Children under stress – COMT genotype and stressful life events predict cortisol increase in an acute social stress paradigm

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Abstract

Dopamine and norepinephrine are key regulators of cognitive and affective processes. The enzyme catechol-O-methyltransferase (COMT) catabolizes catecholamines and the COMT Val¹⁵⁸Met polymorphism has been linked to several neuropsychiatric variables. Additionally, stressful life events (SLEs) contribute substantially to affective processes. We used the stress-induced activation of the hypothalamic-pituitary-adrenal axis to investigate the effects of COMT and SLEs on the cortisol response in 119 healthy children (8–12 yr). Saliva cortisol was measured during and after the Trier Social Stress Test for Children. SLEs were assessed with a standardized interview with one of the children’s parents. Linear regression analysis revealed a significant effect for COMT, with Met allele carriers showing a higher cortisol response ($b = 0.300, p = 0.001$). In turn, more SLEs lead to a less pronounced cortisol increase ($b = -0.192, p = 0.029$) probably indicating increased resilience. Our results further underscore the essential and differential role of genetic variation and environmental factors on stress responsivity.

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Introduction

Stress is an inevitable part of everyday life. Thus, an organism must respond with an adaptive set of reactions in order to cope with a potentially threatening situation and – in the long run – to restore homeostasis. However, there are considerable inter-individual differences in the response to challenges, which are probably based on complex gene × gene and gene × environment interactions (McClearn, 2006). In mammals, activation of the hypothalamic-pituitary-adrenal (HPA) axis constitutes one of the main pathways of the stress response, resulting in the release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus (PVN) of the hypothalamus with a subsequent stimulation of adrenocorticotropic hormone (ACTH) and the secretion of glucocorticoids. Cortisol as the major human stress hormone influences numerous physiological systems, including central nervous system function, metabolism, cardiovascular function, immune system, muscle tissue and bones (Kino & Chrousos, 2005). HPA axis reactivity varies widely even in healthy individuals with genetic as well as environmental factors as likely contributors (Kirschbaum et al. 1992; Linkowski et al. 1993). In this context, the modulation of the HPA axis by additional neural structures, including the brainstem, the amygdala, the hippocampus and the medial prefrontal cortex (PFC; e.g. Dedovic et al. 2009a; Jankord & Herman, 2008) and a number of neurotransmitters innervating these brain regions, suggests several promising candidate genes.

Dopamine and norepinephrine are among those regulators of the stress response (Feldman &
Variations in the gene coding for catechol-O-methyltransferase (COMT), the enzyme facilitating metabolic degradation of catecholamines (Chen et al. 2004; Weinsilboum et al. 1999), have been suggested to impact stress reactivity (Jabbi et al. 2007; Zubieta et al. 2003). COMT exists in two isoforms: soluble, predominantly expressed in tissues such as liver, blood and kidney; membrane-bound, mainly expressed in the brain, particularly in the PFC (Chen et al. 2004; Karoum et al. 1994; Matsumoto et al. 2003; Tenhunen et al. 1993). The COMT gene is located on chromosome 22q11 and contains several single nucleotide polymorphisms (SNPs) including a G/A substitution (rs4680) at codon 158, which results in the substitution of valine (Val) and methionine (Met). The Val^{158}Met SNP changes the thermal stability and activity of COMT. Met/Met homozygotes exhibit 35–50% less COMT efficiency in the PFC at 37 °C compared to Val/V al homozygotes (Chen et al. 2004). Thus, the Met allele probably leads to enhanced catecholaminergic activity (Karoum et al. 1994; Tunbridge et al. 2004) and might therefore impact cortical function.

