibition", "harm avoidance", "OCD", "obsessive compulsive", "panic", "phobia", "social anxiety", "agoraphobia", "posttraumatic stress", "PTSD", "generalized anxiety" or "worry." Identified abstracts were read to select studies examining the association between the COMT val158met polymorphism and anxiety traits. Relevant articles were retrieved and read to determine their appropriateness for inclusion in the meta-analysis; their bibliographies were also searched for potentially eligible studies. We also performed a search for relevant unpublished sources among presentation abstracts[1] from the World Congress on Psychiatric Genetics between 2002 and 2011 and posting a request on the electronic listserv of the Behavioral Genetics Association.

### Selection of Studies for Inclusion in Meta-Analysis

Association studies of the COMT val158met polymorphism with anxiety traits were included in the meta-analysis. We were interested in the full range of anxiety as expressed among adults in the general population. We included population-based studies that did not screen participants for psychiatric diagnoses (Bækken *et al*., 2008; Benjamin *et al*., 2000a; Eley *et al*., 2003; Hatzimanolis *et al*., 2010; Harris *et al*., 2005; Henderson *et al*., 2000; Hettema *et al*., 2008; Middeldorp *et al*., 2010; Olsson *et al*., 2005, 2007; Wray *et al*., 2008) to ensure that the analyzed samples are representative of the general population and to avoid range restriction of anxiety traits.

[1]Data based on three conference posters were incorporated into the meta-analysis reported here (Arias *et al.*, 2010; Hatzimanolis *et al.*, 2010; Ivanova *et al.*, 2006). Data from two are included in peer-reviewed publications that appeared after the cut-off date of our literature search (Alemany *et al.*, 2013; Hatzimanolis *et al.*, 2013).

We excluded studies if the samples were: (A) Pediatric (age <18); (B) exclusively based on clinically anxious samples; (C) samples originally selected for having a non-anxiety phenotype (e.g., alcoholics). We excluded samples with anxiety disorders (Criterion B) because specific diagnoses represent etiologically heterogeneous, disorder-specific characteristics in addition to the anxiety traits of interest here, and they may confound the association with COMT Val158Met. Similarly, the decision to exclude samples selected for having other (non-anxiety) phenotypes (Criterion C) addresses the possibility that any detected association between COMT and anxiety would be attributable to their common association with the non-anxiety phenotype (c.f., Enoch *et al*., 2003). Control samples used in case-control studies (Calati *et al*., 2011; Desmeules *et al*., 2011) were included if the sample did not meet any of the exclusion criteria. We did not exclude studies conducted within one sex or ethnicity group.

## Data Extraction and Data Requests

We extracted the following data from each study: (1) authors, (2) year of publication, (3) sex, (4) ethnicity, (5) country of origin, (6) sample size by genotype (and by sex and ethnicity within genotype, when possible), (7) mean age by sex, (8) relatedness of participants, (9) unselected vs. extreme-scoring design, (10) anxiety measure(s), (11) means and standard deviations of each anxiety measure by genotype and, when provided, by sex and ethnicity within genotype. Alternatively, for a subset of studies, genotype-specific odds ratios (ORs) or cell frequencies (by sex and ethnicity, when available) were extracted. For each study, we further coded (12) whether anxiety data were available as mean scores or ORs, and (13) whether genotype frequencies deviated from Hardy-Weinberg equilibrium (HWE) for each ethnicity and sex-by-ethnicity subgroup.

Our outcome of interest is the *standardized mean differences effect size* ($ES_{SM}$), which reflects the mean difference in anxiety scores between two genotype groups in standard deviation units. Authors were contacted directly to request further data if publications reported: (1) anxiety scores and/or age data collapsed across sexes and/or ethnicity, or (2) results in OR format. Specifically, we requested summary statistics (mean, standard deviation, *N*) for each anxiety measure by genotype, sex and ethnicity, and mean age by sex and ethnicity. Authors were contacted by email at least twice for each data request.

## Data Analysis

Data analysis steps were guided by the work of Lipsey and Wilson (2001) and conducted using the Comprehensive Meta-Analysis statistical software Version 2.2.064 (Borenstein *et al.*, 2011). Hedges (1981) showed that $ES_{SM}$ tends to overestimate the true population parameter, especially in small samples. To correct for this bias, $ES_{SM}$ was multiplied by $\left(1-\frac{3}{4\,(n_1-n_2)\,-9}\right)$, with $n_1$ and $n_2$ defined as the sample sizes for the two genotype groups, to yield Hedge's *g* (1981), the study-specific effect size entered into the meta-analysis. Hedge's *g* is a commonly used mean difference effect size in meta-analyses (e.g., see Borenstein et al., 2009). Three genotypic comparisons were made: Met/Met (MM) vs. Val/Val (VV), Met/Met vs. Val-carriers (Val/*), and Met-carriers (Met/*) vs. Val/Val. A positive *g* indicates higher anxiety scores for the Met group than the Val group.

OR effect sizes ($ES_{OR}$) instead of $ES_{SM}$ were calculated for a subset of studies (see Table 1) because the study sampled participants based on extreme scores on an anxiety measure (Eley *et al*., 2003, Hettema *et al*., 2008, Wray *et al*., 2008), or the anxiety measure had a skewed distribution (Bækken *et al*., 2008; Olsson *et al*., 2005), or we were unable to acquire data in the desired format from the authors (Urata *et al*., 2007). ORs were calculated as the odds of having high anxiety in one genotype versus another genotype. For each OR based on an extreme-scoring sample (e.g., top vs. bottom decile), we calculated an OR based on a continuous distribution (e.g., top 10% vs. bottom 90%) calculated from expected genotypic *N* of unsampled individuals in the middle of the distribution to mitigate the issue of inflated effect size due to extreme groups sampling. Genotypic *N* for unsampled individuals in the middle of the distribution were estimated based on published population frequencies of the COMT val158met polymorphism for that sample's ethnicity (Palmetier *et al*., 1999) while accounting for genotypic frequencies in the extreme groups. Details of this procedure are illustrated with an example in Supplementary Document 1. It is acknowledged that this method of estimating an OR for an extreme-scoring sample is sensitive to the population genotypic frequencies used in the calculation, thus we conducted sensitivity analysis (described later) to test whether any significant associations based on extreme-scoring samples remained after excluding these samples. To allow for direct comparison between effect sizes in mean differences and OR formats, we natural log-transformed each $ES_{OR}$ into $ES_{LOR}$, and applied the Cox (1970) method by dividing $ES_{LOR}$ by the constant 1.65 to yield $ES_{Cox}$. The sampling variance of $ES_{LOR}$ is estimated as $0.367\left[\frac{1}{O_{g1,H}}+\frac{1}{O_{g1,L}}+\frac{1}{O_{g2,H}}+\frac{1}{O_{g2,L}}\right]$, where $O_{g1,H}$ represents the number of individuals with genotype 1 (e.g., Met/Met) and high anxiety, $O_{g2,L}$ represents the number of individuals with genotype 2 (e.g., Val/Vet) and low anxiety, and so on. An example of this transformation is provided in Supplementary Document 1. $ES_{Cox}$ has been found to give a practically unbiased estimation of the population standardized mean difference and closely estimate $ES_{SM}$ when the trait underlying the measure is normally distributed (J. Sánchez-Meca, personal communication, April 2, 2009; Sánchez-Meca *et al.*, 2003).

We used the inverse variance method to aggregate effect sizes across studies, as it adjusts for the error variance and size of each sample. The mean effect size across studies ($\overline{ES}$), was calculated as the sum of inverse variance weighted effect sizes divided by the sum of inverse variance weights. Data were analyzed under a random effects framework, which accounts for between-study variation in effect sizes in determining $\overline{ES}$ and its error variance. We also report study heterogeneity using Cochran's *Q* (1954) quantified with the $I^2$ index for all significant findings. Between-study heterogeneity is considered low with $I^2$ < 25%, moderate with $I^2$ = 25–50% and large with $I^2$ > 50% (Higgins *et al.*, 2003).

