The role of stress-regulation genes in moderating the association of stress and daily-life psychotic experiences

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Objective: The interaction of single nucleotide polymorphisms with both distal and proximal environmental factors across the extended psychosis phenotype is understudied. This study examined (i) the interaction of relevant SNPs with both early-life adversity and proximal (momentary) stress on psychotic experiences (PEs) in an extended psychosis sample; and (ii) differences between early-psychosis and non-clinical groups for these interactions.
Methods: Two hundred and forty-two non-clinical and 96 early-psychosis participants were prompted randomly eight times daily for 1 week to complete assessments of current experiences, including PEs and stress. Participants also reported on childhood trauma and were genotyped for 10 SNPs on *COMT, RGS4, BDNF, FKBP5,* and *OXTR* genes.
Results: Unlike genetic variants, distal and proximal stressors were associated with PEs in both samples and were more strongly associated with PEs in the early-psychosis than in the non-clinical group. The *RGS4* TA and *FKBP5* CATT haplotypes interacted with distal stress, whereas the A allele of *OXTR* (rs2254298) interacted with proximal stress, increasing momentary levels of PEs in the early-psychosis group. No interactions emerged with *COMT* or *BDNF* variants.
Conclusion: Individual differences in relevant stress-regulation systems interact with *both* distal and proximal psychosocial stressors in shaping the daily-life manifestation of PEs across the psychosis continuum.

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Significant outcomes

- Stress-sensitivity mechanisms seemed to be shared across non-clinical and clinical levels of the hypothetical continuum of psychosis.
- Complex gene–environment interactions emerged on the daily-life expression of psychotic phenomena in help-seeking individuals compared with non-clinical individuals.

Limitations

- The cross-sectional nature of the ESM data limits interpretations about causation.
- The sample composition precludes definite conclusions about the role of schizotypy in the GxE interactions.

Introduction

Converging evidence suggests that the psychosis phenotype is expressed across a dynamic continuum spanning from subclinical (e.g., schizotypy, psychotic-like experiences) to full-blown psychotic manifestations (1, 2). In recent years, increasing focus has been placed on studying persons at the early stages of psychosis, such as those with at-risk mental states for psychosis (ARMS) and first episode psychosis (FEP). These populations allow us to examine potentially etiologically relevant mechanisms of psychotic disorders without the marked confounding factors seen in chronic patients (3). Notably, several studies report an overlap of etiological factors, as well as phenomenological and developmental processes, across high schizotypy, clinical risk, and clinical populations (e.g., 4, 5). Among these psychosocial factors, both distal (early-life adversity) and proximal (daily-life momentary) stress have been associated with psychotic features across the extended psychosis phenotype (5–8). At the same time, and consistent with the hypothesized etiopathogenic relevance of these factors, psychosis populations have higher levels of trauma exposure and stress sensitivity (9).

Gene–environment interaction research (GxE) also highlights the synergistic effect between environmental and genetic risk factors across subclinical and clinical expressions of psychosis (4, 10). In this sense, a limited but increasing number of GxE studies have shown that certain single nucleotide polymorphisms (SNPs) interact with distal or proximal stress to heighten risk for psychotic experiences (PEs; e.g., 11). For example, it has been shown that the brain-derived neurotrophic factor (*BDNF*) Val66Met polymorphism moderates the psychosis-inducing effects of distal (12, 13) and momentary stress (14). However, scarce research has examined the interaction of genetic variants with both distal and proximal stress within the same study. Such an approach should offer valuable insights, especially considering recent work indicating that childhood and adult stress interact differently with genetic variants linked to hypothalamus-pituitary-adrenal (HPA) axis reactivity in stress-related phenotypes (15). In particular, previous research showed that some SNPs (e.g., rs3800373, rs9296158, rs1360870, and rs9470080) on the FK506 binding protein 5 (*FKBP5*) gene interacts with distal, but not proximal, stress in the expression of PEs (16–19).

Another important consideration is that only a few studies have employed experience sampling method (ESM) to examine GxE interactions in the realm of daily life, which offers the advantage of minimizing retrospective bias and enhancing ecological validity (20, 21). ESM studies have predominantly examined the interaction of momentary stress with genetic variation in dopamine-related genes, such as the catechol-O-methyltranferase (*COMT*) on the emergence of PEs (22). However, differential effects of *COMT* Val158Met alleles have been found in non-clinical and clinical samples (14, 22–24). Other candidate genes related with dopamine signaling that have been associated previously with PEs, such as the regulator of G-protein signaling 4 (25–27), are also of interest for exploring their possible involvement in the development of such experiences through a stress-reactivity pathway. The oxytocin receptor gene (*OXTR*) is another promising candidate for understanding individual differences in the response of the dopaminergic and stress-response systems. Two *OXTR* SNPs (rs53576, rs2254298) have been identified as relevant in the context of mental disorders associated with social deficits (28). Crucially, the interconnections between the dopamine and oxytocin systems have led to the suggestion that individuals with more efficient variants (i.e., the G alleles of both *OXTR* SNPs) may regulate more adaptively the salience assigned to social stimuli (29), thus diminishing susceptibility to psychopathology. Nonetheless, the role of *OXTR* variability in the context of stress reactivity in psychosis remains unexplored.

