Modification of depression by COMT val\textsuperscript{158}met polymorphism in children exposed to early severe psychosocial deprivation\textsuperscript{\star}

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\textbf{Objective:} To examine the impact of the catechol-O-methyltransferase (COMT) val\textsuperscript{158}met allele on depressive symptoms in young children exposed to early severe social deprivation as a result of being raised in institutions.

\textbf{Methods:} One hundred thirty six children from the Bucharest Early Intervention Project (BEIP) were randomized before 31 months of age to either care as usual (CAU) in institutions or placement in newly created foster care (FCG). At 54 months of age, a psychiatric assessment using the Preschool Age Psychiatric Assessment (PAPA) was completed. DNA was collected and genotyped for the COMT val\textsuperscript{158}met polymorphism. Multivariate analysis examined the relationship between COMT alleles and depressive symptoms.

\textbf{Results:} Mean level of depressive symptoms was lower among participants with the met allele compared to those with two copies of the val allele ($P<0.05$). Controlling for group and gender, the rate of depressive symptoms was significantly lower among participants with the met/met or the met/val genotype [adjusted relative risk (aRR) = 0.67, 95% CI = 0.45, 0.99] compared to participants with the val/val genotype, indicating an intermediate impact for heterozygotes consistent with the biological impact of this polymorphism. The impact of genotype within groups differed significantly. There was a significant protective effect of the met allele on depressive symptoms within the CAU group, however there was no relationship seen within the FCG group.

\textbf{Conclusions:} This is the first study, to our knowledge, to find evidence of a gene $\times$ environment interaction in the setting of early social deprivation. These results support the hypothesis that individual genetic differences may explain some of the variability in recovery amongst children exposed to early severe social deprivation.

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\textbf{Introduction}

Early, severe social deprivation due to institutional rearing has been found to be a risk factor for a variety of cognitive, growth and social/emotional difficulties (Powell, Brasel, & Blizzard, 1967; Zeanah, 2000). Preliminary studies have implicated...
brain structural and functional differences in these children, including reduced metabolic activity in the temporal and frontal cortices and reduced cortico–cortico connections (Chugani et al., 2001; Eluvathingal et al., 2006), reduced EEG power and increased EEG coherence (Marshall, Fox, & Bucharest Early Intervention Core Group, 2004; Marshall, Reeb, Fox, & the BEIP Core Group, 2008), and reduced amplitude of several components of the event-related potential (Moulson, Westerlund, & Nelson, 2009; Parker & Nelson, 2005; Parker, Nelson, & the BEIP Core Group, 2005). Evidence now suggests that early placement of children in enriched foster care environment can, to some extent, minimize or reverse the lasting negative impacts of institutional care on cognitive and behavioral and psychological outcomes (Nelson et al., 2007; Zeanah et al., 2009). Nevertheless, this recovery is not uniform.

Longitudinal and cross-sectional studies demonstrate that although many psychological consequences of early institutionalization resolve with placement in adoptive families, recovery is variable (Chisholm, 1998; Marcovitch et al., 1997; Rutter et al., 2007; Vorria et al., 2006). Additionally, methodological limitations in adoption studies, such as selection bias about who was adopted, differences in the age at which children were adopted, and the lack of systematic baseline assessments prior to adoption, all limit the generalizability of these studies for determining the direct impact and potential psychological recovery from early institutionalization.

The Bucharest Early Intervention Project (BEIP), the first randomized controlled trial of foster care as an alternative to institutional care, was designed to address these shortcomings. This ongoing project has demonstrated that placement in enriched foster care does ameliorate the detrimental impact of early institutionalization in many domains, including cognitive, language, social and emotional expressiveness (Ghera et al., 2009; Nelson et al., 2007; Smyke et al., 2007; Windsor, Glaze, Koga, & the Bucharest Early Intervention Project Core Group, 2007). With regard to psychiatric outcomes at 54 months of age, it was found that children placed into foster care displayed a lower prevalence of internalizing psychiatric disorders compared to children who remained in institutions (Zeanah et al., 2009). In the current study as well as in other studies examining the impact of early institutionalization there remains a wide range of recovery in these children. One hypothesis to explain this variation is that individual genetic differences play a role in these children’s ability to recover from early negative life events; however, no previous studies have examined the impact of genetic variation on either the overall risk of institutional care or the individual response of children to an enriched environment provided by foster care placement.