### Moderator and Construct-Based Analyses

We investigated sex (three subgroups: combined, male, female) and ethnicity (three subgroups: any ethnicity, Caucasians, Asians) as moderators of the association between COMT val158met genotype and anxiety-related traits. Subgroup analysis stratified by sex and ethnicity was conducted only if data from at least three studies were available. Samples

for which genotype frequencies deviated from the Hardy-Weinberg equilibrium (HWE) were excluded from analysis.

Initially, we examined the association of COMT val158met with any anxiety traits across studies. When multiple anxiety measures were administered to a sample, the average effect size across measures for the sample was entered into the meta-analysis (Schinka *et al.*, 2004).

Next, we investigated whether the COMT val158met genotype was associated with specific anxiety traits: (1) Eysenck's neuroticism; (2) NEO neuroticism;(3) harm avoidance; and (4) behavioral inhibition. (See Table 1 for a list of measures assessing each trait included in the meta-analysis.) For some analyses, we combined the Eysenck and NEO measures of neuroticism as these are moderately to strongly correlated ($r = 0.52 – 0.71$; McCrae and Costa, 1983) and have high genetic correlations (0.82 to 0.9; Wray *et al.*, 2007).

### Sensitivity Analysis and Assessment of Publication Bias

When a statistically significant (at $\alpha = 0.05$ level) association was detected, we conducted sensitivity analyses to test whether the association could be attributed to the following design features: (1) use of extreme-scoring samples; (2) effect sizes in OR format; or (3) within-sample relatedness (see Table 1). Of note, for the family-based sample in Middeldorp et al. (2010), meta-analyses included data only from parents, but not offspring.

We assessed publication bias with two methods. First, for each genotypic contrast, we conducted meta-regression of individual effect sizes (collapsed across sex, ethnicity and measures within study) against the year of publication. Second, we created funnel plots by plotting the standard error of effect size against the effect size for each study, and used Egger's test (Egger *et al.*, 1997) to evaluate funnel plot symmetry.

## RESULTS

Of 74 studies identified by our literature search, 43 were excluded for the following reasons: Three studies were based exclusively on clinically anxious individuals (i.e., exclusion criterion B; Hohoff *et al*., 2008; Lochner *et al.*, 2005, 2008; Lonsdorf *et al*., 2010). Four studies were based on clinically anxious individuals and their family members, i.e., individuals with a high genetic risk and therefore "selected" for anxiety disorders (Alsobrook *et al*., 2002; Hamilton *et al*., 2002; Schindler *et al*., 2000; Walitza *et al*., 2008;). Ten studies were selected for a non-anxiety phenotype (i.e., exclusion criterion C; Barr *et al.*, 1999; Birklein *et al.*, 2008; Enoch *et al*., 2003; Kolassa *et al.*, 2010; Gothelf *et al*., 2007a, 2007b; Light *et al.*, 2007; Max *et al*., 2006; Michaelovsky *et al.*, 2008; Zinkstok *et al.*, 2008). Thirteen studies did not include a measure of trait anxiety (Cavallini *et al.*, 2000; Domschke *et al*., 2004; Freitag *et al*., 2006; Karayiorgiou *et al*., 1997; O'Hara *et al*., 1998; Pooley *et al*., 2007; Poyurovsky *et al*., 2005; Rothe *et al*., 2006; Rotondo *et al.*, 2002; Rujescu *et al*., 2003; Samochowiecz *et al*., 2004; Strug *et al*., 2010; Woo *et al*., 2002). In five studies, the target measure reflected an underlying anxiety disorder, such as a checklist of panic disorder symptoms (Erdal *et al*., 2003; McGrath *et al.*, 2004; Maron *et al*., 2008; Meira-Lima *et al*., 2004; Niehaus *et al*., 2001). In three studies, the target phenotype was not

an anxiety trait (Lang *et al*., 2007; Lonsdorf *et al*., 2009; Smolka *et al*., 2005). The sample from one study was already represented by another study included in our meta-analysis (Khan *et al*., 2005). One study appeared to examine a different locus on the COMT gene than Val158Met (Woo *et al*., 2004); attempts to contact the authors for clarification were unsuccessful. Additionally, one study was excluded because the anxiety trait measure was administered only to cases (of irritable bowel syndrome) but not to controls (Karling *et al.*, 2011). Another study was excluded because the experimental procedure (pain induction via infusion of saline into the masseter muscle) possibly affected anxiety ratings (Zubieta *et al*., 2003). Finally, there was insufficient information from one study (Kulikova *et al*., 2008) and one poster abstract (Kenis *et al.*, 2010) to determine their eligibility and we were unable to reach the corresponding authors for clarification.

Of 31 studies deemed eligible for the meta-analysis, attempts to request data from authors of seven studies were unsuccessful. We incorporated partial data from three of the seven based on what was in the publication (Benjamin *et al.*, 2000a; Tochigi *et al.*, 2006; Urata *et al.*, 2007), but had insufficient information for four others so these were not included (Åberg *et al.*, 2011; Drabant *et al*., 2006; Lee *et al.*, 2011; Stein *et al.*, 2005). The remaining 27 studies contributed $k$=29 independent samples, yielding a total sample size of $N$=15,979 for the meta-analysis. . Sex-specific data were unavailable for two samples (Benjamin *et al.*, 2000a; Tochigi *et al.*, 2006). Data were available from $k$=20 independent samples ($N$=6,648) of men and $k$=27 independent samples ($N$=8,630) of women. Of the 29 independent samples, $k$=20 were Caucasian ($N$=13,399), $k$=8 were Asian ($N$=2,126), and $k$ =1 ($N$=454) did not report sample ethnicity (Benjamin *et al*., 2000a). Table 1 provides details for each sample including the country of origin and available measures. Table 2 provides the distribution of genotype frequencies by sex and ethnicity, combined across the available samples.

The first set of meta-analysis considered the overall association of COMT val158met genotype with anxiety traits combined across all studies. In the overall analysis of 20 combined-sex samples of any ethnicity (Table 3a, top left), the association between anxiety-related traits and genotype was non-significant. In subgroup analyses, we found that among Asian male samples ($k$=3) higher anxiety was associated with Val-carriers across all three genotypic contrasts, with mean effect sizes between -0.18 and -0.44 (Table 3a). There was minimal evidence for between-study heterogeneity for any of the genotypic contrasts (MM-VV: $Q$ = 0.74; MM-V*: $Q$ = 0.93; M* - VV: $Q$ = 0.06; all $df$ = 2, $p \geq 0.63$, $I^2$ = 0%). Sensitivity analysis was not applicable to these samples. Results for other sex*ethnicity subgroups were non-significant. (Study-specific effect sizes for the three genotypic contrasts by sex for each sample are available as Supplementary Table 1. Forest plots of the meta-analyses conducted by each sex subgroup and across ethnicity for the MM-VV contrast are available as Supplementary Figures 1a-c.)

## Analyses of Specific Anxiety Traits

**Neuroticism—**Results for neuroticism as measured by variants of the NEO-PI and EPI questionnaires are shown in Table 3b. Across all possible sex-by-ethnicity subgroups, Val-carriers had higher neuroticism than met-carriers among Caucasian male samples, but the difference was statistically significant only for the MM-VV comparison ( $\overline{ES}=-0.13$, $Q$ =

7.23, $df = 7$, $p = 0.41$, $I^2 = 3.13\%$). Sensitivity analysis entailed excluding three studies using an extreme groups design, after which only the MM-V* contrast was significant, $\overline{ES} = -0.14$, 95%*CI* = −0.27, −0.01, $p = 0.04$), with little evidence for between-study heterogeneity ($Q = 3.98$, $df = 4$, $p = 0.41$, $I^2 = 0\%$). Findings among Caucasian females were non-significant and we were unable to examine the association in Asians due to limited data ($k = 0$ to 1 across sex subgroups).

