Shame and Guilt-Proneness in Adolescents: Gene-Environment Interactions

Aurora Szentágotai-Tătar1 *, Adina Chiș2, Romana Vultură2, Anca Dobrean1, Diana Mirela Cândea1, Andrei C. Miu3

1 Department of Clinical Psychology and Psychotherapy, Babeș-Bolyai University, Cluj-Napoca, Cluj, Romania, 2 Department of Cell and Molecular Biology, Iuliu Hațieganu University of Medicine and Pharmacy, Cluj, Cluj-Napoca, Romania, 3 Cognitive Neuroscience Laboratory, Department of Psychology, Babeș-Bolyai University, Cluj-Napoca, Cluj, Romania

* auraszentagotai@psychology.ro

Abstract

Rooted in people’s preoccupation with how they are perceived and evaluated, shame and guilt are self-conscious emotions that play adaptive roles in social behavior, but can also contribute to psychopathology when dysregulated. Shame and guilt-proneness develop during childhood and adolescence, and are influenced by genetic and environmental factors that are little known to date. This study investigated the effects of early traumatic events and functional polymorphisms in the brain-derived neurotrophic factor (BDNF) gene and the serotonin transporter gene promoter (5-HTTLPR) on shame and guilt in adolescents. A sample of N = 271 healthy adolescents between 14 and 17 years of age filled in measures of early traumatic events and proneness to shame and guilt, and were genotyped for the BDNF Val66Met and 5-HTTLPR polymorphisms. Results of moderator analyses indicated that trauma intensity was positively associated with guilt-proneness only in carriers of the low-expressing Met allele of BDNF Val66Met. This is the first study that identifies a gene-environment interaction that significantly contributes to guilt proneness in adolescents, with potential implications for developmental psychopathology.

Introduction

Shame and guilt are negative self-conscious emotions (i.e., involving people’s reactions to their own characteristics and behavior), typically experienced in situations of failure or in which behavioral standards are violated [1,2]. While they are elicited by similar types of situations, shame and guilt differ in terms of how individuals appraise transgressions or errors [2,3], with negative evaluations of the global self in shame, and of specific behaviors in guilt [4].

Research on shame and guilt has mainly focused on childhood [5,6], and relatively little is known about the course and implications of these self-conscious emotions across the life span [7]. Considering that shame and guilt are concerned with how one is being perceived and evaluated by others [8], these emotions may undergo important changes during adolescence [9,10], when emotional reactivity to the social environment increases [11]. Indeed, during
adolescence, concern over social evaluation significantly rises compared to childhood [12], self-consciousness peaks [13], and sensitivity to stimuli relevant for self-conscious emotions is higher than in children and adults [14]. Therefore, while shame and guilt-proneness emerge earlier during childhood, they may undergo important changes during adolescence, taking adaptive or maladaptive forms.

Shame and Guilt-Proneness

Occasional feelings of shame and guilt are functional and serve social goals [1]. For example, shame predicts prosocial behavior and motivation for self-change [15–17]. Likewise, guilt has been associated with higher levels of empathy and prosocial behavior, lower levels of aggression, and lower levels of risky and delinquent behavior in children and adolescents [10,18–20].

However, problems can arise when people's lives are pervaded by shame and guilt, and over the long run, proneness to shame and guilt may play an important role in psychopathology. Studies have consistently linked shame-proneness in children and adolescents with anxiety, depression, eating disorders, externalizing symptoms and delinquent behavior [1,21]. Data regarding the association between guilt-proneness and psychological problems are less consistent [1]. They seem to indicate that guilt over specific behaviors is not associated with poor psychological adjustment [2,22], and that guilt only becomes maladaptive when it is fused with shame, when people develop a distorted sense of responsibility for events beyond their control, and when opportunities for reparation are blocked [2,23,24]. Indeed, similar to shame, maladaptive guilt in children and adolescents correlates with depression [25,26].

Considering the links between shame and guilt-proneness and child and adolescent psychological problems, recent research has focused on factors such as early trauma that may contribute to these emotional dispositions.

Early Trauma, Shame and Guilt

Early adverse experiences may have lasting effects on people's emotional responses [27,28], including proneness to shame and guilt [29]. Retrospective reports of adults, as well as cross-sectional and prospective studies with children and adolescents indicate that feelings of shame are linked with a history of physical and sexual abuse [30–33], and with various forms of psychological maltreatment such as indifference, rejection, abandonment, neglect, devaluation and shaming by parents [24,34–37]. Moreover, state shame is a mediator between trauma and various outcomes such as depression and post-traumatic stress disorder (PTSD) [30,33,34].

The relation between guilt-proneness and early adverse experiences is less consistent. However, a study by Stuewig and McCloskey [37] found an association between harsh parenting and guilt-proneness in adolescents, while studies by Donatelli and colleagues [38], and Rakow and colleagues [39,40] showed that inappropriate guilt induction by depressed parents predicts maladaptive guilt and internalizing symptoms in children and adolescents.

Early experience may have different emotional outcomes depending on genetic dispositions [41–43]. The only available twin study on maternal reports of shame and guilt suggests that both genetic and environmental factors contribute to proneness to these self-conscious emotions in children between 14 and 24 months of age, with relatively higher contributions of heritability in shame and shared environment in guilt [44]. However, these results relied on a small sample of twins and were not replicated or followed up in gene candidate studies. To our knowledge, no study until now investigated specific gene-environment interactions in shame and guilt proneness.
The Current Study

The goal of the current study was to explore gene-environment interactions in adolescent shame and guilt-proneness. While the potential influence of early trauma on shame and guilt-proneness has been examined to some extent, candidate genes that may contribute to shame and guilt-proneness by increasing susceptibility to environmental adversities have not been studied until now. However, shame and guilt-proneness have been linked with depression and anxiety [1,21], and therefore, they may involve some common gene-environment interactions. Although not all studies reported positive or convergent findings, meta-analyses support the view that carrying the low-expressing alleles of the Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene [45] and the 5-HTTLPR polymorphism in the serotonin transporter gene promoter [46,47] is associated with increased depression and anxiety in people with a history of stressful events.

