Associations between the *COMT Val/Met* polymorphism, early life stress, and personality among healthy adults

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Abstract: Efforts to identify genetic factors that confer an increased risk for the expression of psychiatric symptoms have focused on polymorphisms in variety of candidate genes, including the catechol-O-methyltransferase (*COMT*) gene. Results from previous studies that have examined associations between the functional *COMT* polymorphism (*Val158Met*) and mental health have been mixed. In the present study, we examined the relationships between *COMT*, early life stress, and personality in a healthy adult sample. Consistent with previous studies, we hypothesized that individuals with the low-activity genotype would have higher neuroticism and lower extraversion and that this effect would be more pronounced in females. In addition, we extended the previous literature by investigating the potential influence of early life stress. A total of 486 healthy adults underwent genetic testing and personality assessment. Results revealed that individuals homozygous for the *COMT* low enzyme activity allele had lower extraversion on the NEO-FFI and demonstrated a trend toward greater neuroticism. These relationships were not influenced by sex or the presence of reported early life stress. The finding that *COMT* genotype was associated with extraversion, and more weakly with neuroticism, is consistent with previous studies. Future research to clarify the influence of sex and gene–environmental interactions is warranted.

Keywords: anxiety; depression; gene-environment interaction, early life stress

Introduction

Recent genetic linkage and epidemiological studies have focused on the identification of genetic polymorphisms thought to confer an increased risk for psychiatric symptoms, including anxiety and depression. The catechol-O-methyltransferase (*COMT*) gene has been implicated in the expression of anxiety and depression secondary to its role in the enzymatic degradation of adrenaline, noradrenaline, and dopamine (Lannfelt et al 1992; Akil et al 2003). A functional polymorphism characterized by a substitution of methionine (*Met*) in place of valine (*Val*) at codon 158 results in a 2- to 4-fold decrease in the activity of the *COMT* enzyme. Functional effects of the polymorphism for neurotransmission in the brain have been documented (Akil et al 2003; Bray et al 2003) and it has been suggested that the low enzyme activity allele (*Met*) increases susceptibility to a range of psychiatric symptoms (Shifman et al 2004).

Findings from studies examining the association between the *COMT* polymorphism and the expression of affective symptoms in clinical populations are mixed. Although some authors have observed an association between the *Met* allele and affective disorders (Li et al 1997; Kirov et al 1998; Mynett-Johnson et al 1998; Papolos et al 1998), others have found no association (Ohara et al 1998b; Frisch et al

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1999; Henderson et al 2000). The *COMT* polymorphism has also been examined in relation to obsessive-compulsive disorder (Schindler et al 2000; Azzam and Mathews 2003; Erdal et al 2003; Olsson et al 2005), phobic anxiety (Ohara et al 1998a; McGrath et al 2004), and panic disorder (Hamilton et al 2002; Woo et al 2004) with mixed results.

Several recent studies examined the association between *COMT* and personality traits in nonclinical samples. Eley and colleagues (2003) explored the role of monoamine oxidase type A (*MAOA*) and *COMT* on the expression of neuroticism using a selected extremes design. The authors reported an excess of the low-activity genotype among females with high neuroticism. The focus on neuroticism in the study by Eley and colleagues (2003) provided a unique contribution to the literature; however, several aspects of the study warrant further study. First, the authors obtained peer-report of participants' personality using a translated version of the NEO-FFI, rather than using the original standardized self-report measure. In addition, only data from the top and bottom 10% of scores on the neuroticism measure were analyzed in the study. Selecting only those individuals with the most extreme personality scores may have biased the relationships by focusing only on critical aspects of the normal distribution.

Stein and colleagues (2005) extended the findings described above by examining the hypothesis that functional variants in the *COMT* gene would be associated with both high neuroticism and low extraversion among a sample of 497 college students. Results revealed that two of the three single nucleotide polymorphisms examined were associated with low extraversion and high neuroticism, with the effects confined to women. Overall, the authors concluded that the involvement of *COMT* is unlikely to be entirely attributable to the *Val/Met* polymorphism. Future research examining the additional contribution of other factors such as other genetic variation and gene–environment interactions may clarify the relationships.

