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BRIEF REPORT

Child Exposure to Serious Life Events, COMT, and Aggression: Testing Differential Susceptibility Theory

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Both genetic and environmental factors contribute to individual differences in aggression. Catechol-*O*-methyltransferase Val158Met (COMT), a common, functional polymorphism, has been implicated in aggression and aggression traits, as have childhood experiences of adversity. It is unknown whether these effects are additive or interactional and, in the case of interaction, whether they conform to a diathesis-stress or differential susceptibility model. We examined Gene × Environment interactions between COMT and serious life events on measures of childhood aggression and contrasted these 2 models. The sample was composed of community children ($N = 704$); 355 were boys, and the mean age was 54.8 months ($SD = 3.0$). The children were genotyped for COMT rs4680 and assessed for serious life events and by teacher-rated aggression. Regression analysis showed no main effects of COMT and serious life events on aggression. However, a significant interactive effect of childhood serious life events and COMT genotype was observed: Children who had faced many serious life events and were Val homozygotes exhibited more aggression ($p = .02$) than did their Met-carrying counterparts. Notably, in the absence of serious life events, Val homozygotes displayed significantly lower aggression scores than did Met carriers ($p = .03$). When tested, this constellation of findings conformed to the differential susceptibility hypothesis: In this case, Val homozygotes are more malleable to the effect of serious life events on aggression and not simply more vulnerable to the negative effect of having experienced many serious life events.

Keywords: aggression, serious life events, COMT, gene–environment interaction, differential susceptibility

Children generally follow a developmental path whereby aggressive behavior modestly increases during the initial 30 to 42 months of life and peaks at approximately 4 years of age before steadily declining (Côté, Vaillancourt, LeBlanc, Nagin, & Tremblay, 2006; Tremblay et al., 2004). Evidence suggests that a large proportion of aggressive toddlers and preschoolers continue to have problems at school-entry age (Campbell, Pierce, Moore, Marakowitz, & Newby, 1996; Shaw, Winslow & Flanagan, 1999). Moreover, 50% of children displaying aggressive behaviors in preschool maintain these behaviors into adolescence (Campbell, 1995).

Aggression is influenced by both genetic and environmental factors (Rhee & Waldman, 2002; Sarchiapone, Carli, Cuomo,

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Marchetti, & Roy, 2009). The heritability of aggression is high, accounting for at least 40% of the variance (Burt, 2009; Rhee & Waldman, 2002). However, these estimates leave substantial room for environmental effects, and intervention studies demonstrate that aggression is subject to environmental influences (Luntz & Widom, 1994; Tabone et al., 2011). In this study of Gene × Environment (GXE) interaction effects on Norwegian children aged 4 years old, we restrict our focus to a single candidate gene, *COMT*, based on evidence that the dopaminergic system is an important pathway to pathological aggression in childhood (Chen et al., 2005) and that *COMT* may interact with adversity in predicting aggression (Perroud et al., 2010).

COMT

The *COMT* gene carries a single nucleotide polymorphism (Val158Met) that alters a single amino acid in the enzyme and replaces the amino acid valine with methionine (Lachman et al., 1996). *COMT* instructs the production of the enzyme catechol-*O*-methyltransferase, which breaks down dopamine, epinephrine, and norepinephrine. Its activity is located mainly in the frontal areas of the brain, which includes regions important for regulating aggressive behavior. A person who is homozygous for the Val/Val genotype will have fourfold higher COMT activity in the prefrontal cortex (PFC) than homozygous Met allele carriers; heterozygotes would demonstrate intermediate activity (Weinshilboum, Otterness, & Szumlanski, 1999). The low-activity Met allele is associated with better PFC function and associated cognitive processes (Egan et al., 2001; Wirgenes et al., 2010), which is consistent with the view that Val homozygosity is associated with higher levels of aggression in either genotype-phenotype or GXE interaction terms.

There is evidence that *COMT* interacts with child abuse in predicting aggression (Perroud et al., 2010). Furthermore, child characteristics interact with *COMT* to predict aggression, most notably ADHD (Caspi et al., 2008) and disorganized attachment (Hygen, Guzey, Belsky, Berg-Nielsen, & Wichstrøm, 2014). Caspi et al. and Hygen et al. found that Val homozygotes manifest the most aggression in response to such contextual adversity. For this reason, we focused on the heightened susceptibility of Val homozygotes to environmental effects.