These genetic polymorphisms are biologically plausible candidates for emotional development and psychopathology considering their involvement in neural plasticity [48,49] and stress reactivity [50,51]. BDNF Val66Met affects activity-dependent neural release of BDNF and hippocampal activity [48,49], and a recent study [52] suggests that this polymorphism may increase susceptibility to depression in people with a history of early trauma through neural mechanisms involving reduced gray matter in the hippocampus. Work on 5-HTTLPR mostly focused on amygdala-related neural mechanisms [53–55]. The low-expressing S allele of 5-HTTLPR is associated with reduced gray matter in amygdala [55], and impaired functional coupling in an amygdala-prefrontal circuit related to emotion regulation [53,55]. A study on adolescents [56] found that functional coupling between amygdala and the ventromedial prefrontal cortex is also involved in emotional vulnerability to early trauma associated with the low-expressing allele of 5-HTTLPR. Therefore, BDNF Val66Met and 5-HTTLPR, as well as their interaction with early trauma, may involve different pathways to depression and anxiety, related to the structure and function of hippocampal and amygdala-prefrontal circuits, respectively.

Recent studies have also approached some of the psychological mechanisms that may be involved in the influence of BDNF Val66Met and 5-HTTLPR on emotional dispositions. It was found that children carrying the BDNF Met allele, whose mothers suffered from depression [57], as well as children carrying the 5-HTTLPR S allele [57,58] display a memory bias for negative self-descriptive traits. Preliminary evidence also suggests that 5-HTTLPR may be associated with a tendency to make internal, global and stable attributions for negative events [59]. Considering that these cognitive biases affecting memory and appraisal may contribute to the emergence of emotion dispositions [60], and that they have been linked to shame and guilt [61], this study investigated whether BDNF Val66Met and 5-HTTLPR moderated the relation between early trauma and shame and guilt proneness in adolescents. Based on previous literature, we expected that shame and guilt-proneness are increased in adolescents with a history of early trauma who also carry the low-expressing alleles of BDNF Val66Met and 5-HTTLPR polymorphisms.

Materials and Methods

Participants

This study is based on a sample of N = 271 adolescents (165 girls) aged between 14 and 17 years (M = 15.82, SD = 1.169). They were all Caucasians and Romanian was their first language. None of the participants reported diagnosed neuropsychiatric disorders or use of psychoactive medication. Before the study, the procedure was explained to participants and their
parents, and participants’ assent and written parental consent were obtained. The study followed the recommendations of the Declaration of Helsinki regarding participant safety [62] and was approved by the Ethics Committee of Babeș-Bolyai University.

Genotyping

DNA was extracted from buccal epithelial cells using the MasterPure Complete DNA & RNA Purification Kit (Epicentre, Madison, USA) and kept at -20°C. BDNF Val66Met (rs6265) genotyping was performed using tetra primer amplified refractory mutation system (ARMS)-PCR method, as previously described [63]. This polymorphism creates two alleles, Met and Val, the former of which is relatively low-expressing [48]. Considering that the low-expressing Met allele was relatively rare in this sample (frequency: 0.22), which is typical of European samples [64], we aimed to compare Val homozygotes (i.e., Val/Val) and Met carriers (i.e., Val/Met and Met/Met).

Using a previously described protocol [65,66], 5-HTTLPR genotyping included both the insertion/deletion polymorphism, which creates a short (S) allele and a long (L) allele [67], and the neighboring single-nucleotide polymorphism rs25531 that further differentiates the L allele into L_A and L_G [66]. Based on these related polymorphisms, 5-HTTLPR is considered triallelic, with two low-expressing alleles, S and L_G (coded S'), compared to the L_A allele (coded L') [68]. The triallelic 5-HTTLPR genotypes were therefore coded as S'S' (i.e., SS, L_GL_G and S_L_G), S'L' (i.e., S_L_A, L_GL_A) and L'L' (L_A,L_A).

Self-Report Measures

Test of Self-Conscious Affect for Adolescents (TOSCA-A) [69]. Shame-proneness and guilt-proneness were assessed using the corresponding scales from TOSCA-A, a dispositional measure of self-conscious emotions. The TOSCA-A scales consist of 15 scenarios, 10 negative and 5 positive, yielding indices of proneness to shame and guilt. Each scenario (e.g., You and your friend are talking in class, and you get in trouble) is followed by a list of possible responses (e.g., You would think: ’I should know better. I deserve to get in trouble’). Participants rate the likelihood of each response on a scale ranging from 1 (not at all likely) to 5 (very likely). Similar to reliability coefficients reported in previous studies [70], Chronbach’s alpha in this sample was 0.807 for the shame subscale and 0.854 for the guilt subscale. There was a significant, but moderate correlation (r = 0.409, p < 0.001) between shame and guilt scores in this sample.

Childhood Traumatic Events Scale (CTES) [71] is a self-report measure used to identify several types of traumatic events experienced before the age of 17 (or until present in participants of younger ages): (1) physical abuse, such as mugging or assault; (2) sexual abuse, such as rape or molestation; (3) major parental conflicts, divorce or separation; (4) death of a family member or close friend; and (5) severe illness or injury. An additional item refers to other, not specified adverse events. Participants report whether they experienced each type of stressful event and if they did, they are asked to rate its severity on a scale ranging from 1 (not at all) to 7 (extremely). Considering that there is a single item on the occurrence of each stressful event and its severity, it was not possible to analyze the reliability of this scale. However, this scale was used in numerous studies and has shown sensitivity to a wide spectrum of emotional symptoms following early trauma [72,73].

Depression and anxiety symptoms. The depression and anxiety scales from the Depression Anxiety Stress Scales [74] were used to assess depression symptoms (e.g., hopelessness, lack of interest) and anxiety symptoms (e.g., subjective apprehension, autonomic arousal). Each of these scales includes 7 items, which are appropriate for adolescents [75] and show good sensitivity to clinical levels of emotional symptoms [76]. Depression scores over 20 and
anxiety scores over 14 are considered indicative of clinical problems [74]. In this sample, Cronbach’s alpha was 0.710 for the depression scale, and 0.663 for the anxiety scale.

Statistical Analysis
In order to determine whether genotype frequencies in our sample differed from the general population, departures from the Hardy-Weinberg equilibrium were examined [77]. Skewness was investigated using the Shapiro-Wilk test [78] and significantly skewed variables were normalized using the Box-Cox transformation [79]. Sex differences in shame and guilt-proneness were examined using independent-samples Student t tests, and effect sizes were indicated by Cohen’s d [80].

