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Interaction of childhood trauma with rs1360780 of the *FKBP5* gene on trait resilience in a general population sample

Jan Terock[a,b,*], Sandra Van der Auwera[b], Anke Hannemann[c], Deborah Janowitz[b], Georg Homuth[d], Alexander Teumer[e], Hans Jörgen Grabe[b,f]

[a] Department of Psychiatry and Psychotherapy, HELIOS Hanseklinikum Stralsund, Germany
[b] Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Germany
[c] Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Germany
[d] Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Germany
[e] Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany
[f] German Center for Neurodegenerative Diseases DZNE, Site Rostock/ Greifswald, Germany

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1. Introduction

Childhood trauma has been found a major risk factor for the development of psychopathology (Heim and Nemeroff, 2001) and particularly stress related psychiatric disorders including depression (Mandelli et al., 2015), anxiety (Hovens et al., 2015) and posttraumatic stress-disorder (PTSD) (Terock et al., 2016). However, studies also found a substantial proportion of childhood trauma victims showing no particular mental health problems in adulthood (Collishaw et al., 2007). These individuals have been described as 'resilient', a term which refers to the individual psychological and biological predisposition to recover after exposure to stressful life events (Rutter, 1987). Different personality characteristics including secure attachment, sense of coherence and purpose in life as well as self-acceptance were shown to promote individual resilience and to provide relative protection for developing psychiatric conditions in the aftermath of trauma (Bonanno, 2004). Accordingly, different studies found that resilience was negatively associated with stress-related psychiatric disorders like depression and PTSD (Bensimon, 2012) in subjects with exposure to childhood (Poole et al., 2017; Schulz et al., 2014) and adulthood trauma (Wingo et al., 2010). Moreover, there is consistent evidence showing significant negative effects of all types of child maltreatment on resilient functioning (Campbell-Sills et al., 2009; Cicchetti and Rogosch, 2012). Given that resilience is a broad protective factor to stress related psychopathology, diminished resilience may serve as a mechanism underlying the effects of childhood trauma and genetic risk factors common to different psychiatric disorders.

Current etiological concepts of psychiatric disorders emphasize the interplay between environmental and genetic risk factors. One of the most extensively studied genes in the field of stress related psychiatric disorders is *FKBP5* and particularly the common functional polymorphism rs1360780 (Matosin et al., 2018). It is located on chromosome 6p21.31 and codes for the FK506-binding protein 51 (FKBP5), a co-chaperone of the heat shock protein-90 (hsp90). Expression of *FKBP5* is induced by glucocorticoids in an ultrashort intracellular negative feedback loop (Vermeer et al., 2003). In turn, FKBP5 reduces the affinity of the glucocorticoid-receptor (GR) to cortisol and thereby diminishes GR-mediated cortisol effects in the brain (Wochnik et al., 2005). Evidence from previous studies suggests that high-induction alleles of different functional *FKBP5* polymorphisms and particularly of rs1360780 are related to relative GR resistance, impaired negative cortisol feedback, prolonged activation of the stress hormone axis and increased risk for stress-related psychiatric disorders:

For example, Binder et al. (2008) and Zimmermann et al. (2011)

* Corresponding author. Department of Psychiatry and Psychotherapy, University Medicine Greifswald, HELIOS Hanseklinikum Stralsund, Rostocker Chaussee 70, 18437, Stralsund, Germany.
E-mail address: jan.terock@helios-gesundheit.de (J. Terock).

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identified different SNPs including rs1360780 in *FKBP5* that interacted with traumatic events to predict symptoms of PTSD (Binder et al., 2008) and depression (Zimmermann et al., 2011). Appel et al. (2011) found that the rs1360780 polymorphism moderated the effect of childhood physical abuse on the risk for adult depression (Appel et al., 2011). Roy et al. (2010) reported about interacting effects of childhood trauma severity with four *FKBP5* SNPs including rs1360780 on the risk for attempting suicide (Roy et al., 2007). In their recent review and meta-analyses, Wang et al. (2018) investigated gene-environment interactions of early life stress and different polymorphisms of the *FKBP5* gene and reported that carriers of the T-allele of rs1360780 showed significantly increased risks for depression and PTSD (Wang et al., 2018). Finally, Ferrer et al. found that *FKBP5* polymorphisms influence HPA-axis negative feedback independent of major depression and obsessive-compulsive disorder, indicating that this association reflects a transdiagnostic feature for increased stress vulnerability (Ferrer et al., 2018).

Taken together, childhood trauma in interaction with *FKBP5* was repeatedly found a risk factor for the development of various stress related psychiatric disorders. However, it remains unclear how these interacting factors exert their detrimental effects on the different psychopathologies. Considering the concept of resilience as a broad negative predictor for stress related psychopathologies, diminished resilience may contribute to transfer the impact of these factors on psychiatric disorders. Moreover, improving our understanding of the genetic and environmental underpinnings of resilience could help to integrate existing findings of transdiagnostic predictors of mental health conditions.

The genetic underpinnings of resilience and its interaction with environmental factors are only insufficiently understood. Stein et al. (2009) found that the s-allele of a functional polymorphism in the serotonin transporter gene (5-HTTLPR) was associated with lower resilience in a sample of 423 undergraduate students (Stein et al., 2009). In a study on community-dwelling older adults, Rana et al. (2014) investigated putative associations of 65 candidate single nucleotide polymorphisms (SNP) including *5-HTTLPR* with trait resilience and found no significant associations after correction for multiple testing (Rana et al., 2014). Strohmaier et al. (2013) investigated sex-specific associations of the rs1006737 polymorphism of the *CACNA1C* gene with different personality traits and resilience factors in their 10-year follow-up general population study (Strohmaier et al., 2013). Their results showed associations of the A-allele in men with different aspects of low resilience including high emotional lability, lower sense of coherence, lower perceived social support, and higher depressive symptoms, while in women, the same allele was associated with higher resilience factors, indicating that sex-specific effects are involved in the genetic architecture of resilience.

Considering the strong impact of environmental factors and particularly childhood trauma on resilience, gene-environment interactions (GxE) may contribute to explain the currently inconclusive results from candidate gene studies. To date, only few studies on GxE effects on resilience are available: In a first study, Cicchetti et al. (2012) investigated main and interaction effects of four candidate genetic polymorphisms involved in the serotonin, corticotropin releasing hormone, dopamine and oxytocin metabolism with child maltreatment in a sample of maltreated and non-maltreated children (Cicchetti and Rogosch, 2012). Their results showed significant main effects of child maltreatment, while none of the tested SNPs were independently associated with resilience. However, their results revealed a moderating effect of the 5-HTTLPR polymorphism such that nonmaltreated subjects with the ss-genotype were more likely to have a higher resilience whereas maltreated individuals with the same genotype showed a lower resilient functioning. In contrast, in a study based on the same general population sample as this study, Reinelt et al. (2015) found moderating effects of low social support, a well-established chronic stress factor, and genotype of 5-HTTLPR on sense of coherence and resilience (Reinelt et al., 2015). More specifically, their findings showed that carriers of the s-allele and low social support showed more sense of coherence and a higher resilience compared to subjects with the ll-genotype. Finally, Bradley et al. (2013) reported that carriers of the G-allele of the rs53576 polymorphism of the oxytocin receptor gene showed increased resilience if they had experience a more beneficial childhood family environment (Bradley et al., 2013).

Considering the putative impact of childhood trauma on resilience, we aimed at investigating the main effects of childhood trauma and rs1360780 of *FKBP5* and their interaction on adult trait resilience in the general population. Further, based on findings indicating that sex-specific effects are involved in the genetic regulation of the HPA-axis, we sought to examine sex differences in genetic and environmental effects on resilience in secondary analyses.