The aforementioned GXE results indicate that Val can be conceptualized as a "vulnerability" or "risk" allele (Caspi et al., 2003), consistent with the traditional diathesis-stress framework (Zuckerman, 1999). In recent years, however, GXE evidence consistent with an alternative perspective on Person × Environment interactions has emerged, referred to as the *differential susceptibility framework* (Belsky & Pluess, 2009, 2013; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011). In contrast to diathesis-stress thinking, which calls attention to personal characteristics, including genotype, that increases the likelihood that an individual will function poorly when exposed to adverse conditions (e.g., poverty, harsh parenting, negative life events), the differential susceptibility perspective, which is based on evolutionary biological reasoning, regards some individuals as more susceptible to environmental influences "for better and for worse" (Belsky, Bakermans-Kranenburg & van IJzendoorn, 2007). That is, more susceptible or sensitive individuals are more likely to be negatively affected by conditions of adversity than others and to disproportionately benefit from supportive—or even benign—conditions. From the perspective of child development, these highly susceptible children are more developmentally plastic. Accordingly, carriers of the Val allele, especially those carrying two such alleles, are predicted to be especially sensitive to the rearing environment, making them particularly susceptible to both the negative effects of adversity and the (often unmeasured) beneficial effects of supportive-or merely benign-contextual conditions. Therefore, the core prediction tested in the present study is that children homozygous for the Val allele will exhibit higher levels of aggression than their Met-carrying counterparts when exposed to traumatic events, and the reverse will be true in the absence of such trauma. To test these predictions, we used a newly developed model-testing approach that compares the fit of the data to diathesis-stress and differential susceptibility models (Widaman et al., 2012; Belsky, Pluess, & Widamann, 2013).

Method

Participants and Recruitment

Two birth cohorts of children (born in 2003 or 2004) and their parents living in the city of Trondheim, Norway were invited to participate in the Trondheim Early Secure Study. Details of the procedure and recruitment have been presented elsewhere (Wichstrøm et al., 2012); only a brief outline is provided here. The Strengths and Difficulties Questionnaire (SDQ) 4–16 version (Goodman, 1997), together with an invitation letter, was mailed to the parents (N = 3,456). Completed SDQs were returned at the routine community health check-up for 4-year-olds at Well Child Clinics, which all Norwegian children (are expected to) attend (3,358 families attended). Parents with inadequate proficiency in Norwegian were excluded (n = 176), and the health nurses failed to ask 166 parents. At the Well Child Clinic, eligible parents (n = 3,016) were informed of the study through procedures approved by the Regional Committee for Medical and Health Research Ethics. Written consent was obtained from the parents of 2,475 children (82.1% of those eligible).

The SDQ total scores were divided into four strata. Using a random number generator, the defined proportions of parents in each stratum were selected to participate in a further study. The selection probabilities increased with increasing SDQ scores. Of the 1,250 parents invited to participate, we tested 936 (74.9%). The subsequent dropout rate did not vary according to the SDQ strata (χ^2 = 5.70, df = 3, p = .13) or gender (χ^2 = .23, df = 1, p = .63). Of all children, 704 were successfully genotyped for the *COMT* Val158Met polymorphism; these children formed this report's analysis sample. There were 355 (50.4%) males among the participating children; most lived with their biological parents, who were of Norwegian ethnicity (see Table 1). Teacher data were collected by means of questionnaires sent to day care centers. The teacher response rate was 90.6%. The teachers had known the children for an average of 13 months.

Table 1
Sample Characteristics (N = 704)

Variable	*M*	*SD*	Minimum	Maximum	*n*
Demographics					
Child age (months)	54.79	2.97	48.17	67.81	656
Male children (%)	50.4%				355
Age of parent at clinic (in years)	35.03	4.72	21.00	57.00	666
Relation to the child					
Biological parents (%)	98.2%				654
Adoptive parents (%)	1.2%				8
Stepparents (%)	0.2%				1
Foster parents	0.5%				3
Ethnicity					
Ethnicity male parent (%) Norwegian	94.8%				633
Ethnicity female parent (%) Norwegian	96.4%				644
Descriptive statistics for variables in the analyses					
Teacher-rated aggression	4.21	6.44	.00	38.00	626
Serious life events	.74	.92	.00	5.00	668
Children with 0 SLEs					344
Children with 1 SLE					197
Children with 2 SLEs					95
Children with 3 SLEs					26
Children with 4 SLEs					4
Children with 5 SLEs					2
Genotype					704
Genotype Val/Val (%)	21.4%				151
Genotype Val/Met (%)	50.4%				355
Genotype Met/Met (%)	28.1%				198

Note. SLE = serious life events.