The COMT Val allele has been linked to insufficient prefrontal activation during tasks measuring cognitive control and working memory (Blasi et al. 2005; Dumontheil et al. 2011; Egan et al. 2001; Winterer et al. 2006) and to poorer performance in prefrentally mediated tasks (Barnett et al. 2007; Goldberg et al. 2003; Joober et al. 2002; Malhotra et al. 2002). Conversely, the COMT Met allele has been associated with heightened scores of negative emotionality measured with self-reports (Lang et al. 2007; Reuter & Hennig, 2005; Stein et al. 2005), although inconsistent findings exist (Wray et al. 2008). In addition, Met allele carriers show an increased proneness for the development of anxiety disorders (Enoch et al. 2003; Olsson et al. 2005; Woo et al. 2004) and depression (Aberg et al. 2011). Psychophysiological studies support these findings: the Met allele resulted in elevated startle responses (Armbruster et al. 2011; Montag et al. 2008) and in increased limbic and prefrontal activation in response to negative stimuli in functional magnetic resonance imaging (fMRI) studies (Drabant et al. 2006; Rasch et al. 2010; Smolka et al. 2005; Williams et al. 2010). A recent meta-analysis on fMRI data concluded that Val allele carriers show advantages in emotional but disadvantages in cognitive paradigms while the opposite pattern applies to Met allele carriers (Mier et al. 2010). This trade-off had been earlier termed the warrior/worrier model (Goldman et al. 2005; Stein et al. 2006). However, while there are numerous studies on emotional regulation, fewer studies have investigated the link between COMT and the stress response in general and HPA axis reactivity in particular. Recently, Jabbi et al. (2007) reported higher plasma epinephrine levels and elevated subjective stress ratings in response to a modified version of the Trier Social Stress Test (TSST) in COMT Met/Met homozygotes. Furthermore, an interaction effect between COMT Val^{158}Met and a functional variable number of tandem repeats (VNTR) polymorphism in the dopamine transporter gene (DAT1 VNTR) – but no COMT main effect – was found in response to a public speaking paradigm in healthy young men (Alexander et al. 2011). Met/Met homozygotes, who also carried the DAT1 10R/10R genotype, showed a stronger cortisol stress response and impaired recovery. Met/Met homozygotes also showed a more pronounced secretion of ACTH and cortisol than Val allele carriers after administration of the opioid antagonist naloxone (Oswald et al. 2004). Opioid blockade was chosen because COMT Val^{158}Met had been previously linked to changes in μ-opioid receptor binding potential, which, in turn, lead to differences in pain responses (Zubieta et al. 2003). COMT Val^{158}Met has also been associated with post-traumatic stress disorder (PTSD) after the experience of severe stressors. In survivors of the Rwandan genocide, COMT Val allele carriers showed a typical dose–response relationship while Met/Met homozygotes exhibited a heightened PTSD risk independently of the severity of traumatic load (Kolassa et al. 2010).

Thus, although overall the COMT Met allele seems to be associated with deficits in the stress response, results are not entirely consistent. In addition, the existing studies mainly focus on adult populations. Since genetic variations exist from the very beginning of development it seems important to determine whether such differences are already present in younger individuals. Recently, Waldcr et al. (2010) reported effects of COMT on changes in morning cortisol levels in healthy and at-risk adolescents. As expected, there was an increase in cortisol secretion over the course of 1 yr, which was further modulated by COMT. Met/Met homozygotes showed a marked increase while there was no increase in Val/Val individuals. In sum: (a) there are numerous studies on the effects of COMT on negative emotionality but only few studies on the stress response, non of which was conducted in children; (b) COMT is expressed in the PFC, a region that has been found to be involved in HPA axis regulation; (c) COMT catabolizes dopamine and norepinephrine, which have been reported to regulate HPA axis activity.
As there is evidence from animal studies that the brain-derived neurotrophic factor (BDNF) influences structure and function of the dopaminergic system (Horger et al. 1999; Hyman et al. 1991; Narita et al. 2003; Spina et al. 1992), the BDNF Val<sup>8</sup>Met SNP was also included, mainly to investigate possible COMT × BDNF interactions. Furthermore, there is already a number of studies showing that variation in this gene is associated with HPA axis reactivity (e.g. Colzato et al. 2011; Elzinga et al. 2011; Schule et al. 2006; Shalev et al. 2009; Vinberg et al. 2009). Moreover, animal studies provided evidence that early life stress in turn decreases BDNF expression, resulting in neuronal atrophy and degeneration in the cortex and the hippocampus (Murakami et al. 2005; Roceri et al. 2002; Song et al. 2006).