Gene-environment interactions were analyzed by multiple regressions [81], using the PROCESS macro for SPSS [82]. The two genotypes (i.e., BDNF Val66Met, 5-HTTLPR) were separately tested as moderators in the relations between mean intensity of traumatic events (CTES) as predictor, and either shame or guilt-proneness (TOSCA) as outcomes. One dummy code was created for BDNF Val66Met, contrasting Met carriers (coded with 1) and Val homozygotes (coded with 0), and two dummy codes were created for 5-HTTLPR, contrasting either SS’ (coded with 1) with the other genotypes (coded with 0), or SL’ (coded with 1) with the other genotypes (coded with 0) [83]. Slope analysis was used to describe the relations between trauma intensity and shame/guilt-proneness for each genotype [81,83]. Effect sizes for significant moderator effects were indicated by Cohen’s $f^2$, indicating the ratio of systematic variance accounted for by the moderator relative to unexplained variance in the criterion [84]. While a priori estimations of statistical power were not performed, post-hoc power estimations for moderator effects were run using the G*Power software [85].

We report significant effects at the traditional level of significance ($p < 0.05$). However, considering that the effects of the two genotypes were investigated in three regression models, which may have inflated the type I error, the survival of significant effects at a Bonferroni-corrected ($p/3$) level of significance ($p < 0.017$) is also reported.

Results
Genotypes
BDNF Val66Met genotyping indicated that there were 171 participants with Val/Val genotype, 82 with Val/Met genotype and 18 with Met/Met genotype. These genotypes were in Hardy-Weinberg equilibrium ($\chi^2 = 3.380, p > 0.05$). Due to the low number of Met homozygotes, they were included together with heterozygotes in a Met carrier group and compared to Val homozygotes.

Triallelic 5-HTTLPR genotyping indicated that there were 65 participants with L'L' genotype, 110 with SL' genotype, and 68 with SS' genotype. Due to insufficient DNA, 5-HTTLPR genotyping could not be performed for 28 participants. Considering that the number of girls and boys excluded was similar (15 girls, 13 boys), the sex ratio in the remaining sample was not affected. In addition, shame and guilt proneness and trauma intensity were not significantly different in excluded participants compared to the rest of the sample (all $p$'s > 0.175). The distribution of 5-HTTLPR genotypes in this sample was in Hardy-Weinberg equilibrium ($\chi^2 = 2.171, p > 0.05$).

Early Trauma
Most participants (62%) reported at least one traumatic event. Death of family or close friend was the most frequent trauma (39.48%), followed by severe illness or injury (22.87%), other
traumatic event not specified (22.14%), major parental conflicts or separation (18.08%), physical abuse (8.11%) and sexual abuse (1.47%). Death of family or close friend had the highest traumatic intensity (M = 4.046, SD = 1.723), followed by other traumatic events not specified (M = 3.466, SD = 1.534), major parental conflicts or separation (M = 3.061, SD = 1.795), sexual abuse (M = 3.000, SD = 2.708), physical abuse (M = 2.863, SD = 1.780) and severe illness or injury (M = 2.354, SD = 1.146).

Genes and Environment

BDNF Val66Met and 5-HTTLPR (dummy coded) were separately tested as potential moderators in the relations between mean trauma intensity as predictor and shame and guilt-proneness as outcomes. Considering that girls reported higher levels of shame-proneness (t[269] = 3.504, p = 0.001, d = 0.435) and guilt-proneness (t[181.379] = 5.876, p < 0.001, d = 0.752) compared to boys, sex was included as covariate in all analyses.

Guilt-proneness (Shapiro-Wilk’s W[266] = 0.961, p < 0.001), but not shame-proneness was significantly skewed. Normalized (i.e., Box-Cox transformed) scores were therefore used in all analyses on the former outcome.

None of the participants reported depression symptoms (M = 4.780, SD = 4.143) and anxiety symptoms (M = 5.631, SD = 3.822) over the clinical cut-offs, and these variables were therefore not used as covariates in the moderation analyses. However, shame-proneness significantly correlated with both depression (r = 0.308, p < 0.001) and anxiety (r = 0.254, p < 0.001), whereas guilt-proneness only correlated significantly with anxiety (r = 0.169, p = 0.006).

Results of moderator analyses with shame-proneness as outcome (Table 1) indicated that the main effects of BDNF Val66Met and trauma intensity on shame-proneness were not significant, but their interaction was significant (model 1 in Table 1). Slope analysis indicated that the positive relation between trauma intensity and shame-proneness was significant in BDNF Met carriers (B = 0.981, p = 0.045), but not Val homozygotes (B = -0.373, p = 0.244) (Fig 1). However, this effect did not survive at the Bonferroni-corrected level of significance. In addition, there was a main effect of 5-HTTLPR on shame-proneness when S’S’ was contrasted with the other genotypes (model 2 in Table 1), but not when S'L’ was contrasted with the other genotypes (model 3 in Table 1). This main effect did not survive at the Bonferroni-corrected level of significance.

Table 1. Coefficients for regressing self-reported shame on mean intensity of traumatic events, BDNF Val66Met genotype and 5-HTTLPR genotype, while controlling for sex.

| Model 1 | BDNF Val66Met dummy (Met carriers coded 1, Val homozygotes coded 0) | B | SE B | 95% CI |
|---------|-------------------------------------------------|---|------|--------|
|         | Mean intensity of traumatic events (centered)   | -0.373 | 0.320 | -1.003, 0.256 |
|         | BDNF Val66Met dummy × Mean intensity of traumatic events | 1.354* | 0.582 | 0.208, 2.501 |
| Model 2 | 5-HTTLPR dummy 1 (S’S’ coded 1, all other coded 0) | 2.754* | 1.307 | 0.180, 5.327 |
|         | Mean intensity of traumatic events (centered)   | 0.232 | 0.338 | -0.434, 0.899 |
|         | 5-HTTLPR dummy 1 × Mean intensity of traumatic events | -0.581 | 0.602 | -1.767, 0.604 |
| Model 3 | 5-HTTLPR dummy 2 (S'L’ coded 1, all other coded 0) | -1.373 | 1.190 | -3.718, 0.971 |
|         | Mean intensity of traumatic events (centered)   | -0.245 | 0.366 | -0.966, 0.477 |
|         | 5-HTTLPR dummy 2 × Mean intensity of traumatic events | 0.623 | 0.580 | -0.520, 1.766 |

Note. Abbreviations: B, unstandardized regression coefficient; CI, confidence interval; SE, standard error.

*p< 0.05

doi:10.1371/journal.pone.0134716.t001
The interactions between trauma intensity and 5-HTTLPR on shame-proneness were not significant. Table 2 shows the results of moderator analyses with guilt-proneness as outcome. The main effect of BDNF Val66Met and trauma intensity were not significant (model 1 in Table 2), but their interaction was significant and survived at the Bonferroni-corrected level of significance ($f^2 = 0.022$). Slope analysis indicated that trauma intensity was positively related to guilt in BDNF Met carriers ($B = 1.731, p < 0.001$), but not Val homozygotes ($B = 0.184, p = 0.538$) (Fig 1). The main effects of 5-HTTLPR and its interactions with trauma intensity were not significant. Guilt-proneness scores were normalized using the Box-Cox transformation. Abbreviations: B, unstandardized regression coefficient; CI, confidence interval; SE, standard error.