Early life stress represents one important environmental condition that may affect genetic vulnerabilities to adult psychosocial health. In a recent study, Henderson and colleagues (2000) examined *COMT* and *DRD3* polymorphisms in a large community sample. In this study, there was no relationship between *COMT* and *DRD3* polymorphisms and personality traits conferring vulnerability to anxiety or depression. Results also revealed no relationship between *DRD3* genotype and exposure to childhood and recent environmental stressors; interestingly, the relationships between *COMT* polymorphism, early life stress, and mental health were not examined.

In the present study we examined the association between *COMT* genotype and personality among a cohort of healthy adults. Consistent with previous studies, we hypothesized that individuals with the *Met/Met* genotype (low enzyme activity) would report higher levels of neuroticism and lower extraversion on the NEO-FFI than individuals with the *Val/Val* genotype (high activity enzyme). We also examined the relationship between *COMT* and personality traits by sex. We expected that the association between *COMT* and neuroticism and extraversion would be stronger for females than for males. In addition, to further clarify the association between *COMT* genotype and anxiety-related personality traits, we examined the interaction between genotype and environmental exposure to early life stress. Exposure to early life stress was expected to moderate the association between *COMT* genotype and neuroticism and extraversion. Specifically, we hypothesized that individuals with both the *Met/Met* genotype and a history of early life stress would endorse greater neuroticism and lower extraversion.

Methods

Procedures

All individuals in the present study were participants in a large multi-site, multi-national study of brain function, including, in part, emotional and genetic data (Brain Resource International Database, BRID www.brainresource.com; Gordon 2003; Gordon et al 2005). As part of the parent study, individuals were excluded if they had a history of any medical (eg, diabetes, hypertension, stroke, degenerative disease, thyroid disease), or psychiatric condition (eg, psychosis, mood disorder). The screening procedure included a comprehensive web-based medical history questionnaire and the SPHERE (Hickie et al 2001). Participants were examined at one of five research sites in Australia, North America, and Europe. Written informed consent was obtained for all individuals after receiving a thorough explanation of the study. The parent study was approved by local IRBs at each of the participating research sites. Participants were financially compensated for participation.

Genotyping

Genomic DNA was extracted from cheek swabs. Buccal cells were pelleted by centrifugation and digested overnight

at 42ºC in a 420 µl volume containing 1 µg/ml Proteinase K, 6 mM Tris-Cl pH 7.5, 6 mM EDTA, 0.3% Na Sarkosyl, 1.2 M guanidine HCl, and 0.5 M ammonium acetate. DNA was purified from the digest by standard chloroform extraction and EtOH precipitation, and resuspended in de-ionised water. *COMT* genotypes were determined by restriction fragment length polymorphism method. A 109-base-pair polymerase chain reaction product was generated using the primers Comt1 nt 1881 5′ CTCATCACCATCGA GATCAA 3′ and Comt2 nt 1989 5′ CCAGGTCTGACAAC GGGTCA 3′. The *Val* and *Met* alleles were discriminated by digesting the PCR product with *Nla*III, followed by agarose gel electrophoresis and visualization by ethidium bromide staining.

Psychological measures

Early life stress questionnaire (ELSQ)

Early life stress was measured using the ELSQ, which was developed for use in an international cohort (Gordon et al 2005; McFarlane et al 2005; Paul et al 2005). The ELSQ is based on the Child Abuse and Trauma Scale, which has been shown to have strong internal consistency, test-retest reliability, and validity, as it correlates with adult outcome and psychopathology (Sanders and Becker-Lausen 1995). The measure consists of 19 events shown to have psychological impact in childhood in previous studies (eg, Sanders and Becker-Lausen 1995). Participants reported whether they experienced a broad range of specific early life stressors and the age at which it occurred. Specific events covered on the questionnaire are listed in Table 1. For the current study, participants were grouped based on the number of early life stressors that they reported (ie, "low early life stress" = 0 early life events, and "high early life stress" = 2 or more early life events).