Aims of the study

The first aim was to concurrently examine the interaction of both distal (childhood trauma) and proximal (momentary) stress with genetic variation on psychotic experiences (PEs). The second aim was to examine whether the interaction of early-life adversity or real-life assessments of momentary stress (situational and social stress) with genetic variation on PEs differed between early-psychosis and non-clinical groups.

We predicted that the interaction of both distal and proximal environmental factors with the variability of *COMT* (Val158Met Met allele), *RGS4* (rs951436—rs2661319 TA haplotype), *BDNF* (Val66Met Met allele), *FKBP5* (rs3800373—rs9296158—rs1360780—rs4470080 CATT haplotype), and *OXTR* genes (rs2554298 A allele and rs53576 A allele) would be associated with increased PEs and that these associations would be greater in an early-psychosis sample than in a non-clinical sample, given previous reports of increased levels of trauma exposure and stress sensitivity in persons with psychosis.

Methods

Participants

The data were collected as part of an ongoing longitudinal investigation examining psychosis risk and resilience. The non-clinical sample was drawn from an original unselected sample of 808 young adults, which included 547 undergraduate students from the Universitat Autònoma de Barcelona (UAB) and 261 students from technical training schools in Barcelona. A subset of these participants was invited to take part in an in-depth assessment including self-report, interview, laboratory, and ESM measures. We successfully recruited 136 participants who had standard scores based upon sample norms of at least 1.0 on the positive or negative schizotypy dimensions of the Wisconsin Schizotypy Scales (WSS; 30–33), the suspiciousness scale of the Schizotypal Personality Questionnaire (SPQ; 34), or the positive symptom subscale of the Community Assessment of Psychic Experiences (CAPE; 35), and randomly selected 106 participants who had standard scores below 1.0 on each of these. The goal of this enrichment procedure was to insure adequate variability of schizotypy traits and avoid having a 'super healthy' control sample. The final non-clinical sample comprised 242 participants (206 from UAB and 36 from technical schools). None of the university or technical school participant had a

psychotic disorder according to SCID-I, and only eight participants met diagnostic criteria for Cluster A disorders: three with Schizotypal, three with Paranoid, and one with Schizoid personality disorder (one qualified for more than one disorder).

The early-psychosis sample was recruited in the Sant Pere Claver-Early Psychosis Program (SPC-EPP; 36) in Barcelona. A total of 96 early-psychosis participants (60 ARMS and 36 FEP) were included in this study. Patients' inclusion criteria were age between 14 and 40 years old and IQ ≥ 75. ARMS criteria were established by the Comprehensive Assessment of At-Risk Mental States (CAARMS; 37) and/or the Schizophrenia Proneness Instrument-Adult version (SPI-A; 38). FEP patients met DSM-IV-TR criteria for any psychotic disorder or affective disorder with psychotic symptoms as established by the Structured Clinical Interview for DSM-IV (SCID-I; 39). All participants had full capacity to consent to participation in research and provided written informed consent prior to taking part in the study. The study was developed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Ethical approval for the study was granted by the university and the local ethics committees. Descriptive characteristics of the whole sample are displayed in supplementary material (Table S1).

Material and procedure

Distal stress

Participants were administered the Childhood Trauma Questionnaire (CTQ; 40), a self-report measure that assesses emotional, physical, and sexual abuse and emotional and physical neglect during childhood and adolescence. CTQ items are answered on a 5-point Likert-type scale ranging from 'never true' to 'very often true'. In this study, the total CTQ score was used for analyses (Cronbach's $\alpha = 0.89$).

ESM proximal stress and PEs measures

Experience sampling method data were collected on personal digital assistants (PDAs) that signaled participants randomly eight times daily (between 10 a.m. and 10 p.m.) for 1 week to complete brief questionnaires. All ESM items reported in the current study were answered on 7-point scales from 'not at all' to 'very much'. The analyses used ESM items assessing PEs and appraisals of proximal (situational and social) stress. We created an index of PEs using the following 10 items: feeling suspicious, feeling mistreated, unusual senses, unusual thoughts,

feeling weird, losing control, difficulty controlling thoughts, familiar things seeming strange, hearing/seeing things others could not, and passivity feelings. A principal components analysis (PCA) on the PE items yielded one factor that explained 69.4% of the variance (Cronbach's α = 0.94). The Kaiser-Meyer-Olkin measure also confirmed the sampling adequacy for the analysis (KMO = 0.87), and Bartlett's Test of Sphericity, χ^2 (df = 45) = 3274.069, $P < 0.001$ revealed that there were patterned relationships between the items (see Table S3). Regarding proximal stress, the appraisal of situational stress was assessed with the item 'My current situation is stressful'. Social stress appraisals during social contact were assessed by two items: 'I feel close to this person (people)' (reversed) and 'Right now I would prefer to be alone'.