Table 2. Coefficients for regressing self-reported guilt mean intensity of traumatic events, BDNF Val66Met genotype and 5-HTTLPR genotype, while controlling for sex.

| Model | Dummy | B    | SE B | 95% CI          |
|-------|-------|------|------|-----------------|
| Model 1 | BDNF Val66Met dummy (Met carriers coded 1, Val homozygotes coded 0) | -0.101 | 1.137 | -2.339, 2.138  |
|       | Mean intensity of traumatic events (centered) | 0.184 | 0.342 | -0.489, 0.857  |
|       | BDNF Val66Met dummy × Mean intensity of traumatic events | 1.547** | 0.564 | 0.436, 2.658  |
| Model 2 | 5-HTTLPR dummy 1 (S’S’ coded 1, all other coded 0) | 2.175 | 1.335 | -0.455, 4.806  |
|       | Mean intensity of traumatic events (centered) | 0.889* | 0.347 | 0.205, 1.572  |
|       | 5-HTTLPR dummy 1 × Mean intensity of traumatic events | -0.211 | 0.613 | -1.419, 0.997  |
| Model 3 | 5-HTTLPR dummy 2 (S’L’ coded 1, all other coded 0) | -1.956 | 1.171 | -4.263, 0.350  |
|       | Mean intensity of traumatic events (centered) | 0.720 | 0.373 | -0.014, 1.455  |
|       | 5-HTTLPR dummy 2 × Mean intensity of traumatic events | 0.199 | 0.598 | -0.979, 1.377  |

Note. Guilt-proneness scores were normalized using the Box-Cox transformation. Abbreviations: B, unstandardized regression coefficient; CI, confidence interval; SE, standard error.

* $p < 0.05$

** $p < 0.01$
significant (models 1 and 2 in Table 2). Trauma intensity had a significant main effect in one of the models, when SS’ was contrasted with the other 5-HTTLPR genotypes (model 2 in Table 2), but the effect did not survive at the Bonferroni-corrected level of significance.

Supplementary Analyses

We investigated shame and guilt-proneness in relation to each type of traumatic event. Participants who reported experiences of severe illness or injury had increased shame-proneness compared to those who did not have such experiences (t[264] = 2.204, p = 0.028, Cohen’s d = 0.317). There were no other significant differences between participants who reported other types of traumatic events (i.e., physical abuse; sexual abuse; major parental conflicts or separation; death of family of close friend) and those who did not.

Discussion

The main finding of this study is that the intensity of early trauma in adolescents is positively related to guilt-proneness only in carriers of the low-expressing Met allele of BDNF Val66Met. Other positive relations between the 5-HTTLPR SS’ genotype and shame-proneness, and trauma intensity and guilt proneness, as well as the interaction between BDNF Val66Met and early trauma on shame-proneness were also found, but these effects did not survive at the level of significance corrected for multiple testing and are thus less reliable.

This is the first gene-environment interaction study on shame and guilt-proneness, but it adds to a recent line of research that has linked early trauma and BDNF Val66Met to negative self-evaluation. For example, maternal depression has been associated with a memory bias toward negative self-descriptive traits in children carrying the Met allele of BDNF Val66Met [57]. Using a similar approach, another study found that adult men with a history of early trauma and the BDNF Met allele show reduced memory for positive self-referential descriptors [86]. These results, along with the present findings, suggest that the low-expressing allele of BDNF Val66Met may increase emotional vulnerability following early trauma through biased negative self-evaluation and related emotional dispositions such as guilt-proneness. Guilt-proneness in adolescents may be an important facet of this “depressogenic” phenotype, considering its prospective association with depression [37]. In this study, which focused on healthy adolescents, guilt-proneness correlated with subclinical anxiety symptoms, which suggests that higher levels of guilt are maladaptive. Shame-proneness was also positively associated with subclinical depression and anxiety symptoms, and like guilt-proneness, this emotional disposition was affected by the BDNF Val66Met and early trauma interaction. However, this effect did not survive at the corrected level of significance and should be interpreted with caution until more convincing evidence emerges. Post-hoc power analyses based on effect sizes and sample characteristics indicated that power to detect a gene-environment interaction on shame-proneness was suboptimal (0.515) and lower than for guilt-proneness (0.995) in this study, which suggests that future attempts to replicate potential effects on the former outcome should be based on larger samples.

The present finding raises the question of the neural mechanisms by which the BDNF Val66Met and early trauma interaction influences guilt-proneness in adolescents. Recent neuroimaging work suggested that the hippocampus plays a central role in the neural pathway that links BDNF Val66Met and emotional vulnerability following early trauma. A history of early trauma in adults carrying the BDNF Met allele is associated with reduced hippocampal gray matter and depression [52]. In addition, a functional study found increased hippocampal activity during processing of emotional facial expressions in adolescents suffering from depression who also carried the BDNF Met allele [87]. Other neural structures such as the insula may be
involved in the link between maladaptive guilt and depression [88], but their anatomical and functional modulation by BDNF Val66Met and early trauma has not been studied. To date, neuroimaging genetics research shows that the BDNF Val66Met and early trauma interaction affects brain structure and function, and its influence on the hippocampus may be particularly relevant for long-term emotional vulnerability.

Trauma intensity in adolescents was not related to shame-proneness, but was positively related to guilt-proneness. However, this effect was significant in only one of the models (i.e., 5-HTTLPR, with S'S' vs. all others x trauma intensity) and did not survive at the corrected level of significance. This is in line with recent evidence suggesting that childhood trauma influences shame and guilt-proneness only indirectly. In a study conducted by Stuewig and McCloskey [37], the authors investigated the longitudinal paths between child maltreatment, parenting and shame and guilt-proneness during adolescence. They found that sexual abuse and parental conflict, two forms of early trauma also investigated in this study, were not significantly associated with shame and guilt-proneness, but that harsh parenting (i.e., punitive practices of yelling, hitting, and spanking) during childhood contributed to shame and guilt-proneness in adolescence, through later parental rejection (i.e., excessive criticism and humiliation) [37]. Therefore, early trauma may not have direct effects on proneness to shame and guilt, which is not surprising considering that it is temporally distal relative to emotional dispositions in adolescence. An earlier cross-sectional study in adults also found that emotional, but not physical abuse was related to shame-proneness, and neither was related to guilt-proneness [89]. In apparent contrast, there are studies reporting that shame is associated with sexual and physical abuse, and plays a mediator role in the relation between abuse and depression or PTSD [30–33]. However, these studies did not assess shame-proneness, but domain-specific feelings, such as bodily shame [30], or event-specific feelings, such as shame about being the victim of a violent crime [31] or sexual abuse [32,33]. In this study, we found that only adolescents with a history of severe illness or injury have increased shame-proneness. Overall, while it is possible that the limited effects of early trauma intensity on shame and guilt-proneness may be related to the small cell sizes of certain abuse groups (e.g., sexual abuse, physical abuse) in this study, these results are in line with the two other studies that also assessed dispositional shame and guilt [37,89].