To follow up on the significant association, we separately explored genotype in relation to neuroticism as measured by versions of the EPI versus the NEO scales. Figure 1 is a forest plot of the Met/Met vs. Val/* results by sex. It can be seen that all samples with Eysenck neuroticism data were Caucasian. As shown in Table 3c, significant associations were identified in male samples: men with Val/Val genotype had higher neuroticism than men with Met/Met (MM-VV: $\overline{ES} = -0.17$) and Met-carrying genotypes (M*-VV: $\overline{ES} = -0.17$). Between-study heterogeneity was large (MM-VV: $Q = 26.55$, $df = 5$, $p < 0.001$, $I^2 = 81.17\%$; M*-VV: $Q = 42.77$, $df = 5$, $p < 0.001$, $I^2 = 88.3\%$). As shown in Figure 1, sensitivity analysis would have required repeating the meta-analysis after eliminating three samples with extreme-sampling design and $ES_{OR}$, but this was not feasible due to the limited number of remaining studies ($k$=2). No other significant association was observed for Caucasian female or combined-sex samples.

Table 3d summarizes meta-analysis results for neuroticism as measured by the NEO scales. We were unable to test the association in Asians due to limited samples. In the remaining sex*ethnicity subgroups, there was no significant association of genotype with NEO-neuroticism.

**Harm Avoidance—**Table 3e summarizes the meta-analysis results and Figure 2 is a forest plot for the Met/Met vs. Val/* contrast by sex for harm avoidance. Significant associations were initially detected among male samples of any ethnicity, such that Val-carrying men had higher levels of harm avoidance than their Met/Met counterpart (MM-V*: $\overline{ES} = -0.20$). There was little between-study heterogeneity ($Q = 2.42$, $df = 6$, $p = 0.88$, $I^2 = 0\%$) and no sensitivity analysis was warranted. Further stratifying the male samples by ethnicity showed that the significant association was unique to Asians and evident across all three genotypic contrasts: MM-VV: $\overline{ES} = -0.43$; MM-V*: $\overline{ES} = -0.34$ M*=VV, $\overline{ES} = -0.23$. Again, there was little between-study heterogeneity (MM-VV: $Q = 0.63$; MM-V*: $Q = 0.51$; M*-VV: $Q = 1.01$; all $df = 2$, $p \geq 0.60$, $I^2 = 0\%$). No sensitivity analysis was warranted. The association was not significant in any female and combined-sex subgroups.

**Behavioral Inhibition—**Data on COMT val158met polymorphism and behavioral inhibition were available on $k$=3 combined sex samples, $k$=3 male samples, and $k$=4 female samples (see Table 3f). Among samples of any ethnicity, there was no evidence of an association in any of the three sex groupings. Due to limited data, stratified analysis by ethnicity was possible only for Caucasian females ($k$=3), for whom the association was not significant.

### Publication Bias

To examine these data for publication bias, we first conducted a meta-regression of average effect size across all anxiety measures for each independent sample against year of publication. There was no evidence of an association between effect size and publication year for each genotypic contrast: MM-VV: $b_{pub\_yr} = -0.006$ (0.01), $p = 0.39$; MM-V*: $b_{pub\_yr} = -0.002$ (.01), $p = 0.78$; M*-VV: $b_{pub\_yr} = -0.003$ (0.01), $p = 0.56$.

Next, we inspected funnel plots for evidence that effect sizes were biased in a particular direction by studies with small sample sizes or large error variances. Funnel plots are shown in Figures 3a–c. Results from Egger's test were consistent with the null hypothesis of symmetrical funnel plots because the intercepts did not significantly deviate from (0, 0): MM-VV: intercept = 0.99 (0.72), 2-tailed $p = 0.18$; MM-V*: intercept = 0.59 (0.55), 2-tailed $p = 0.30$; M*-VV: intercept = 1.08 (0.94), 2-tailed $p = 0.26$. In sum, we did not find any evidence for publication bias across all samples entered into the meta-analysis.

## DISCUSSION

We conducted a meta-analysis of 27 studies ($N$=15,979) to examine the association of the COMT val158met polymorphism with anxiety traits. Overall, our findings indicate sex-specific effects and some variation associated with anxiety phenotype. Compared to men who were Met homozygotes, Val-carrying men had higher levels of anxiety as measured by neuroticism in Caucasians and harm avoidance in Asians. The ethnic specificity of these effects could not be evaluated fully as there were no studies of neuroticism in Asian males. However, there was evidence suggesting the absence of a COMT-harm avoidance association in Caucasian men was not due to low statistical power, but the association was specific to Asian males. There was no evidence for an association between COMT val158met polymorphism and any anxiety traits in women, regardless of ethnicity.

### Association of COMT Val Allele with Anxiety Traits

The association between the COMT Val allele and higher anxiety may be related to COMT effects on dopaminergic tone in the prefrontal cortex (PFC) and their relation to cognition. As mentioned earlier, the stronger phasic response to external stimuli and higher D2 transmission linked to the Val allele has led to speculations that Val protects against distressing stimuli via rapid disengagement of the cortical circuits from the stimuli (e.g., Bilder *et al.*, 2004). Supporting this hypothesis, a recent meta-analysis concluded that Met homozygotes were less efficient than Val homozygotes when engaging in tasks requiring emotional processing, but more efficient on tasks based primarily on cognitive processing (Mier *et al.*, 2010). Specifically, Mier *et al.* (2010) reported a large effect ($d = -1.0$) indicating stronger PFC activation by Met homozygotes than Val homozygotes on emotion processing paradigms. Examining the details of the emotional processing tasks used in the four studies included in the Mier *et al.* (2010) meta-analysis (Domschke *et al.*, 2008; Drabant *et al.*, 2006; Smolka *et al.*, 2005; Yacubian *et al.*, 2007) and more recent works suggests a more nuanced interpretation of these findings. Carriers of the Met allele tended to have greater limbic response in emotional processing tasks that are less effortful, as evidenced by the stronger PFC activation during passive viewing of affectively valenced vs.

neutral pictures (e.g., Smolka *et al.* 2005) and during a facial matching task (Drabant *et al.* 2006). Domschke *et al*. (2008) also used a passive-viewing paradigm; however, in contrast to findings by Smolka *et al*. (2005) and Drabant *et al*. (2006), they found that Val carriers have greater amygdala and PFC activation in response to emotional faces than Met homozygotes. It may be that a passive facial viewing task was more effortful for the clinically anxious sample in Domschke *et al*.'s (2008) study than for the healthy controls in the other two studies. Yacubian *et al.*'s (2007) examined PFC activation in response to reward anticipation during a gambling task. Their task is less comparable to other emotional processing paradigms included in Mier *et al.*'s (2010) meta-analysis.

One speculation is that during emotional tasks with a high cognitive load, Val carriers may be at a disadvantage. For example, using an affect labeling task that is more effortful in nature than the aforementioned passive viewing paradigms, Kempton *et al.* (2009) reported less amygdala deactivation in Val/Val men compared to Met/Met men, suggesting less efficient prefrontal inhibition by Val homozygotes. On an attentional task with negatively valenced distractors, Val allele dosage was positively associated with PFC activation to negative distractors relative to neutral distractors (Bishop *et al.*, 2006), suggesting inefficient resource allocation by Val carriers while engaging in a cognitive task and being simultaneously distracted by unpleasant stimuli. One interpretation of these findings is that whereas Met carriers may initially exhibit an exaggerated limbic response to affective stimuli, Val carriers are less efficient at subsequently modulating or inhibiting amygdala response when required to manipulate the emotional information.

Although higher COMT activity and lower PFC dopaminergic tone of Val carriers have been considered as mechanisms that protect against anxiety based on a cognitive advantage, our finding of an association between higher anxiety and the COMT Val allele contradicts this notion. We suggest that our results may be partly attributable to a cognitive profile marked by greater distractibility and unstable cognitive sets among Val carriers. This is consistent with earlier work linking lower cortical dopamine and D1 stimulation (associated with Val) to low cortical signal-to-noise ratio and poor differentiation of target from background in cognitive tasks (Winterer and Weinberger, 2004). Additionally, Val allele dosage has been associated with poor sensorimotor gating (Roussos *et al.*, 2008) and poor accuracy and efficiency in attentional tasks (Blasi *et al.*, 2005). Both neuroticism and harm avoidance are characterized by irritability, hypervigilance, and poor concentration. The higher distractibility associated with the Val allele may facilitate a hypervigilant attentional style and threat-scanning behaviors. Difficulties staying "on task" or engaging in complex cognitive tasks when faced with emotional stimuli may exacerbate distress and increase tendencies toward neurotic and harm avoidant behaviors. If the effect of COMT val158met on anxiety is mediated through cognitive mechanisms, the modest effect sizes observed here are not surprising.

