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COMT Val[158]Met moderation of stress-induced psychosis

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ABSTRACT

Background. Exposure to stressful life events increases the risk of developing a psychotic disorder. Moreover, increased reactivity to stress seems to represent part of the vulnerability for psychosis. This study aimed to investigate whether a functional polymorphism in the catechol-*O*-methyltransferase (COMT Val[158]Met) gene moderates the psychosis-inducing effects of stress.

Method. A semi-experimental stress exposure paradigm was used in a sample of 306 genotyped young men (aged 19–24 years), in whom measures of psychotic symptoms were obtained at recruitment in the Greek army (exposed condition) and again after 18 months of military training (unexposed condition).

Results. Stress exposure at army induction was associated with an increased level of psychotic symptoms. In addition, carriers of the COMT Val[158]Met Val allele were more susceptible to the effect of stress on the psychosis outcome than those with the Met/Met genotype (test for interaction: $\chi^2 = 5{\cdot}02$, df = 1, $p = 0{\cdot}025$).

Conclusion. The COMT Val[158]Met genotype may moderate the effect of stress on psychotic symptoms.

INTRODUCTION

Exposure to stressful life events increases the risk of developing a psychotic disorder in proportion to the intensity of the stressful experiences (Lukoff *et al.* 1984; Bebbington *et al.* 1993; Myin-Germeys *et al.* 2003). Powerful evidence for the role of stress in the aetiology of psychosis comes from the study of psychosis after semi-experimental stressful conditions such as army induction (Steinberg & Durell, 1968). In addition, stresses of urban life (van Os *et al.* 2001), as well as victimization and childhood trauma (Lataster *et al.* 2006), have consistently been found to be associated with increased clinical and subclinical levels of psychosis (Bebbington *et al.* 1993; Read *et al.* 2005). As dopamine is thought to play an important role in mediating stress-related responses (Laruelle, 2000) and attributing salience to meaningful environmental stimuli (Kapur, 2003), the hypothesis of stress-induced hyperdopaminergic states, resulting in aberrant assignment of salience and development of hallucinatory and delusional experiences, can be put forward. In support of this hypothesis is work showing that patients with an established

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psychotic disorder display greater psychosis reactivity to small daily stressors compared to healthy controls, as do their first-degree relatives, albeit to a lesser extent (Myin-Germeys *et al*. 2005). Part of the abnormal sensitivity to stress-induced psychosis may thus be due to a familial liability to dysregulation of dopamine neurotransmission. Recently, it was found that a functional polymorphism in the catechol-*O*-methyltransferase (COMT Val^{158}Met) gene may moderate the psychosis-inducing effect of the dopamine agonist delta-9-tetrahydrocannabinol (Δ-9-THC) (Caspi *et al*. 2005; Henquet *et al*. 2006). The COMT gene encodes catechol-*O*-methyltransferase, which is an enzymatic inactivator of dopamine, in particular in the prefrontal cortex. The functional polymorphism involves a methionine (Met) to valine (Val) substitution at codon 158, which results in two common allelic variants, Val and Met, associated respectively with high *versus* low enzyme activity (Lotta *et al*. 1995; Lachman *et al*. 1996). In Caucasian populations, this results in a distribution of individuals with the Met/Met (approximately 25%), Val/Met (50%) and Val/Val (25%) genotype. As the COMT Val^{158}Met genotype alone is not associated with overall greater risk for psychotic illness (Fan *et al*. 2005; Flint & Munafo, 2007) and reported environmental risk factors for psychosis have weak effect sizes at best, more environmental risk factors may interact with the COMT Val^{158}Met genotype in causing psychosis. Gene–environment interaction occurs when the effect of an environmental stressor on a person's health is conditional upon his or her genotype (Caspi & Moffitt, 2006). In complete gene–environment interaction, the effects of genes and environment are dependent on each other in such a way that exposure to neither, or either one alone, does not result in disease, whereas exposure to both does (van Os *et al*. 2003). To determine gene–environment interaction, gene–environment correlation (the degree to which exposure to environmental factors may be caused by an individual's genetic vulnerability) needs to be considered as well (Bergeman *et al*. 1991).

In the current study, the interaction between the COMT Val^{158}Met genotype and environmental stress on psychosis outcomes was therefore studied in an observational semi-experimental design. We investigated whether (i) an intense and datable increase in stress (young men at the start of a compulsory army induction programme) was associated with an increase in psychotic symptoms and (ii) whether any increase in psychotic symptoms was moderated by the COMT Val^{158}Met genotype.