In addition to genetic variation, stressful life events (SLEs) also contribute to the long-term regulation of the stress response (Tarloilo & Gunnar, 2006). Furthermore, exposure to SLEs results in an enhanced risk of developing neuropsychiatric disorders (Paykel, 2003). Particularly, SLEs during critical stages of early development might lead to persisting harmful effects over the course of life. For instance, early social stressors (i.e. low maternal care) in rats lead to increased stress responses in adult individuals via epigenetic processes (Weaver, 2007). Consistently, the crucial role of early SLEs has also been confirmed in humans (Fumagalli et al. 2007; Kaufman et al. 2000). Additionally, gene × environment interactions have been reported, although not always consistently. With regard to COMT, there are, for instance, reports of interaction effects with: (a) cannabis use on the later development of psychosis with Val allele carriers at greater risk (Caspi et al. 2005); (b) maternal cigarette smoking during pregnancy on aggressive behaviour at ages 15 and 20 yr, with Val/Val homozygotes displaying the greatest risk (Brennan et al. 2011); (c) childhood abuse and anger traits in adulthood, again with Val allele carriers at greater risk (Perroud et al. 2010) or (d) less sufficient parenting practices, resulting in more alcohol consumption during adolescence in Met/Met homozygotes (Laucht et al. 2011).

In order to further examine genetic and environmental underpinnings of stress reactivity, we investigated a sample of children to discover whether: (1) COMT Met allele carriers already show a heightened cortisol stress response during childhood; (2) past SLEs affect the cortisol response in this age group; (3) there are COMT × SLE interaction effects; (4) BDNF Val<sup>8</sup>Met affects the stress response independently or jointly with COMT and SLEs.

**Method**

**Participants**

All participants were of German/Middle European ancestry and originally consisted of 52 girls and 71 boys. Of these, 122 participants were successfully genotyped for COMT and BDNF. From the remaining sample, two participants had to be excluded due to extreme cortisol responses (see below) and for one participant cortisol data were not available for the crucial measurement points to calculate cortisol increase, leaving 52 girls and 67 boys for the final sample (mean age 9.32 yr, s.d. = 1.03, range 8–12 yr). All participants were reported to be in good health. The children were screened for psychiatric or neurological disorders or treatment in a telephone interview with their parents before participation. In addition, a semi-structured interview was conducted with one of the parents in order to assess children’s SLEs (for details, see below). As part of this interview medical problems were determined and participants whose parents reported a history of mental illness would have been excluded. Participants and their parents were informed about the aims of the study and parents gave written informed consent. The study design was approved by the Ethics Committee of the German Psychological Association.

**TSST psychosocial stress protocol**

An age appropriate version of the TSST (Kirschbaum et al. 1993) for the induction of psychosocial stress was adapted which has been described in details elsewhere and which has been found to elicit a strong and reliable cortisol response [Trier Social Stress Test for Children (TSST-C); Buske-Kirschbaum et al. 1997]. This standardized laboratory stressor consists of a preparation period (3 min), followed by a speech task (5 min), during which children had to finish telling a story, and a mental arithmetic task (5 min) to be performed in front of an audience.

**Cortisol analysis**

Salivary cortisol samples were obtained using ‘Salivettes’ (Sarstedt; Germany) and kept at −20 °C until analysis. Samples were repeatedly collected for determination of the biologically active ‘free’ fraction of cortisol before onset of the stress sessions, as well as 2, 10, 20 and 30 min after cessation of stress. Salivary cortisol samples were prepared for biochemical analysis by centrifuging at 1800 g for 5 min, which resulted in a clear supernatant of low viscosity. Salivary free cortisol concentrations were determined...
by employing a chemiluminescence immunoassay with high sensitivity of 0.16 ng/ml (IBL, Germany). Intra- and inter-assay coefficients of variation were <8%.

Life history calendar

The life history calendar (LHC) is a semi-structured interview method for collecting detailed retrospective data about life events and activities (Axinn et al. 1999; Freedman et al. 1988).