Genetic data

All subjects were asked to provide a biological sample consisting of buccal mucosa on cotton swabs or blood. Genomic DNA was extracted using the Realpure genomic DNA extraction kit for buccal mucosa or blood samples (Durviz S.L.U., Valencia, Spain). Ten SNPs within the *COMT*, *BDNF*, *OXTR*, *FKBP5*, and *RGS4* genes were genotyped using TaqMan 5′ exonuclease assay (Applied Biosystems). Details on the SNPs are given in Table S2. Compliance with Hardy–Weinberg equilibrium was assessed for each SNP (all $P > 0.05$).

Linkage disequilibrium (LD) between SNPs within the same gene was examined by pairwise comparisons of r^2 and D' using Haploview version 4.2 (41). High LD was observed between the four *FKBP5* SNPs and between the two *RGS4* SNPs (both with $r^2 > 0.7$ and $D' > 0.9$), but not between the *OXTR* SNPs ($r^2 < 0.04$; $D' < 0.6$). Estimation of *FKBP5* and *RGS4* haplotype combination per subject was conducted using a Bayesian approach implemented with PHASE software (42). To better examine our hypotheses, participants were divided into the following groups based on previous studies (19, 26, 27, 43): (i) carriers of at least one risk haplotype, (ii) carriers of one risk haplotype and one protective haplotype, and (iii) carriers of at least one protective haplotype. Specifically, the groups were as follows: (i) AGCC/-, (ii) AGCC/CATT, and (iii) CATT/- for the *FKBP5* haplotype, and (i) TA/-, (ii) TA/GG, and (iii) GG/- for the *RGS4* haplotype. Haplotypic frequencies are presented in Table S2.

Statistical method

Descriptive statistics were performed on the childhood trauma and ESM variables using the Statistical Package for Social Sciences (SPSS) Version 19.0 (44). ESM data have a hierarchical structure in which repeated daily-life ratings (level 1 data) are nested within participants (level 2 data). Linear mixed models were used to control for within-subject clustering of multiple observations using the 'xtmixed' command in STATA 12 (45). Graphs were generated with the R program (www.r-project.org). Analyses were performed on the total pool of participants, that is, on a total sample comprising non-clinical and early-psychosis participants, treating group as a variable when necessary.

The multilevel analyses examined two types of relations between genetic and environmental variables on PEs across the extended psychosis phenotype. First, to examine whether the interactions between environmental (distal and proximal stress) and genetic (four SNPs and two haplotypes) variables on PEs were significant in the total sample, the main effects of environmental and genetic variables (e.g., distal stress and *FKBP5* haplotype) were entered simultaneously at the first step, and the interaction term (e.g., distal stress x *FKBP5* haplotype) was entered at the second step to examine its contribution over and above the main effects.

Second, we examined whether the interactions between environmental and genetic variables on PEs differ between non-clinical and early-psychosis groups. Therefore, the three main effects (e.g., distal stress, *FKBP5* haplotype, and group variables) were entered at the first step, the three-two-way interaction terms (e.g., distal stress x group, *FKBP5* haplotype x group, and distal stress x *FKBP5* haplotype) were entered at the second step, and the three-way interaction term was entered at the third step (e.g., distal stress x *FKBP5* haplotype x group). When a significant interaction was found, the effect of the interaction was examined using simple slopes analyses. Distal and proximal stresses were used as continuous variables for analyses. Genotypes were coded 0, 1, and 2 using an additive genetic model. However, when genotype comparison was required, we also used a dummy variable coding. Six sets of multilevel models, one for each genetic variant investigated, were conducted to test each hypothesis; therefore, the P-value was set at $P = 0.05/6 = 0.0083$.

Results

GxE interactions in the total sample

As shown in Table 1, distal stress and both situational and social proximal stress were associated with PEs in daily life in the total sample, whereas

Table 1. Two-way interactions of environmental stress variables and genetic variables on psychotic experiences