2. Materials and methods

2.1. Sample

Data from the “Study of Health in Pomerania (SHIP)” were used (Völzke et al., 2011). The target population was comprised of adult German residents in northeast Germany living in 3 cities and 29 communities, with a total population of 212,157. A two-stage stratified cluster sample of adults aged 20–81 years had been drawn from local population registration files. The net sample comprised 6267 eligible subjects, of which 4308 Caucasian subjects participated at baseline SHIP-0 between 1997 and 2001. Follow-up examination (SHIP-1) was conducted 5 years after baseline and included 3300 subjects. From June 2007 until August 2010, the “**L**ife-**E**vents and **G**ene-**En**vironment Interaction in **De**pression (LEGENDE)” study was carried out (Appel et al., 2011; Völzke et al., 2011). Among the 3669 subjects of SHIP-0 that were invited to take part in the LEGENDE study, 2400 participated.

The investigations in SHIP and LEGENDE were carried out in accordance with the Declaration of Helsinki, including written informed consent of all participants. The survey and study methods of both the studies were approved by the institutional ethical committee of the University of Greifswald.

2.2. Phenotypic data

Childhood trauma was assessed using the German 28-item version of the Childhood Trauma Questionnaire (CTQ) (Bernstein and Putnam, 1986; Wingenfeld et al., 2010). Participants self-rate exposure to traumatic events during childhood (defined younger than 16 years) on 28 items on a five-point Likert scale ranging from ‘never true’ = 1 to very often true’ = 5. The 28 items form 5 subscales reflect different dimensions of childhood trauma including ‘sexual abuse’, ‘physical abuse’, ‘emotional abuse’, ‘physical neglect’ as well as ‘emotional neglect’. In addition to a dimensional scoring procedure, the manual provides threshold scores to determine the severity of abuse and neglect (none = 0, mild = 1, moderate = 2, and severe-to-extreme = 3). In detail, classification of the different subscale dimensions is as follows: Emotional abuse: none = 5–8, mild = 9–12; moderate = 13–15; severe = 16 and more points, sexual abuse: none = 5; mild = 6–7; moderate = 8–12; severe = 13 and more; physical abuse: none = 5–7; mild = 8–9; moderate = 10–12; severe = 13 and more; emotional neglect: none = 5–9; mild = 10–14; moderate: 15–17; severe: 18 and more; physical neglect: none = 5–7; mild = 8–9; moderate: 10–12; severe = 13 and more. Based on the subscales, we created variables for overall abuse (range 0–3) and neglect (range 0–2) as the number of subscales with at least moderate trauma.

We measured resilience applying the German version of the resilience scale (RS-25) (Schumacher et al., 2005; Wagnild and Young, 1993). It is comprised of 25 items with 7-point Likert scale and it is used to measure scores of five components which have been conceptualized to form a so called ‘Resilience Core’ (Wagnild, 2009). The components

of the RS-25 include a 'purposeful life', 'perseverance', 'equanimity', 'self-reliance' and 'the awareness of being on your own in a lot of situations in life' (Existential aloneness). Scores range from 25 to 175 with higher scores indicating a higher degree of resilience. While the original American version was comprised of the two factors 'Acceptance of Self and Life' and 'Personal Competence', this two factor model could not be replicated in the German version (Schumacher et al., 2005). The German RS-25 showed good values for reliability and confirmed significant construct validity.

Symptoms of depression for our sensitivity analyses were measured using the validated German translation of the Beck Depression Inventory (BDI-II) (Beck et al., 1961; Kühner et al., 2007). This is a widely used 21 item self-rated instrument showing excellent psychometric properties. Participants are asked to rate symptoms of depression on a 4-point (0–3) Likert scale. Sum scores range from 0 to a maximum of 63 with higher scores reflecting a higher severity of depression.

The diagnosis of lifetime MDD according to DSM-IV criteria was determined using the standardized and computerized Munich-Composite International Diagnostic Interview (M-CIDI) (Schulz et al., 2014).

Additional adjustment for the number of traumatic events and current diagnosis of PTSD was performed using the PTSD module of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (Elhai et al., 2008). In the interview subjects were asked if they had been exposed to one of the following events which are enlisted as traumatic events in the DSM-IV: combat or war-zone experience, physical assault, rape, childhood sexual abuse, natural disaster, life-threatening illness, serious or nearly fatal accident, imprisonment and/or torture, sudden and unexpected death of a loved one, as well as witnessing or learning about traumas to others. The number of traumatic events was counted in order to estimate the severity of traumatic stress. If the participant answered with "no" to each of these questions, the module was terminated. If a participant affirmed exposure to more than one traumatic event, the person was asked to identify the most distressing experience and to relate to this event when answering the subsequent questions. The PTSD symptoms according the DSM-IV were then continuously asked in the interview. If the respondent did not pass the required diagnostic threshold (e. g. at least one re-experiencing symptom), the interview was also terminated.

2.3. Genetic data

Blood samples from the SHIP study were genotyped using the Affymetrix Human SNP Array 6.0. The overall genotyping efficiency was 98.55%. Imputation of genotypes was performed using the HRCv1.1 reference panel and the Eagle and minimac3 software implemented in the Michigan Imputation Server for pre-phasing and imputation, respectively. SNPs with a Hardy-Weinberg-Equilibrium (HWE) p-value < 0.0001, a call rate < 0.95, and a minor allele frequency (MAF) $< 1\%$ were removed before imputation. The *FKBP5* single nucleotide polymorphism (SNP) rs1360780 (C/T) had a MAF of 30%, a HWE p-value of 0.02 and an imputation quality of nearly 1.

Among the 2400 subjects who participated in the SHIP-LEGENDE study, N = 253 subjects were excluded from the analyses because of missing values in the analyzed variables.

2.4. Statistical analyses

Multiple linear regression analyses with robust standard errors were applied in order to calculate predictive effects of childhood trauma (and subscales) and *FKBP5* genotype rs1360780 on resilience. As the number of homozygote TT carriers was very small, especially in the interaction analyses, we dichotomized the SNP into non T-allele carriers (N = 1031) versus T-allele carriers (N = 1116) (T dominant genetic model) prior to analyses. The childhood trauma questionnaire was used as overall metric trauma score. Abuse and neglect as well as the subscales were treated ordinal. For overall abuse and neglect, we used the number of subscales with at least moderate trauma. The five subscales were taken as none, mild, moderate, severe (scaled 0–3) as suggested in the manual of the CTQ (Bernstein and Putnam, 1986). Subsequently, we investigated multiplicative interaction effects of trauma variables and rs1360780 on resilience. All analyses were adjusted for age and sex as baseline confounders. In sensitivity analyses we also adjusted for current depressive symptoms measured with the BDI-II or for lifetime major depressive disorder (MDD) to account for measurements of state and trait depression. As the BDI-II was by far a better predictor of resilience than MDD (explained R^2 25.54% for BDI-II versus 3.36% for MDD) we focused on the analyses adjusted for BDI-II.

The CTQ sum score and the different subscales were tested separately. To account for the effects of multiple testing we corrected for N = 6 tests for the direct associations (5 CTQ subscales and rs1360780 on resilience), and for N = 5 tests in the interaction analyses (5 CTQ subscales*SNP). The threshold for significance was set at $p < 0.0045$ (0.05/11 tests).

2.5. Sensitivity analyses

Because of the ongoing discussion on confounder–environment interaction in gene × environment interaction studies initiated by Keller (2014), we examined the influence of additional C × E (confounder–environment) and C × G (confounder–gene) interaction terms on the G × E effect (Keller, 2014). In addition, we also controlled for the influence of current PTSD diagnosis.