There was only one main effect of 5-HTTLPR, with higher shame-proneness in adolescents with the S'S' genotype. However, this effect did not survive the correction for multiple testing. Failing to find an interaction between 5-HTTLPR and early trauma in relation to shame and guilt may seem surprising considering the literature supporting the effect of this interaction on depression and anxiety [46]. However, a recent meta-analysis [47] emphasized that most studies on 5-HTTLPR, stress and depression are focused on adults between 21 and 50 years of age, and life stressors rather than childhood stressors and illnesses. Therefore, differences in age of participants and type of trauma may explain the apparent divergence from the depression literature. In addition, this study took a triallelic approach to 5-HTTLPR genotyping, which has only recently started to be employed in gene candidate studies [66]. By differentiating two functionally distinct L alleles, genotyping rs25531 contributes to more accurate identification of 5-HTTLPR genotypes and reduces the likelihood of false positive findings [65,66]. The lack of evidence for a significant 5-HTTLPR and early trauma interaction may suggest that the neural mechanisms (e.g., amygdala-prefrontal circuits) underlying its influence on depression and anxiety [56] may differ from those involved in gene-environment interactions influencing shame and guilt-proneness.

The implications of these results are related to the possibility of targeting shame and guilt-proneness in prevention programs aiming to reduce the risk of psychopathology in adolescents [37]. Based on this study, adolescents with higher levels of childhood trauma and the BDNF
low-expressing allele are primary candidates for prevention programs focused on anxiety and depression and other forms of psychopathology related to increased guilt. Recent studies in therapygenetics [90] have also started to examine the influence of BDNF Val66Met on psychotherapy outcomes [91,92] and in the future, they might uncover clinical aspects of the interaction between BDNF Val66Met and early trauma. However, one must consider that the effect size of this interaction is small [80] in this study, which is not surprising considering that like most psychological characteristics [93,94], shame and guilt-proneness are complex or polygenic phenotypes that probably involve hundreds or thousands of gene polymorphisms and their interactions with environment. With an increasing interest in shame and guilt-proneness as potential markers of risk for developmental psychopathology [1,21], future studies might take the challenge of uncovering other relevant gene-environment interactions.

This study has at least three limits. First, the sample is small in light of estimated sizes that would be needed in gene candidate studies focused on functional polymorphisms with small effects [95]. Therefore, these results should be taken with caution until they are independently replicated. Second, three-way interactions between BDNF Val66Met, 5-HTTLPR and early trauma could not be tested in this study because of limited statistical power. While the interaction between BDNF and the serotonin transporter molecule is biologically plausible [96] and relevant for emotional disorders [97], larger sample sizes are needed in order to examine gene × gene and gene × gene × environment interactions. A recent study [98] indicates that the moderator effects of BDNF Val66Met and 5-HTTLPR in the relation between childhood adversity and depression are independent. This suggests that not including three-way interactions in statistical models does not affect the potential of uncovering gene-environment interactions separately implicating the two polymorphisms. Finally, the recency of trauma was not assessed in this study. The questionnaire that we have used is typical for the early life stress literature and has been previously employed in adolescent studies [73], but it did not allow us to control for developmental timing of trauma [99]. However, recent studies that have differentiated between childhood adversity and recent stress found that only the former interacts with BDNF Val66Met in relation to emotional responses [100,101], which suggests that this study may have tapped the effect of early trauma.

In conclusion, our results indicate that BDNF Val66Met is a significant moderator of the relation between early trauma and guilt-proneness in healthy adolescents. Should these results be replicated in independent samples, future studies might focus on the neural mechanisms underlying the effect of this gene-environment interaction on proneness to negative self-conscious emotions and their impact on developmental psychopathology.

Acknowledgments
We thank Dr. Lavinia Cheie for her help with data collection.

Author Contributions
Conceived and designed the experiments: AST ACM. Performed the experiments: AC RV DMC. Analyzed the data: AST AD ACM. Wrote the paper: AST ACM.