Psychotic experiences

	COMT rs4680	BDNF rs6265	OXTR rs2254298	OXTR rs53576	FKBP5 Haplotype	RGS4 Haplotype
Distal variable	n = 316	n = 318	n = 319	n = 309	n = 309	n = 315
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Childhood trauma	0.016 (0.002)***	0.018 (0.003)***	0.018 (0.003)***	0.018 (0.003)***	0.018 (0.003)***	0.018 (0.003)***
Genetic variation (G)	0.008 (0.034)	0.057 (0.043)	0.020 (0.044)	−0.031 (0.037)	0.010 (0.035)	0.029 (0.032)
Childhood trauma x G	0.005 (0.004)	−0.008 (0.005)	−0.003 (0.005)	−0.004 (0.004)	0.009 (0.003)*	0.009 (0.004)*
Proximal variables	n = 325	n = 328	n = 329	n = 319	n = 319	n = 325
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Situational stress	0.054 (0.049)***	0.053 (0.005)***	0.055 (0.005)***	0.053 (0.005)***	0.056 (0.005)***	0.055 (0.005)***
Genetic variation (G)	0.006 (0.024)	0.023 (0.034)	−0.005 (0.034)	−0.051 (0.029)	0.023 (0.027)	0.029 (0.025)
Situational stress x G	0.001 (0.007)	0.001 (0.008)	0.015 (0.009)	0.002 (0.007)	0.007 (0.007)	−0.001 (0.006)
Close to other	−0.023 (0.004)***	−0.019 (0.004)***	−0.023 (0.004)***	−0.019 (0.004)***	−0.023 (0.005)***	−0.023 (0.004)***
Genetic variation (G)	−0.003 (0.030)	0.013 (0.043)	0.015 (0.043)	0.033 (0.037)	0.038 (0.035)	0.027 (0.032)
Close to other x G	0.002 (0.006)	0.000 (0.006)	−0.003 (0.008)	−0.004 (0.005)	−0.000 (0.006)	−0.005 (0.006)
Prefer to be alone	0.034 (0.006)***	0.032 (0.005)***	0.035 (0.006)***	0.034 (0.005)***	0.036 (0.006)***	0.036 (0.006)***
Genetic variation (G)	−0.023 (0.023)	0.058 (0.033)	0.005 (0.033)	0.032 (0.029)	0.009 (0.027)	0.024 (0.025)
Prefer to be alone x G	0.007 (0.008)	−0.017 (0.009)	0.002 (0.010)	0.003 (0.008)	0.006 (0.008)	0.008 (0.008)

$*P \leq 0.01$, $***P \leq 0.001$. In order to examine the two-way interaction between genetic and environmental variables, we first assessed the two main effects of E and G in the same model and then entered the interaction term over and above the two main effects.

no main effects of genetic variation on PEs were found. The two-way interactions between genetic and environmental variables on PEs indicated that only the interaction of distal stress with the *FKBP5* ($P = 0.007$) and *RGS4* ($P = 0.008$) risk haplotypes were associated with increased PEs. As expected, simple slopes analyses indicated that distal stress was associated with greater increases in PEs for individuals carrying the *FKBP5* risk haplotype (CATT/-: 0.028, $SE = 0.008$, $P < 0.001$; AGCC/CATT: 0.022, $SE = 0.005$, $P < 0.001$; AGCC/-: 0.010, $SE = 0.003$, $P < 0.001$). Additionally, dummy-coded variables were created for genotype comparison purposes. Participants carrying the *FKBP5* risk haplotype (CATT/- and AGCC/CATT) showed greater increases in PEs compared to non-risk individuals (CATT/- vs. AGCC/-: 0.018, $SE = 0.007$, $P = 0.011$; AGCC/CATT vs. AGCC/-: 0.012, $SE = 0.006$, $P = 0.035$; CATT/- vs. AGCC/CATT: 0.006, $SE = 0.007$, $P = 0.402$). Similarly, simple slopes analyses indicated that distal stress was associated with greater increases in PEs for individuals carrying the *RGS4* risk haplotype (TA/-:0.029, $SE = 0.005$, $P = 0.000$; TA/GG: 0.017, $SE = 0.002$, $P = 0.000$; GG/-:0.015, $SE = 0.004$, $P = 0.000$). Participants carrying the risk haplotype (TA/-) experienced more PEs than TA/GG carriers (TA/- vs. TA/GG: 0.020, $SE = 0.006$, $P < 0.001$) and, at a trend level, than non-risk individuals (TA/- vs. GG/-: 0.014, $SE = 0.007$, $P = 0.057$). No differences were found between TA/GG and GG/- haplotype groups (TA/GG vs. GG: −0.006, $SE = 0.007$, $P = 0.416$).

Group differences in the interaction between environmental (distal and proximal) and genetic variables

As shown in Tables 2 and 3, the group variable was also associated with PEs, indicating that early-psychosis participants reported more PEs in daily life than non-clinical participants. The two-way interactions between environmental and group variables showed that, in most models (except for *COMT* and *RGS4*), environmental variables (both distal and proximal) were more strongly associated with PEs in the early-psychosis group. None of the two-way interactions of genetic variation with group were associated with PEs.

The three-way interaction of distal stress, *FKBP5* haplotype, and group was significantly associated with PEs, such that childhood trauma was associated with increased PEs for participants with the *FKBP5* risk haplotype in the early-psychosis group. Simple slope analyses indicated that the *FKBP5* risk haplotype moderated the association between distal stress and PEs in the early-psychosis, but not in the non-clinical group (early-psychosis: 0.024, $SE = 0.09$, $P = 0.007$; non-clinical: −0.004, $SE = 0.002$, $P = 0.114$). In addition, analyses of the *FKBP5* haplotype in the early-psychosis group showed that distal stress was associated with increased PEs for CATT/- and AGCC/CATT participants (CATT/-: 0.057, $SE = 0.019$, $P = 0.002$; AGCC/CATT: 0.029, $SE = 0.014$, $P = 0.044$), but not for those carrying the AGCC/- haplotype (AGCC/: 0.003, $SE = 0.006$, ns; see Fig. 1).