Evidence is increasing that common variations in gene sequences (polymorphisms) and exposure to early life stress may interact to impact an individual’s risk for developing depression in adulthood, but few studies have explored this relation in young children with recent traumatic or stressful exposure, and no previous studies have examined genetic variation in the setting of early institutionalization (Binder et al., 2008; Caspi et al., 2003; Eley et al., 2004; Kaufman et al., 2004, 2006). Examining the interaction between individual differences in polymorphisms in the DNA and changes in the environment during early development will provide new insight into the neurobiological mechanisms through which gene × environment interactions lead to both resilience and vulnerability in the setting of early life stress.

The catechol-O-methyltransferase (COMT) gene is located on chromosome 22q11, and the gene product is densely expressed in the hippocampus and the prefrontal cortex. COMT is the main regulator of dopamine and other catecholamine degradation in the prefrontal cortex (PFC) (Gogos et al., 1998; Karoum, Chrapusta, & Egan, 1994). COMT's expression pattern is complex and differs during development with the highest levels of the enzyme found early in life and decreasing with age (Guldberg & Marsden, 1975). Located within the COMT gene are multiple polymorphic sites that impact its expression and function. The most studied of the polymorphic sites is the val158 or 108met amino acid substitution in exon four, which results from a guanine to an adenosine change in the DNA sequence. The difference in numerical reference position of the polymorphism depends on whether one is considering the membrane bound (158) or soluble protein sequence (108); hence either number refers to the same DNA sequence variation. The met variant has a four-fold decreased enzyme activity, resulting in slower degradation of dopamine in the prefrontal cortex, and studies show a co-dominant effect of these alleles such that heterozygotes have an intermediate phenotype of enzyme level, and thus levels of dopamine in the PFC (Lachman et al., 1996; Lotta et al., 1995). Deficiencies in serotonin, norepinephrine and dopamine are thought to be involved in the pathophysiology of depression and medications impacting the levels of these neurotransmitters have been found to function as antidepressants (Nutt, 2006; Pani & Gess, 2002). As catecholamines are implicated in the etiology of depression and other psychological disorders, and COMT is one of the main regulators of catecholamine levels, particularly dopamine, it has been explored as a vulnerability factor for mood disorders (Schilldkraut, 2006).

A variety of studies have examined the association of the COMT val158met polymorphism and vulnerability to depression and mood disorders, however, replication of findings has been inconsistent (Burdick et al., 2007; Funke et al., 2005; Gutierrez et al., 1997; Kirov et al., 1998; Kunugi et al., 1997; Massat et al., 2005; O’hara, Hnagai, Suzuki, & Ohara, 1998; Papulos, Veit, Faedda, Saito, & Lachman, 1998; Rotondo et al., 2002; Shifman et al., 2004). Notably, it is not clear that one particular allele (i.e., the met or val) represents the vulnerable allele for the development of depression. The majority of these studies examined the impact of COMT on adult mood disorders. Nevertheless, in a study exploring the relations between COMT and early onset mood disorders (defined as age of onset less than 25) the val allele was associated with an increased risk of the development of a mood disorder (Massat et al., 2005). One hypothesis for these discrepant results is that there exists either alternative polymorphisms in linkage disequilibrium with the COMT val158met polymorphism or specific haplotypes of COMT that are responsible for COMT’s association with mood disorders. It has also been postulated that there exists
an optimal intermediate dopamine level, and that either too much or too little dopamine can result in deficits (Diamond, 2007; Diamond, Briand, Fossella, & Gehlbach, 2004; Volkow et al., 1996). This would suggest that different alleles would be beneficial at different developmental time points, and in different environmental settings. Thus an alternative hypothesis is that these discrepant results are due to differences in the age of the populations examined and potentially the stress exposure levels as well.

