Interaction of both positive and negative daily-life experiences with *FKBP5* haplotype on psychosis risk

Author for correspondence:
Neus Barrantes-Vidal,
E-mail: neus.barrantes@uab.cat

Paula Cristóbal-Narváez[1,2], Tamara Sheinbaum[3], Araceli Rosa[2,4,5],
Marta de Castro-Catala[4,5], Tecelli Domínguez-Martínez[6], Thomas R. Kwapil[7] and
Neus Barrantes-Vidal[2,8,9]*

[1]Parc Sanitari Sant Joan de Déu, Institut de Recerca Sant Joan de Déu, Barcelona, Spain; [2]Centre for Biomedical Research Network on Mental Health (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain; [3]Department of Psychology, University of Southern California, Los Angeles, California, USA; [4]Secció de Zoologia i Antropologia, Departament de Biologia Evolutiva, Ecologia i Ciències Ambientals, Facultat de Biologia, Universitat de Barcelona (UB), Barcelona, Spain; [5]Institut de Biomedicina de la Universitat de Barcelona (IBUB), Barcelona, Spain; [6]Centro de Investigación en Salud Mental Global, Dirección de Investigaciones Epidemiológicas y Psicosociales, Instituto Nacional de Psiquiatría 'Ramon de la Fuente Muñiz', México; [7]Department of Psychology, University of Illinois at Urbana-Champaign, Champaign, Illinois, USA; [8]Departament de Psicologia Clínica i de la Salut, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain and [9]Sant Pere Claver—Fundació Sanitària, Barcelona, Spain

Abstract

Background. There is limited research on the interaction of both positive and negative daily-life environments with stress-related genetic variants on psychotic experiences (PEs) and negative affect (NA) across the extended psychosis phenotype. This study examined whether the FK506 binding protein 51 (*FKBP5*) variability moderates the association of *positive* and *negative* experiences in the moment with PEs and NA in participants with incipient psychosis and their nonclinical counterparts.

Methods. A total of 233 nonclinical and 86 incipient psychosis participants were prompted for a 1-week period to assess their day-to-day experiences. Participants were genotyped for four *FKBP5* single nucleotide polymorphisms (rs3800373, rs9296158, rs1360780, and rs9470080).

Results. Multilevel analyses indicated that, unlike the risk haplotype, the protective *FKBP5* haplotype moderated all the associations of positive experiences with diminished PEs and NA in incipient psychosis compared with nonclinical group.

Conclusions. Participants with incipient psychosis showed symptomatic improvement when reporting positive appraisals in the interpersonal domain, which suggests that these act as a powerful coping mechanism. The fact that this occurred in daily-life underscores the clinical significance of this finding and pinpoints the importance of identifying protective mechanisms. In addition, results seem to concur with the vantage sensitivity model of gene–environment interaction, which poses that certain genetic variants may enhance the likelihood of benefiting from positive exposures.

Introduction

Extensive evidence indicates that the psychosis phenotype is expressed across a dynamic continuum that ranges from nonclinical to clinical manifestations [1, 2]. Individuals with nonclinical, subclinical, and early-stage manifestations offer important assets for the study of both risk and protective mechanisms, as they are less affected by the wide array of confounding effects associated with overt psychopathology and chronicity. Thus, investigating continuities as well as discontinuities between clinical and nonclinical expressions may help to elucidate the heterogeneity that characterizes pathways to psychosis and the identification of protective factors [3]. In this regard, the study of patterns of gene–environment interactions (G × E) in clinical and nonclinical populations may contribute to our understanding of common and differential mechanisms operating across the psychosis continuum [4].