Additional factors may explain the small effect sizes of the association between the COMT val158met polymorphism and anxiety. Other COMT functional loci may account for additional variation in anxiety that is not captured in this study. Cis-regulatory elements (Zhu *et al.*, 2004) and interactions of COMT val158met with two non-synonymous COMT SNPs (Diatchenko *et al*., 2005) contribute to COMT gene expression beyond the effect of

val158met. . For example, association studies of anxiety traits have identified COMT haplotypes containing the val158met polymorphism that were more strongly related to neuroticism than val158met alone (Hettema *et al*., 2008; Stein *et al*., 2005). Genetic epistasis and gene-environment interactions are other pathways by which COMT may influence anxiety (e.g., Benjamin *et al.*, 2000b; Kolassa *et al.*, 2010). Research investigating genetic networks may help identify how multiple variants are co-expressed and influence behavioral phenotypes (e.g., Zhang and Horvath, 2005).

The small effect sizes in the current meta-analysis highlight the challenges that exist when conducting association studies of single functional variants with complex phenotypes. The self-report paper-and-pencil measures used to assess anxiety in the studies included in this meta-analysis are indirect indices of a psychological trait. Effect sizes for genetic association are typically larger as one moves from complex behaviors and traits to endophenotypes such as neuroimaging and molecular phenotypes (Zhou *et al*, 2008).

## Sex Differences in the COMT-Anxiety Association

There are several possible explanations for our finding of sex differences in the association of COMT genotype with neuroticism and harm avoidance, including insufficient statistical power, methodological differences and true differences. For each significant association reported for men, the sample size for the corresponding subgroup analysis in women was always larger. All male-based analyses had comparable female samples assessed with the same methodology. Given the reported interaction of COMT val158met genotype and endogenous estrogen fluctuation on cognitive functioning in women (Jacobs and D'Esposito, 2011), a lack of adjustment for female participants' menstrual phase or use of hormonal birth control in most studies in our meta-analysis might contribute to greater measurement error in female-specific findings. However, the effect sizes estimated for female and male samples within the same studies were generally of similar precision, suggesting the observed sex differences are not due to power or methodological variation.

Several studies have identified sex differences in COMT activity in dopamine-related pathways, including higher COMT enzyme activity in blood and liver tissues among males than females (Cohn and Axelrod, 1971; Boudíková *et al.*, 1990) and lower proportion of dopamine neurons making up mesocortical projections in male than female rats (Kritzer and Creutz, 2008). This implies Val/Val males relative to Met-carrying males or to females are more likely to have low PFC dopaminergic transmission and the associated cognitive and emotional processing vulnerability. Relatedly, greater affective sensitivity to dopamine has been found in men compared to women (Riccardi *et al.*, 2011). The finding of higher anxiety in Val-carrying men but not women may therefore be attributable to their lower levels of PFC dopamine and greater affective sensitivity to dopamine.

Our null finding of a lack of association between COMT val158met genotype and any anxiety traits in women differs from the report by Enoch *et al.* (2003) of elevated harm avoidance scores in Met/Met women compared to Val-carrying women[2]. Enoch *et al.* (2003) used pedigrees that had been selected for alcoholism and an alcohol-related electroencephalogram trait. Differences in sampling may therefore explain the different findings.

Our findings are in contrast to Papaleo *et al.*'s (2008) finding of blunted stress response, lower pain sensitivity, less exploration and more avoidant behaviors when exposed to novel objects in male mice with lower COMT activity. Our findings and those of Papaleo et al.'s (2008) are in contrast to Gogos *et al*.'s (1998) report of COMT-deficient female mice exhibiting greater anxiety-like behaviors than wild-type females. In Gogo *et al*.'s (1998) study, the effect of COMT on anxiety-like behaviors was nonsignificant in male mice. Complete COMT deficiency, as in the knock-out mice used in these animal studies, is not directly analogous to low COMT activity among human Met homozygotes; the same can be said for the comparison between transgenic mice overexpressing the COMT Val allele in Papaleo *et al.*'s study and human Val homozygotes. Mouse models of anxiety were developed primary in males and sex differences on the same phenotypes can be attributable to numerous factors (see review by Palanza, 2001). For these reasons, we believe that these landmark studies are best used to implicate COMT variation as contributing to risk for neuropsychiatric disorders, but caution is warranted in extrapolating specific findings to humans.

## Ethnicity- and Measure-Specific Findings

We found evidence that ethnicity moderates the association between COMT and harm avoidance in men, with higher levels of harm avoidance in Val-carriers than non-Val carriers among males of East Asian descent. The absence of a parallel finding in Caucasian males does not appear to be due to lower statistical power. Calculations using G-power (Faul *et al.*, 2007) and taking ethnic differences in genotype frequency into consideration found the Caucasian male sample size of $N$=174 had 80% power to detect an effect as large as that found for the MM-VV comparison in the Asian sample (−0.43 based on $N$=397 Asians). For the MM-V* and M*-VV comparisons, the Caucasian sample size of $N$=332 had 79% and 43% power, respectively, to detect the corresponding effect sizes found in the Asian sample of $N$=634.

Another goal of our study was to explore whether several anxiety-related traits differed in their strength of the association with the COMT val158met polymorphism. For neuroticism, the association with COMT val158met was significant for studies using the Eysenck scale but not the NEO scales. Between neuroticism and harm avoidance, the strength of association with COMT val158met was somewhat stronger for the latter. As discussed below, differences in the strength of association is likely attributable to true differences, study methodology and ethnic differences in COMT action on anxiety. However, it was impossible to directly compare the strength of association across constructs because the use of different measures was confounded with ethnicity.

For neuroticism, effect sizes for the MM-VV contrast was −0.13 in the analysis considering both Eysenck and NEO scales, and slightly higher (−0.17) when only considering Eysenck neuroticism. The somewhat higher effect sizes in the Eysenck-only analysis may be due to

[2]Of note, after consultation with the study's lead author, we chose not to include the Enoch *et al.* (2003) study in our meta-analysis primarily because it met our exclusion criterion C (sample selection based on a non-anxiety phenotype). Both samples included individuals selected for alcoholism or a putative alcoholism-related phenotype (low voltage alpha EEG) Consequently, any association observed between COMT and measures of trait anxiety could be due to a common association with alcoholism.

the inclusion of extreme-scoring samples, as evidenced by the significant between-study heterogeneity in effect sizes. For the MM-V* and M*-VV contrasts, effect sizes of the COMT-neuroticism (Eysenck+NEO, Eysenck only) association ranged from −0.05 to −0.17. The nonsignificant association between COMT val158met polymorphism and NEO neuroticism is likely due to a combination of a weaker true effect and smaller sample sizes in the NEO-only analysis.

For harm avoidance in Asian males, the effect size was −0.43 for the MM-VV contrast, −0.34 and −0.23 in the MM-V* and M*-VV contrasts, respectively. Ethnic differences in COMT action on anxiety and smaller measurement error in the harm avoidance measures may explain the slightly larger effect size for harm avoidance than neuroticism. In particular, despite language differences, all three studies contributing to the significant harm avoidance finding used the same version of the scale (TCI; Cloninger *et al.*, 1993). For Eysenck neuroticism, different versions of the scale (EPQ-R-S vs. EPI) used across studies may contribute to greater effect size heterogeneity across studies, thus reducing the pooled effect size. A twin study investigating the genetic overlap across measures found that 53% and 65% of the covariance between neuroticism and harm avoidance was attributable to genetic factors in men and women, respectively (Heath *et al.*, 1994), so it is not surprising that we found an association of COMT with both traits.

## Limitations

There are several limitations to this study. First, despite our attempts to locate all relevant studies, we had insufficient information for several. It is likely that there are others we missed. Our analyses of publication bias indicated that publication year, sample size and error variance were not associated with effect sizes, thus alleviating concerns regarding biased samples entered into the meta-analysis.