Table 2. Three-way interactions of group status (early-psychosis vs. non-clinical), environmental (distal and proximal) stress variables, and genetic variables on psychotic experiences

Psychotic experiences

Psychosocial stress	COMT rs4680	BDNF rs6265	OXTR rs2254298	OXTR rs53576	FKBP5 Haplotype	RGS4 Haplotype
Distal variable	n = 316	n = 318	n = 319	n = 309	n = 309	n = 315
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Childhood trauma	0.012 (0.002)***	0.013 (0.002)***	0.013 (0.002)***	0.014 (0.003)***	0.013 (0.003)***	0.013 (0.003)***
Genetic variation (G)	0.014 (0.032)	0.055 (0.040)	0.012 (0.041)	−0.018 (0.035)	0.008 (0.033)	0.024 (0.030)
Group	0.343 (0.055)***	0.345 (0.056)***	0.360 (0.057)***	0.350 (0.057)***	0.365 (0.058)***	0.358 (0.057)***
Childhood trauma x group	0.011 (0.005)+	0.015 (0.005)**	0.014 (0.005)**	0.015 (0.005)**	0.014 (0.005)**	0.011 (0.005)+
G x group	−0.006 (0.080)	0.242 (0.098)+	0.021 (0.095)	−0.075 (0.083)	0.021 (0.079)	0.121 (0.074)
Childhood trauma x G	0.002 (0.004)	−0.010 (0.005)+	−0.002 (0.004)	0.002 (0.004)	0.008 (0.003)+	0.005 (0.004)
Childhood trauma x G x group	−0.001 (0.009)	−0.020 (0.010)+	−0.009 (0.009)	0.003 (0.008)	0.030 (0.006)***	0.023 (0.007)**
Proximal variables	n = 325	n = 328	n = 329	n = 319	n = 319	n = 325
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Situational stress	0.054 (0.005)***	0.053 (0.004)***	0.055 (0.005)***	0.054 (0.005)***	0.056 (0.005)***	0.056 (0.005)***
Genetic variation (G)	0.010 (0.023)	0.033 (0.032)	−0.006 (0.032)	−0.038 (0.028)	0.023 (0.026)	0.022 (0.024)
Group	0.202 (0.038)***	0.250 (0.041)***	0.247 (0.041)***	0.245 (0.042)***	0.248 (0.042)***	0.245 (0.041)***
Situational stress x group	0.075 (0.011)***	0.068 (0.010)***	0.073 (0.010)***	0.069 (0.010)***	0.074 (0.011)***	0.073 (0.010)***
G x group	0.018 (0.054)	0.097 (0.076)	−0.039 (0.072)	−0.122 (0.062)+	0.116 (0.058)+	0.110 (0.054)+
Situational stress x G	0.003 (0.007)	0.003 (0.008)	0.013 (0.008)	0.006 (0.007)	0.007 (0.007)	−0.002 (0.006)
Situational Stress x G x group	0.008 (0.015)	0.019 (0.018)	0.051 (0.018)**	0.004 (0.015)	0.018 (0.015)	0.012 (0.014)

+$P \leq 0.05$, **$P \leq 0.005$, ***$P \leq 0.001$

Table 3. Three-way interactions of group status (early-psychosis vs. non-clinical), distal environmental social stress variables, and genetic variables on psychotic experiences