Recent G × E studies indicate that the interaction of genetic variants on the FK506 binding protein 5 (*FKBP5*) gene with psychosocial stressors is associated with psychotic experiences (PEs) in clinical and nonclinical samples [5-8]. Compelling evidence has suggested that individual variation in the *FKBP5* gene is linked to the dysregulation of the hypothalamus–pituitary–adrenal (HPA) axis, which has been identified as a critical neurobiological mechanism underlying the emergence of psychotic symptoms [9]. In particular, the minor risk alleles (C, A, T, T) of at least 4 *FKBP5* single nucleotide polymorphisms (SNPs; rs3800373, rs9296158, rs1360780, and

rs9470080, respectively), as compared with the nonrisk or protective alleles (A, G, C, C), have been associated with a decreased sensitivity of the glucocorticoid receptor to circulating cortisol, entailing a diminished negative feedback regulation of the HPA axis that results in an abnormal prolongation of the stress response [10]. Importantly, the rs1360780 SNPs included in a functional haplotype confers differential effects in *FKBP5* mRNA and protein levels mediated by a differential chromatin conformation, resulting in different transcriptional effects between risk and protective alleles [11]. So far, research has predominantly focused on analyzing the effects of the interplay of *FKBP5* variation with adverse environmental exposures on psychotic phenomena guided by diathesis-stress model for schizophrenia [12], greatly understudying the interaction of genetic variation with *positive*, and thus putative protective, environmental factors. However, individuals may differ in their susceptibility to the environment across a range of exposures (not just negative ones) and, therefore, moderation effects by genetic variation should also be expected in relation to the *benefit* that individuals may obtain from positive experiences [13]. In light of this, new frameworks under which to consider G × E interactions have been developed. For example, the *differential susceptibility model* [14] highlights that individuals traditionally considered to carry greater vulnerability may be better conceptualized as being more plastic, sensitive, or malleable to the environment ("for worse and for better"). That is, it suggests that the same genetic variants involved in increasing the negative effects of adverse experiences could also be involved in enhancing the likelihood of benefiting from positive ones. Another relevant model of G × E interactions is *vantage sensitivity* [15], which poses that certain genetic variants may enhance the likelihood of benefiting from positive exposures (without also implying an increase in the susceptibility to negative exposures)—that is, vantage sensitivity is more than the "bright side" of environmental sensitivity as covered in differential susceptibility models. Although these approaches have been scarcely considered within the psychosis field, the pertinence of incorporating the assessment of positive environmental experiences and examining potential beneficial effects is underscored by G × E investigations in other stress-related phenotypes. For instance, in depression research, it has been shown that the impact of *BDNF* Val[66]Met genotype on stress sensitivity may be dependent on the experience of daily-life positive emotions [16].

Another relevant issue that has received increasing attention in the context of G × E research has been the importance of refining environmental measures [17]. In this regard, the enhancement of precision, reliability, and ecological validity offered by the use of ambulatory assessment strategies (such as experience sampling methodology [ESM] or ecological momentary assessment) should be helpful for examining genetic moderation of the effects of both positive and negative microlevel experiences (i.e., those occurring in the moment in real-life contexts; [18]). To the best of our knowledge, there are no ambulatory assessment studies investigating the potential moderation of individual genetic variation involved in the regulation of the stress system, such as *FKBP5* variants, in the association of positive and negative momentary experiences on the psychosis phenotype. Importantly, there is also a lack of studies with ecological validity that examine plausible genetic-environmental interplay differences between nonclinical and clinical individuals, which should allow to identify risk and resilience mechanisms and targets for prophylactic interventions [19].

Therefore, the present study used ESM to elucidate the extent to which the interplay of *FKBP5* variability with both positive and negative exposures impacts the expression of PEs, as well as

negative affect (NA), in daily-life across nonclinical and clinical levels of expression of the extended psychosis phenotype. Specifically, we examined whether the interaction effects of positive and negative experiences with the *FKBP5* haplotype on PEs and NA differed between subjects with and without need for care, that is, in incipient psychosis and nonclinical groups. We predicted that the association of both positive and negative momentary experiences with symptoms and NA would be greater in an incipient psychosis group than in a nonclinical group, and that these associations would be moderated by *FKBP5* variability.

