FKBP5 moderation of the relationship between childhood trauma and maladaptive emotion regulation strategies in adolescents

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ABSTRACT

Maladaptive emotion regulation strategies, such as rumination and catastrophizing, are transdiagnostic risk factors for psychopathology. FK506-binding protein 51 (*FKBP5*) has been found to moderate the relationship between stressful life events and various psychiatric disorders. Given the cross-disorder moderation effect of *FKBP5* at the diagnostic level, the aim of the current study was to examine whether the relationship between exposure to childhood trauma and transdiagnostic maladaptive emotion regulation processes would also be moderated by genetic *FKBP5* variation in a community sample of adolescents. We hypothesized that adolescent carriers of the *FKBP5* CATT haplotype composed of rs9296158, rs3800373, rs1360780, and rs9470080, that has been associated with increased risk for psychiatric disorders in adulthood, would also show higher levels of rumination and catastrophizing. Participants included 1345 genotyped adolescents (M_{age} = 13.95, 64.2% female; 100% European Caucasians of Portuguese descent) who completed self-report measures on exposure to childhood trauma and emotion regulation strategies. Genotypes of rs9296158, rs3800373, rs1360780, and rs9470080 were used to estimate the CATT haplotype (carriers versus non-carriers). Consistent with our hypotheses and previous findings, adolescent CATT haplotype carriers with higher levels of childhood trauma endorsed higher levels of both rumination and catastrophizing compared to non-carriers. Given the association of these maladaptive emotion regulation processes and psychiatric disorders, the findings suggest possible psychological mechanisms why *FKBP5* haplotype carriers exposed to childhood trauma are more vulnerable to developing a psychiatric disorder later in life.

1. Introduction

Due to the rising prevalence of depression and anxiety (Mathers and Loncar, 2006), investigating factors associated with increased risk of these disorders in premorbid adolescent populations is important. Adolescence is a high-risk period for the onset of psychiatric disorders due to the accelerated psychological, biological and endocrine development occuring during this time in the lifespan, which interacts with the intensified stress and emotional responsiveness to the social environment (Paus et al., 2008). Accordingly, an increased understanding of risk and resilience factors during this sensitive developmental stage may be crucial in developing effective preventative interventions.

Maladaptive emotion regulation strategies, such as rumination and catastrophizing, have been identified as transdiagnostic risk factors for psychopathology (Gellatly and Beck, 2016; Ottaviani et al., 2016). Rumination refers to the tendency to perseverate on negative cognitions and the potential causes and consequences of distress (Nolen-Hoeksema, 2000; Ottaviani et al., 2016). Catastrophizing, on the other hand, is the tendency to overestimate negative consequences associated with an event (Gellatly and Beck, 2016). Both rumination and catastrophizing have been associated with the onset, maintenance, and recurrence of mood and anxiety disorders (Gellatly and Beck, 2016; Ottaviani et al., 2016).

Overall, risk for psychiatric disorders is associated with

Table 1
Sample demographics.

Characteristic	Homozygous CATT carrier N = 114	Heterozygous CATT carrier N = 530	Homozygous non-carrier N = 701	Total N = 1345
Age M(SD)	13.94(.95)	13.91(.88)	13.97(.91)	13.95(.90)
Sex N(%)				
Females	76(66.7)	341(64.3)	447(63.8)	864(64.2)
Males	38(33.3)	189(35.7)	254(36.2)	481(35.7)
SES N(%)[a]				
Low	66(57.9)	303(57.2)	402(57.3)	771(57.3)
Medium	26(22.8)	144(27.2)	178(25.4)	348(25.9)
High	22(19.3)	79(14.9)	109(15.5)	210(15.6)
Childhood trauma M (SD)	31.75(7.64)	32.55(8.74)	32.25(8.33)	32.33(8.44)
Rumination M(SD)	11.48(3.83)	11.31(3.63)	11.54(3.74)	11.44(3.70)
Catastrophizing M (SD)	9.20(3.71)	8.87(3.66)	9.01(3.76)	8.97(3.72)

Note: Socioeconomic status (SES) based on the parents' profession and education level according to Simões classification (Simões, 1995). SES = socioeconomic status.