All analyses were performed using STATA 14.

3. Results

3.1. Descriptive statistics

Sociodemographic and health related characteristics of SHIP-LEGENDE are given in Table 1. Among the 2147 subjects 48% were males. Comparison of males and females revealed that the females in our sample were significantly younger, reported higher BDI-II scores as well as higher rates of sexual and emotional abuse and lower rates of physical abuse and neglect subscales. There were no significant differences in the overall CTQ sum score, resilience or *FKBP5* genotype.

3.2. Resilience and childhood trauma

Table 2 presents the findings of the associations between CTQ score, its subscales and *FKBP5* rs1360780 as predictors of resilience adjusted for age and sex. We also conducted sensitivity analyses adjusting for BDI-II sum score because resilience and BDI-II ($r = -0.49$) and for MDD lifetime ($r = -0.20$) were highly correlated.

Without additional adjustment for all CTQ subscales as well as the overall CTQ sum score were negatively associated with resilience. When also adjusting for BDI-II sum score only emotional neglect remained significant ($\beta = -1.91$, $p = 8.1E\text{-}5$) after correction for multiple testing. CTQ sum score was at least nominal significant ($\beta = -0.11$, $p = 0.021$) after adjusting for BDI-II. When adjusting for MDD instead of BDI-II all CTQ variables were negatively associated with resilience except of physical and sexual abuse.

3.3. Resilience and FKBP5 rs1360780

No statistical significant association between rs1360780 of *FKBP5* and resilience could be observed (see Table 2).

3.4. Interaction between FKBP5 rs1360780 and CTQ on resilience

Table 3 presents the results of the interaction between CTQ sum

Table 1
Descriptive statistic of outcome, predictor and covariables used in the statistical models for the analytic sample.

Characteristic	Males (N = 1023)	Females (N = 1124)	Comparison
Age (mean, sd)	57 (14.3)	54 (13.5)	T = 5.1 P < 0.001
RS-25 (mean, SD) Range: 25-175	145.9 (17.7)	144.9 (19.3)	T = 1.2 P = 0.24
CTQ (mean, SD) Range: 25-119	34.1 (8.4)	33.6 (10.4)	T = 1.1 P = 0.27
Abuse[a]			Chi2 = 6.4
0	947 (92.6%)	1009 (89.8%)	P = 0.096
1	59 (5.8%)	82 (7.3%)	
2	14 (1.4%)	25 (2.2%)	
3	3 (0.3%)	8 (0.7%)	
Emotional abuse			Chi2 = 13.6
None	929 (90.8%)	969 (86.2%)	P = 0.003
Mild	70 (6.8%)	103 (9.2%)	
Moderate	15 (1.5%)	26 (2.3%)	
Severe	9 (0.9%)	26 (2.3%	
Physical abuse			Chi2 = 11.1
None	913 (89.2%)	1041 (92.6%)	P = 0.011
Mild	56 (5.5%)	35 (3.1%)	
Moderate	35 (3.4%)	24 (2.1%)	
Severe	19 (1.9%)	24 (2.1%)	
Sexual abuse			Chi2 = 25.
None	981 (95.9%)	1017 (90.5%)	P < 0.001
Mild	24 (2.3%)	51 (4.5%)	
Moderate	15 (1.5%)	40 (3.6%)	
Severe	3 (0.3%)	16 (1.4%)	
Neglect[a]			Chi2 = 8.8
0	775 (75.8%)	910 (81.0%)	P = 0.012
1	174 (17.0%)	146 (13.0%)	
2	74 (7.2%)	68 (6.0%)	
Emotional neglect			Chi2 = 14.8
None	599 (58.6%)	733 (65.2%)	P = 0.002
Mild	287 (28.1%)	269 (23.9%)	
Moderate	71 (6.9%)	47 (4.2%)	
Severe	66 (6.5%)	75 (6.7%)	
Physical neglect			Chi2 = 17.3
None	588 (57.5%)	734 (65.3%)	P = 0.001
Mild	250 (24.4%)	230 (20.5%)	
Moderate	141 (13.8%)	108 (9.6%)	
Severe	44 (4.3%)	52 (4.6%)	
BDI-II (mean, SD) Range: 0-58	5.8 (6.7)	7.1 (8.0)	T = −3.8 P < 0.001
PTSD	6 (0.6%)	21 (1.9%)	Chi2 = 7.1 P = 0.008
MDD lifetime	115 (11.2%)	243 (21.6%)	Chi2 = 41.2 P < 0.001
rs1360780			Chi2 = 2.3
CC	507 (49.6%)	524 (46.6%)	P = 0.32
CT	433 (42.3%)	512 (45.6%)	
TT	83 (8.1%)	88 (7.8%)	

RS-25: Resilience Scale-25; CTQ: Childhood Trauma Questionnaire; BDI-II: Beck Depression Inventory-II.
[a] number of subscales with at least moderate trauma.

score and its subscales with rs1360780 as predictor of resilience. No CTQ variable revealed a significant interaction with rs1360780 on resilience after correction for multiple testing. CTQ sum score as well as all neglect variables were at least nominal significant in their interaction with rs1360780. However, when also adjusting for BDI-II the CTQ sum score (see Fig. 1) as well as all neglect variables revealed a significant interaction with *FKBP5* genotype. In subjects carrying at least one T-allele a higher CTQ score/more severe neglect was associated with a reduced score in resilience whereas this association was absent in non T-allele carriers. When adjusting for MDD all significant interactions did not reach corrected significance anymore.

3.5. Sensitivity analyses

Neither additional adjustment for PTSD diagnosis nor the GxE adjustment by Keller (2014) did change the significance of the findings (see Supplementary Tables S1–S4) (Keller, 2014).

3.6. Post-hoc analyses: Gender specific effects

Sex-stratified interaction analyses adjusted for age and BDI-II revealed that the observed GxE effects for CTQ and rs1360780 were only present in females (Table 4), especially for neglect and its subscales (see Fig. 2). But also for abuse and subscales the interactions showed borderline significance ($p < 0.1$). In males none of the interactions became at least nominal significant. When adjusting for MDD instead of BDI-II only the interaction between rs1360780 and physical neglect remained significant (see Supplementary Table S5).

4. Discussion

Based on findings from previous GxE studies suggesting a role of *FKBP5* in stress-related psychiatric disorders, we sought to investigate main and interaction effects of the rs1360780 polymorphism with childhood trauma on trait resilience in the adult general population. We found that all dimensions of childhood trauma were negatively associated with trait resilience. After adjusting for BDI-II scores which showed a strong correlation with RS-25 scores only childhood emotional neglect remained as a significant predictor of resilience. In contrast, rs1360780 of *FKBP5* did not show significant main effects on resilience. However, interaction analyses revealed an interaction effect of childhood trauma and rs1360780 with the T allele enhancing the negative impact of childhood trauma on resilience. This effect was carried by both subscales of childhood neglect and remained stable after adjusting for BDI-II scores, number of adult traumas and after exclusion of PTSD patients. Finally, sex-stratified analyses revealed that GxE effects were specific to female participants.

Finding significant negative associations of all facets of childhood trauma with adult resilience in a dose-response fashion is in line with previous research showing lower resilience following childhood

Table 2
Results for the primary associations between CTQ and its subscales as well as *FKBP5* rs1360780 on resilience sum score in LEGENDE (N = 2147).