Materials and Methods

Participants

Data were collected as part of an ongoing longitudinal investigation examining psychosis risk and resilience [20]. The present study included a total of 319 participants reflecting different levels of expression of the psychosis phenotype for which ESM and genetic data were available. The nonclinical group was comprised of 233 students recruited from university and technical schools who scored across a range on questionnaire assessments of schizotypy and psychosis-proneness questionnaires (mean age = 20.0 years, SD = 2.9 years; 25.3% males). We invited participants from our screening samples 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 [21], the suspiciousness scale of the Schizotypal Personality Questionnaire [22], or the positive symptom subscale of the Community Assessment of Psychic Experiences [23], and randomly selected participants who had standard scores below 1.0 on each of these. The goal of this enrichment procedure was to ensure adequate variability of schizotypy traits and avoid having a "super healthy" control sample. The final nonclinical sample contained 198 university and 35 technical school students.

The incipient psychosis group included 86 patients recruited at the Sant Pere Claver Health Foundation (mean age = 22.3 years, SD = 4.7 years; 69.8% males). Specifically, the sample for this study consisted of 55 diagnosed with at-risk mental states for psychosis (ARMS) and 31 first episode psychosis (FEP) patients (6 of them met criteria for affective psychoses including 4 with bipolar I disorder and 2 with unipolar depression with psychosis). Patients' inclusion criteria were age between 14 and 40 years and IQ ≥ 75. ARMS-criteria were established by the Comprehensive Assessment of At-Risk Mental States [24] and/or the Schizophrenia Proneness Instrument-Adult version [25]. 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 [26]. Ethical approval was obtained from the University Ethics committee and participants provided written informed consent.

Measures

Participants received personal digital assistants that signaled them randomly eight times daily for 1 week to complete brief assessments of affect, cognition, activities, and PEs on 7-point scales ranging from 1 (not at all) to 7 (very much). A detailed description of the ESM assessment and validation data can be found in previous studies [20]. The positive and negative experience items used in the present study focused on two main domains of daily-life: situational and interpersonal. We focused on two content areas

that have been shown as highly relevant in psychosis and tested out in ESM research: situational stress and appraisals of social rejection [20]. Thus, the negatively valenced items were: "My current situation is stressful" and (when alone) "I am alone because people do not want to be with me." The positively valenced items were: "My current situation is positive" and "Right now I feel that others care about me." Two ESM indices were created and used as outcome measures: (i) PEs was computed by averaging the scores for 10 items: unusual senses, unusual thoughts, feeling weird, losing control, difficulty controlling thoughts, familiar things seeming strange, feeling suspicious, feeling mistreated, hearing/seeing things others could not, and passivity (coefficient $\alpha = 0.95$); (ii) NA was the mean of four items: feeling anxious, sad, angry, and guilty (coefficient $\alpha = 0.89$).

Genetic data

Genomic DNA was extracted from saliva in the nonclinical sample and blood in the incipient psychosis samples. Four single-nucleotide polymorphisms (SNPs) included in a previously described functional *FKBP5* haplotype [27] were genotyped using TaqMan 5′ exonuclease assay (Applied Biosystems): rs3800373, rs9296158, rs1360780, and rs9470080. Compliance with Hardy–Weinberg equilibrium was verified for all polymorphisms in both samples (all $p > 0.05$). Haplotypes were estimated using PHASE, after confirming that the four SNPs were in high linkage-disequilibrium ($D' > 0.9$; $r^2 > 0.7$). Participants were classified into three groups for analyses based on previous studies [19,28]: (i) carriers of at least one protective haplotype and no risk haplotypes (AGCC/−, $n = 157$), (ii) carriers of one risk haplotype and one protective haplotype (AGCC/CATT, $n = 118$), and (iii) carriers of at least one risk haplotype and no protective haplotypes (CATT/−, $n = 44$). Haplotypic frequencies are presented in Table S1).