[a] Seventeen participants were missing SES information (4 heterozygous CATT carriers and 13 homozygous non-carriers).

environmental and genetic factors, as well as their interactions (Halldorsdottir and Binder, 2017). One of the most consistent risk factors for psychopathology in adulthood is exposure to childhood trauma, and various genetic polymorphisms have been described to moderate this relationship. Among these genetic markers are variants within the gene encoding the FK506-binding protein 51 *FKBP5*, which plays an important role in the hypothalamic-pituitary-adrenal (HPA) axis through its regulatory role of glucocorticoid receptor sensitivity (Binder, 2009). Gene-by-environment interaction (G × E) studies have found that minor allele carriers of a haplotype derived of 4 variants (rs9296158, rs3800373, rs1360780, and rs9470080), referred to as CATT carriers, are at greater risk of developing a range of psychiatric disorders in adulthood following childhood trauma relative to major allele carriers (Zannas et al., 2016). Only few studies have, however, examined the moderating role of *FKBP5* on transdiagnostic psychological risk factors for psychopathology in youth, especially adolescents (Comasco et al., 2015; Isaksson et al., 2016). Toward bridging this gap, the current study investigated the combined predictive effect of this *FKBP5* haplotype and exposure to childhood trauma on the maladaptive emotion regulation strategies described above. Given that this *FKBP5* haplotype has shown moderating effects of childhood adversities across psychiatric disorders, we hypothesized that these transdiagnostic emotion regulation processes would also be affected in that CATT haplotype carriers exposed to higher levels of childhood trauma would present with the higher level of rumination and catastrophizing compared to non-carriers.

2. Method

2.1. Participants

Participants were drawn from a larger study comprising 1459 students between the ages 12–17 and their parents recruited from 31 schools in Portugal in 2011–2012 and 2013–2014. A total of 1345 genotyped adolescents between the ages 12–17 (M_{age} = 13.95, 64.2% female; 100% European Caucasians of Portuguese nationality) completed the measures required for the present study (see Table 1 for sample characteristics). All subjects' parents completed consent forms and students completed assent forms prior to participation. Trained research assistants (master's students and licensed psychologists) administered the assessment battery and extracted saliva in the school classroom setting. Genetic samples were genotyped at the Max Planck Institute of Psychiatry (MPIP) in Germany. De-identified phenotypic

data[1] were also supplied to the researchers at MPIP for analyses. All protocols were approved by the Portuguese National Committee for Data Protection and the Ethical Committee of the Faculty of Psychology and Educational Psychology of the University of Coimbra.

2.2. Psychometric measures

The Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003) was used to assess childhood trauma. Participants rated each item about his/her childhood experience on a 5-point scale (*Never true* to *Always true*). In the current study, a total score of the abuse (emotional, physical, and sexual abuse) and neglect (emotional and physical neglect) subscales was used (Cronbach's α = 0.745), with higher ratings indicating higher levels of childhood trauma. The psychometric properties of the CTQ were adequate in Portuguese samples (Dias et al., 2014).

The Cognitive Emotion Regulation Questionnaire (CERQ; Garnefski et al., 2001) assessed self-reported rumination (4 items on 1–5 scale, *Never* to *Always*; Cronbach's α = 0.792), and catastrophizing (4 items on 1–5 scale, *Never* to *Always*; Cronbach's α = 0.794). Higher scores indicate greater frequency of engagement in the maladaptive cognitive strategy. The CERQ has been translated to Portuguese and its psychometric properties have proven adequate (Castro et al., 2013).

2.3. Genotyping methods for the FKBP5 gene

DNA was extracted from saliva from each participant using Oragene Saliva kits (DNA Genotek). Genotyping was performed with the Infinium Global Screening Array protocol (for a detailed description of the protocol, see www.illumina.com). Single-nucleotide polymorphisms (SNPs) with Hardy-Weinberg equilibrium (HWE) < 0.0001, minor allele frequency (MAF) < 0.05 and call rate < 95% were excluded for quality control. With the SNPs surviving this quality control, imputation for additional variants was performed using IMPUTE version 2 (Howie, Donnelly, & Marchini, 2009) and the 1000 Genomes Project reference genome. Imputed SNPs were excluded if their posterior probability averages were less than 90% for the most likely imputed genotype (INFO ≥ 0.9). After the imputation process, SNPs with call rate < 98%, HWE p < 0.0001 and MAF < 0.05 were excluded. This yielded a total of 3.779.545 SNPs.