Measures

Aggressive behavior was measured by the 25-item Aggression subscale of the Teacher's Report Form (TRF/5–18; Achenbach, 1991), which assesses tendencies to physically or verbally attack other people, destroy property, and defy authority (α = .93). Teachers rate how well an item describes the target child currently or within the last 2 months: 1 = not true (as far as I know), 2 = somewhat or sometimes true, and 3 = very true or often true.

Serious life events (SLEs) were measured by parent interviews using the Preschool Age Psychiatric Assessment (PAPA; Egger & Angold, 2004) to determine whether their child had ever experienced any of 26 stressors that could potentially cause posttraumatic stress disorder, such as being in a vehicular accident, getting burned, nearly drowning, having a serious fall, witnessing violence or death, or enduring physical and/or sexual abuse. All experienced events were summed to create a total number of SLEs. Table 1 presents the distribution of scores.

COMT genotyping was conducted using 2 milliliters of saliva collected from the children using the Oragene DNA saliva kit (DNA Genotek, Ottawa, Canada). DNA was later extracted and stored according to the manufacturer's protocol. The genotypes of the *COMT* Val158Met polymorphism were determined using a LightCycler Real-Time PCR machine (Roche Diagnostics, Scandinavia AB, Bromma, Sweden; Wittwer et al., 1997)). The PCR was performed in 20 μl of reagent in a LightCycler System using 2 μl of genomic DNA and a LightCycler-FastStart DNA Master Hybridization Probes kit (Roche Diagnostics, Bromma, Sweden) with previously published PCR primers and hybridization probes (Holmen et al., 1990). Based on the melting curve profiles, the genotypes of the participants were classified as Val/Val, Val/Met, or Met/Met. The children's genotypes proved to be in the Hardy–Weinberg equilibrium (χ^2 = 0.12, df = 1, p = .73): Val/Val (n = 151, 21.4%), Val/Met (n = 355, 50.4%), and Met/Met (n = 198, 28.1%).

Statistical Analysis

We used linear regression analysis with the aggression score as the dependent variable and the *COMT* Val158Met polymorphism (coded as Val/Val vs. Met carriers) and serious life events and their interaction as the primary predictors. Child gender served as a covariate because boys generally behave more aggressively than girls, at least in early childhood (Bjørkqvist, Lagerspetz, & Kaukiainen, 1992), which proved to be the case in this study (see first paragraph of Results below).

With a screen-stratified sample, all parameters were weighted with the inverse of the drawing probability for each participant (i.e., low-screen scorers were "weighted up," and high scorers were weighted down). This method provides unbiased general population estimates (Horvitz & Thompson, 1952). Two-sided p values < 0.05 are regarded as statistically significant, and 95% confidence intervals (CI) are reported where relevant. Analyses were performed in SPSS 21. To determine whether an interaction effect reflects diathesis-stress or differential susceptibility, we evaluated whether the regression slopes for the Met carriers and the Val homozygotes crossed within the range of available data of SLEs using the competitive model-testing procedures of Widaman et al. (2012) and Belsky, Pluess, & Widaman, 2013. To do this, nonlinear regression must be used; it is not possible to conduct this analysis in SPSS in conjunction

with weighted data. We therefore modeled this crossing point using model constraints and a robust maximum likelihood estimator in Mplus 7.2 (Muthén & Muthén, 2009).