Predictor	Initial analysis (adjusted for age, sex)	Sensitivity analysis (adjusted for age, sex, BDI-II)	Sensitivity analysis (adjusted for age, sex, MDD)
CTQ score	β = −0.38, p = 6.3E-14	β = −0.11, p = 0.021	β = −0.33, p = 6.4E-11
Abuse	β = −4.78, p = 3.8E-5	β = 0.18, p = 0.84	β = −3.74, p = 1.1E-3
Emotional abuse	β = −4.33, p = 3.3E-6	β = 0.14, p = 0.85	β = −3.28, p = 2.5E-4
Physical abuse	β = −1.80, p = 0.019	β = 0.89, p = 0.18	β = −1.27, p = 0.09
Sexual abuse	β = −3.21, p = 3.8E-3	β = −0.49, p = 0.54	β = −2.75, p = 0.014
Neglect	β = −4.50, p = 1.5E-9	β = −1.26, p = 0.061	β = −3.77, p = 2.6E-7
Emotional neglect	β = −4.06, p = 6.0E-14	β = −1.91, p = 8.1E-5	β = −3.55, p = 3.1E-11
Physical neglect	β = −2.33, p = 1.7E-6	β = −0.21, p = 0.62	β = −1.93, p = 6.0E-5
rs1360780	β = 0.15, p = 0.85	β = −0.20, p = 0.78	β = 0.47, p = 0.55

CTQ: Childhood Trauma Questionnaire, Abuse (range 0–3), Neglect (range 0–2), CTQ subscales (range 0–3); BDI-II: Beck Depression Inventory-II; MDD: major depressive disorder; significant results are highlighted in bold.

Table 3
Results for the interaction analyses between CTQ and subscales with rs1360780 on resilience sum score in LEGENDE (N = 2147).

Predictor	Initial analysis (adjusted for age, sex)	Sensitivity analysis (adjusted for age, sex, BDI-II)	Sensitivity analysis (adjusted for age, sex, MDD)
CTQ score*rs1360780	β = −0.27, p = 5.4E-3	β = −0.27, p = 9.5E-4	β = −0.25, p = 0.009
Abuse*rs1360780	β = −3.11, p = 0.17	β = −2.94, p = 0.093	β = −3.15, p = 0.16
Emotional abuse*rs1360780	β = −2.67, p = 0.15	β = −2.43, p = 0.091	β = −2.51, p = 0.16
Physical abuse*rs1360780	β = −1.50, p = 0.32	β = −1.60, p = 0.22	β = −1.17, p = 0.44
Sexual abuse*rs1360780	β = −0.97, p = 0.66	β = −1.33, p = 0.40	β = −1.84, p = 0.41
Neglect*rs1360780	β = −3.54, p = 0.015	β = −3.69, p = 4.5E-3	β = −3.03, p = 0.034
Emotional neglect*rs1360780	β = −2.50, p = 0.018	β = −2.63, p = 4.3E-3	β = −2.37, p = 0.023
Physical neglect*rs1360780	β = −2.58, p = 5.8E-3	β = −2.93, p = 4.2E-4	β = −2.22, p = 0.016

CTQ: Childhood Trauma Questionnaire, Abuse (range 0–3), Neglect (range 0–2), CTQ subscales (range 0–3); BDI-II: Beck Depression Inventory-II; MDD: major depressive disorder; significant results are highlighted in bold.

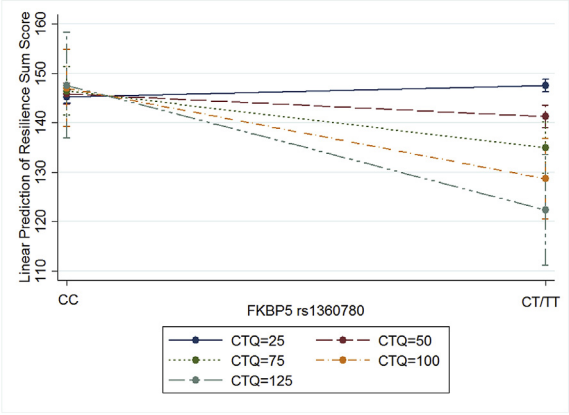

Fig. 1. Interaction between CTQ and rs1360780 on RS-25 sum score.

Table 4
Results for the sex separated interaction analyses between CTQ and subscales with rs1360780 on resilience sum score in LEGENDE.

Predictor	Males (N = 1023)	Females (N = 1124)
CTQ score*rs1360780	β = −0.08, p = 0.47	β = −0.39, p = 4.0E-4
Abuse*rs1360780	β = −0.99, p = 0.68	β = −4.09, p = 0.081
Emotional abuse*rs1360780	β = −0.31, p = 0.87	β = −3.57, p = 0.059
Physical abuse*rs1360780	β = 0.34, p = 0.82	β = −3.72, p = 0.068
Sexual abuse*rs1360780	β = −1.03, p = 0.74	β = −1.30, p = 0.48
Neglect*rs1360780	β = −0.90, p = 0.59	β = −6.75, p = 8.7E-4
Emotional neglect*rs1360780	β = −1.35, p = 0.24	β = −3.92, p = 5.4E-3
Physical neglect*rs1360780	β = −0.60, p = 0.60	β = −5.25, p = 2.2E-5

CTQ: Childhood Trauma Questionnaire, Abuse (range 0–3), Neglect (range 0–2), CTQ subscales (range 0–3); BDI-II: Beck Depression Inventory-II; significant results are highlighted in bold. Analyses adjusted for age and BDI-II sum score.

maltreatment (Campbell-Sills et al., 2009; Collishaw et al., 2007). The results of our sensitivity analyses revealed that the effects were carried by the emotional neglect dimension, while the other CTQ subscales lost significance after adjusting for BDI-II scores. This finding is particularly interesting in the context of a general paucity of studies on the specific effects of childhood neglect on resilience (Ben-David and Jonson-Reid, 2017). Interestingly, results by Campbell-Sills et al. (2006) showed that resilience moderated the effects of childhood emotional neglect but not of other forms of childhood trauma on psychiatric symptoms (Campbell-Sills et al., 2006).

While the mechanism for the relation of childhood trauma and low resilience is not fully understood, it may be partly explained by the correlation of childhood maltreatment with various psychosocial predictors of low resilience including poor social support (Bonanno et al., 2007), insecure attachment, family dysfunction (Riggs and Riggs, 2011) and low socioeconomic status in childhood (Sameroff and Rosenblum, 2006). Moreover, resilience has been reported to be negatively associated with specific coping skills and personality factors like neuroticism (Campbell-Sills et al., 2006) alexithymia (Armstrong et al., 2011) and poor optimism (Tusaie et al., 2007), which are linked to history of childhood trauma (Terock et al., 2018). However, as the results of our study were driven by the emotional neglect component, mechanisms over and above psychosocial correlates like impaired emotion regulation strategies may possibly contribute to the relation of childhood trauma and resilience (Min et al., 2013). Given that emotional neglect is the most prevalent form of childhood trauma in the United States (Taillieu et al., 2016) and considering the growing body of research highlighting the role of emotional neglect as a specific predictor for psychopathologies like depression (Infurna et al., 2016) and dissociation (Terock et al., 2016), our findings underscore the relevance of more emotional and omitting aspects of childhood trauma for resilience function and may contribute to understand the differential impact of trauma types on the development of psychiatric disorders.

Consistent with previous research (Rana et al., 2014), the rs1360780 polymorphism did not emerge as an independent predictor of trait resilience in our sample. However, we identified an interaction of rs1360780 with childhood trauma such that the T-allele as compared to the CC-genotype enhanced the negative effects of childhood trauma on RS-25 scores. Sensitivity analyses showed that this effect was carried by both dimensions of childhood neglect, while the abuse subscales did not significantly interact with rs1360780. All significant interaction effects showed robust effect sizes and remained stable after adjusting for BDI-II scores.