As our previous work had found that children with a history of institutionalization had greater internalizing symptoms compared to typically developing community age-matched controls, we sought to extend these findings and explore two additional hypotheses. First, we hypothesized that the COMT val158met polymorphism would influence the development of depressive symptoms in these children. Second, we hypothesized that the impact of COMT variation would differ between the Institutionalized Group (CAU) and the Foster Care Group (FCG), such that in those children exposed to a more negative and stressful environment, such as the CAU group, there would be a larger impact of genetic variation.

Methods

Participants

The participants in this study were enrolled in the Bucharest Early Intervention Project (Zeanah et al., 2003). The study was reviewed and approved by Institutional Review Boards at each of the US universities for the three PIs (NF, CN, and CZ). In addition, the study was approved by the local commissions on child protection in Bucharest and in 2002 by an Ethics commission of the Ministry of Health. Local child commissioners in each sector in Bucharest were the legal guardians for institutionalized children and those in foster care. They consented to each child’s participation, and caregivers or foster parents assented to all procedures. The ethical issues in the project have been considered in some detail elsewhere (Nelson et al., 2007; supplemental online material; Zeanah et al., 2006a, 2006b).

In the BEIP, children less than 31 months of age and residing in any of 6 institutions for young abandoned children in Bucharest, Romania, were screened with a pediatric and neurological exam, growth measurements, auditory assessment, and assessment of physical abnormalities. Of the 187 children screened, 51 were excluded for medical reasons, including genetic syndromes, frank signs of fetal alcohol syndrome (based largely on facial dysmorphology), and microcephaly (Nelson et al., 2007). After assessment of all 136 children, 68 children (33 males and 35 females) were randomly assigned to remain in institutional care and were designated the CAU group, and 68 (34 males and 34 females) were randomly assigned to foster care and were designated the FCG (Nelson et al., 2007). For detailed description of baseline measures, and attrition and group placement please see Zeanah et al. (2009) and Fig. 1. At 54 months of age, there were 111 children available who underwent PAPA (Preschool Age Psychiatric Assessment) assessment (52 CAU and 59 FCG) (Zeanah et al., 2009). Buccal swabs and genetic data were available for 98 of these children (47 CAU and 51 FCG). Due to the design of the project we did not interfere with the natural course of placement with these children. For all analyses, we used intent-to-treat, such that children were considered part of their originally assigned group (FCG vs. CAU) despite any changes in status as this is the most stringent statistical approach and would likely underestimate the impact of findings related to environment changes. Therefore at 54 months of age in the FCG 83% \( (n = 45) \) remained in their initial foster care placement, 7% \( (n = 4) \) were adopted, 3% \( (n = 2) \) were in newly created government foster care, and 14% \( (n = 8) \) were returned to their biological families. In the CAU group 40% \( (n = 21) \) remained in institutional care while the remaining children were either adopted \( (4\%, n = 2) \), in foster care \( (35\%, n = 18) \), returned to their biological families \( (17\%, n = 9) \), or in family care \( (4\%, n = 2) \). Ethnicity was characterized as Romanian, Gypsy (Roma), other or unknown. Analysis is based on a final study sample of 98. There were no differences in gender or ethnicity between the 98 children who are included in these analyses and the 38 children in the original sample who are not. There were also no differences in gender, ethnicity or depression scores between the 98 children from whom DNA samples were collected and the remaining 13 children for whom PAPA data was obtained at 54 months but genetic data was not obtained. This study was approved by the Institutional Review Boards at Tulane University Medical Center, Harvard School of Medicine, and the University of Maryland. Informed consent was obtained from all caregivers at the time of DNA collection.

Genotyping

DNA was extracted from MasterAmp buccal swabs from Epicentre Biotechnologies using the MasterAmp DNA Extraction Solution following manufacturer’s recommendations. PCR was performed using the following primers (Massat et al., 2005): 5′-ACT GTG CCT ACT CAG CGT TG-3′ and 5′-CCT TTT TCC AGG TCT GAC AA-3′. PCR was carried out in a 50 μl reaction with 10 pmol of each primer, 1.25 U unit of Ex Taq™ DNA Polymerase (TaKara Bio USA), 1 × Ex Taq™ Buffer, 200 μM dNTPs. Thermal cycling conditions were an initial denaturation for 5 min followed by 33 cycles of 94 for 30 s, 58 for 30 s, and 72 for 45 s. 20 μl of the PCR was digested with Nla III (New England Biolabs) and size fractionated on a 4% agarose gel. Allele status was determined by fragment size. A random selection of samples was sequenced for confirmation of allele status. Repeat analysis was performed on 100% of the samples. Any ambiguities in amplification product or allele status were subsequently directly sequenced.
Psychiatric diagnosis