Psychotic experiences

	COMT rs4680	BDNF rs6265	OXTR rs2254298	OXTR rs53576	FKBP5 Haplotype	RGS4 Haplotype
Proximal variables	n = 325	n = 328	n = 329	n = 319	n = 319	n = 325
	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)	Coefficient (SE)
Close to other	−0.023 (0.004)***	−0.019 (0.003)***	−0.022 (0.004)***	−0.019 (0.004)***	−0.022 (0.005)***	−0.022 (0.004)***
Genetic variation (G)	0.005 (0.029)	0.028 (0.041)	0.011 (0.041)	0.018 (0.035)	0.035 (0.033)	0.023 (0.030)
Group	0.272 (0.048)***	0.353 (0.053)***	0.349 (0.052)***	0.353 (0.054)***	0.351 (0.053)***	0.349 (0.052)***
Close to other x group	−0.049 (0.010)***	−0.033 (0.008)***	−0.043 (0.010)***	−0.033 (0.008)***	−0.045 (0.010)***	−0.043 (0.010)***
G x group	0.018 (0.070)	0.080 (0.098)	−0.004 (0.092)	0.105 (0.079)	0.166 (0.074)+	0.121 (0.069)+
Close to other x G	0.005 (0.006)	−0.001 (0.006)	−0.003 (0.008)	−0.002 (0.005)	0.001 (0.006)	−0.004 (0.006)
Close to other x G x group	0.032 (0.015)+	−0.015 (0.016)	0.003 (0.019)	−0.025 (0.012)+	0.004 (0.014)	0.001 (0.013)
Prefer to be alone	0.035 (0.006)***	0.033 (0.004)***	0.035 (0.006)***	0.034 (0.005)***	0.036 (0.006)***	0.036 (0.006)***
Genetic variation (G)	−0.014 (0.022)	0.065 (0.032)+	0.001 (0.032)	0.020 (0.028)	0.007 (0.026)	−0.001 (0.023)
Group	0.215 (0.037)***	0.267 (0.041)***	0.262 (0.041)***	0.266 (0.042)***	0.262 (0.042)***	0.263 (0.041)***
Prefer to be alone x group	0.051 (0.013)***	0.040 (0.011)***	0.051 (0.012)***	0.040 (0.011)***	0.052 (0.013)***	0.050 (0.013)***
G x group	0.005 (0.053)	0.105 (0.076)	−0.052 (0.071)	0.109 (0.062)	0.086 (0.058)	0.021 (0.054)
Prefer to be alone x G	0.008 (0.008)	−0.016 (0.009)	0.002 (0.010)	0.001 (0.008)	0.005 (0.008)	0.007 (0.007)
Prefer to be alone x G x group	−0.024 (0.018)	0.013 (0.020)	0.021 (0.021)	0.009 (0.016)	0.008 (0.018)	0.029 (0.016)

+$P \leq 0.05$, ***$P \leq 0.001$

Similarly, the three-way interaction among distal stress, *RGS4* haplotype, and group was significantly associated with PEs. This indicated that distal stress was associated with increased PEs for participants with the *RGS4* risk haplotype in the early-psychosis compared to the non-clinical group. Simple slopes analyses indicated a consistent trend for the early-psychosis group although it did not reach statistical significance (early-psychosis: 0.017, *SE* = 0.010, ns; non-clinical: −0.003,

SE = 0.003, *P* = 0.204). Additionally, analyses of the *RGS4* haplotype in the early-psychosis group showed that distal stress was associated with increased PEs for the risk haplotype TA/- participants (0.034, *SE* = 0.009, *P* < 0.001), but not for those carrying the GG/- or TA/GG haplotype (GG/-: 0.750, *SE* = 0.929, *P* = 0.42; TA/GG: 1.170, *SE* = 0.161, *P* = 0.055).

The three-way interactions also examined whether the interaction of proximal stress (both

Fig. 1. Interaction between distal stress and *FKBP5* haplotype on psychotic experiences in early-psychosis individuals. [Colour figure can be viewed at wileyonlinelibrary.com]
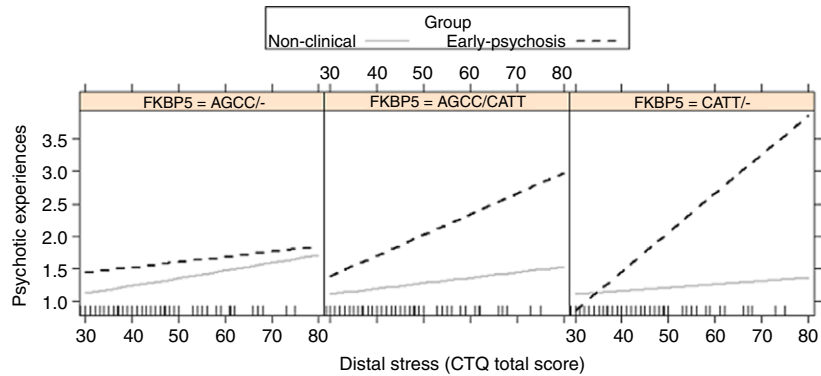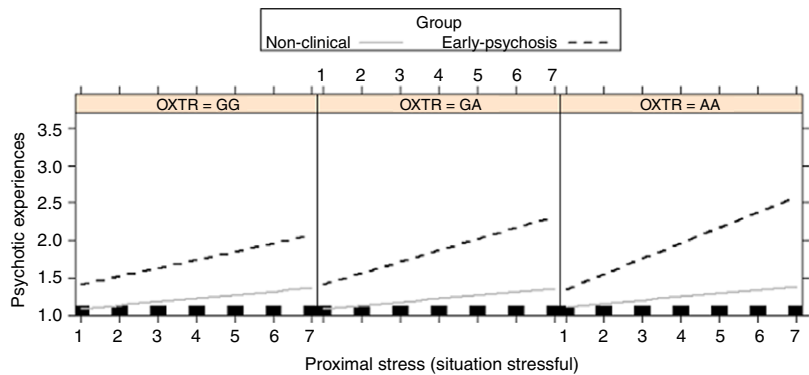