References
1. Muris P, Meesters C (2014) Small or big in the eyes of the other: on the developmental psychopathology of self-conscious emotions as shame, guilt, and pride. Clin Child Fam Psychol Rev 17: 19–40. doi: 10.1007/s10567-013-0137-z PMID: 23712881
2. Tangney JP, Tracy JL (2012) Self-conscious emotions In: Leary M, Tangney JP, editors. Handbook of self and identity. 2nd ed. New York: Guilford. pp. 446–478.
3. Tangney JP (1996) Conceptual and methodological issues in the assessment of shame and guilt. Behav Res Ther 34: 741–754. PMID: 8936757
4. Lewis HB (1971) Shame and guilt in neurosis. New York: International Universities Press.
5. Lagattuta KH, Thompson RA (2007) The development of self-conscious emotions. In: Tracy JL, Robins RW, Tangney JP, editors. The self-conscious emotions: Theory and research New York: Guilford. pp. 91–113.
6. Lewis M (2007) Self-conscious emotional development. In: Tracy JL, Robins RW, Tangney JP, editors. The self-conscious emotions: Theory and research New York: Guilford. pp. 134–149.
7. Orth U, Robins RW, Soto CJ (2010) Tracking the trajectory of shame, guilt, and pride across the life span. J Pers Soc Psychol 99: 1061–1071. doi: 10.1037/a0021342 PMID: 21114354
8. Leary MR (2004) Digging deeper: The fundamental nature of “Self-conscious” emotions. Psychol Inq 15: 129–131.
9. Grazzani Gavazzi, Ornaghi V, Antoniotti C (2011) Children’s and adolescents’ narratives of guilt: Antecedents and mentalization. Eur J Dev Psychol 8: 311–330
10. Olthof T, Ferguson T, Bloemers E, Deij M (2004) Morality-related antecedents of children’s guilt and shame attributions in events involving physical illness. J Pers Soc Psychol 86: 391–404.
11. Blakemore SJ, Mills KL (2014) Is adolescence a sensitive period for sociocultural processing? Annu Rev Psychol 65: 193–217. doi: 10.1146/annurev-psych-100213-115202 PMID: 24016274
12. Westenberg PM, Drewes MJ, Goedhart AW, Treffers PD (2004) A developmental analysis of self-reported fears in late childhood through mid-adolescence: social-evaluative fears on the rise? J Child Psychol Psychiatry 45: 481–495. PMID: 15055368
13. Rankin JL, Lane DJ, Gibbons FX, Gerrard M (2004) Adolescent self-consciousness: Longitudinal age changes and gender differences in two cohorts. J Res Adolesc 14: 1–21.
14. Somerville LH, Jones RM, Ruberry EJ, Dyke JP, Glover G, Casey BJ (2013) The medial prefrontal cortex and the emergence of self-conscious emotion in adolescence. Psychol Sci 24: 1545–1562. doi: 10.1177/0956797612475633 PMID: 23804962
15. de Hooge IE, Zeelenberg M, Breugelmans SM (2007) Moral sentiments and cooperation: Differential influences of shame and guilt. Cogn Emot 21: 1025–1042.
16. de Hooge IE, Zeelenberg M, Breugelmans SM (2008) Restore and protect motivations following shame. Cogn Emot 22: 111–127.
17. Lickel B, Kushlev K, Savalei V, Matta S, Schmader T (2014) Shame and the motivation to change the self. Emotion 14: 1049–1061. doi: 10.1037/a0038235 PMID: 25401288
18. Roberts W, Strayer J, Denham S (2014) Empathy, Anger, Guilt: Emotions and Prosocial Behaviour. Can J Behav Sci 46: 465–474.
19. Roos S, Hodges EV, Salmivalli C (2014) Do guilt- and shame-proneness differentially predict prosocial, aggressive, and withdrawn behaviors during early adolescence? Dev Psychol 50: 941–946. doi: 10.1037/a0033904 PMID: 23895166
20. Stuewig J, Tangney JP, Kendall S, Folk JB, Meyer CR, Dearing RL (2015) Children’s Proneness to Shame and Guilt Predict Risky and Illegal Behaviors in Young Adulthood. Child Psychiatry Hum Dev 46: 217–227. doi: 10.1007/s10578-014-0467-1 PMID: 24842762
21. Mills RSL (2005) Taking stock of the developmental literature on shame. Dev Rev 25: 26–63.
22. Tangney JP, Stuewig J, Mashek DJ (2007) Moral emotions and moral behavior. Annu Rev Psychol 58: 345–372. PMID: 16953797
23. Ferguson TJ, Stegge H, Eyre HL, Vollmer R, Ashbaker M (2000) Context effects and the (mal)adaptive nature of guilt and shame in children. Genet Soc Gen Psychol Monogr 126: 319–345. PMID: 10950200
24. Webb M, Heisler D, Call S, Chickering SA, Colburn TA (2007) Shame, guilt, symptoms of depression, and reported history of psychological maltreatment. Child Abuse Negl 31: 1143–1153. PMID: 18023873
25. Luby J, Belden A, Sullivan J, Hayen R, McCadney A, Spitznagel E (2009) Shame and guilt in preschool depression: evidence for elevations in self-conscious emotions in depression as early as age 3. J Child Psychol Psychiatry 50: 1156–1166. doi: 10.1111/j.1469-7610.2009.02077.x PMID: 19490311
26. Tilghman-Osborne C, Cole DA, Felton JW (2012) Inappropriate and excessive guilt: instrument validation and developmental differences in relation to depression. J Abnorm Child Psychol 40: 607–620. doi: 10.1007/s10802-011-9591-8 PMID: 22086497
27. Briggs-Gowan MJ, Carter AS, Clark R, Augustyn M, McCarthy KJ, Ford JD (2010) Exposure to potentially traumatic events in early childhood: differential links to emergent psychopathology. J Child Psychol Psychiatry 51: 1132–1140. doi: 10.1111/j.1469-7610.2010.02256.x PMID: 20840502

28. Mongillo EA, Briggs-Gowan M, Ford JD, Carter AS (2009) Impact of traumatic life events in a community sample of toddlers. J Abnorm Child Psychol 37: 455–468. doi: 10.1007/s10802-008-9283-z PMID: 19034643

29. Fletcher KE (2011) Understanding and Assessing Traumatic Responses of Guilt, Shame, and Anger among Children, Adolescents, and Young Adults. Journal of Child and Adolescent Trauma 4: 339–360.

30. Andrews B (1995) Bodily shame as a mediator between abusive experiences and depression. J Abnorm Psychol 104: 277–285. PMID: 7790630

31. Andrews B, Brewin CR, Rose S, Kirk M (2000) Predicting PTSD symptoms in victims of violent crime: the role of shame, anger, and childhood abuse. J Abnorm Psychol 109: 69–73. PMID: 10740937

32. Feiring C, Taska L, Chen K (2002) Trying to understand why horrible things happen: attribution, shame, and symptom development following sexual abuse. Child Maltreat 7: 26–41. PMID: 11838512

33. Feiring C, Taska L, Lewis M (2002) Adjustment following sexual abuse discovery: the role of shame and attributional style. Dev Psychol 38: 79–92. PMID: 11806704

34. Bennett DS, Sullivan MW, Lewis M (2010) Neglected children, shame-proneness, and depressive symptoms. Child Maltreat 15: 305–314. doi: 10.1177/1077559510379634 PMID: 20724372

35. Claesson K, Sohberg S (2002) Internalized shame and early interactions characterized by indifference, abandonment and rejection: Replicated findings. Clin Psychol Psychother 9: 277–284.

36. Mills RS, Hastings PD, Serbin LA, Stack DM, Abela JR, Arbeau KA, et al. (2015) Depressogenic Thinking and Shame Proneness in the Development of Internalizing Problems. Child Psychiatry Hum Dev 46: 194–208. doi: 10.1007/s10578-014-0416-4 PMID: 24198082

37. Stuewig J, McCloskey LA (2005) The relation of child maltreatment to shame and guilt among adolescents: psychological routes to depression and delinquency. Child Maltreat 10: 324–336. PMID: 16204735

38. Donatelli J-AL, Bybee JA, Buka SL (2007) What Do Mothers Make Adolescents Feel Guilty About? Incidents, Reactions, and Relation to Depression. J Child Fam Stud 16: 859–875.