Second, despite the relatively large number of studies and pooled sample size contributing to the overall meta-analysis, some of the sex-by-ethnicity subgroup analyses for specific constructs were underpowered. This restricted our ability to evaluate whether the COMT-neuroticism association among Caucasian males also applies to Asian males. Similarly, we were unable to directly compare the magnitude of the association across constructs as the use of different measures was confounded with differences in ethnicity.

Third, we observed significant heterogeneity among studies included in the analysis of Eysenck neuroticism in Caucasian men. Such heterogeneity is likely due to inclusion of three studies that used an extreme-groups design. We were unable to formally estimate the effect size after excluding these samples as only two samples remained. We used two strategies to ameliorate the impact of these studies: calculation of $ES_{OR}$ after imputing the genotypes of unsampled individuals in the middle of these distributions and use of a random-effects analytic framework. Furthermore, in the Eysenck+NEO neuroticism analyses, we obtained similar results before and after excluding the extreme samples.

## Summary

This is the first meta-analysis of genetic association of the COMT val158met polymorphism with anxiety-related traits. The total sample of more than 15,000 individuals provided an opportunity to assess whether the association differed by sex and ethnicity. There was a sex-specific association across anxiety traits, such that Val-carriers had higher anxiety than Met homozygotes only among males. The COMT-harm avoidance association was observed among Asian but not Caucasian men. These findings highlight the importance of considering sex and ethnicity in genetic association studies.


## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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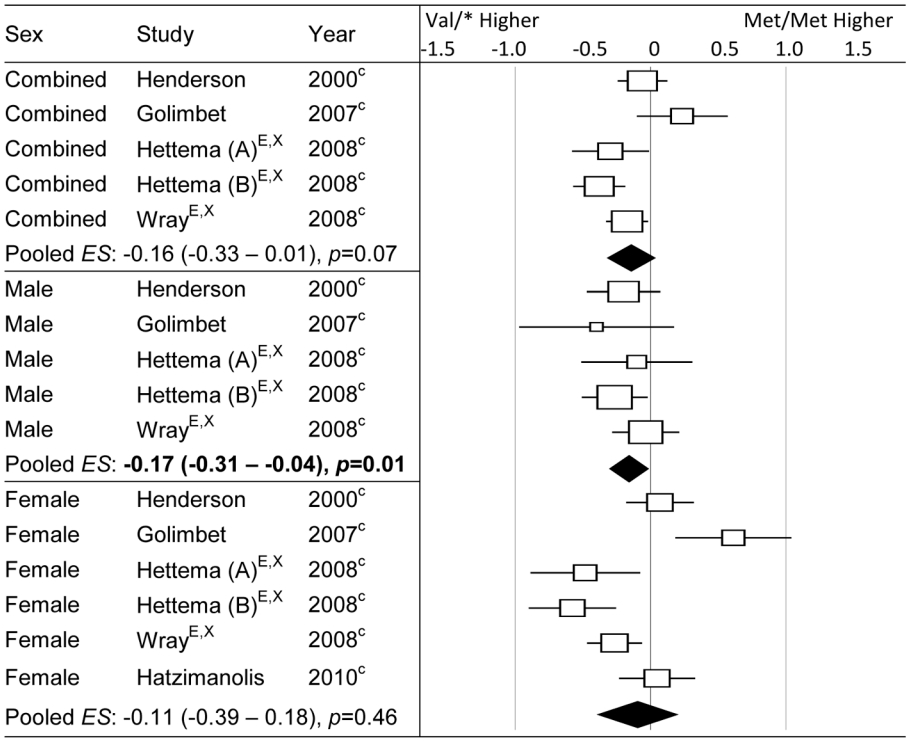
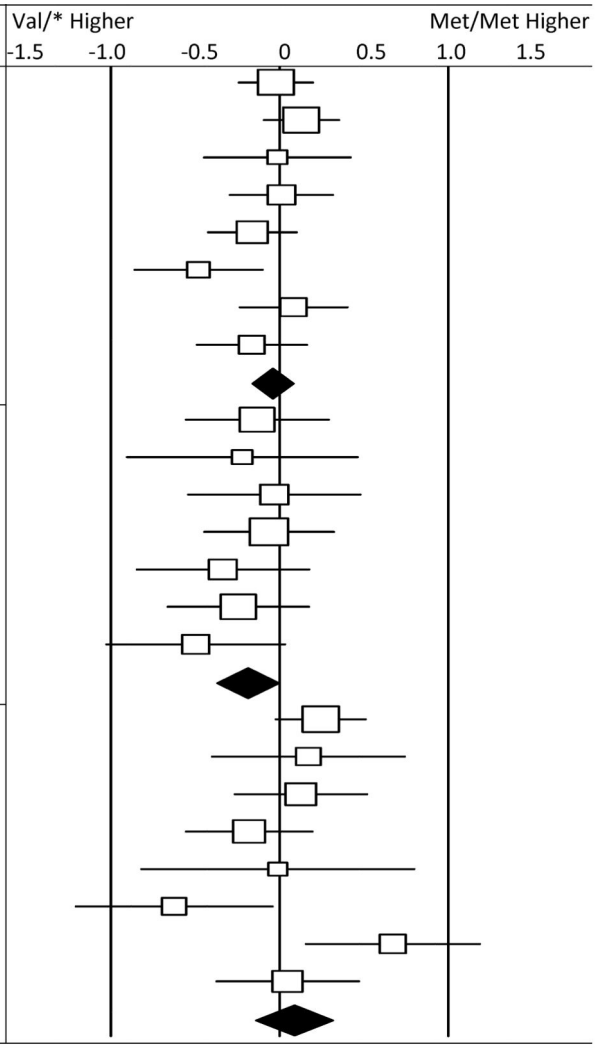



*Notes:*

1. Studies subsequently removed in sensitivity analysis due to the following characteristics are denoted by superscripts: $^{E}$=extreme sampling, $^{X}$=Cox method used to convert logged odds ratio effect sizes.
2. Sample ethnicity is denoted by a superscript: $^{c}$=Caucasian.
3. Bold font indicates effect size is significant at $p \leq .05$.

**Figure 1.**
Forest plot of meta-analysis results by sex for Eysenck Neuroticism measures; Met/Met vs. Val/* contrast.

| Sex | Study | Year |
|---|---|---|
| Combined | Benjamin[R] | 2000a[u] |
| Combined | Reuter | 2005[c] |
| Combined | Ivanova | 2006[c] |
| Combined | Golimbet | 2007[c] |
| Combined | Calati | 2011[c] |
| Combined | Kim | 2006[a] |
| Combined | Ishii | 2007[a] |
| Combined | Chen | 2011[a] |
| Pooled *ES*: -0.05 (-0.17 – 0.07), *p*=0.40 | | |
| Male | Reuter | 2005[c] |
| Male | Ivanova | 2006[c] |
| Male | Golimbet | 2007[c] |
| Male | Calati | 2011[c] |
| Male | Kim | 2006[a] |
| Male | Ishii | 2007[a] |
| Male | Chen | 2011[a] |
| Pooled *ES*: **-0.20 (-0.38 – -0.02), *p*=0.03** | | |
| Female | Reuter | 2005[c] |
| Female | Ivanova | 2006[c] |
| Female | Golimbet | 2007[c] |
| Female | Calati | 2011[c] |
| Female | Tsai | 2004[a] |
| Female | Kim | 2006[a] |
| Female | Ishii | 2007[a] |
| Female | Chen | 2011[a] |
| Pooled *ES*: 0.08 (-0.15 – 0.30), *p*=0.51 | | |




*Notes:*

1. One study subsequently removed in sensitivity analysis due to sample relatedness was denoted by the superscript [R].
2. Sample ethnicity is denoted by superscripts: [a]=Asian, [c]=Caucasian, [u]=unknown.
3. Bold font indicates effect size is significant at $p \leq .05$.