METHOD

Subjects

A total of 2243 male recruits, aged 19–24 years, participated in the Athens Study of Psychosis Proneness and Incidence of Schizophrenia (Stefanis *et al*. 2004), a study of newly recruited conscripts undergoing basic training as part of their compulsory military service in Greece. Subjects were assessed at two measurements in time. The first assessment took place after the first 2 weeks of admission to the military service. A second measurement in a subset of the sample took place at completion of the military training (18 months later). To increase statistical power, high and average schizotypy scores were consecutively oversampled, *a priori* based on high (above the 90th percentile) or medium (around the 50th percentile) scores on the Schizotypal Personality Questionnaire (SPQ), a self-rated schizotypy scale (Raine, 1991), or either high (above the 95th percentile) or medium (around the 50th percentile) scores on the Perceptual Aberration Scale (PAS; Chapman *et al*. 1978). Analyses were thus conducted on a risk set of 306 subjects of which 34% scored above the 90th and 27% around the 50th percentile of the SPQ at the first assessment. At both assessments, subjects completed demographic questionnaires and self-rated psychometric evaluations. DNA was extracted from a mouthwash mixture. Genotyping was performed using polymerase chain reaction (PCR) amplification and digestion with the restriction enzyme NiaII and 3% agarose electrophoresis as described by Kirov *et al*. (1998). The mean age of these subjects was 20·6 years (S.D. = 1·8, range = 19–24 years).

The period of induction into compulsory military service compared to the period of conclusion of the training 18 months later was hypothesized to be a proxy measure of stress (Steinberg & Durell, 1968; Hatzitaskos *et al*. 1997). Army induction was considered to be associated with increases in stress caused by

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being away from home for the first time and being exposed to combat scenarios, sleep deprivation and the rules and regime of initiation into the army corps. Several studies have shown increases in stress levels during the first weeks of military training (Clemons, 1996; Larson *et al*. 2001), followed by a subsequent reduction of stress upon leaving the army (Lerew *et al*. 1999; Schmidt *et al*. 2000; Martin *et al*. 2006). The compulsory aspect of the military training offers a unique natural setting to study genetic differences in stress sensitivity, as the level of environmental exposure to stress was datable, similar for all recruits and not associated with genetic variation (i.e. no evidence of gene–environment correlation). Assessment upon conclusion of military training was hypothesized to be associated with lower levels of stress, as the trainees would be better equipped to face up to the stresses of military life and related assignments. For the current analyses, the level of stress by period (0 = low stress condition at conclusion of military training; 1 = high stress condition at army induction) served as the environmental exposure.

To capture psychotic symptoms during the first 2 weeks of military training, the self-report Symptom Checklist-90 – Revised (SCL-90-R) was used. The 'paranoid ideation' and 'psychoticism' subscales were used to assess state-related psychotic symptoms (Henquet *et al*. 2005). Mean scores of both subscales were combined into a mean total score (hereafter the SCL-90-R psychosis score; Henquet *et al*. 2005). Psychotic symptoms at conclusion of military training were assessed similarly. To investigate whether any moderating effects of the COMT Val^{158}Met genotype on stress sensitivity would specifically result in increased levels of psychosis, or would contribute to variation in psychological distress in general, symptoms of anxiety were also assessed at both measurements, using the SCL-90-R subscale 'anxiety' (hereafter the SCL-90-R anxiety score).

Analyses

As each individual had two observations (0, low stress condition at army conclusion; 1, high stress condition at army induction), multilevel random regression analyses were conducted, examining the effects of stress (low *versus* high stress condition) and the COMT Val^{158}Met genotype (0 = Met/Met, 1 = Val/Met, 2 = Val/Val) on the SCL-90-R psychosis symptom score. The stress × genotype interaction was fitted with genotype as dummy variables with Met/Met as reference category and regressed on the SCL-90-R psychosis symptom score. This allowed estimation of stress effect sizes for each genotype separately. Based on these results, the stress × genotype interaction was *post hoc* simplified to a stress × Val dominance term as described below (0 = no Val alleles, 1 = one or two Val alleles). Similarly, main effects of stress and the COMT Val^{158}Met genotype, as well as their interaction, were regressed on the *a priori* selected SCL-90-R anxiety outcome, to determine whether any interaction between stress and the COMT Val^{158}Met genotype was specific for psychosis. Main effects of the COMT Val^{158}Met genotype on SCL-90-R symptom outcomes were examined in the low stress condition exclusively. Main effects and interactions were *a priori* adjusted for age and assessed by the Wald test.

