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Short Communication

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

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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 $\alpha = 0.745$), 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 $\alpha = 0.792$), and catastrophizing (4 items on 1–5 scale, *Never* to *Always*; Cronbach's $\alpha = 0.794$). 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

[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.