In accordance with prior studies on the relation of rs1360780 and risk for psychiatric disorders (Appel et al., 2011; Matosin et al., 2018; Wang et al., 2018), the status of being a T allele carrier was found to enhance the detrimental effects of childhood trauma on adult resilience. The high-induction T allele was previously found to be associated with increased expression of *FKBP5* in response to elevated cortisol levels (Ising et al., 2008). In turn, enhanced FKBP5 binding to brain glucocorticoid receptors results in reduced cortisol sensitivity in the negative feedback loop and thereby leads to impaired recovery from psychosocial stress-induced cortisol release (Binder et al., 2008; Ising et al., 2008). Considering results on altered endocrine activity in response to childhood trauma (Heim et al., 2008; Terock et al., 2019) and particularly on the crucial role of the HPA-axis in the pathophysiology of stress-related psychiatric diseases, reduced GR sensitivity to cortisol and thus diminished functioning of the negative cortisol feedback loop in the brain may well represent a neurobiological mechanism underlying the interaction of childhood trauma with rs1360780 on resilience.

Findings from neuroimaging studies could provide insight into the neural basis of the interactional effects found in our study: For example, Grabe et al. (2016) reported about an interaction of childhood abuse with rs1360780 resulting in reduced gray matter volumes in three clusters relevant to emotion processing including the insula, bilateral hippocampus and right amygdala as well as the anterior cingulate cortex in homozygote carriers of the T-allele (Grabe et al., 2016). However, our results suggested that rs1360780 moderated the effects of

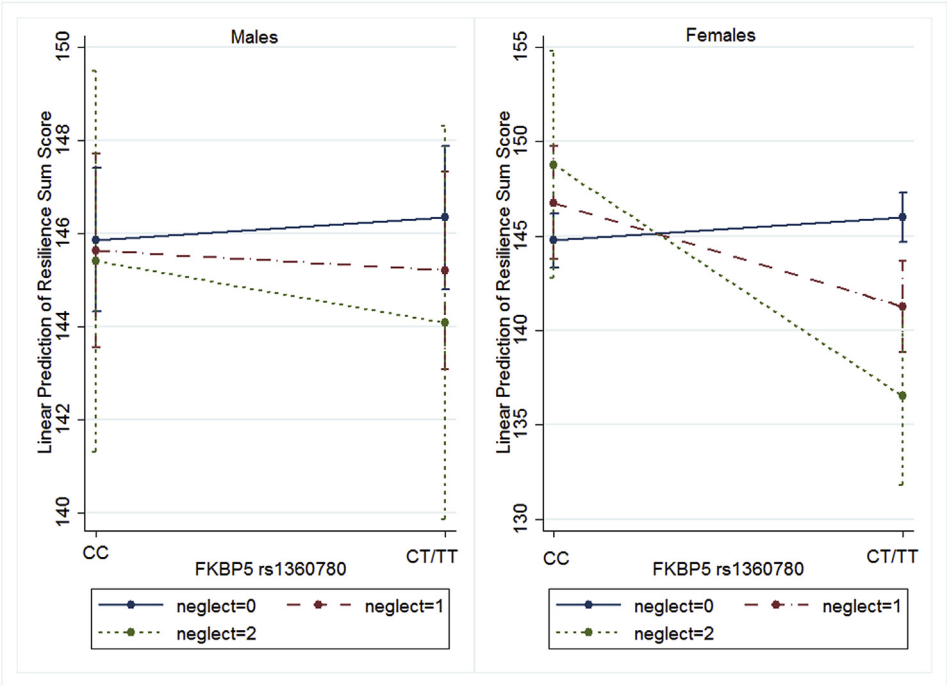

Fig. 2. Sex separated interaction between neglect and rs1360780 on RS-25 sum score.

childhood neglect, but not of abuse on resilience. Converging evidence from functional and structural brain studies suggesting a specific impact of neglect on the amygdala could help to integrate these findings: For example, White et al. (2012) found that risk alleles of different *FKBP5* SNPs including the T allele of rs1360780 showed interactional effects with childhood emotional neglect on acute stress-induced amygdala reactivity (White et al., 2012). Specifically, T allele carriers showed increased dorsal amygdala reactivity in response to threat-related stimuli. The amygdala is considered a key region for emotion processing and altered amygdala activity is associated with stress related psychiatric disorders (Beesdo et al., 2009). Moreover, different studies found an involvement of the amygdala in the use of emotion regulation strategies which promote resilience (Feder et al., 2009). The amygdala closely interacts with the HPA-axis in stress response and Gillespie et al. (2009) pointed out that these interactions are particularly sensitive to factors like developmental support and maternal care during critical periods for emotional learning (Gillespie et al., 2009). In the context of our findings, it could be speculated that experiences of childhood neglect like a lack of emotional support and maternal care during periods of emotional learning interact with risk genes like *FKBP5* in their effects on the amygdala-HPA-axis and thereby diminish psychological resilience. In a second step reduced resilience may increase the risk for psychiatric disorders in the aftermath of childhood abuse. However, trait resilience is likely to be based on complex neurobiological mechanisms which are currently only insufficiently understood, which is why the interplay between FKBP5, the HPA-axis and different brain regions including the amygdala needs to be addressed in future studies. Finding sex-specific effects in the interaction of childhood trauma and rs1360780 such that lower resilience was only observed in female participants adds to previous findings on sex-related differences in FKBP5-mediated regulation of the HPA-axis (Mahon et al., 2013). Moreover, many studies investigating the association of *FKBP5* polymorphisms with clinical outcomes failed to report sex-stratified results (Appel et al., 2011; Binder et al., 2008; Zimmermann et al., 2011). Therefore, our result of a female-specific GxE effect may contribute to explain the consistently reported differences in prevalence rates of depression (Chapman et al., 2004; Weissman et al., 1996) and PTSD (Walker et al., 2004), particularly in relation to childhood trauma. Our findings are also consistent with results from previous studies which showed sex-specific effects in their interaction analyses. For example, VanZomeren-Dohm et al. (2015) investigated the interaction of peer victimization and rs1360780 in post-institutionalized youths and found differential effects such that girls but not boys with the T-allele and higher levels of victimization showed more severe symptoms of depression (VanZomeren-Dohm et al., 2015). Likewise, Isaksson et al. (2016) reported that the minor alleles of different polymorphisms of the *FKBP5* gene including rs1360780 were associated with higher ratings of anxiety and depression in the presence of violence in females, but not males (Isaksson et al., 2016), indicating that *FKBP5* may moderate sex-specific differences in the HPA-axis regulation. The results of Isaksson et al. also revealed that age influenced the sex-specific effects. Findings from Matosin et al. may speculatively provide a working mechanism on a molecular level for these findings: the authors found a developmental pattern of *FKBP5* mRNA expression which may be related to reduced *FKBP5* methylation with age (Matosin et al., 2018). Similar methylation processes could conceivably be involved in sex-specific regulation of *FKBP5* gene expression. This female-specific interaction may also be partly explained by results from Hertel et al. (2017) showing stress-like activation of the HPA-axis in women taking oral contraceptives (Hertel et al., 2017). Interestingly, the authors also found increased whole-blood *FKBP5* mRNA levels of in women taking oral contraceptives and that the association of oral contraceptives and increased *FKBP5* mRNA was modified by rs1360780.