The genotypes of four SNPs of the *FKBP* locus (rs9296158, rs3800373, rs1360780, and rs9470080) in linkage disequilibrium (r^2 > 0.78 for all SNPs) previously found to be associated with a host of psychiatric disorders (Zannas et al., 2016) were use to compute the number of CATT haplotype (carriers versus non-carriers) copies using PLINK (version 1.07; Purcell et al., 2007), an open-source whole genome association analysis software program. Consistent with the previous literature, the CATT haplotype was coded based on the dominant model (0 = homozygous non-carrier; 1 = homozygous or heterozygous CATT haplotype carrier). See Table 1 for genotype frequencies. Principal components (PCAs) to account for population stratification were calculated using genome-wide complex trait analysis (Yang et al., 2013). Three clusters were identified and, thus, the first 3 PCAs were included in all analyses to control for population stratification.

2.4. Data analysis

Chi-square and *t*-test analyses were used to examine genotype differences and regression analyses were conducted to investigate the association of demographic and clinical characteristics with the

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[1] Each participant was assigned a subject number, and the psychometric measures were scored and put into databases with only subject numbers as identifiers. Original measures with individual identifying data were kept in double locked storage in the research offices of the principal investigator (APM) in Portugal.

dependent variables (i.e., rumination and catastrophizing). The main effects and interaction of exposure to childhood trauma and CATT haplotype on rumination and catastrophizing were examined with multivariate analysis of variance (MANOVA) using SPSS software for Windows (IBM SPSS version 22). The interaction was composed of the cross-product term for exposure to childhood trauma (CTQ total score) × CATT haplotype (0 = non-carrier; 1 = heterozygous or homozygous CATT haplotype carrier). As secondary analyses, we also examined a three-way interaction including biological sex (i.e., childhood trauma × CATT haplotype × biological sex). In accordance with the recommendation of Keller (2014), significant group differences and characteristics significantly associated with the dependent variables and their interaction with the independent variables (i.e., CTQ total score and CATT haplotype) were also included as covariates in all analyses (Keller, 2014). To correct for multiple testing, two-tailed $p < 0.025$ was considered significant. For significant interactions, a test of region of significance (RoS) was performed using an SPSS macro developed by Prof. Johannes Ullrich. Power analyses indicated the ability to detect a small effect ($f^2 \leq 0.10$) with an alpha probability of 0.025 and power of 80%.

3. Results

Demographic and clinical characteristics of the sample are presented in Table 1. No significant differences were noted based on *FKBP5* genotype. Higher levels of rumination and catastrophizing were however observed among participants with lower socioeconomic status (SES) status ($p < 0.001$). Additionally, females endorsed higher levels of rumination and catastrophizing than males ($p < 0.001$). SES and biological sex and their interaction with the independent variables (i.e., exposure to childhood trauma and CATT haplotype) were therefore controlled for in all analyses (Keller, 2014). Consistent with previous findings (Garnefski et al., 2001), rumination and catastrophizing were significantly correlated ($r = 0.587$, $p < 0.001$).

Controlling for sex and SES, gene-environment correlation revealed a nonsignificant correlation between CATT haplotype and exposure to childhood trauma ($rGE = 0.014$, $p = 0.615$). Partial correlations, adjusting for sex and SES, revealed a significant correlation between exposure to childhood trauma and rumination for both CATT haplotype carriers and non-carriers. The correlation however was higher among CATT haplotype carriers ($r = 0.231$, $p < 0.001$) than non-carriers ($r = 0.168$, $p < 0.001$). The same pattern was observed for the correlation between exposure to childhood trauma and catastrophizing (CATT haplotype carriers: $r = 0.324$, $p < 0.001$; non-carriers: $r = 0.294$, $p < .001$). The significant correlations were to be expected due to the positive relationship between exposure to childhood trauma and maladaptive emotion regulation strategies, in addition to the large sample size in the current study.