Table 1 Events on the early life stress questionnaire

1. Emotional abuse
2. Physical abuse
3. Sexual abuse
4. Domestic violence
5. Severe family conflict
6. Neglect
7. Divorce
8. Separated from family
9. Death in family
10. Major illness in family
11. Fire destroyed home
12. War
13. Natural disaster
14. Major personal illness
15. Hospitalization/surgery
16. Bullied
17. Premature birth
18. Adoption
19. Describe other events

NEO-Five Factor Inventory (NEO-FFI)

The NEO-FFI, a 60-item self-report questionnaire, was used to assess personality. The NEO-FFI is a short form of the NEO-Personality Inventory-Revised (NEO-PI; Costa and McCrae 1992), a measure of the Five Factor Model of Personality composed of Neuroticism, Extraversion, Openness to experience, Agreeableness, and Conscientiousness scales.

Sample

From the larger dataset, we identified all individuals over the age of 18 who had data for the relevant genetic and psychological measures. This resulted in a sample of 486 individuals. Participants had an average age of 38.52 (SD = 16.6; range 18–82), an average education of 14.5 years (SD = 2.6; range 8–18), and the sample was 53% male. Seventy-three percent of the sample was collected in Australia, 15% was collected in the US, and 12% was collected in Europe. The majority of the sample was of European descent (83.1%). Approximately 5% reported having "mixed" ethnicity, 3.1% were Asian, 2.1% were Middle Eastern, and the remaining 7% were either Indian, African, indigenous American, indigenous Australian, or Pacific Islander. Approximately 20% of the sample had a *Val/Val* genotype and 37% percent had a *Met/Met* genotype and allele frequencies were in Hardy-Weinberg equilibrium. This is commensurate with the frequency of the low enzyme activity allele reported in previous psychiatrically screened Caucasian control samples (Karayiorgou et al 1997).

Data analysis

Univariate comparisons of demographic characteristics between *COMT* genotype groups were carried out using independent samples t-tests for continuous variables and χ^2 tests for categorical variables. To examine the comparability of the *Val/Met* allele frequencies across subsamples collected on each of the three continents, a χ^2 test was conducted. Analysis of variance (ANOVA) was used to examine differences in personality dimensions on the NEO-FFI between the low (*Met/Met*) and high (*Val/Val*) *COMT* genotype groups. MANOVA was used to examine the potential interaction between *COMT*, sex, and personality. A second MANOVA was carried out to examine the possible

interaction between *COMT* genotype, exposure to early life stress, and personality. *COMT* genotype and ELS severity (high vs low) were entered as fixed factors, with NEO-FFI personality dimensions entered as the dependent variables. An alpha level of 0.05 was retained for all analyses, as specific a priori hypotheses were tested, and the relative risk of Type I error was deemed to be more acceptable than Type II error given the fact that relatively subtle effects were anticipated.

Results

There were no significant differences on key demographic variables (ie, age, education, sex, number of early life stressful events) between the *COMT* genotype groups. Allele frequencies did not differ across subsamples collected on each of the continents; thus, all individuals were grouped for the primary analysis. Mean scores on the NEO-FFI are presented in Tables 2 and 3 by *COMT* genotype and severity of early life stress. Those individuals who were homozygous for the low-activity *COMT* enzyme allele (*Met/Met*) had lower scores on the extraversion personality dimension than those participants with the high-enzyme genotype (*Val/Val*) ($F(1,253) = 5.10$, $p < 0.05$); there was a nonsignificant trend for individuals with the low-activity genotype to have higher neuroticism ($F(1,252) = 0.10$, $p = 0.08$). The *COMT* polymorphism accounted for 2.0% of the variance in extraversion and 1.2% of the variance in neuroticism scores. There were no significant statistically significant interactions between *COMT* genotype and sex for any of the personality dimensions.

Approximately 69% of the sample reported exposure to early life stress, with the most common events including hospitalization, severe personal illness, natural disaster, and major family conflict. Of the sample, 54.5% were classified as "low ELS" and 45.5% classified as "high ELS." Regarding the association between environmental exposure to early life stress and mental health, individuals who were exposed to high early life stress endorsed higher neuroticism ($F(1,442) = 15.66$, $p < 0.001$) and openness to experience ($F(1,445) = 6.71$, $p < 0.05$) on the NEO-FFI than those participants who were not exposed to early life stressful events. The level of exposure to early life stress accounted for 3.4% of the variance in neuroticism scores and 2.0% of the variance in openness to experience. Finally, the interaction between *COMT* genotype and severity of early life stress was examined. The interaction terms were not statistically significant for any of the NEO-FFI personality dimensions.