Some limitations of our study need to be acknowledged: First, resilience was only measured in a subset (SHIP-LEGENDE) of the SHIP study with only 55.7% participation rate compared to the baseline sample. Therefore, selection processes due to clinical or psychosocial correlates cannot be ruled out. Second, only cross-sectional data were available and an independent sample for replication was missing. As childhood trauma is associated with increased burden of life stressors and psychological distress in later life which may additionally compromise resilience, longitudinal studies accounting for these factors and replication in independent samples are warranted. Third, childhood trauma was measured based on retrospective self-reporting only. Participants may have limited access to memories from early traumatic experiences or may choose not to disclose information on traumatic

events, for example in an attempt to avoid painful remembering. Therefore, the number of childhood traumatic events may even be higher than reported, which could lead to an overestimation of the found effects. Finally, previous studies included diverse other functional *FKBP5* polymorphisms in their analyses. For example, in a recent study from our working group, Klinger-Koenig et al. investigated 22 other SNPs of *FKBP5* in addition to rs1360780 (Klinger-König et al., 2019). However, in order to keep the number of our analyses small, we decided to concentrate on the most frequently studied polymorphism of *FKPB5* in psychiatric diseases.

In conclusion, as resilience is considered to reflect generally diminished vulnerability to life stressors, our finding supports the concept of the T allele of rs1360780 as a broad risk factor to different stress-related psychiatric conditions like depression and PTSD in traumatized individuals. Childhood neglect emerged has the most prominent predictor in main and interaction analyses underscoring the relevance of this trauma dimensions in the etiology of psychiatric disease. Finding sex-specific effects in *FKBP5* x trauma analyses may contribute to explain different prevalence rates in stress-related psychiatric disorders. Considering the physiological function of FKBP5, our findings further support the role of altered cortisol sensitivity as a risk factor for stress-related psychopathologies.

Contributions

J. T. and H. J. G. conceived of the presented idea, S. V. developed the statistical approach and performed the computations, J. T. and S. V. wrote the manuscript with support from A. H. and D. J., H. J. G. encouraged J. T. and S. V. to perform additional sex-stratified analyses, G. H. and A. T. verified the conceptual and statistical approach.

Conflicts of interest

DJ received travel grants and speakers honoraria from Janssen CILAG.

HJG has received travel grants and speakers honoraria from Fresenius Medical Care and Janssen Cilag.

All other authors declare no conflicting interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.06.008.

References

Appel, K., Schwahn, C., Mahler, J., Schulz, A., Spitzer, C., Fenske, K., Stender, J., Barnow, S., John, U., Teumer, A., Biffar, R., Nauck, M., Völzke, H., Freyberger, H.J., Grabe, H.J., 2011. Moderation of adult depression by a polymorphism in the *FKBP5* gene and childhood physical abuse in the general population. Neuropsychopharmacology 36, 1982–1991. https://doi.org/10.1038/npp.2011.81.

Armstrong, A.R., Galligan, R.F., Critchley, C.R., 2011. Emotional intelligence and psychological resilience to negative life events. Pers. Indiv. Differ. 51, 331–336.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatr. 4, 561–571.

Beesdo, K., Lau, J.Y., Guyer, A.E., McClure-Tone, E.B., Monk, C.S., Nelson, E.E., Fromm, S.J., Goldwin, M.A., Wittchen, H.-U., Leibenluft, E., 2009. Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. Arch. Gen. Psychiatr. 66, 275–285.

Ben-David, V., Jonson-Reid, M., 2017. Resilience among adult survivors of childhood neglect: a missing piece in the resilience literature. Child. Youth Serv. Rev. 78, 93–103. https://doi.org/10.1016/j.childyouth.2017.05.014.

Bensimon, M., 2012. Elaboration on the association between trauma, PTSD and posttraumatic growth: the role of trait resilience. Pers. Indiv. Differ. 52, 782–787. https://doi.org/10.1016/j.paid.2012.01.011.

Bernstein, E.M., Putnam, F.W., 1986. Development, reliability, and validity of a dissociation scale. J. Nerv. Ment. Dis. 174, 727–735.

Binder, E.B., Bradley, R.G., Liu, W., Epstein, M.P., Deveau, T.C., Mercer, K.B., Tang, Y., Gillespie, C.F., Heim, C.M., Nemeroff, C.B., Schwartz, A.C., Cubells, J.F., Ressler, K.J., 2008. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. J. Am. Med. Assoc. 299, 1291–1305. https://doi.org/10.1001/jama.299.11.1291.

Bonanno, G.A., 2004. Loss, trauma, and human resilience: have we underestimated the human capacity to thrive after extremely aversive events? Am. Psychol. 59, 20.

Bonanno, G.A., Galea, S., Bucciarelli, A., Vlahov, D., 2007. What predicts psychological resilience after disaster? The role of demographics, resources, and life stress. J. Consult. Clin. Psychol. 75, 671.

Bradley, B., Davis, T.A., Wingo, A.P., Mercer, K.B., Ressler, K.J., 2013. Family environment and adult resilience: contributions of positive parenting and the oxytocin receptor gene. Eur. J. Psychotraumatol. 4, 21659. https://doi.org/10.3402/ejpt.v4i0.21659.

Campbell-Sills, L., Cohan, S.L., Stein, M.B., 2006. Relationship of resilience to personality, coping, and psychiatric symptoms in young adults. Behav. Res. Ther. 44, 585–599. https://doi.org/10.1016/j.brat.2005.05.001.

Campbell-Sills, L., Forde, D.R., Stein, M.B., 2009. Demographic and childhood environmental predictors of resilience in a community sample. J. Psychiatr. Res. 43, 1007–1012. https://doi.org/10.1016/j.jpsychires.2009.01.013.

Chapman, D.P., Whitfield, C.L., Felitti, V.J., Dube, S.R., Edwards, V.J., Anda, R.F., 2004. Adverse childhood experiences and the risk of depressive disorders in adulthood. J. Affect. Disord. 82, 217–225.

Cicchetti, D., Rogosch, F.A., 2012. Gene$\ imes$ Environment interaction and resilience: effects of child maltreatment and serotonin, corticotropin releasing hormone, dopamine, and oxytocin genes. Dev. Psychopathol. 24, 411–427.

Collishaw, S., Pickles, A., Messer, J., Rutter, M., Shearer, C., Maughan, B., 2007. Resilience to adult psychopathology following childhood maltreatment: evidence from a community sample. Child Abuse Negl. 31, 211–229. https://doi.org/10.1016/j.chiabu.2007.02.004.

Elhai, J.D., Franklin, C.L., Gray, M.J., 2008. The SCID PTSD module's trauma screen: validity with two samples in detecting trauma history. Depress. Anxiety 25, 737–741. https://doi.org/10.1002/da.20318.

Feder, A., Nestler, E.J., Charney, D.S., 2009. Psychobiology and molecular genetics of resilience. Nat. Rev. Neurosci. 10, 446–457. https://doi.org/10.1038/nrn2649.

Ferrer, A., Costas, J., Labad, J., Salvat-Pujol, N., Segalàs, C., Urretavizcaya, M., Real, E., de Arriba-Arnau, A., Alonso, P., Crespo, J.M., Barrachina, M., Soriano-Mas, C., Carracedo, Á., Menchón, J.M., Soria, V., 2018. FKBP5 polymorphisms and hypothalamic-pituitary-adrenal axis negative feedback in major depression and obsessive-compulsive disorder. J. Psychiatr. Res. 104, 227–234. https://doi.org/10.1016/j.jpsychires.2018.08.003.

Gillespie, C.F., Phifer, J., Bradley, B., Ressler, K.J., 2009. Risk and resilience: genetic and environmental influences on development of the stress response. Depress. Anxiety 26, 984–992. https://doi.org/10.1002/da.20605.