**Figure 2.**
Forest plot of meta-analysis results by sex for harm avoidance measures; Met/Met vs. Val/* contrast.

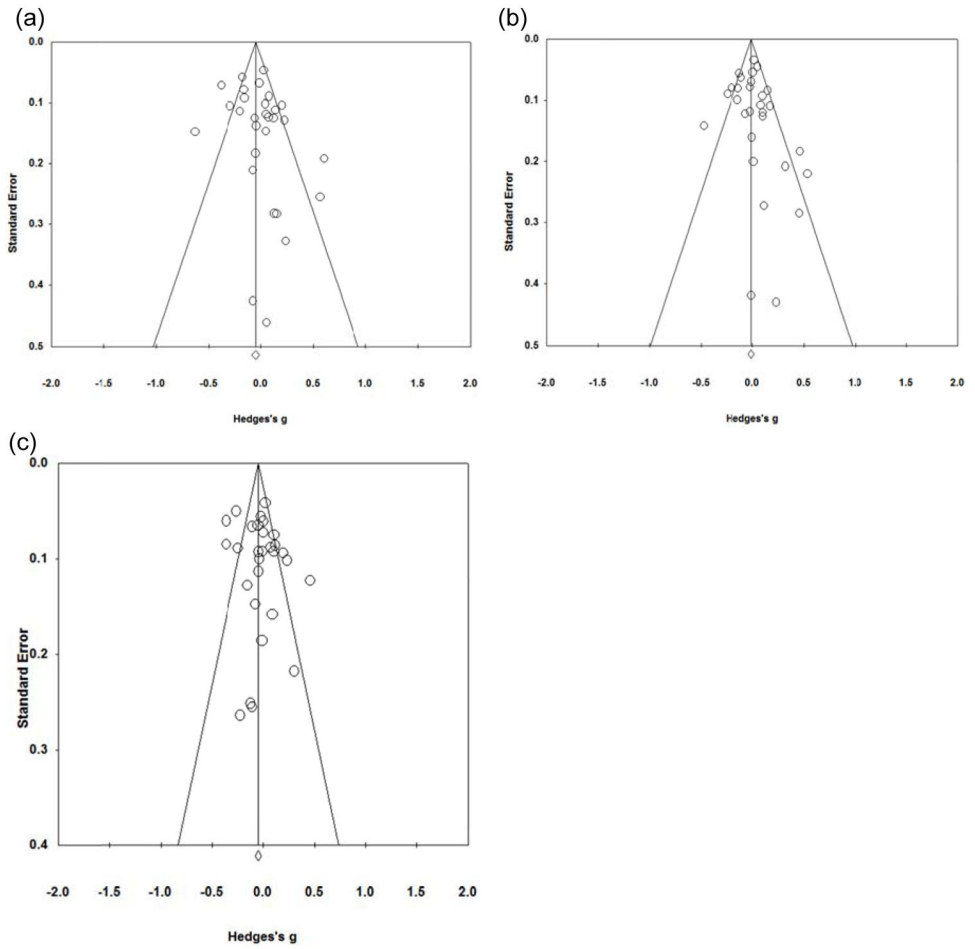



**Figure 3.**

Funnel plots of meta-analysis results across *k*=29 independent samples: (a) Met/Met vs. Val/Val, (b) Met/Met vs. Val/*, (c) Met/* vs. Val/Val.

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**Table 1**

Descriptive information on studies included in the meta-analysis.

| Study | Year | Sex | Mean Age | Location | Measure (construct) | All N | Male N | Female N |
|---|---|---|---|---|---|---|---|---|
| Benjamin | 2000a[R] | MF▲ | 26.95 | Israel[u] | TPQ (HA) | 454 | -- | -- |
| Henderson | 2000 | MF | 42.05 | Australia[c] | BIS (BI) | 870 | 407 | 463 |
| | | | | | DSSI (Anx) | 870 | 407 | 463 |
| | | | | | EPQ-R-S (N) | 868 | 405 | 463 |
| | | | | | Goldberg (Anx) | 870 | 407 | 463 |
| | | | | | PANAS (NA) | 965 | 502 | 463 |
| Eley | 2003[E,X] | F | 36.59 | Germany[c] | NEO-FFI (N) | 71 | -- | 71 |
| Kim (A) | 2004[H] | MF | 25.77 | US[c] | TCI (HA) | 349 | 164 | 185 |
| Kim (B) | 2004 | F | 24.73 | US[a] | TCI (HA) | 64 | -- | 64 |
| Tsai | 2004 | F | 20.00 | Taiwan[a] | TPQ (HA) | 120 | -- | 120 |
| Harris | 2005 | MF | 79.06 | Scotland[c] | HADS (Anx) | 533 | 223 | 310 |
| Olsson | 2005[X] | MF | 24.09 | Australia[c] | CIS-R (Anx) | 803 | 338 | 465 |
| | 2007 | | | | NEO (N) | 801 | 338 | 463 |
| Reuter | 2005 | MF | 24.39 | Germany[c] | NEO-FFI (N) | 363 | 101 | 262 |
| | | | | | TCI (HA) | 363 | 101 | 262 |
| Hoth | 2006 | MF | 39.68 | (mixed)[c] | DASS (Anx) | 402 | 221 | 181 |
| | | | | | NEO-FFI (N) | 374 | 204 | 170 |
| Ivanova | 2006 | MF | 36.82 | Bulgaria [c] | TCI (HA) | 102 | 40 | 62 |
| Kim | 2006 | MF | 23.00 | Korea[a] | TCI (HA) | 286 | 138 | 148 |
| Reuter | 2006 | MF | 25.57 | Germany[c] | BIS (BI) | 295 | 143 | 152 |
| Tochigi | 2006 | MF▲ | 37.40 | Japan[a] | NEO-PI-R (N) | 248 | -- | -- |

| Study | Year | Sex | Mean Age | Location | Measure (construct) | All N | Male N | Female N |
|---|---|---|---|---|---|---|---|---|
| Golimbet | 2007 | MF | 31.55 | Russia[c] | EPI (N) | 270 | 98 | 172 |
| | | | | | MMPI (Pt) | 269 | 99 | 170 |
| | | | | | TCI (HA) | 211 | 68 | 143 |
| Hashimoto | 2007[H] | MF | 36.32 | Japan[a] | TCI (HA) | 139 | 47 | 92 |
| Ishii | 2007 | MF | 29.30 | Japan[a] | TCI (HA) | 478 | 246 | 232 |
| Urata | 2007[X] | F | 20.00 | Japan[a] | NEO-FFI (N) | 235 | -- | 235 |
| Bækken | 2008[X] | MF | 50.61 | Norway[c] | HADS (Anx) | 5,651 | 2,629 | 3022 |
| Hettema (A) | 2008[E,X] | MF | 37.41 | US[c] | EPQ-R-S (N) | 359 | 186 | 173 |
| Hettema (B) | 2008[E,X] | MF | 36.47 | US[c] | EPQ-R-S (N) | 712 | 471 | 241 |
| Montag | 2008[C] | F | 22.11 | Germany[c] | BIS (BI) | 96 | -- | 96 |
| Wray | 2008[E,X] | MF | 40.14 | Australia[c] | EPQ-R-S (N) | 954 | 403 | 551 |
| Arias | 2010 | MF | 21.87 | Spain[c] | STAI-T (Anx) | 456 | 200 | 256 |
| Hatzimanolis | 2010 | F | 39.60 | Greece[c] | EPQ (N) | 381 | -- | 381 |
| Middeldorp | 2010 | MF | 56.46 | Netherlands[c] | YASR (Anx) | 274 | 124 | 150 |
| Calati | 2011 | MF | 45.22 | Germany[c] | TCI (HA) | 289 | 123 | 166 |
| Chen | 2011 | MF | 20.47 | China[a] | BAI (Anx) | 556 | 250 | 306 |
| | | | | | BIS (BI) | 556 | 250 | 306 |
| | | | | | TCI (HA) | 556 | 250 | 306 |
| Desmeules | 2011 | F | 50.00 | Switzerland[c] | STAI-T (Anx) | 74 | -- | 74 |
| TOTAL (27 studies / 29 independent samples) | | | | | | 15,979 | 6,648 | 8,630 |