Validity and reliability of the LHC is enhanced through its use of memory cues. It elicits easily recalled memories and uses this information to aid the retrieval of less easily recalled information. The LHC uses a calendar format, which combines chronological and theme-based structures that support sequencing as well as parallel retrieval approaches. Agreement between retrospectively obtained LHC data and data obtained 5 yr earlier about the respondent’s then current situation have been found to range from 72 to 92% (Freedman et al. 1988) and, over a 3-yr period, Caspi et al. (1996) found 90% agreement. Based on the interview data, a cumulative score representing the total number of reported SLEs can be calculated. However, since the impact of any event might vary between different individuals, parents were also asked to rate each SLE according to the following classification, mild = 1, moderate = 2 or severe = 3, allowing the calculation of a weighted SLE score (SLE-W). Additionally, the LHC data can be grouped in the following subcategories: (1) illness; (2) family problems (e.g. separation or divorce of parents, severe conflicts with parents or siblings, new step-parent); (3) problems related to schooling; (4) negative socio-economic circumstances; (5) social problems with peers (e.g. end of important friendship); (6) disaster (e.g. severe accidents, fires, floods); (7) death of significant others; (8) other.

Procedure

After a telephone interview with the parents of participating children regarding basic inclusion criteria (e.g. age, health or medication), participants were scheduled for a laboratory session starting between 14:00 and 16:00 hours. Upon arrival, participants were given an overview about the study goals and protocol. The children were accompanied by a parent who stayed with the child during most resting phases and the preparations for the experiments. All participants were instructed that they could decline to participate at any time. After a short resting period, children first underwent a startle experiment (data not reported). The LHC was then conducted with the parent by a trained interviewer (D.A.) while the child had a further resting period of 30 min, after which the TSST-C was conducted. Thus, all TSST-Cs were performed between 15:45 and 18:00 hours. To assess cortisol levels, saliva samples were obtained before and after the startle experiment as well as 2 min before and 2, 10, 20 and 30 min after the TSST-C. A final saliva sample was obtained for later DNA extraction. Participants were subsequently debriefed, reimbursed for participation and thanked.

Genotyping

For genotyping, DNA was isolated from saliva samples using the ORAgene DNA Extraction kits (DNA Genotek, Canada). COMT and BDNF genotypes were determined by polymerase chain reaction (PCR) followed by digestion of the PCR products and agarose gel size fractionation as described in detail elsewhere (COMT: Armbruster et al. 2011; BDNF: Hünnerkopf et al. 2007).

Statistical analysis

All analyses were performed using SPSS for Windows 15.0 (SPSS Inc., USA).

Cortisol variables were examined for outliers using boxplots. Two participants were excluded: one with an extremely strong cortisol increase after the TSST-C of 51.03 nmol/l and the other with a very atypical cortisol time course manifesting itself in a marked cortisol decrease of −12.14 nmol/l. In order to determine whether the TSST-C did result in a sufficient cortisol increase, a repeated-measures analysis of variance (ANOVA) was performed with the six measure points as within subject variable. COMT and BDNF genotype were entered as independent between-subject variables for a first assessment of genotype group differences. A difference score was then computed between cortisol concentrations 20 min after cessation of stress (when cortisol levels had reached their peak) and immediately before the TSST-C (raw variables). A linear regression analysis was performed with COMT, BDNF and SLE-Ws as predictors and the cortisol difference score as the dependent variable. In order to assess gene × gene and gene × environment interactions, a moderated regression was conducted. Beforehand, SLE-W as a continuous predictor was centred and COMT as threefold categorical predictor was recoded as two variables according to the recommendations of West et al. (1996). In addition, the products of the transformed independent variables were calculated and entered (West et al. 1996). Since
older children might have experienced more SLEs and thus age might confound this predictor, correlations between age and the number of reported SLEs ($p=0.991$) and the weighted SLEs ($p=0.552$) were assessed. Since there were no significant correlations, age was excluded as a possible predictor. Furthermore, an additional regression analysis was performed with COMT, BDNF and the SLE subcategories as predictors to investigate possible differential effects of the various types of SLEs (e.g. illness, death of significant others, family problems).