Results

Table 1 presents the descriptive statistics for all variables included in the primary linear regression analysis. The average score for aggression was 4.21, whereas the average score for traumatic life-events was low at 0.74 in this population-based Norwegian sample. Boys had higher aggression scores than girls did (*M* difference = 1.96, 95% CI: 1.11 to 2.81, $p < .001$). Neither experiences of serious life events (b = 1.85, 95% CI: 0.88 to 2.82, $p = .55$) nor being homozygous for the Val allele (b = 0.15, 95% CI: − 0.32 to 0.60, $p = .78$) predicted aggression when controlling for gender. However, the GXE interaction proved significant (b = −1.33, 95% CI: −2.23 to −0.43, $p = .004$) and is graphically depicted in Figure 1. For children with no SLEs, the Met carriers had a mean aggression score of 1.11 (95% CI: 0.09 to 2.14, $p = .03$), which is higher than Val/Val. For children with three SLEs, the mean difference was −2.86 (95% CI: −5.28 to −0.44, $p = .02$). The negative sign for SLE = 3 indicates that for these children, Val/Val homozygotes had the higher and highest aggression scores. As can be seen, the two regression lines cross each other. This crossing point (C) was different from zero ($M_c = 0.82$, 95% CI: 0.06 to 1.58, $p = .03$), which supports the differential susceptibility theory (Widaman et al., 2012). For the Val/Val carriers, the mean aggression score increased by 0.94 (95% CI: 0.17 to 1.70, $p = .02$) per increase in one SLE. For the Met carriers, the mean aggression score changed much less and in the opposite direction, 0.39 per increase in one SLE.

The decision to treat all Met-carriers as members of a single group was based on previous GXE studies and on association studies in which aggression was the measured outcome (Frigerio et al., 2009; Albaugh et al., 2010; Langley, Heron, O'Donovan, Owen, & Thapar, 2010; Hygen et al., 2014). Moreover, this approach is based on the premise that the effects of SLEs on aggressive behavior would not vary across heterozygote and homozygote Met-carriers. To test this premise, we reran the analyses investigating the possible differences between the two Met-carrying groups, and no differences were observed ($p = .20$).

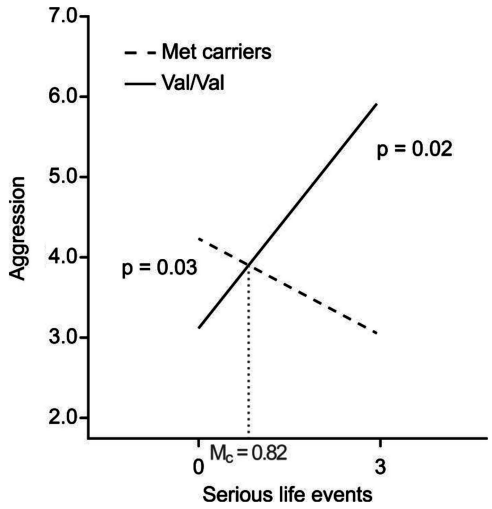

Figure 1. Estimated mean aggression score as function of number of serious life events for the two genotype groups. *p* values for differences in aggression at 0 and 3 serious life events are included.

Discussion

To our knowledge, this is the first study to evaluate whether a GXE that involves *COMT* predicts aggression while comparing diathesis-stress and differential susceptibility models, two alternative models of Person × Environment interaction. Notably, *COMT* was found to moderate the effect of exposure to serious life events on teacher-rated aggression at age four (in the absence of main effects of either *COMT* or SLEs). Moreover, the use of new statistical techniques that focus on the crossover point of the interaction revealed the data to be more consistent with differential susceptibility than with diathesis stress, as has proven with several other polymorphisms that were long conceptualized by psychiatric geneticists as "vulnerability genes" (Belsky et al., 2009; Belsky & Pluess, 2009, 2013; Ellis et al., 2011). Thus, it was not only that Val homozygotes were more vulnerable to adversity, evincing greater aggression than Met carriers under conditions of three or more SLEs, but that they were also generally more developmentally plastic or malleable. Recall that Val homozygotes also manifested less aggression than Met carriers when both groups experienced no SLEs.

Our GXE finding regarding Val homozygotes' vulnerability to adversity is consistent with the results of other GXE studies focused on *COMT* Val158Met, including Nobile et al.'s (2010) study, which showed that problematic behavior increases among Val homozygotes raised under conditions of socioeconomic disadvantage. Further studies indicate that low birth weight (Thapar et al., 2005) and ADHD (Caspi et al., 2008; Langley et al., 2010) increase the risk of antisocial behavior among Val homozygotes. Likewise, Perroud et al. (2010) reported that Val allele carriers displayed a greater inclination toward anger when exposed to sexual abuse than did Met homozygotes, and Hygen et al. (2014) found the Val/Val genotype to be associated with increasing levels of aggression in individuals with higher levels of disorganized attachment. None of these studies, however, tested whether the detected GXE effects were more or less consistent with diathesis-stress or differential susceptibility models of Person × Environment interaction, as was done in the present study.