RESULTS

The COMT Val^{158}Met genotype distribution in the whole sample was 21% Met/Met, 49% Val/Met and 30% Val/Val and in Hardy–Weinberg equilibrium. Genotype was not associated with age [$\beta = 0{\cdot}24$, 95% confidence interval (CI) $-0{\cdot}03$ to $0{\cdot}51$, $p = 0{\cdot}085$], nor with the SCL-90-R psychosis score in the low stress condition ($\beta = -0{\cdot}01$, 95% CI $-0{\cdot}24$ to $0{\cdot}22$, $p = 0{\cdot}94$ and $\beta = -0{\cdot}11$, 95% CI $-0{\cdot}36$ to $0{\cdot}14$, $p = 0{\cdot}37$ for Val/Met and Val/Val respectively) or with the SCL-90-R anxiety score ($\beta = 0{\cdot}09$, 95% CI $-0{\cdot}12$ to $0{\cdot}30$, $p = 0{\cdot}39$ and $\beta = 0{\cdot}03$, 95% CI $-0{\cdot}20$ to $0{\cdot}26$, $p = 0{\cdot}80$ for Val/Met and Val/Val respectively). The SCL-90-R psychosis score increased significantly with increasing level of stress ($\beta = 0{\cdot}40$, 95% CI $0{\cdot}31 - 0{\cdot}49$, $p < 0{\cdot}001$), as did the SCL-90-R anxiety score ($\beta = 0{\cdot}49$, 95% CI $0{\cdot}40 - 0{\cdot}57$, $p < 0{\cdot}001$). Carriers of the Val allele were more sensitive to the psychosis-inducing effects of stress than individuals of the Met/Met genotype (interaction for Val/Met: $\beta = 0{\cdot}27$, 95% CI $0{\cdot}02 - 0{\cdot}51$, $\chi^2 = 4{\cdot}42$, df = 1, $p = 0{\cdot}035$ and interaction for Val/Val: $\beta = 0{\cdot}26$, 95% CI $-0{\cdot}01$ to $0{\cdot}53$, $\chi^2 = 3{\cdot}50$, df = 1, $p = 0{\cdot}061$; Table 1). The effect of stress on the psychosis outcome was similar for the Val/Met

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Table 1. *Mean SCL-90-R psychosis scores (subscales 'paranoid ideation' and 'psychoticism') stratified by COMT Val[158]Met genotype*

COMT Val[158]Met genotype	Low stress (conclusion of army training) Mean score (S.D.)	High stress (first 2 weeks of army training) Mean score (S.D.)	Stress effect size (β[a], 95% CI, p)
Met/Met ($n=64$)	0·72 (0·58)	0·91 (0·53)	$\beta=0{\cdot}19$, 95% CI −0·01 to 0·39, $p=0{\cdot}062$
Val/Met ($n=150$)	0·70 (0·61)	1·12 (0·65)	$\beta=0{\cdot}46$, 95% CI 0·31−0·60, $p<0{\cdot}001$
Val/Val ($n=92$)	0·59 (0·60)	1·05 (0·62)	$\beta=0{\cdot}44$, 95% CI 0·27−0·62, $p<0{\cdot}001$
Stress × Val dominance term interaction[b]		($\beta=0{\cdot}26$, 95% CI 0·03−0·50, $\chi^2=5{\cdot}02$, df=1, $p=0{\cdot}025$)	

SCL-90-R, Symptom Checklist-90-Revised; COMT, catechol-*O*-methyltransferase; Met, methionine; Val, valine; S.D., standard deviation; CI, confidence interval; df, degrees of freedom.

[a] Regression coefficient indicates change in SCL-90-R psychosis score associated with high stress *versus* low stress, analyses adjusted for age.