Results

**Genotype frequencies**

The genotype frequencies of the COMT Val$^{158}$Met were 27.7% ($n=33$) for Val/Val, 49.6% ($n=59$) for Val/Met and 22.7% ($n=27$) for Met/Met. The genotype frequencies of the BDNF Val$^{66}$Met were 62.2% ($n=74$) for Val/Val, 35.3% ($n=42$) for Val/Met and 2.5% ($n=3$) for Met/Met. BDNF Met/Met and Val/Met individuals were grouped together for statistical analysis. Age and sex did not differ by COMT (age: ANOVA, $p=0.323$; sex: $x^2$ test, $p=0.521$) or BDNF (age: ANOVA, $p=0.765$; sex: $x^2$ test, $p=0.254$). The genotypes were in Hardy–Weinberg equilibrium (COMT: $p=0.949$; BDNF: $p=0.295$).

**Impact of COMT on the cortisol response**

ANOVA revealed a significant time effect indicating that the TSST-C had led to significant changes in cortisol levels ($F_{1,2,66.4}=47.62$, $p<0.001$, $\eta^2=0.300$). In addition, there was a main effect of COMT genotype ($F_{2,58}=3.79$, $p=0.026$, $\eta^2=0.064$) with Val/Val homozygotes showing the smallest and Met/Met homozygotes the strongest cortisol response while heterozygotes fell in between (Fig. 1). Contrast analyses revealed a significant difference between Val/Val and Met/Met ($p=0.007$), while the differences between Val/Met and Met/Met ($p=0.120$) and Val/Met and Val/Val ($p=0.122$) fell short of reaching significance.

Linear regression ($R=0.350$) also revealed a significant effect for COMT genotype ($p=0.001$) with the Met allele being associated with a stronger cortisol response ($\beta=0.300$). The average cortisol increase was more than twice as high in Met/Met compared to Val/Val homozygotes (8.379 nmol/l vs. 2.907 nmol/l; Figs. 1 and 2) while Val/Met heterozygotes showed intermediate levels (4.351 nmol/l; Figs. 1 and 2). This effect was not due to baseline differences before the TSST-C (ANOVA, $p=0.658$).

**Impact of SLEs on the cortisol response**

The average number of SLEs as reported by the parents was 7.28 (s.d. = 4.10, range 0–21) and the average score of SLE-Ws was 12.23 (s.d. = 6.71, range 0–35). There was no difference between the sexes and
the COMT genotype groups regarding SLE-Ws (sex: ANOVA, \( p = 0.233 \); COMT: ANOVA, \( p = 0.727 \)) and, as reported in detail above, SLEs were also unrelated to age (\( p \geq 0.552 \)). There was a significant effect for SLE-Ws: the more SLE-Ws had been reported the smaller was the cortisol increase (\( p = 0.029; \beta = -0.192 \); Fig. 3). Again, this effect was not due to baseline differences since there was no influence of SLE-Ws on cortisol levels before the TSST-C (linear regression, \( p = 0.337 \)).

Regarding the differential effects of various types of life events on the cortisol stress response, the most pronounced effect was found for death of significant others, which, however, failed to reach the conventional significance level by a narrow margin (\( p = 0.054, \beta = -0.180 \)). All other SLE subcategories did not predict cortisol stress response (all \( p \geq 0.127 \)). Furthermore, moderated multiple regression revealed no SLE \( \times \) COMT genotype interaction effect (all \( p \geq 0.494 \)).

**Impact of BDNF on the cortisol response**

Repeated-measurements ANOVA revealed no significant effect of BDNF (\( p = 0.209 \)) on cortisol levels over time. However, in regression analyses, there was a significant BDNF effect on cortisol increase (\( p = 0.005, \beta = 0.245 \)) with Met allele carriers showing a stronger cortisol response. However, moderated regression revealed no SLE \( \times \) BDNF interaction (\( p = 0.133 \)) or COMT \( \times \) BDNF interaction (\( p = 0.587 \)). The three-way interaction COMT \( \times \) BDNF \( \times \) SLE was also not significant (\( p = 0.136 \)).