*Abbreviations (measures)*: BAI = Beck Anxiety Inventory (Beck and Steer, 1990); BIS = Behavioral Inhibition System Scale (Carver and White, 1994); CIS-R = Clinical Interview Schedule – Revised (Lewis *et al.*, 1988); DASS = Depression Anxiety Stress Scales (Anxiety subscale; Lovibond and Lovibond, 1995); DSSI = Delusions-Symptoms-States Inventory (Anxiety scale; Bedford *et al.*, 1976); EPI = Eysenck Personality Inventory (Eysenck and Eysenck, 1964); EPQ = Eysenck Personality Questionnaire (Eysenck and Eysenck, 1975); EPQ-R-S = EPQ-Revised-short form (Eysenck and Eysenck, 1991); Goldberg = Goldberg anxiety scale (Goldberg *et al.*, 1988); HADS = Hospital Anxiety and Depression Scale (anxiety subscale; Zigmond and Snaith, 1983); MMPI-Pt = Minnesota Multiphasic

Personality Inventory (Psychasthenia subscale) (Hathaway and McKinley, 1940); NEO = Neuroticism, Extraversion, and Openness Personality Inventory (Costa & McCrae, 1985); NEO-FFI = NEO Five Factor Inventory (Costa & McCrae, 1992); NEO-PI-R = NEO Revised (Costa *et al.*, 1991); PANAS = Positive and Negative Affect Schedule (short form; Mackinnon *et al.*, 1999); STAI-T = State Trait Anxiety Inventory (trait form; Spielberger, 1983); TCI = Temperament and Character Inventory (Cloninger *et al.*, 1994); TPQ = Tridimensional Personality Questionnaire (Cloninger *et al.*, 1991); YASR = Young Adult Self-Report (anxious depression scale; Achenbach, 1990).

*Abbreviations (constructs)*: HA = harm avoidance; N = neuroticism; BI = behavioral avoidance; Anx = anxiety; Dep = depression.

*Abbreviations (others)*:[a] = Asian, [c] = Caucasian, [u] = unknown ethnicity. [H] = HWE flag indicates deviation of genotype frequency from HWE, [X] = effect sizes provided in odds ratio format and transformed with the Cox method; [E] = extreme-scoring samples; [R] = related participants. M = male, F = female, MF = both sexes included; ▲ = studies that did not provide separate statistics for males and females.

Notes:

1. When a sample included multiple measures, *N* for measure with biggest sample size was used to calculate the total *N* reported here. Sex-specific *N* only includes studies that provided sex-specific data. For clarity, each independent sample is placed within the same shaded/unshaded row.
2. Olsson *et al.* (2005) and Olsson *et al.* (2007) were treated as one study because of the nearly identical samples; they were based on the same study sample (Victorian Adolescent Health Cohort Study. Effect sizes on CIS-R, but not NEO-FFI, were provided in odds ratio format and transformed with the Cox method. On the CIS-R, individuals who reported heightened generalized anxiety symptoms for =>3 waves were coded as “high anxiety” to approximate a median split of the sample.In the 2005 sample, “cases” vs. controls were coded as individuals with 3+ vs. 0–3 waves of generalized anxiety.
3. Kim (A) and Kim (B) represent the Caucasian and Asian samples in Kim *et al.* (2004), respectively. In this study, Hardy-Weinberg equilibrium (HWE) was violated in the Caucasian sample. We excluded the entire sample (Caucasian and Asian) from HWE sensitivity analyses. This study included Asian males, but this subgroup was excluded from our meta-analysis due to N=0 with the rs4680 met/met genotype.
4. Hettema (A) and Hettema (B) represent the two-stage independent samples in Hettema *et al.* (2008).
5. In Hashimoto *et al.* (2007), deviation from HWE was observed only in the combined sex sample, but to be conservative, we removed the study from all HWE sensitivity analyses.

**Table 2**

Genotype frequencies by sex and ethnicity.

| | Met/Met | Val/Met | Val/Val | Met/Met | Val/Met | Val/Val | Total |
|---|---|---|---|---|---|---|---|
| ALL INDEPENDENT SAMPLES (*k*=29)* | | Any Ethnicity | | | -- | | |
| | 4,064 (25.43%) | 7,713 (46.26%) | 4,202 (26.30%) | -- | -- | -- | 15,979 |
| ALL INDEPENDENT SAMPLES (*k*=28) | | Caucasians (*k*=20) | | | Asians (*k*=8)^ | | (*k*=28) |
| | 3,796 (28.33%) | 6,650 (49.63%) | 2,953 (22.04%) | 181 (8.51%) | 833 (39.18%) | 1,112 (52.30%) | Caucasians: 13,399<br>Asians: 2,126<br>Total: 15,525 |
| MALE (*k*=20) | | Caucasians (*k*=16) | | | Asians (*k*=4) | | (*k*=20) |
| | 1,749 (29.31%) | 2,969 (49.76%) | 1,249 (20.93%) | 58 (8.52%) | 250 (36.71%) | 373 (54.77%) | Caucasians: 5,967<br>Asians: 681<br>Total: 6,648 |
| FEMALE (*k*=27) | | Caucasians (*k*=20) | | | Asians (*k*=7) | | |
| | 2,047 (27.54%) | 3,683 (49.55%) | 1,703 (22.91%) | 95 (7.94%) | 478 (39.93%) | 624 (52.13%) | Caucasians: 7,433<br>Asians: 1,197<br>Total: 8,630 |

Notes:

*See list in Table 1.

^Includes one study that did not specify genotype frequencies by sex.

1. When a sample included multiple measures, *N* for measure with biggest sample size (specific to each sex category) was used to calculate the *N*s reported here. Sex-specific *N*s are only based on studies that provided sex-specific data.

2. Percentages given as row total for each ethnicity.

**Table 3a–f**

Summary of effect sizes (95% UCI, 95% LCI) by sex, ethnicity and genotypic contrasts; by constructs.

**(a) Any anxiety-related traits:**

| | **Any Ethnicity** | **Caucasian** | **Asian** |
|---|---|---|---|
| Both Sexes | *k*=20 | *k*=15 | *k*=4 |
| MM - VV | −0.06 (−0.14, 0.02), *p*=0.14 | −0.05 (−0.14, 0.04), *p*=0.30 | −0.17 (−0.46, 0.13), *p*=0.26 |
| MM - V* | −0.02 (−0.07, 0.02), *p*=0.34 | −0.02 (−0.07, 0.03), *p*=0.49 | −0.10 (−0.34, 0.14), *p*=0.41 |
| M* - VV | −0.05 (−0.12, 0.02), *p*=0.16 | −0.03 (−0.12, 0.06), *p*=0.52 | −0.13 (−0.28, 0.03), *p*=0.10 |
| Male | *k*=18 | *k*=15 | *k*=3 |
| MM - VV | −0.09 (−0.20, 0.01), *p*=0.07 | −0.06 (−0.16, 0.04), *p*=0.21 | **−0.44 (−0.73, −0.15), *P*=0.003** |
| MM - V* | −0.05 (−0.12, 0.02), *p*=0.16 | −0.03 (−0.10, 0.04), *p*=0.42 | **−0.36 (−0.65, −0.08), *P*=0.01** |
| M* - VV | −0.07 (−0.15, 0.01), *p*=0.07 | −0.04 (−0.13, 0.05), *p*=0.38 | **−0.18 (−0.34, −0.03), *P*=0.02** |
| Female | *k*=24 | *k*=19 | *k*=5 |
| MM - VV | 0.02 (−0.11, 0.14), *p*=0.78 | −0.001 (−0.13, 0.12), *p*=0.99 | 0.08 (−0.42, 0.58), *p*=0.75 |
| MM - V* | 0.05 (−0.04, 0.13), *p*=0.28 | 0.04 (−0.05, 0.12), *p*=0.41 | 0.11 (−0.31, 0.52), *p*=0.61 |
| M* - VV | −0.03 (−0.13, 0.06), *p*=0.50 | −0.04 (−0.14, 0.07), *p*=0.51 | −0.03 (−0.26, 0.21), *p*=0.83 |