This is not the first study to document differential susceptibility-like findings when predicting aggressive behavior (e.g., externalized behavior, conduct problems). In fact, this finding has now emerged in research that treats the temperament factor of negative emotionality as a moderator of contextual effects (Pluess & Belsky, 2009; Poehlmann et al., 2011, 2012) and physiological reactivity (Conradt, Measelle, & Ablow, 2013; Obradović, Bush, & Boyce, 2011), 5-HTTLPR (Brody et al., 2011), DRD4 (Zohsel et al., 2014), and OXTR (Johansson et al., 2012) as genetic predictors. For example, Brody and colleagues (2011) observed that higher and lower levels of perceived racial discrimination predicted more and less conduct problems among rural African American youth, respectively, but only if they carried one or more short alleles of 5-HTTLPR. Such results clearly indicate that *COMT* is

not the only candidate gene to moderate environmental influences in a differential susceptibility-related manner.

How might the reported results be explained? COMT is a critical determinant of prefrontal dopamine flux (Tunbridge, Bannerman, Sharp, & Harrison, 2004), and *COMT* Val158Met accounts for much of the dopamine degradation in the PFC (Karoum, Chrapusta, & Egan, 1994), playing an important role in regulating dopamine concentration in this brain region. The PFC is involved in complex mental processes (Benton, 1991; Fuster, 2011), including the assessment and control of appropriate social behavior (Allen, 2009; Yang & Raine, 2009). The *COMT* polymorphism has been related to self-regulation and attention (Diamond, Briand, Fossella, & Gehlbach, 2004; Egan et al., 2001). Different levels of *COMT* activity conferred by the Val158Met genotypes may therefore influence the stress response and self-regulating mechanisms, which in turn affect the development of aggressive behavior, particularly in the case of children who have experienced severe life events, as the findings of this study indicate.

More specifically, the Val allele is associated with lower tonic dopamine, especially in the case of Val homozygotes, which is hypothesized to reduce executive function (Bilder, Volavka, Lachman, & Grace, 2004; Goldberg et al., 2003) and thus may facilitate the propensity for reactive aggression when facing adversity. Carriers of the Met allele have higher D1 and D2 transmission and thus more stable networks for short-term memory (Bilder et al., 2004). Better short-term memory among Met carriers may facilitate problem-focused coping in stressful situations, thereby enabling children to act in a deliberate and planned manner rather than one of impulse and emotion, including aggressive reactions. Children who were homozygous for the Val allele displayed the lowest aggression scores in the absence of SLEs. Consistent with the differential susceptibility theory, this suggests that this particular genotype and the dopamine turnover it reflects confer plasticity for better and for worse, not just during adversity. Thus, when the environment is benign or supportive, Val/Val homozygotes prove especially susceptible to such environmental input and behave less aggressively, whereas the opposite is the case in the presence of adversity. Moreover, carriers of the Met allele seem to be less affected by environmental factors, at least with respect to the aggression reported herein.

Although the primary results are consistent with differential susceptibility theory (Belsky et al., 2007), more research is necessary before strong conclusions and interpretations can be drawn from our results. One of the limitations of this study is that our measures do not encompass both negative and positive aspects of the environment or the measured outcome, which affords the best test of differential susceptibility theorizing. After all, the absence of SLEs does not reflect the presence of positive ones, and lack of aggression is not the same as positive social functioning. Moreover, our focus was exclusively on the COMT Val158Met polymorphism. Future research should consider other candidate genes implicated in the development of aggression and environmental sensitivity. Another limitation of our study is the low prevalence of SLEs, which may be balanced by the large, community-based sample. Nevertheless, future research could benefit from a focus on higher-risk populations. It is also important to note that this is an observational study; thus, causal effects of the environment cannot be inferred with confidence. Therefore, experimental intervention research provides an excellent means of testing GXE hypotheses. Such research is being conducted and is providing additional support for the differential susceptibility framework, which predicts that some individuals will be more susceptible to positive environmental effects than others (Belsky & van Ijzendoorn, 2015; van Ijzendoorn & Bakermans-Kranenburg, 2015). Despite these limitations, our findings strengthen previous reports on the moderating role of COMT Val158Met and add to the growing body of evidence that supports the differential susceptibility hypothesis.

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