3.1. Interaction between FKBP5 genotype and childhood abuse predicting rumination

Exposure to childhood trauma ($F(1) = 42.706$, $p < 0.001$, $\eta^2 = 0.031$) significantly predicted rumination but CATT haplotype did not ($F(1) = 1.454$, $p = 0.228$, $\eta^2 = 0.001$). Specifically, youth exposed to higher levels of childhood trauma endorsed higher levels of rumination than did youth with lower levels of exposure to childhood trauma. The interaction between exposure to childhood trauma and CATT haplotype also significantly predicted rumination ($F(1) = 6.418$, $p = 0.011$, $\eta^2 = 0.005$). Specifically, CATT haplotype carriers exposed to higher levels of childhood trauma showed higher levels of rumination than haplotype carriers exposed to lower levels of childhood trauma and non-carriers with and without a history of childhood trauma (see Fig. 1A). Interestingly, higher exposure to childhood trauma was associated with lower rumination ratings in non-carriers. The interaction between exposure to childhood trauma and CATT

haplotype predicting rumination was not further moderated by biological sex ($p = 0.978$).

For the two-way interaction, RoS analyses revealed that the interaction of *FKBP5* haplotype and exposure to childhood trauma predicting rumination was significant across the entire range of the CTQ score. Specifically, the regression analyses extrapolated that the interaction would be significant if the exposure to childhood trauma was above 4.205.

3.2. Interaction between FKBP5 genotype and childhood abuse predicting catastrophizing

The main effect for exposure to childhood trauma ($F(1) = 137.296$, $p < 0.001$, $\eta^2 = 0.093$) was significantly associated with catastrophizing. That is, higher levels of catastrophizing were endorsed by adolescents exposed to higher levels of childhood trauma. The main effect of CATT haplotype ($F(1) = 0.290$, $p = 0.590$, $\eta^2 < 0.001$) on catastrophizing was not significant. The interaction between exposure to childhood trauma and CATT haplotype ($F(1) = 5.949$, $p = 0.015$, $\eta^2 = 0.005$) significantly predicted catastrophizing in that higher levels of catastrophizing were endorsed by CATT haplotype carriers exposed to higher levels of childhood trauma compared to haplotype carriers with lower levels of exposure to childhood trauma and non-carriers independent of the exposure to childhood trauma (see Fig. 1B). The three-way interaction with childhood trauma, CATT haplotype, and biological sex ($p = 0.107$) did not significantly predict catastrophizing.

Again, RoS analyses for the two-way interaction showed that the interaction between *FKBP5* haplotype and exposure to childhood trauma predicting catastrophizing was significant across the entire range of the CTQ, namely the interaction was significant if the exposure to childhood trauma was 4.065 or above.

4. Discussion

We found that *FKBP5* haplotype interacted with exposure to childhood trauma to predict both rumination and catastrophizing in adolescents. Consistent with our hypotheses and previous findings (Zannas et al., 2016), CATT haplotype carriers exposed to higher levels of childhood trauma reported higher levels of both rumination and catastrophizing, whereas this pattern was not observed in non-carriers. As noted previously, rumination and catastrophizing have been identified as transdiagnostic risk factors for psychopathology (Garnefski et al., 2001; Gellatly and Beck, 2016; Ottaviani et al., 2016). Accordingly, the findings may suggest that adolescent CATT haplotype carriers exposed to childhood trauma display altered emotion regulation, and they are therefore more susceptible to developing a psychiatric disorder than non-carriers independent of exposure to childhood trauma. Longitudinal studies are needed, however, to determine whether this is indeed the sequence of events. Such findings could have important clinical implications in terms of identifying at-risk individuals for psychopathology in premorbid populations.