Fig. 2. Interaction between proximal stress and *OXTR*-rs2254298 on psychotic experiences in early-psychosis individuals. [Colour figure can be viewed at wileyonlinelibrary.com]

situational and social appraisals) with genetic variation on PEs differed between non-clinical and early-psychosis groups. As shown in Table 2, only the three-way interaction of situational stress, *OXTR* rs2254298, and group was significantly associated with PEs. This interaction indicated that situational stress was associated with increased PEs for participants with the A allele in the early-psychosis group. Simple slope analyses indicated that the A allele of the *OXTR* gene moderated the association between situational stress and PEs in the early-psychosis group but not in the non-clinical group (early-psychosis: 0.048, $SE = 0.022$, $P = 0.031$; non-clinical: -0.001, $SE = 0.008$, $P = 0.927$). In addition, analyses of the *OXTR* in the early-psychosis group showed that situational stress was associated with greater increases in PEs for AA and AG participants (AA: 0.255, $SE = 0.063$, $P = 0.000$; GA: 0.138, $SE = 0.028$, $P < 0.001$) as compared with those carrying the GG genotype (GG: 0.089, $SE = 0.014$, $P < 0.001$; see Fig. 2). As expected, dummy coding indicated that A allele carriers (AA and AG) experienced more PEs than GG subjects (AA vs. GG: 0.135, $SE = 0.037$, $P = 0.000$; GA vs. GG: 0.057, $SE = 0.015$, $P = 0.000$; AA vs. GA: 0.078, $SE = 0.038$, $P = 0.038$).

Finally, although some three-way interactions also seemed to emerge in *COMT* (rs4680), *OXTR* (rs53576), and *BDNF* (rs6265) models, these results did not reach significance after controlling for multiple testing.

Discussion

Findings

The present study extended previous GxE reports in psychosis by examining with ecological validity the interplay of genetic variants with both distal and proximal psychosocial environmental factors on the real-life expression of PEs. Both early-life and momentary (situational and social) stress were associated with increased levels of PEs, whereas none of the genetic variants studied were directly associated with PEs. GxE interactions of the risk haplotype of *RGS4* and *FKBP5* with distal, but not proximal, stress were associated with the expression of PEs in the total sample. Moreover, when both groups were compared, results indicated that both factors were more strongly associated with PEs in the early-psychosis group as compared with the non-clinical group. In the early-psychosis group, the interactions of distal stress with the risk haplotype of *RGS4* and *FKBP5* were associated with increased levels of PEs, whereas the interaction of momentary situational stress with the A allele of *OXTR* (rs2254298) was associated with PEs.

The association of both distal and proximal environmental factors with PEs is consistent with a

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growing body of research showing that psychosocial stress—such as childhood trauma and momentary situational and social stress—is associated with schizotypy traits and subclinical and clinical expressions of the psychosis phenotype (7, 46–48). As expected, and consistent with previous studies (e.g., 9, 49), the association of both types of stressors with PEs was also greater in the early-psychosis group compared to the non-clinical group (even if the latter was oversampled for elevated scores on schizotypy to include a wide range of variability in terms of psychosis liability). Results thus seem to indicate that, although comparable mechanisms, such as stress sensitivity, operate across different levels of psychotic liability, and expression, there is also a differential impact of stressors in both groups reflecting individual differences in risk and resilience factors, some of which may pave the way toward psychotic outcomes. In addition, it may be that once PEs reach certain severity levels and need for care status the effect of stressors is of greater magnitude.

Our analysis of the moderating role of stress-regulation SNPs on environmental stress exposures showed that the interactions of the risk haplotypes of *RGS4* and *FKBP5* genes with distal, but not proximal, stress were associated with PEs in the total sample. Importantly, the group comparison indicated that such GxE findings only held for the early-psychosis group and, again, only for distal stress. This resonates with a recent study showing that, unlike momentary stress, the exposure of early-life stress may lead to long-lasting molecular mechanisms in relevant stress-response systems, shaping individual differential trajectories and resulting in a greater risk for the development of psychopathological outcomes (50). Prior studies have consistently demonstrated that exposure to childhood trauma increases the risk for several stress-related phenotypes for carriers of the minor alleles (C, A, T, T) of *FKBP5* SNPs (rs3800373, rs9296158, rs1360870, and rs9470080; e.g., 51) or for the risk haplotype including these three or four alleles (e.g., 15, 52). Specifically, these risk alleles have been associated with decreased sensitivity of the glucocorticoid receptor (GR) to circulating cortisol, entailing a diminished negative feedback regulation of the HPA axis and hence, enduring responses to stress (51). Notably, a relevant finding consistent with the discrepancy of both stressors with *FKBP5* variability is that specifically early-life stress (but not current cortisol levels or adult trauma exposure) in interaction with *FKBP5* risk alleles induce epigenetic changes that result in individual differences in GR sensitivity, ultimately leading to the dysregulation of the stress response

and an increased vulnerability for psychopathological phenotypes (15). These authors suggested that there may exist a sensitive development stage for such epigenetic changes altering the homeostasis of the HPA axis and causing subsequent abnormal responses to stress.