Psychiatric morbidity at 54 months of age was assessed using the Preschool Age Psychiatric Assessment (PAPA). The PAPA is a caregiver-report instrument with a detailed and structured protocol that requires interviewers to confirm that the caregiver has a clear understanding of the questions being asked, are provided with examples, and provide sufficient detail to determine if symptom meets a pre-specified level of severity. Test–retest reliability of the PAPA is comparable to structured psychiatric interviews used to assess older children and adults (Egger et al., 2006). The PAPA 1.3 was translated into Romanian, back-translated into English, and assessed for meaning at each step by bilingual research staff. The BEIP lead interviewer was trained in administration of the PAPA by the group who developed the measure, and he subsequently trained other Romanian interviewers. For those children in the Institution the PAPA interview was conducted with the individual who knew the child best, while foster parents were interviewed for those children in foster care. As there is a low incidence of depression disorder in this age group in other, non-clinical populations, and this was replicated in the BEIP
sample, we examined the impact of the COMT val$^{158}$met polymorphism on all symptoms of depression as a continuous variable.

**Statistical analysis**

The presence of Hardy–Weinberg equilibrium was determined with a chi-square test for goodness of fit. Bivariate relationships were examined through basic correlations (Pearson or Spearman where appropriate), likelihood ratio chi-square ($\chi^2$) or Fisher’s exact test of independence, or one-way ANOVA or Mann–Whitney U-test, where appropriate. Bivariate tests were used to confirm that there was no association between genotype and group or genotype and demographic characteristics (i.e., sex and ethnicity) prior to analysis. Crude and adjusted Poisson regressions were run to examine the relationship between the sum of depressive and dysthymia symptoms (a count) and COMT allele status. Primary multivariate models compared influence of allele status while accounting for group (intervention) and sex. Two-way interactions were also examined for group $\times$ allele. Analysis was done considering all individuals originally assigned to the Institutional group as the care as usual (CAU) group, following the last observation carried forward statistical approach, even though many of the CAU children were in foster care at 54 months (Fig. 1).

**Results**

**Preliminary analyses**

Two buccal swabs were obtained in Romania and shipped via room temperature to the United States. Approximately 5% of swabs did not generate an amplification product. However, as two buccal swabs were collected, COMT allele status was determined from all children from whom consent for DNA analysis was obtained. Initial analysis confirmed that the alleles were in Hardy–Weinberg equilibrium and that allele status was approximately consistent with Eastern European estimates from NCBI data base with a val allele frequency of 0.61 and a met allele frequency of 0.39 compared to the reported mixed European descent frequencies at this loci of .62/.38 (dbSNP rs 4680). Table 1 presents the characteristics of participants by COMT allele status. As shown, there were no statistical differences in allele status by intervention group, which was assigned randomly at entrance into the study, ethnicity, or sex. Examining dose of deprivation (the percent of the child’s life at 54 months spent in an institution) also was not significantly different across allele status supporting the effectiveness of randomization from the view point of allele status.

**Vulnerability to depression**

The impact of COMT val$^{158}$met on depressive symptoms was explored in two ways. First, we collapsed genotypes and compared individuals with any copies of the met allele (i.e. met/met and met/val) with homozygote val/val individuals (Table 2). The rate of depressive symptoms was significantly lower among those with at least one copy of the met allele, even after adjusting for group, and sex adjusted relative risk (aRR = 0.67, 95% CI = 0.45, 0.99, P < 0.05). A significant interaction between COMT genotype status and group was revealed, with the met allele being protective only for participants in the CAU group (aRR = 0.48, 95% CI = 0.28, 0.83, P < 0.01) (Model 3, Table 2) and not those in the FCG group (aRR = 0.92, 95% CI = 0.53, 1.60, P = 0.47) (Model 4, Table 2).