As noted above, adolescence is a crucial and fragile developmental period in multiple ways, including brain development (Paus et al., 2008). The combination of risk-increasing genes and environmental influences likely results in pathophysiological disturbance in molecular pathways and consequently may influence the neural circuits associated with psychopathology. Pertinent to the current findings, brain regions associated with emotion processing and memory, such as the amygdala and hippocampus, are believed to be involved in *FKBP5*-related vulnerability to psychopathology (Zannas et al., 2016). Interestingly, rumination has also been associated with increased activation of the default mode network, which includes the amygdala and hippocampus (Belzung et al., 2015). Future studies are needed to determine whether this association between these brain regions and rumination and catastrophizing are moderated by *FKBP5* genotype. Such an increased understanding of the underlying pathophysiology could lead to more
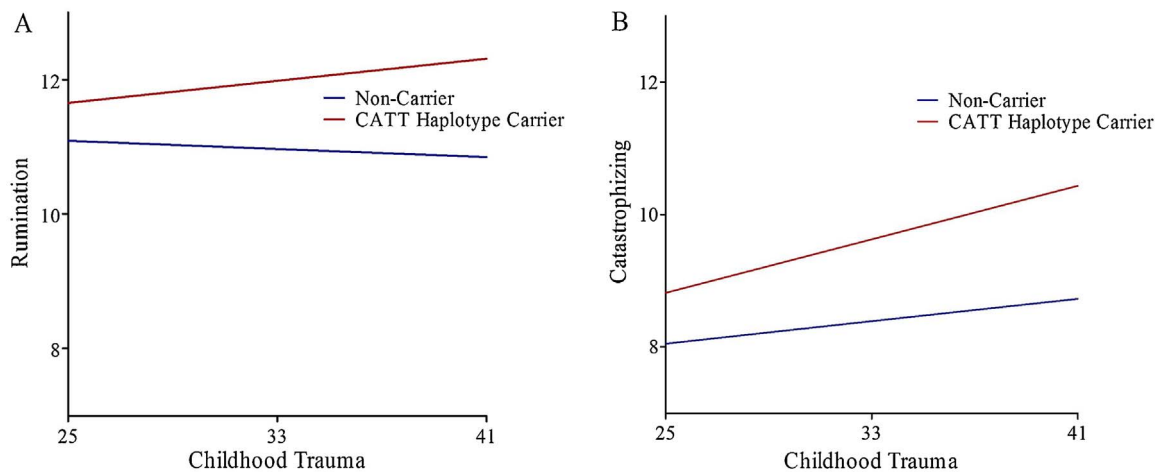
Fig. 1. A & B. Exposure to childhood trauma against rumination (Fig. 1A) and catastrophizing (Fig. 1B) by *FKBP5* haplotype. The rumination and catastrophizing score have been adjusted for socioeconomic status and biological sex.

targeted prevention efforts and treatments.

Strengths of the study include the relatively large sample size and the incorporation of transdiagnostic processes associated with the development of psychiatric disorders that were dimensionally conceptualized as recommended in the National Institute of Mental Health's Research Domain Criteria and DSM-5. The current study, however, also has several limitations. For instance, all of the participants were Caucasian; as such, generalizability to other ethnicities is limited. Furthermore, our analyses were limited to rumination and catastrophizing, which have been associated primarily with internalizing disorders. Future studies should investigate the relationship between genetic and environmental factors with other transdiagnostic processes associated with the development of externalizing disorders and psychotic symptoms. Lastly, the study investigated a composite score of the exposure to emotional, physical and sexual abuse and emotional and physical neglect. It is possible that specific subtypes of childhood trauma interact differently with the *FKBP5* genotype in predicting maladaptive emotion regulation strategies. Further delineation of potential moderation effects of *FKBP5* based on the type of childhood trauma shaping the risk for psychopathology will therefore be needed.

To conclude, the current study brings novelty and expands upon previous G × E studies by examining the moderating effect of *FKBP5* and stressful life events on transdiagnostic risk factors of psychopathology, namely rumination and catastrophizing. The findings may have important clinical implications towards a neurobiological informed nosology and more targeted identification of at-risk adolescents given that such maladaptive emotion regulation strategies are transdiagnostic precursors of psychiatric disorders.

Conflict of interest/disclosure

WEC is a board member of Hugarheill ehf, an Icelandic company dedicated to the prevention of depression, and he receives book royalties from John Wiley & Sons. His research is also supported by the NIH, the Mary and John Brock Foundation, and the Fuqua family foundations. He is a consultant to the George West Mental Health Foundation that oversees Skyland Trail, a residential treatment facility in Atlanta, Georgia.

EBB is co-inventor on *FKBP5*: a novel target for antidepressant therapy, *European Patent# EP* 1687443 B1, and receives a research grant from Böhringer-Ingelheim for a collaboration on functional investigations of *FKBP5*.

TH, **APM**, YA, and **EOA** have nothing to disclose.

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