39. Rakow A, Forehand R, Haker K, McKee LG, Champion JE, Potts J, et al. (2012) The Association of Parental Depressive Symptoms with Child Internalizing Problems: The Role of Parental Guilt Induction. J Fam Psychol 25: 147–151.

40. Rakow A, Forehand R, McKee L, Coffelt N, Champion J, Fear J, et al. (2009) The Relation of Parental Guilt Induction to Child Internalizing Problems When a Caregiver Has a History of Depression. J Child Fam Stud 18: 367–377. PMID: 20090853

41. Caspi A, Moffitt TE (2006) Gene-environment interactions in psychiatry: joining forces with neuroscience. Nat Rev Neurosci 7: 583–590. PMID: 16791147

42. Lesch KP (2004) Gene-environment interaction in psychiatry: principles and examples. Dialogues Clin Neurosci 6: 314–325.

43. Rutter M, Dunn J, Plomin R, Simonoff E, Pickles A, Maughan B, et al. (1997) Integrating nature and nurture: implications of person-environment correlations and interactions for developmental psychopathology. Dev Psychopathol 9: 335–364. PMID: 9201448

44. Zahn-Waxler C, Robinson J (1995) Empathy and guilt: early origins of feelings of responsibility. In: Tangney JP, Fisher KW, editors. Self-conscious emotions: The psychology of shame, guilt, embarrassment, and pride. New York: Guilford Press. pp. 143–173.

45. Hosang GM, Shiles C, Tansey KE, McGuffin P, Uher R (2014) Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis. BMC Med 12: 7. doi: 10.1186/1741-7015-12-7 PMID: 24433458

46. Karg K, Burmeister M, Shedden K, Sen S (2011) The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. Arch Gen Psychiatry 68: 444–454. doi: 10.1001/archgenpsychiatry.2010.189 PMID: 21199959

47. Sharpley CF, Palanisamy SK, Glyde NS, Dillingham PW, Agnew LL (2014) An update on the interaction between the serotonin transporter promoter variant (5-HTTLPR), stress and depression, plus an exploration of non-confirming findings. Behav Brain Res 273: 69–105. doi: 10.1016/j.bbr.2014.07.030 PMID: 25078292

48. Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, et al. (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112: 257–269. PMID: 12953913
49. Karabeg MM, Grauthoff S, Kollert SY, Weidner M, Heiming RS, Jansen F, et al. (2013) 5-HTT deficiency affects neuropaecity and increases stress sensitivity resulting in altered spatial learning performance in the Morris water maze but not in the Barnes maze. PLoS One 8: e78238. doi: 10.1371/journal.pone.0078238 PMID: 24167611

50. Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, et al. (2006) Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science 314: 140–143. PMID: 17023662

51. Holmes A, Yang RJ, Lesch KP, Crawley JN, Murphy DL (2003) Mice lacking the serotonin transporter exhibit 5-HT(1A) receptor-mediated abnormalities in tests for anxiety-like behavior. Neuropsychopharmacology 28: 2077–2088. PMID: 12968128

52. Gatt JM, Nemeroff CB, Dobson-Stone C, Paul RH, Bryant RA, Schofield R, et al. (2009) Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. Mol Psychiatry 14: 681–695. doi: 10.1038/mp.2008.143 PMID: 19153574

53. Drabant EM, Ramel W, Edge MD, Hyde LW, Kuo JR, Goldin PR, et al. (2012) Neural mechanisms underlying 5-HTTLPR-related sensitivity to acute stress. Am J Psychiatry 169: 397–405. doi: 10.1176/appi.ajp.2011.10111699 PMID: 22362395

54. Miu AC, Vulturar R, Chis A, Ungureanu L, Gross JJ (2013) Reappraisal as a mediator in the link between 5-HTTLPR and social anxiety symptoms. Emotion 13: 1012–1022. doi: 10.1037/a0033383 PMID: 23795589

55. Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, et al. (2005) 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci 8: 828–834. PMID: 15880108

56. Burghy CA, Stodola DE, Ruttle PL, Molloy EK, Armstrong JM, Oler JA, et al. (2012) Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. Nat Neurosci 15: 1736–1741. doi: 10.1038/nn.3257 PMID: 23143517

57. Hayden EP, Olin TM, Bufferd SJ, Miller A, Dougherty LR, Sheikh HI, et al. (2013) The serotonin transporter linked polymorphic region and brain-derived neurotrophic factor valine to methionine at position 66 polymorphisms and maternal history of depression: associations with cognitive vulnerability to depression in childhood. Dev Psychopathol 25: 587–598. doi: 10.1017/S0954579413000035 PMID: 23980378

58. Hayden EP, Dougherty LR, Maloney B, Olin TM, Sheikh H, Durbin CE, et al. (2008) Early-emerging cognitive vulnerability to depression and the serotonin transporter promoter region polymorphism. J Affect Disord 107: 227–230. PMID: 17804080

59. Sheikh HI, Hayden EP, Singh SM, Dougherty LR, Olin TM, Durbin CE, et al. (2008) An examination of the association between the 5-HTT promoter region polymorphism and depressogenic attributional styles in childhood. Pers Individ Dif 45: 425–428. PMID: 19122945

60. Scherer KR, Borsch T (2009) Culture-Specific Appraisal Biases Contribute to Emotion Dispositions. Eur J Pers 23: 265–288.

61. Tracy JL, Robins RW (2004) Putting the self into self-conscious emotions: A theoretical model. Psychol Inq 15: 103–125.

62. World Medical Association (2013) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310: 2191–2194. doi: 10.1001/jama.2013.281053 PMID: 24141714

63. Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, et al. (1996) Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274: 1527–1531. PMID: 8929413
68. Hu XZ, Lipsky RH, Zhu G, Akhtar LA, Taubman J, Greenberg BD, et al. (2006) Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. Am J Hum Genet 78: 815–826. PMID:16642437

69. Tangney JP, Wagner PE, J. G, Gramzow R (1991) The Test of Self-Conscious Affect for Adolescents (TOSCA-A). Fairfax, VA: George Mason University.