Second, to further define the impact of genotype on depressive symptoms, recognizing the limitations of the sample size and the impact this would have on the ability to detect statistically significant changes, we then examined the interaction

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between specific genotype (met/met compared to met/val compared to val/val) and intervention group and depressive symptoms (Table 3). Depressive symptoms were lower in individuals with the met/met genotype (aRR = 0.57, 95% CI = 0.29, 1.10) or the met/val allele (aRR = 0.70, 95% CI = 0.46, 1.05) compared to participants with the val/val allele. Here again the impact of genotype was influenced by group, with the protective impact of the met allele seen only in the CAU group, although the interaction was only marginally significant for the met/val by group (P < 0.10). These results also demonstrated a dose response effect for met allele, with its protective effect strongest for participants with met/met versus met/val (aRR = 0.57 vs. 0.70). The protective effect of the met allele was only seen in the CAU group, although the met/met allele difference was not significant due to the small size after multiple stratifications (genotype and intervention group). There was no significant interaction in the FCG. The significant aRR 0.48 indicates a 108% lower risk for depressive symptoms in the CAU in individuals with the met/met genotype, and a 60% lower risk of depressive symptoms in heterozygotes.

Discussion

This study explored the interaction between the COMT val158met polymorphism and early social deprivation on depressive symptoms in children at 54 months of age. The met allele was a protective factor for the development of depression, but only in those children in institutional care. The protective effect was dose dependent relative to the number of met alleles and thus consistent with a co-dominant allele system. This protective effect was not seen in those children placed in the improved social and emotional environment of foster care. To our knowledge, this is the first report of a gene × environment interaction in a setting of early severe social deprivation and supports the hypothesis that common genetic polymorphisms may explain some of the variation in children's vulnerability to caregiving contexts as well as their potential for recovery.

This study provides support for the role of COMT val158met in the etiology of depressive symptoms, especially in the context of negative early life exposure. The met allele was only protective in the group of children who were raised in the adverse context of an institutional environment and the effect not apparent for those being raised in foster care families.
This is similar to the findings of Caspi et al. (2003) regarding the serotonin transporter gene where the short allele conferred vulnerability to depression, but only with significant negative life stress exposure (Caspi et al., 2003).

COMT clearly has complex and pleiotropic effects and this study adds further support to the role of COMT val<sup>158</sup>met variation in the etiology of affective disorders. While some previous studies have found the met allele to be a risk factor for mood disorders and depression, we found the met allele provided a protective factor in the setting of severe social deprivation. Two previous studies have identified the val allele as a risk factor for affective symptoms, one exploring early onset mood disorders and the second looking at affective symptoms in individuals at risk for schizophrenia (Massat et al., 2005; McClay et al., 2006). Twin studies have found that the heritability of anxious/depression is greater earlier in development and it may be that some of the discrepant findings examining COMT’s contribution to affective disorders is the result of differential developmental impact, such that COMT’s influence may be more pronounced, and therefore more easily identifiable, in younger study populations (Boomsma, van Beijsterveldt, & Hudziak, 2005).

In addition to developmental differences it may be that the impact of COMT val<sup>158</sup>met polymorphism is the result of more complex interactions. One hypothesis to explain these differences in COMT’s findings in affective disorders stems from an idea that there may be an optimal dopamine level, or “set point” that varies with age. If the “ideal” concentration of dopamine in the PFC is high in younger individuals and decreases as the individual ages, this would resolve some previous discrepant findings. Also, there is evidence that stress impacts PFC dopamine levels, and therefore, the “ideal” dopamine level in an individual exposed to early life stress may be different than an individual with no significant stress exposure (Deutsh & Roth, 1990; Roth, Tam, Ida, Yang, & Deutsh, 1988). Either too much or too little dopamine may result in elevated risk, with the threshold varying according to the age and exposure to stressors. Therefore, in those children exposed to early severe social deprivation, the COMT val<sup>158</sup>met allele may elevate the dopamine level in the PFC to the needed “ideal” set point in young children with stress exposure and thus protect them from depressive symptoms. Once the stress exposure is removed the COMT val<sup>158</sup>met variation would be less important, and a different dopamine “set point” for affective symptoms may prevail.