Table 2 Mean scores on the NEO-FFI by *COMT* genotype

Measure	COMT genotype Val/Val (n = 96)	Met/Met (n = 182)	F	p value (ANOVA)
NEO-FFI[a]				
Neuroticism	16.66 (6.65)	18.22 (6.74)	3.10	0.08
Extraversion	31.28 (4.87)	29.72 (5.44)	5.10	0.03
Openness	30.62(6.10)	30.72 (6.24)	0.02	0.90
Agreeableness	32.23 (5.69)	31.61 (5.04)	0.78	0.38
Conscientiousness	32.73 (6.10)	32.18 (7.00)	0.40	0.53

[a] NEO-Five Factor Inventory

Table 3 Mean scores on the NEO-FFI by severity of early life stress

	ELS[a] severity Low ELS (n = 261)	High ELS (n = 211)	F	p value (ANOVA)
NEO-FFI[b]				
Neuroticism	16.69 (6.38)	19.21 (7.03)	15.66	0.001
Extraversion	30.35 (5.66)	29.79 (5.65)	0.711	0.40
Openness	29.97 (5.98)	31.47 (6.21)	6.71	0.010
Agreeableness	31.96 (5.14)	31.53 (5.50)	0.74	0.39
Conscientiousness	32.56 (6.89)	31.88 (6.38)	1.16	0.28

[a] Early life stress.
[b] NEO-Five Factor Inventory

Discussion

The current study extends previous research associating the *COMT* polymorphism and mental health by assessing personality traits associated with negative affect in a sample of healthy adults, and examining the potential moderating effects of sex and early life stress on these relationships. The results provide weak support for an association between the *COMT* polymorphism and individual differences in extraversion and neuroticism among a sample of 486 medically and psychiatrically screened healthy adults. Specifically, findings revealed that participants who were homozygous for the *COMT* low-enzyme-activity allele (*Met/Met*) endorsed significantly lower extraversion and a tendency toward higher neuroticism on the NEO-FFI than those with the high-enzyme-activity genotype (*Val/Val*), though the magnitude of the effect was small. In contrast with previous studies, no sex-specific effects were observed. Finally, exposure to early life stress did not moderate the influence of the *COMT* low-enzyme-activity genotype on personality.

Examining the role of candidate genes on the expression of normally distributed anxiety related traits in healthy individuals provides a strategy to identify underlying genetic

vulnerabilities to developing anxiety and mood disorders. Studies have indicated that anxiety and depression share a common genetic diathesis that renders certain individuals vulnerable to develop both types of disorder (Kendler et al 1992). It has been proposed that individual differences in neuroticism may result in vulnerability to subjective distress and negative affect and ultimately development of anxiety and depression (Mineka et al 1998). In an effort to examine underlying genetic vulnerabilities for anxiety and depression, previous studies have observed associations between the serotonin transporter promoter polymorphism and neuroticism (see Schinka et al 2004 for a review). Other studies have examined monoamine oxidase type A (Eley et al 2003), *GABA-A* (Sen et al 2004), and *COMT* (Henderson et al 2000; Eley et al 2003; Stein et al 2005).

Variations in the *COMT* polymorphism have been associated with several normally distributed personality traits including harm avoidance (Enoch et al 2003), aggression (Rujescu et al 2003), and neuroticism in some (Eley et al 2003; Stein et al 2005) but not all (Henderson et al 2000) studies. Extraversion has been less studied in association with anxiety; however, Stein and colleagues (2005) observed that *COMT* polymorphism was associated with lower extraversion among female college students. These authors point out that extraversion is heritable (Jang et al 1996) and has been associated with several anxiety disorders (eg, agoraphobia and social phobia; Bienvenu et al 2001; Bienvenu and Stein 2003). Findings from the current study provide limited support to the associations between the low-enzyme-activity variation of the *COMT* polymorphism, lower extraversion, and higher neuroticism. The variance in the expression of the personality dimensions that was accounted for by *COMT* polymorphism is small, consistent with previous literature finding that specific polymorphisms examined alone account for limited variation in the phenotype (eg, Berrettini 1997, 2000). It is important to note that the sample that was examined in the current study included a highly selected healthy subset of the overall population, as individuals with a history of psychiatric disorders and chronic medical illnesses were excluded. This likely reduced the variability in personality traits by excluding individuals with clinically significant anxiety and depression. However, examining the relationships within a sample of healthy individuals extends findings in clinical populations in an important way. Differences in the expression of "normal" personality traits may reflect a subtle association between the low-activity genotype and individual vulnerability to subjective distress among adults free of anxiety or mood disorders. Furthermore, there is evidence that neuroticism and to a lesser extent extraversion, are risk factors for mood and anxiety disorders and that in the presence of exposure to stress the personality disorders interact to yield psychopathology.