**Discussion**

We found that COMT Val158Met genotype and (weighted) SLEs impacted the cortisol stress response in children, but no interaction was found between the two factors. The presence of the COMT Met allele led to a stronger cortisol response, while the occurrence of more SLEs resulted in a less pronounced cortisol increase after the TSST-C. These effects were not due to differences in cortisol baseline levels. The main effect of COMT is in line with findings indicating that the Met allele is (a) a risk factor for deficits in emotional regulation and mood disorders and (b) associated with heightened HPA axis activity. The COMT Met allele has been linked to insufficient affective regulation, especially anxiety-related traits and disorders (Enoch et al. 2003; Mier et al. 2010; Olsson et al. 2005; Rasch et al. 2010; Stein et al. 2005; Williams et al. 2010; Woo et al. 2004) while the Val allele has been associated with less efficient PFC activation during cognitive control and working memory and poorer performance on prefrontally mediated tasks (Dumontheil et al. 2011; Egan et al. 2001; Mier et al. 2010).

This trade-off between enhanced anxiety proneness but better cognitive performance in Met allele carriers and increased resilience but poorer performance in executive tasks in Val allele carriers has been summarized as the warrior/worrier model (Goldman et al. 2005; Stein et al. 2006).

So far, fewer studies have investigated the link between COMT and stress reactivity. Existing findings also mainly suggest the Met allele as a risk factor for deficits in stress responses. Met/Met homozygotes showed higher plasma epinephrine levels and higher subjective stress ratings after confrontation with a psychosocial stressor (Jabbi et al. 2007). Furthermore, an interaction effect has been reported between COMT Val158Met and DAT1 VNTR. COMT Met/Met homozygotes also carrying the DAT1 10R/10R genotype showed a stronger cortisol stress response and impaired recovery (Alexander et al. 2011). Met/Met homozygotes also responded with greater ACTH and cortisol secretion after the administration of an opioid antagonist (Oswald et al. 2004). Additionally, COMT Met/Met homozygotes had a higher risk of developing PTSD after extreme stress exposure independent of traumatic load (Kolassa et al. 2010). Although not all...
of these studies investigated actual cortisol increase, overall our results point in the same direction. COMT Met allele carriers (worriers) show an allele dosage dependent stronger cortisol stress response. Intriguingly, these differences between genotype groups were already present in healthy children before the onset of puberty.

COMT is mainly expressed in the PFC (Chen et al. 2004; Karoum et al. 1994; Matsumoto et al. 2003; Tenhunen et al. 1993), where it is the most important source for the termination of dopaminergic signalling, a neurotransmitter that has been previously suggested to impact the stress response (Sullivan & Dufresne, 2006). However, it should be noted that COMT also metabolizes norepinephrine, which is an additional potential regulator of stress reactivity (Feldman & Weidenfeld, 2004). The PFC, in turn, has been implicated to be involved in the processing of psychological stressors (Dedovic et al. 2009b), thus suggesting a mechanism through which COMT might exert an influence on peripheral stress parameters. However, the PFC is also involved in cognitive functions and COMT has been found to impact working memory and cognitive flexibility (Barnett et al. 2007; Bilder et al. 2004; Joaner et al. 2002; Malhotra et al. 2002). Since the TSST-C is not only a stressful situation, but also a cognitive challenge, this potentially confounding factor needs to be acknowledged. Hence, the effects of COMT on HPA axis reactivity should additionally be investigated with stress paradigms that do not require such a degree of cognitive processing. Furthermore, as Oswald et al. (2004) pointed out, COMT might also exert its influence on the HPA axis via its actions on the opioid neurotransmission.

Since the dopaminergic system is further modulated by BDNF (Horger et al. 1999; Hyman et al. 1991; Narita et al. 2003; Spina et al. 1992), we included the BDNF Val*Met SNP in our analysis. While there was no significant effect of BDNF on cortisol levels across the different points in time, regression analysis revealed a stronger cortisol increase in Met allele carriers. The latter finding is in line with other studies reporting stronger cortisol responses in BDNF Met allele carriers (Colzato et al. 2011; Shalev et al. 2009; Vinberg et al. 2009). However, there was no COMT x BDNF interaction. In addition to the potentially moderating role of BDNF, a recent rodent study demonstrated that the well-known link between HPA axis activity and a further neurotransmitter – serotonin (5-HT) – was modulated by 5-HT<sub>AC</sub> receptors (Heisler et al. 2007). 5-HT<sub>AC</sub> was found to be expressed in CRH-containing neurons in the PVN and affected CRH regulation and expression. Since interactions between the serotonergic and dopaminergic system are well documented (review in di Giovanni et al. 2010), this raises the likelihood of an additional possible route of influence for COMT through CRH regulation via 5-HT<sub>AC</sub>. Recently, COMT Val<sup>158</sup>Met x 5-HT<sub>AC</sub> – 759 C/T interactions were reported on BMI, fat BMI, waist circumference and cholesterol levels (Kring et al. 2009), pointing to joint influence in metabolic disorders, which, in turn, are linked to mood disorders and stress regulation.