Grabe, H.J., Wittfeld, K., Auwera, S.V. der, Janowitz, D., Hegenscheid, K., Habes, M., Homuth, G., Barnow, S., John, U., Nauck, M., Völzke, H., Schwabedissen, H.M.zud., Freyberger, H.J., Hosten, N., 2016. Effect of the interaction between childhood abuse and rs1360780 of the FKBP5 gene on gray matter volume in a general population sample. Hum. Brain Mapp. 37, 1602–1613. https://doi.org/10.1002/hbm.23123.

Heim, C., Nemeroff, C.B., 2001. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol. Psychiatry 49, 1023–1039.

Heim, C., Newport, D.J., Mletzko, T., Miller, A.H., Nemeroff, C.B., 2008. The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology 33, 693–710. https://doi.org/10.1016/j.psyneuen.2008.03.008.

Hertel, J., König, J., Homuth, G., Van der Auwera, S., Wittfeld, K., Pietzner, M., Kacprowski, T., Pfeiffer, L., Kretschmer, A., Waldenberger, M., Kastenmüller, G., Artati, A., Suhre, K., Adamski, J., Langner, S., Völker, U., Völzke, H., Nauck, M., Friedrich, N., Grabe, H.J., 2017. Evidence for stress-like alterations in the HPA-Axis in women taking oral contraceptives. Sci. Rep. 7, 14111. https://doi.org/10.1038/s41598-017-13927-7.

Hovens, J.G., Giltay, E.J., Spinhoven, P., van Hemert, A.M., Penninx, B.W., 2015. Impact of childhood life events and childhood trauma on the onset and recurrence of depressive and anxiety disorders. J. Clin. Psychiatry 76, 931–938.

Infurna, M.R., Reichl, C., Parzer, P., Schimmenti, A., Bifulco, A., Kaess, M., 2016. Associations between depression and specific childhood experiences of abuse and neglect: a meta-analysis. J. Affect. Disord. 190, 47–55. https://doi.org/10.1016/j.jad.2015.09.006.

Isaksson, Johan, et al., 2016. Associations between the FKBP5 haplotype, exposure to violence and anxiety in females. Psychoneuroendocrinology 72, 196–204.

Ising, M., Depping, A.-M., Siebertz, A., Lucae, S., Unschuld, P.G., Kloiber, S., Horstmann, S., Uhr, M., Müller-Myhsok, B., Holsboer, F., 2008. Polymorphisms in the FKBP5 gene region modulate recovery from psychosocial stress in healthy controls. Eur. J. Neurosci. 28, 389–398.

Keller, M.C., 2014. Gene × environment interaction studies have not properly controlled for potential confounders: the problem and the (simple) solution. Biol. Psychiatry 75, 18–24. https://doi.org/10.1016/j.biopsych.2013.09.006.

Klinger-König, J., Hertel, J., Auwera, S.V.der, Frenzel, S., Pfeiffer, L., Waldenberger, M., Golchert, J., Teumer, A., Nauck, M., Homuth, G., Völzke, H., Grabe, H.J., 2019. Methylation of the FKBP5 gene in association with FKBP5 genotypes, childhood maltreatment and depression. Neuropsychopharmacology 1. https://doi.org/10.1038/s41386-019-0319-6.

Kühner, C., Bürger, C., Keller, F., Hautzinger, M., 2007. Reliabilität und validität des revidierten beck-depressionsinventars (BDI-II). Nervenarzt 78, 651–656.

Mahon, P.B., Zandi, P.P., Potash, J.B., Nestadt, G., Wand, G.S., 2013. Genetic association of FKBP5 and CRHR1 with cortisol response to acute psychosocial stress in healthy adults. Psychopharmacology 227, 231–241. https://doi.org/10.1007/s00213-012-2956-x.

Mandelli, L., Petrelli, C., Serretti, A., 2015. The role of specific early trauma in adult depression: a meta-analysis of published literature. Childhood trauma and adult depression. Eur. Psychiatry 30, 665–680.

Matosin, N., Halldorsdottir, T., Binder, E.B., 2018. Understanding the molecular mechanisms underpinning gene by environment interactions in psychiatric disorders: the FKBP5 model. Biol. Psychiatry, Molecular Signatures of Stress and Posttraumatic Stress Disorder 83, 821–830. https://doi.org/10.1016/j.biopsych.2018.01.021.

Min, J.-A., Yu, J.J., Lee, C.-U., Chae, J.-H., 2013. Cognitive emotion regulation strategies contributing to resilience in patients with depression and/or anxiety disorders. Compr. Psychiatr. 54, 1190–1197. https://doi.org/10.1016/j.comppsych.2013.05.008.

Poole, J.C., Dobson, K.S., Pusch, D., 2017. Childhood adversity and adult depression: the protective role of psychological resilience. Child Abuse Negl. 64, 89–100. https://doi.org/10.1016/j.chiabu.2016.12.012.

Roy, Alec, et al., 2010. Interaction of FKBP5, a stress-related gene, with childhood trauma increases the risk for attempting suicide. Neuropsychopharmacology 35.8, 1674.

Rana, B.K., Darst, B.F., Bloss, C., Shih, P.B., Depp, C., Nievergelt, C.M., Allison, M., Parsons, J.K., Schork, N., Jeste, D.V., 2014. Candidate SNP associations of optimism and resilience in older adults: exploratory study of 935 community-dwelling adults. Am. J. Geriatr. Psychiatry, Genotyping 22, 997–1006. e5. https://doi.org/10.1016/j.jagp.2014.03.009.

Reinelt, E., Barnow, S., Stopsack, M., Aldinger, M., Schmidt, C.O., John, U., Grabe, H.J., 2015. Social support and the serotonin transporter genotype (5-HTTLPR) moderate levels of resilience, sense of coherence, and depression. Am. J. Med. Genet. B Neuropsychiatr. Genet. 168, 383–391.

Riggs, S.A., Riggs, D.S., 2011. Risk and resilience in military families experiencing deployment: the role of the family attachment network. J. Fam. Psychol. 25, 675.

Roy, A., Hu, X.-Z., Janal, M.N., Goldman, D., 2007. Interaction between childhood trauma and serotonin transporter gene variation in suicide. Neuropsychopharmacology 32, 2046–2052. https://doi.org/10.1038/sj.npp.1301331.

Rutter, M., 1987. Psychosocial resilience and protective mechanisms. Am. J. Orthopsychiatry 57, 316–331. https://doi.org/10.1111/j.1939-0025.1987.tb03541.x.

Sameroff, A.J., Rosenblum, K.L., 2006. Psychosocial constraints on the development of resilience. Ann. N. Y. Acad. Sci. 1094, 116–124. https://doi.org/10.1196/annals.1376.010.

Schulz, A., Becker, M., Van der Auwera, S., Barnow, S., Appel, K., Mahler, J., Schmidt, C.O., John, U., Freyberger, H.J., Grabe, H.J., 2014. The impact of childhood trauma on depression: does resilience matter? Population-based results from the Study of Health in Pomerania. J. Psychosom. Res. 77, 97–103.

Schumacher, J., Leppert, K., Gunzelmann, T., Strau\s s, B., Brähler, E., 2005. Die Resilienzskala–Ein Fragebogen zur Erfassung der psychischen Widerstandsfähigkeit als Personmerkmal. Z. Klin. Psychol. Psychiatr. Psychother. 53, 16–39.

Stein, M.B., Campbell-Sills, L., Gelernter, J., 2009. Genetic variation in 5HTTLPR is associated with emotional resilience. Am. J. Med. Genet. B Neuropsychiatr. Genet. 150B, 900–906. https://doi.org/10.1002/ajmg.b.30916.