70. Tangney JP, Dearing R (2002) Shame and Guilt. New York: Guilford.

71. Tangney JP, Dearing R (2002) Shame and Guilt. New York: Guilford.

72. Camuta M, Crisan LG, Vultură R, Opre A, Miu AC (2015) Emotional non-acceptance links early life stress and blunted cortisol reactivity to social threat. Psychoneuroendocrinology 51: 176–187. doi: 10.1016/j.psyneuen.2014.09.026 PMID:25462891

73. Smyth JM, Hockemeyer JR, Heron KE, Wonderlich SA, Pennebaker JW (2008) Prevalence, type, disclosure, and severity of adverse life events in college students. J Am Coll Health 57: 69–76. doi: 10.3200/JACH.57.1.69-76 PMID: 18682348

74. Lovibond SH, Lovibond PF (1995) Manual for the Depression Anxiety Stress Scales. Sidney: Psychology Foundation.

75. Szabo M (2010) The short version of the Depression Anxiety Stress Scales (DASS-21): factor structure in a young adolescent sample. J Adolesc 33: 1–8. doi: 10.1111/j.1467-8683.2009.00814.x PMID:19560196

76. Brown TA, Chorpita BF, Korotitsch W, Barlow DH (1997) Psychometric properties of the Depression Anxiety Stress Scales (DASS) in clinical samples. Behav Res Ther 35: 79–88. PMID:9009048

77. Rodríguez S, Gaunt TR, Day IN (2009) Hardy-Weinberg equilibrium testing of biological ascertainment for Mendelian randomization studies. Am J Epidemiol 169: 505–514. doi:10.1093/aje/kwn359 PMID: 19126586

78. Box GEP, Cox DR (1964) An analysis of transformations. J R Stat Soc Series B 26: 211–252. PMID:9009048

79. Frazier PA, Tix AP, Barron KE (2004) Testing Moderator and Mediator Effects in Counseling Psychology Research. J Couns Psychol 51: 115–134.

80. Hayes AF (2013) Introduction to Mediation, Moderation, and Conditional Process Analysis. A Regression-Based Approach. New York: The Guilford Press.

81. West SG, Aiken LS, Krull JL (1996) Experimental personality designs: analyzing categorical by continuous variable interactions. J Pers 64: 1–48. PMID:8656311

82. Aiken LS, West SG (1991) Multiple regression: Testing and interpreting interactions. Newbury Park, CA: Sage.

83. Faul F, Erdfelder E, Buchner A, Lang AG (2009) Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods 41: 1149–1160. doi:10.3758/BRM.41.4.1149 PMID:19897823

84. van Oostrom I, Franke B, Rijpkema M, Gerritsen L, Arias-Vasquez A, Fernandez G, et al. (2012) Interaction between BDNF Val66Met and childhood stressful life events is associated to affective memory bias in men but not women. Biol Psychol 89: 214–219. doi: 10.1016/j.bip psychosis.2011.10.012 PMID: 22033217

85. Lau JY, Goldman D, Buzas B, Hodgkinson C, Leibenluft E, Nelson E, et al. (2010) BDNF gene polymorphism (Val66Met) predicts amygdala and anterior hippocampus responses to emotional faces in anxious and depressed adolescents. Neuroimage 53: 952–961. doi: 10.1016/j.neuroimage.2009.11.026 PMID: 19931400

86. Belden AC, Barch DM, Oakberg TJ, April LM, Harms MP, Botteron KN, et al. (2015) Anterior insula volume and guilt: neurobehavioral markers of recurrence after early childhood major depressive disorder. JAMA Psychiatry 72: 40–48. doi: 10.1001/jamapsychiatry.2014.1604 PMID:25390502

87. Hoglund CL, Nicholas KB (1995) Shame, Guilt, and Anger in College-Students Exposed to Abusive Family Environments. J Fam Violence 10: 141–157.

88. Lester KJ, Eley TC (2013) Therapypathetics: Using genetic markers to predict response to psychological treatment for mood and anxiety disorders. Biol Mood Anxiety Disord 3: 4. doi: 10.1186/2045-5380-3-4 PMID:23388219

89. Lester KJ, Hudson JL, Tropeano M, Creswell C, Collier DA, Farmer A, et al. (2012) Neurotrophic gene polymorphisms and response to psychological therapy. Transl Psychiatry 2: e108. doi: 10.1038/tp. 2012.33 PMID: 22832952
92. Perroud N, Salzmann A, Prada P, Nicastro R, Hoepli ME, Furrer S, et al. (2013) Response to psychotherapy in borderline personality disorder and methylation status of the BDNF gene. Transl Psychiatry 3: e207. doi: 10.1038/tp.2012.140 PMID: 23422958

93. Plomin R, Haworth CM, Meaburn EL, Price TS, Wellcome Trust Case Control C, Davis OSP (2013) Common DNA markers can account for more than half of the genetic influence on cognitive abilities. Psychol Sci 24: 562–568. doi: 10.1177/0956797612457952 PMID: 23501967

94. Vinkhuyzen AA, Pedersen NL, Yang J, Lee SH, Magnusson PK, Iacono WG, et al. (2012) Common SNPs explain some of the variation in the personality dimensions of neuroticism and extraversion. Transl Psychiatry 2: e102. doi: 10.1038/tp.2012.27 PMID: 22832902

95. Duncan LE, Keller MC (2011) A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. Am J Psychiatry 168: 1041–1049. doi: 10.1176/appi.ajp.2011.11020191 PMID: 21890791

96. Martinowich K, Lu B (2008) Interaction between BDNF and serotonin: role in mood disorders. Neuropsychopharmacology 33: 73–83. PMID: 17882234

97. Duman RS, Monteggia LM (2006) A neurotrophic model for stress-related mood disorders. Biol Psychiatry 59: 1116–1127. PMID: 16631126

98. Carver CS, Johnson SL, Joormann J, Lemoult J, Cuccaro ML (2011) Childhood adversity interacts separately with 5-HTTLPR and BDNF to predict lifetime depression diagnosis. J Affect Disord 132: 89–93. doi: 10.1016/j.jad.2011.02.001 PMID: 21420735

99. Nugent NR, Tyrka AR, Carpenter LL, Price LH (2011) Gene-environment interactions: early life stress and risk for depressive and anxiety disorders. Psychopharmacology (Berl) 214: 175–196.

100. Elzinga BM, Molendijk ML, Oude Voshaar RC, Bus BA, Prickaerts J, Spinboven P, et al. (2011) The impact of childhood abuse and recent stress on serum brain-derived neurotrophic factor and the moderating role of BDNF Val66Met. Psychopharmacology (Berl) 214: 319–328.

101. Perea CS, Paternina AC, Gomez Y, Latig MC (2012) Negative affectivity moderated by BDNF and stress response. J Affect Disord 136: 767–774. doi: 10.1016/j.jad.2011.09.043 PMID: 22044630