**(b) Neuroticism:**

| | **Any Ethnicity** | **Caucasian** | **Asian** |
|---|---|---|---|
| Both Sexes | *k*=9 | *k*=8 | *k*=1 |
| MM - VV | −0.08 (−0.22, 0.05), *p*=0.23 | −0.08 (−0.23, 0.06), *p*=0.27 | -- |
| MM - * | −0.04 (−0.11, 0.03), *p*=0.28 | −0.04 (−0.12, 0.04), *p*=0.30 | -- |
| M* - V | −0.06 (−0.20, 0.08), *p*=0.37 | −0.05 (−0.21, 0.10), *p*=0.50 | -- |
| Male | (all Caucasian) | *k*=8 | *k*=0 |
| MM - V | -- | **−0.13 (−0.25, −0.02), *P*=0.03** | -- |
| MM - V* | -- | −0.07 (−0.17, 0.03), *p*=0.18 | -- |
| M* - V | -- | −0.10 (−0.21, 0.004), *p*=0.06 | -- |
| Female | *k*=11 | *k*=10 | *k*=1 |
| MM - VV | −0.03 (−0.21, 0.16), *p*=0.79 | −0.04 (−0.23, 0.16), *p*=0.72 | -- |
| MM - V* | 0.02 (−0.07, 0.11), *p*=0.67 | 0.02 (−0.08, 0.11), *p*=0.71 | -- |

**(b) Neuroticism:**

| | Any Ethnicity | Caucasian | Asian |
|---|---|---|---|
| M* - V | −0.04 (−0.22, 0.14), *p*=0.66 | −0.05 (−0.25, 0.14), *p*=0.59 | -- |

**(c) Neuroticism as measured by Eysenck scales:**

| | Caucasian |
|---|---|
| Both sexes | *k*=5 |
| MM-VV | −0.16 (−0.33, 0.01), *p*=0.07 |
| MM-V* | −0.04 (−0.11, 0.04), *p*=0.33 |
| M* - VV | −0.13 (−0.33, 0.07), *p*=0.21 |
| Male | *k*=5 |
| MM-VV | **−0.17 (−0.31.−0.04), *p*=0.01** |
| MM-V* | −0.05 (−0.16, 0.06), *p*=0.39 |
| M* - VV | **−0.17 (−0.29, −0.05), *p*=0.004** |
| Female | *k*=6 |
| MM-VV | −0.11 (−0.39, 0.18), *p*=0.46 |
| MM-V* | −0.004 (−0.12, 0.11), *p*=0.95 |
| M* - VV | −0.11 (−0.40, 0.19), *p*=0.47 |

**(d) Neuroticism as measured by the NEO scales:**

| | Any Ethnicity | Caucasian | Asian |
|---|---|---|---|
| Both sexes | *k*=4 | *k*=3 | *k*=1 |
| MM - VV | 0.02 (−0.19, 0.24), *p*=0.83 | 0.05 (−0.22, 0.32), *p*=0.72 | -- |
| MM - V* | −0.02 (−0.19, 0.15), *p*=0.84 | −0.02 (−0.23, 0.19), *p*=0.87 | -- |
| M* - VV | 0.02 (−0.14, 0.18), *p*=0.80 | 0.07 (−0.11, 0.24), *p*=0.44 | -- |
| Male | (all Caucasian) | *k*=3 | *k*=0 |
| MM - VV | -- | −0.01 (−0.33, 0.31), *p*=0.96 | -- |
| MM - V* | -- | −0.09 (−0.33, 0.15), *p*=0.45 | -- |
| M* - VV | -- | 0.06 (−0.16, 0.28), p=0.60 | -- |
| Female | *k*=5 | *k*=4 | *k*=1 |
| MM - VV | 0.06 (−0.11, 0.23), *p*=0.47 | 0.06 (−0.13, 0.25), *p*=0.53 | -- |
| MM - V* | 0.07 (−0.10, 0.23), *p*=0.42 | 0.07 (−0.12, 0.27), *p*=0.46 | -- |

**(d) Neuroticism as measured by the NEO scales:**

| | Any Ethnicity | Caucasian | Asian |
|---|---|---|---|
| M* - VV | 0.04 (−0.09, 0.18), *p*=0.53 | 0.03 (−0.12, 0.18), *p*=0.67 | -- |

**(e) Harm avoidance:**

| | Any Ethnicity | Caucasian | Asian |
|---|---|---|---|
| Both sexes | *k*=8 | *k*=4 | *k*=3 |
| MM - VV | −0.06 (−0.22, 0.10), *p*=0.47 | 0.08 (−0.10, 0.25), *p*=0.40 | −0.25 (−0.63, 0.14), *p*=0.21 |
| MM - V* | −0.05 (−0.17, 0.07), *p*=0.40 | 0.01 (−0.14, 0.15), *p*=0.95 | −0.17 (−0.48, 0.14), *p*=0.27 |
| M* - VV | −0.04 (−0.15, 0.07), *p*=0.52 | 0.10 (−0.04, 0.24), *p*=0.16 | −0.14 (−0.32, 0.03), *p*=0.10 |
| Male | *k*=7 | *k*=4 | *k*=3 |
| MM - VV | −0.17 (−0.43, 0.08), *p*=0.19 | 0.10 (−0.20, 0.40), *p*=0.52 | **−0.43 (−0.72, −0.14), *P*=0.004** |
| MM - V* | **−0.20 (−0.38, −0.02), *P*=0.03** | −0.10 (−0.34, 0.14), *p*=0.43 | **−0.34 (−0.62, −0.06), *P*=0.02** |
| M* - VV | −0.06 (−0.26, 0.14), *p*=0.54 | 0.19 (−0.06, 0.45), *p*=0.13 | **−0.23 (−0.39, −0.07), *P*=0.004** |
| Female | *k*=8 | *k*=4 | *k*=4 |
| MM - VV | 0.08 (−0.20, 0.35), *p*=0.58 | 0.15 (−0.07, 0.37), *p*=0.19 | −0.01 (−0.64, 0.63), *p*=0.99 |
| MM - V* | 0.08 (−0.15, 0.30), *p*=0.51 | 0.11 (−0.08, 0.30), *p*=0.26 | 0.035 (−0.50, 0.57), *p*=0.90 |
| M* - VV | 0.01 (−0.15, 0.16), *p*=0.91 | 0.09 (−0.09, 0.26), *p*=0.32 | −0.06 (−0.35, 0.23), *p*=0.68 |

**(f) Behavioral inhibition:**

| | Any Ethnicity | Caucasian | Asian |
|---|---|---|---|
| Both sexes | *k*=3 | *k*=2 | *k*=1 |
| MM - VV | 0.02 (−0.13, 0.16), *p*=0.83 | -- | -- |
| MM - V* | 0.03 (−0.10, 0.15), *p*=0.69 | -- | -- |
| M* - VV | 0.01 (−0.10, 0.11), *p*=0.91 | -- | -- |
| Male | *k*=3 | *k*=2 | *k*=1 |
| MM - VV | −0.08 (−0.64, 0.48), *p*=0.78 | -- | -- |
| MM - V* | −0.06 (−0.51, 0.38), *p*=0.78 | -- | -- |
| M* - VV | −0.02 (−0.31, 0.27), *p*=0.90 | -- | -- |
| Female | *k*=4 | *k*=3 | *k*=1 |
| MM - VV | 0.21 (−0.07, 0.49), *p*=0.15 | 0.15 (−0.20, 0.51), *p*=0.39 | -- |
| MM - V* | 0.19 (−0.07, 0.45), *p*=0.16 | 0.15 (−0.18, 0.47), *p*=0.37 | -- |

**(f) Behavioral inhibition:**

| | Any Ethnicity | Caucasian | Asian |
|---|---|---|---|
| M* - VV | 0.09 (−0.04, 0.23), $p$=0.18 | 0.06 (−0.12, 0.23), $p$=0.52 | -- |

Notes for Tables 3a–f:

1. COMT val158met genotype: MM = Met/Met, VV = Val/Val, M* = Met-carriers, V* = Val-carriers.

2. Bold font indicates significant effect size at $p \leq .05$.

3. Samples with genotype frequency in violation of Hardy-Weinberg equilibrium have been excluded.

4. Analyses were not conducted when the number of available samples (*k*) was lower than three.

5. For (c), all samples administered the Eysenck scales were Caucasian.