Strohmaier, J., Amelang, M., Hothorn, L.A., Witt, S.H., Nieratschker, V., Gerhard, D., Meier, S., Wüst, S., Frank, J., Loerbroks, A., Rietschel, M., Stürmer, T., Schulze, T.G., 2013. The psychiatric vulnerability gene *CACNA1C* and its sex-specific relationship with personality traits, resilience factors and depressive symptoms in the general population. Mol. Psychiatry 18, 607–613. https://doi.org/10.1038/mp.2012.53.

Taillieu, T.L., Brownridge, D.A., Sareen, J., Afifi, T.O., 2016. Childhood emotional maltreatment and mental disorders: results from a nationally representative adult sample from the United States. Child Abuse Negl. 59, 1–12. https://doi.org/10.1016/j.chiabu.2016.07.005.

Terock, J., Van der Auwera, S., Janowitz, D., Spitzer, C., Barnow, S., Miertsch, M., Freyberger, H.J., Grabe, H.-J., 2016. From childhood trauma to adult dissociation: the role of PTSD and alexithymia. Psychopathology 49, 374–382. https://doi.org/10.1159/000449004.

Terock, J., Van der Auwera, S., Janowitz, D., Homuth, G., Hannemann, A., Schmidt, C.O., Meyer Zu Schwabedissen, H., Freyberger, H.J., Grabe, H.J., 2018. Childhood trauma and functional variants of 5-HTTLPR are independently associated with alexithymia in 5,283 subjects from the general population. Psychother. Psychosom. 87, 58–61. https://doi.org/10.1159/000484143.

Terock, J., Hannemann, A., Janowitz, D., Van der Auwera, S., Bahls, M., Völzke, H., Grabe, H.J., 2019. Differential activation of the renin-angiotensin-aldosterone-system in response to childhood and adulthood trauma. Psychoneuroendocrinology 107, 232–240. https://doi.org/10.1016/j.psyneuen.2019.05.026.

Tusaie, K., Puskar, K., Sereika, S.M., 2007. A predictive and moderating model of psychosocial resilience in adolescents. J. Nurs. Scholarsh. 39, 54–60. https://doi.org/10.1111/j.1547-5069.2007.00143.x.

VanZomeren-Dohm, A.A., Pitula, C.E., Koss, K.J., Thomas, K., Gunnar, M.R., 2015. FKBP5 moderation of depressive symptoms in peer victimized, post-institutionalized children. Psychoneuroendocrinology 0, 426–430. https://doi.org/10.1016/j.psyneuen.2014.10.003.

Vermeer, H., Hendriks-Stegeman, B.I., van der Burg, B., van Buul-Offers, S.C., Jansen, M., 2003. Glucocorticoid-induced increase in lymphocytic FKBP51 messenger ribonucleic acid expression: a potential marker for glucocorticoid sensitivity, potency, and bioavailability. J. Clin. Endocrinol. Metab. 88, 277–284.

Völzke, H., Alte, D., Schmidt, C.O., Radke, D., Lorbeer, R., Friedrich, N., Aumann, N., Lau, K., Piontek, M., Born, G., Havemann, C., Ittermann, T., Schipf, S., Haring, R., Baumeister, S.E., Wallaschofski, H., Nauck, M., Frick, S., Arnold, A., Jünger, M., Mayerle, J., Kraft, M., Lerch, M.M., Dörr, M., Reffelmann, T., Empen, K., Felix, S.B., Obst, A., Koch, B., Gläser, S., Ewert, R., Fietze, I., Penzel, T., Dören, M., Rathmann, W., Haerting, J., Hannemann, M., Röpcke, J., Schminke, U., Jürgens, C., Tost, F., Rettig, R., Kors, J.A., Ungerer, S., Hegenscheid, K., Kühn, J.-P., Kühn, J., Hosten, N., Puls, R., Henke, J., Gloger, O., Teumer, A., Homuth, G., Völker, U., Schwahn, C., Holtfreter, B., Polzer, I., Kohlmann, T., Grabe, H.J., Rosskopf, D., Kroemer, H.K., Kocher, T., Biffar, R., John, U., Hoffmann, W., 2011. Cohort profile: the study of health in Pomerania. Int. J. Epidemiol. 40, 294–307. https://doi.org/10.1093/ije/dyp394.

Wagnild, G., 2009. A review of the resilience scale. J. Nurs. Meas. 17, 105–113.

Wagnild, G., Young, H., 1993. Development and psychometric. J. Nurs. Meas. 1, 165–178.

Walker, J.L., Carey, P.D., Mohr, N., Stein, D.J., Seedat, S., 2004. Gender differences in the prevalence of childhood sexual abuse and in the development of pediatric PTSD. Arch. Wom. Ment. Health 7, 111–121. https://doi.org/10.1007/s00737-003-0039-z.

Wang, Q., Shelton, R.C., Dwivedi, Y., 2018. Interaction between early-life stress and FKBP5 gene variants in major depressive disorder and post-traumatic stress disorder: a systematic review and meta-analysis. J. Affect. Disord. 225, 422–428.

Weissman, M.M., Bland, R.C., Canino, G.J., Faravelli, C., Greenwald, S., Hwu, H.-G., Joyce, P.R., Karam, E.G., Lee, C.-K., Lellouch, J., Lépine, J.-P., Newman, S.C., Rubio-Stipec, M., Wells, J.E., Wickramaratne, P.J., Wittchen, H.-U., Yeh, E.-K., 1996. Cross-national epidemiology of major depression and bipolar disorder. J. Am. Med. Assoc. 276, 293–299. https://doi.org/10.1001/jama.1996.03540040037030.

White, M.G., Bogdan, R., Fisher, P.M., Muñoz, K.E., Williamson, D.E., Hariri, A.R., 2012. FKBP5 and emotional neglect interact to predict individual differences in amygdala reactivity. Genes Brain Behav. 11, 869–878. https://doi.org/10.1111/j.1601-183X.2012.00837.x.

Wingenfeld, K., Spitzer, C., Mensebach, C., Grabe, H.J., Hill, A., Gast, U., Schlosser, N., Höpp, H., Beblo, T., Driessen, M., 2010. [The German version of the childhood trauma questionnaire (CTQ):Preliminary psychometric properties.]. Psychother. Psychosom. Med. Psychol. 60, e13. https://doi.org/10.1055/s-0030-1253494.

Wingo, A.P., Wrenn, G., Pelletier, T., Gutman, A.R., Bradley, B., Ressler, K.J., 2010. Moderating effects of resilience on depression in individuals with a history of childhood abuse or trauma exposure. J. Affect. Disord. 126, 411–414. https://doi.org/10.1016/j.jad.2010.04.009.

Wochnik, G.M., Rüegg, J., Abel, G.A., Schmidt, U., Holsboer, F., Rein, T., 2005. FK506-binding proteins 51 and 52 differentially regulate dynein interaction and nuclear translocation of the glucocorticoid receptor in mammalian cells. J. Biol. Chem. 280, 4609–4616. https://doi.org/10.1074/jbc.M407498200.

Zimmermann, P., Brückl, T., Nocon, A., Pfister, H., Binder, E.B., Uhr, M., Lieb, R., Moffitt, T.E., Caspi, A., Holsboer, F., Ising, M., 2011. Interaction of FKBP5 gene variants and adverse life events in predicting depression onset: results from a 10-year prospective community study. Am. J. Psychiatry 168, 1107–1116. https://doi.org/10.1176/appi.ajp.2011.10111577.