While the genetic effects are in line with existing findings, our results concerning SLEs might appear contradictory to previous results. SLEs have been indicated as a risk factor for neuropsychiatric outcomes (Paykel, 2003). Thus, one might expect a positive association between stressful events and the cortisol stress response. However, there are two additional points to consider. First, dysfunctional HPA activity does not necessarily manifest itself in an exaggerated cortisol secretion. Blunted cortisol responses have, for instance, been reported in patients with panic disorder (Petrovski et al. 2010) or depression (Burke et al. 2005a, b). Second, and more importantly, reported SLEs were mild to moderate. There were no maltreated children in our sample. Rather, a positive selection is to be expected since it seems highly unlikely that abusive parents would participate in a study aiming to investigate SLEs in their children’s life – events about which they would be questioned in an interview. In addition, participants were pre-selected to be healthy. Also, although some parents reported financial problems, these were at the lower end of the range. Notably, the SLE effect was apparently mainly driven by death of significant others and, to a lesser degree, by family problems.

In sum, our sample consisted of very healthy children from overall functioning social backgrounds, who, although differing with regard to past stressors, certainly did not experience the entire range of possible SLEs. This restriction in variability might have obscured possible associations, including gene x environment interactions. Clearly, replications in more heterogeneous samples are warranted. Furthermore, longitudinal studies are needed to shed light on the dynamic processing of stressful events and on their influence on shaping future stress responses and the development of coping strategies. Based on the mild to moderate SLE burden, we interpret our finding of an inverse relationship between SLEs and the cortisol response as a sign of resilience. Children who had experienced more stressors, but were apparently able to handle them well enough since there were no signs of impaired health or social functioning, appeared to be better prepared to deal with a new
stressor (TSST-C). Findings in animal and human studies suggest that mild to moderate stressors during development might be beneficial since they may lead to a more adaptive phenotype, including diminished HPA axis activation after acute stress exposure (for a review, see Lyons & Parker, 2007). Thus, the relationship between SLEs and stress-related outcomes might follow a U-shaped profile (e.g. Macri & Würbel, 2006). However, stress reactivity does not solely depend on encountered SLEs but also on individual genotype composition. This notion is supported by reports of subgroups that have been found to ‘benefit’ even from traumatic events, showing what has been described as post-traumatic growth (Tedeschi & Calhoun, 2004) while others might develop PTSD. Although we did not observe a COMT × SLE interaction, which might be due to the aforementioned restricted SLE variance, such an effect was found at the other end of the SLE spectrum. The development of PTSD in survivors of the Rwandan Genocide was moderated by COMT (Kolassa et al. 2010).

There are several limitations to our study. The sample size was comparatively small for a genetic association study. Furthermore, the relatively strict selection procedure may have reduced representativeness and may have also led to a restriction of variability of the cortisol stress response. This restriction of variability might, in turn, have obscured possible associations, which, however, could have also been obscured by additional confounding factors, such as the use of medication or physical and mental disorders. Thus, we chose to exclude known or likely confounding factors and take the risk that some effects might not become significant due to restriction of variability rather than the opposite. Clearly, however, future studies should examine whether the present results hold true in more heterogeneous populations.

Taken together, our findings provide further evidence that the cortisol stress response is sensitive for genetic variation in COMT. The Met allele, which leads to enhanced catecholaminergic activity, resulted in a stronger response. In addition, a less pronounced cortisol increase was related to more (mild to moderate) stressful events, probably representing increased resilience and an enhanced ability to deal with new stressors. However, the exact underlying biological pathways by which COMT Val158Met and SLEs impact the stress response need to be investigated further.

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Statement of Interest

None.

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