Similarly, the *RGS4* risk haplotype moderated the association between distal, but not proximal, stress and PEs. Although, to the best of our knowledge, this is the first GxE study showing evidence of the interplay between psychosocial stress and *RGS4* genetic variation on PEs, neurobiological research has indicated that the *RGS4* gene, because of its function and biological properties, may be a relevant candidate gene for psychotic outcomes (25). *RGS4* is highly expressed in important brain regions involved in the pathophysiology of schizophrenia (e.g., PFC) and, importantly, it also shows an increased responsiveness to environmental stimuli, can modulate the function of G-protein-coupled neurotransmitter receptors critically implicated in schizophrenia-related disorders (53, 54). Evidence from animal studies has also indicated that differential regulation of *RGS4* expression may contribute to the dysregulation of the glucocorticoid-induced negative feedback regulation and thus, the prolongation of stress responses (55). In this context, our significant results of distal stress with the *FKBP5* and *RGS4* risk haplotypes suggest that after childhood trauma exposure, both variants may be involved in the HPA axis dysregulation associated with the risk for PEs across the extended psychosis phenotype. This is consistent with compelling evidence suggesting that the dysregulation of HPA axis may play a critical role in the expression of the positive dimension of psychotic phenomena (56, 57) due to the synergistic relation between glucocorticoid secretion and an elevated dopaminergic activity in mesolimbic regions (e.g., 58).

Conversely, the interaction of *OXTR* (rs2254298) A allele with momentary stress was associated with PEs in the early-psychosis group. Compelling evidence has shown that oxytocin administration has stress-buffering effects decreasing subjective stress experiences (28) and also diminishes amygdala activation in response to stressors (e.g., 59, 60). Notably, the two SNPs on *OXTR* (rs2254298, rs53576) have been associated with individual differences in intermediate mechanisms (e.g., affiliation, stress regulation, and empathy) underlying the risk for psychopathological phenotypes—especially those with social dysfunction features (e.g., 61). Although there is no prior evidence showing that, in particular, allelic variation (rs2254298) may moderate the association of

stress with PEs, several studies have linked this polymorphism with an increased risk for psychopathological outcomes (e.g., 62) and with alterations in important brain areas involved in stress reactivity and emotional responses, such as the hypothalamus and amygdala (e.g., 63). Interestingly, one study revealed that A carriers of rs225498 showed higher PANSS general symptom scores than GG individuals in a group of persons with schizophrenia, whereas no differences were found within a healthy control group (64). In light of these findings, it is attractive to speculate that early-psychosis individuals carrying at least one A allele of rs225498 may present a maladaptive regulation to negative environmental factors in the realm of daily life (e.g., stressful situations), increasing the susceptibility to psychopathology.

Conclusions and future directions

Overall, our results provide new insights into how the interplay of genetic variation within *FKBP5, RGS4,* and *OXTR* genes with distal or proximal environmental factors impacts the expression of PEs in early-psychosis compared to the non-clinical group. In addition, some interactions of environmental factors with *BDNF* and *COMT* variability also seemed to be associated with PEs; however, they did not reach statistical significance after controlling for multiple testing.

From a clinical view-point, the findings of this study add further support to the validity of the ESM approach in psychosis research by showing that early-psychosis individuals are able to meaningfully inform about their internal experiences, both in terms of symptoms and psychological appraisals of both context and interpersonal interactions. These issues are relevant for informing etiological models of symptom formation and may assist the development of ecological momentary interventions in psychiatry. In this regard, the ecological momentary interventions (EMIs) using experience sampling methodology recently devised in the field of psychosis constitute a promising and an innovative assessment and intervention approach, allowing to tailor-personalized interventions toward individual needs such as decreasing daily-life stress in the specific moment that are needed (65).

Strengths and limitations

The strengths of this study include the comparison of a non-clinical and early-psychosis sample, the use of ecologically valid measures of symptoms, and stress in real-life during multiple time points over a week enhancing the reliability of GxE research (66) and the estimation of two risk haplotypes increasing the power to detect genetic associations (67). Limitations of the study include its cross-sectional nature, which limits interpretations about the causal effects of GxE interactions. Similarly, causal inferences examining the effects of stress cannot be definitively drawn, given that predictor and criterion ESM variables were measured concurrently. It should also be noted that although the non-clinical sample was oversampled for schizotypy to insure adequate variance in psychosis liability, it does not constitute a homogenously high schizotypy sample. That is, the sample is composed of high, medium, and low schizotypy scorers, and the high scores refer to both the positive and negative schizotypy dimensions (which may involve different etiological mechanisms). Therefore, the sample composition precludes us from drawing precise conclusions of the role of schizotypy in the GxE interactions examined in the present study. Future research may focus on the examination of these GxE interactions in high and low schizotypy groups, analyzing the positive and negative dimensions independently.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Demographic characteristics, ESM and genetic variables across the extended psychosis phenotype.

Table S2. Details on the genetic polymorphisms included in the present study.

Table S3. Principal component analysis (PCA) of ESM PEs measure.