An alternative hypothesis arises from consideration of the COMT val<sup>158</sup>met’s relation with memory and attention (Diamond et al., 2004). If children with the met allele, who have been found to have better working memory and better attention, are better able to emotionally and neurodevelopmentally benefit from the limited caregiving that they do receive, then this variant allele may provide some protection from the detrimental impact of severe social deprivation. When the environment is changed and there is no longer a limited amount of social stimulation the importance of sustained attention and memory is less important to the development of symptoms of depression and therefore no effect is seen in the FCG. One final possibility is that the association with depression is dependent on an alternative polymorphism in COMT and the val<sup>158</sup>met‘ polymorphism is not causative of the associated depressive phenotype.

Several limitations of this study exist. First, the sample is small, thus limiting the power of this study, especially when considering stratification by group and specific genotype. Second, we did not correct for genetic admixture. This is always a concern in genetic studies; however, the absence of statistically significant difference between genotype frequencies and ethnicity supports our findings. In order for population stratification to present a statistical difficulty for this study two conditions would need to be met. The first condition is that significant differences in allele frequencies for the COMT polymorphism exist between ethnic groups, which has not been definitively demonstrated in our sample as we did not find statistical differences in the allele frequencies. The second condition is that baseline differences in depressive symptoms between Roma and Romanian children exist. This was not seen in our control population nor in an ongoing epidemiologic study in Romania (Hutchison, Stallings, McGeary, & Bryan, 2005). Replication of this finding in other populations of children at the same age would further support our findings. We are currently performing a second psychological assessment of this same sample at 8 years of age and if this protective effect continues at this second time point this would provide further support for our findings. A second limitation of this study is that, as with most genetic association studies, we cannot exclude the possibility of the association between this polymorphism and depression symptoms is the result of other polymorphisms in linkage disequilibrium with this polymorphism, another polymorphism in a nearby gene, or specific haplotypes of COMT that have previously been shown to have specific functional significance (Nackley et al., 2006). Future studies exploring other polymorphisms in COMT and haplotype analysis would provide further definitive support for our hypothesis and better define the role of COMT in the development of depression. A final limitation of this study is that this is a young population of children and depressive symptoms in this age group are uncommon though by no means unheard of (Egger et al., 2006). In support of our results, and the clinical relevance of even low frequency of depressive symptoms in preschool children, a recent study exploring depression in preschool children found a significant impact of chronic medical illness on symptoms of depression and importantly found that depressive symptoms mediated the relationship between medical illness and social functioning (Curtis & Luby, 2008). Thus even though the mean of depressive symptoms is small they may be functionally impairing and therefore relevant for these children’s care. It will be important to monitor their levels of symptoms over time, longitudinally explore this gene × environment interaction, and explore the impact upon these children as they age across social, emotional and cognitive growth and development.

These limitations notwithstanding, there are important implications of this study. The finding of a gene × environment interaction in the setting of an randomized controlled trial of alterations of early caregiving environments provides clear evidence for the impact of both inherent genetic predisposition and environmental conditions on the development of affective symptoms, even in very young children, and highlights the importance of early and appropriate intervention for children at risk for limited social and emotional support such as children in institutional care or in child protective custody.
These findings have implications beyond the Romanian institutional context. Children who experience deprivation or neglect in many different environments are vulnerable to various types of psychopathology. Determining whether allelic variations of the COMT gene confer protection from other adverse environments is an important direction for future research on resilience. Identifying the genetic contributions to resilience in different environmental settings may better define the underlying neurobiology of resilience as well as the neural pathways impacted by early experiences.

Understanding COMT’s role in depression will require an exploration of the impact of COMT on intermediate phenotypes and endophenotypes related to depression as well as a careful consideration of the differential developmental impact of COMT. Future research should consider the relations between psychological outcomes, electrophysiological measures, and cognitive function to begin to create a complete neurobiological model that relates genetic variation, neurologic and cognitive endophenotypes, environmental alterations, and psychological outcomes.

References