[b] Stress × COMT Val[158]Met genotype interaction fitted with Val dominance term (0 = no Val alleles, 1 = one or two Val alleles), analysis adjusted for age.

and Val/Val genotypes ($\chi^2=0{\cdot}01$, df=1, $p=0{\cdot}94$), suggesting Val allele dominance. Thus, the *post hoc* model using the stress × Val dominance term interaction (0 = no Val alleles, 1 = one or two Val alleles) displayed significant interaction (Table 1). No interaction effects were observed for the SCL-90-R anxiety score (interaction for Val/Met $\beta=0{\cdot}20$, 95% CI −0·05 to 0·44, $\chi^2=2{\cdot}52$, df=1, $p=0{\cdot}11$ and interaction for Val/Val $\beta=0{\cdot}17$, 95% CI −0·10 to 0·43, $\chi^2=1{\cdot}52$, df=1, $p=0{\cdot}22$).

DISCUSSION

Exposure to environmental stressful changes associated with induction into compulsory military service was associated with increases in psychotic symptoms as measured with the SCL-90-R. The COMT Val[158]Met genotype moderated the psychotic response to environmental stress, in that carriers of the Val allele were more sensitive to stress than individuals of the Met/Met genotype. These results suggest that gene–environment interactions, in which the dopamine system may play an important role, partly underlie the complex aetiology of psychotic symptoms.

The finding that psychosis reactivity to stress was greater in the Val/Val and Val/Met subjects compared to Met/Met subjects confirms the hypothesis that lower levels of constant background tonic dopamine, associated with higher COMT enzyme activity in Val carriers, exhibit less control over state-related high-amplitude phasic (subcortical) dopamine release (Grace, 1991; Akil *et al*. 2003; Bilder *et al*. 2004; Meyer-Lindenberg *et al*. 2005). It is attractive to further hypothesize that, as a consequence, stress-induced phasic dopamine release may be greater in those who carry the Val allele, given equal levels of environmental exposure. As the mesolimbic (phasic) dopamine system plays an important role in regulating salience to environmental stimuli, a hyperdopaminergic state may facilitate abnormal salience to ambiguous environmental stimuli, leading to erroneous interpretations and subsequent development of psychotic symptoms (Kapur, 2003). This would explain why, at the level of general population, the COMT Val[158]Met genotype alone does not mediate psychosis risk (Fan *et al*. 2005), whereas significant increases in psychotic symptoms may be observed by the synergistic action of the COMT Val[158]Met genotype (alone or in combination with other genetic risk factors) and environmental stimulation of the dopamine system.

Several methodological issues should be considered. We hypothesized that increases in psychotic symptoms at induction compared to symptom level upon conclusion of the military training were attributable to stress (Stefanis *et al*. 2006). Other factors, however, such as developmental expression of subclinical psychotic symptoms associated with age, or increases in use of cannabis or other factors known to be associated with entry into military training, may nevertheless have also played a role. Adjustment

for age did not change the results. The fact that all subjects were male may limit generalizability of the findings, and replication using female subjects is necessary.

The current findings partly contrast with those from other studies in which an increased sensitivity to stress and anxiety was identified only in carriers of the Met, and not of the Val, allele (Smolka *et al*. 2005; Drabant *et al*. 2006). Other studies, however, have shown that the moderating effects of the COMT Val[158]Met genotype may be gender specific, and that lower emotional resilience associated with the Met allele may be specific to females (Enoch *et al*. 2003; Stein *et al*. 2005). In addition, the current analyses did not show that carriers of the Val allele were overall more reactive to stress (i.e. no interaction was observed between the COMT Val[158]Met genotype and stress for the SCL-90-R anxiety score), but rather that increased stress had a specific psychotogenic effect in carriers of the Val allele. As stated previously by Tunbridge *et al*. (2006), with respect to prefrontal function, the relationship between the COMT Val[158]Met genotype and stress sensitivity may be more complex than a simple 'Met-good/Val-bad', and each allele may be vulnerable to, or benefit from, different environments. The phenotypic expression of the COMT Val[158]Met polymorphism with respect to psychosis is likely to be similarly diverse, affecting a broad range of behaviours. What this study and other studies suggest is that it is only in interaction with specific environmental factors that the Val allele may have an impact on psychosis outcomes. Carriers of the Val and the Met allele may be equally sensitive to developing psychosis, although by separate pathways and in interaction with different genetic and environmental factors. Replication of the current finding, including more (interacting) single nucleotide polymorphisms within the COMT gene as well as other genes, is required to further investigate the stress response system in relation to psychosis.

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DECLARATION OF INTEREST

None.

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