Several studies have observed sex-specific effects of the *COMT* polymorphism on anxiety; specifically, the associations between the low activity *COMT* genotype and symptoms of anxiety have been found to be pronounced for females (Eley et al 2003; Olsson et al 2005; Stein et al 2005). In contrast with these previous findings, in the present study there was no evidence of differential sex effects. It is possible that the current study was limited by a relatively small sample size, reducing power to detect subtle effects. Previous studies have examined the association between the *COMT* polymorphism and anxiety related personality traits by examining females and males separately. In the current study, we investigated potential sex specific effects by statistically testing the interaction between *COMT* and sex, thus using a more conservative test. Future studies in larger samples of healthy adults will help to clarify potential sex effects.

An important contribution of the present study was the examination of the potential interaction between *COMT* genotype, early life stress, and personality traits associated with anxiety and negative affect. Multiple authors have pointed out that inconsistencies in the neuropsychiatric genetics literature are likely due, in part, to the fact that the expression of behavioral syndromes result from complex gene–environment interactions (eg, Berrettini 1997, 2000). Systematically examining interactions between genetic vulnerabilities and environmental exposure provides an important approach to clarify the multiple factors that influence the expression of anxiety. Exposure to early life stress has been associated with a range of adult psychopathology (eg, Harrison et al 1997; Friedman et al 2002). Alterations in the HPA axis and mesolimbic dopamine pathways have been implicated as a potential mechanism by which stress influences the expression of anxiety (Sapolsky 1996; Heim et al 2000). Given that the *COMT* polymorphism alters dopamine metabolism, the polymorphism may confer an underlying sensitivity to effects of early life stress via this neurotransmitter system. However, the effects of *COMT* on dopamine metabolism and subsequently anxiety and depression require further study at the neurochemical level.

Our data suggest that exposure to early life stress in itself was associated with higher scores on the personality

dimensions of neuroticism and openness to experience. These effects were statistically significant, but were extremely subtle as exposure to early life stress accounted for only 2%–3% of the variance in the expression of the personality dimensions. This indicates that additional factors including other genes and/or environmental influences underlie the expression of these anxiety-related personality traits. However, we found no evidence for an interaction between *COMT* genotype and early life stress measured using a life events questionnaire. This may not be surprising, given that that the expression of psychological traits results from the interaction of multiple genes and environmental influences. The current study was limited by examining a single functional polymorphism in one gene rather then functional polymorphisms from multiple genes, which would provide a more realistic model.

Some other studies have observed interaction effects between polymorphism variations in genes affecting dopamine neurotransmission and environmental exposure. Caspi and colleagues (2003) tested the moderating effects of variations in the serotonin transporter (*5-HTT*) gene on whether stressful experiences lead to depression in a prospective-longitudinal investigation. Analyses revealed that the serotonin transporter gene interacted with life events to predict depressive symptoms, diagnosis of depression, and suicidality. The authors discussed the fact that many candidate genes fail replication and account for little variation in the phenotype being examined. Differing levels of exposure to environmental risk may explain some of the mixed findings. In addition, Caspi and colleagues speculate that some multifactorial disorders may results from variations in multiple genes that have small effects, and some may result from variations in relatively fewer genes that are influenced by environmental risk. Caspi observed that in their sample, the moderation of life stress and depression by *5-HTT* was not affected by the individuals' *MAOA* status. Future studies in larger samples examining both interaction between *5-HTT*, *COMT*, and environmental influences will provide an important contribution toward clarifying these relationships.

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