Statistical analyses

ESM data have a hierarchical structure in which ESM 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 [29]. Graphs were generated with the R program (www.r-project.org).

Two types of multilevel analyses were conducted in the present study. First, in order to examine whether the effect of the *FKBP5* haplotype on PEs and NA differed between nonclinical and incipient psychosis groups, we assessed the main effects of level 2 predictors on level 1 outcome variables (PEs and NA). The level 2 predictors were the *FKBP5* haplotype (0 = AGCC/−; 1 = AGCC/CATT; 2 = CATT/−), the group status (incipient psychosis vs nonclinical groups), and the interaction term (*FKBP5* haplotype × group status).

Second, to examine whether the potential moderating role of the *FKBP5* haplotype in the association of momentary appraisals with daily-life outcomes differed between nonclinical and incipient psychosis groups, cross-level interactions were conducted. Cross-level interactions tested whether level 1 slopes (i.e., the association of positive and negative experiences with symptoms and NA) varied as a function of level 2 variables *FKBP5* haplotype, group status, and *FKBP5* haplotype × group status). Finally, when a level 2 interaction was significant, the effect of the interaction was examined in each *FKBP5* haplotype group using simple slopes analyses. Please note that multiple comparisons in multilevel modeling do not present the risk of alpha inflation that is seen in traditional unilevel analyses, so following Gelman et al. [30] multiple testing corrections were not conducted.

Results

Main effects of level 2 predictors (FKBP5 and group)

Results indicated that the *FKBP5* haplotype was not associated with momentary PEs or NA (Table 1). However, as expected, participants in the incipient psychosis group experienced more PEs and NA than individuals in the nonclinical group ($p < 0.001$). No interaction effects were found between the *FKBP5* haplotype and group on PEs or NA in daily-life. Thus, haplotype risk and protective groups were unassociated with the overall reports of symptoms and affect in daily life.

Cross-level interactions

Cross-level interaction analyses examined whether the *FKBP5* haplotype, group status, and their interaction moderated the associations of positive and negative experiences with PEs and NA in daily-life (Table 2). All negative appraisals in the moment (situational stress and feeling unwanted by others) were associated with increased PEs and NA in the moment, whereas all positive experiences (current situation being positive and feeling cared for by others) were associated with decreased PEs and NA.

Regarding moderation effects, the *FKBP5* haplotype did not moderate the associations of positive or negative appraisals with PEs or

Table 1. Main effects of the *FKBP5* haplotype, group status, and their interaction on psychotic experiences and negative affect ($n = 319$).

| | Level 2 predictors | | |
| | *FKBP5* haplotype | Group: early-psychosis vs nonclinical | *FKBP5* haplotype × group |
Level 1 criterion	γ_{01} ($df = 316$)	γ_{02} ($df = 316$)	γ_{03} ($df = 315$)
ESM psychosis			
Psychotic experiences index	0.026 ($SE = 0.036$)	0.447 ($SE = 0.058$)***	0.138 ($SE = 0.082$)
ESM affect			
Negative affect index	−0.031 ($SE = 0.051$)	0.425 ($SE = 0.081$)***	0.122 ($SE = 0.114$)

*$p < 0.050$.

**$p < 0.010$.

***$p < 0.001$.

The effect of the *FKBP5* haplotype × group interaction term was examined over and above the main effects.

Table 2. Moderation by *FKBP5* haplotype, group, and the *FKBP5* × group interaction of the association between both positive and negative appraisals with psychotic experiences and negative affect (*n* = 319).

Level 1 criterion	Appraisals	Level 1 predictor[a] ESM momentary appraisals γ_{10} (*df* = 316) Coeff. (*SE*)	Level 2 predictors *FKBP5* haplotype γ_{11} (*df* = 316) Coeff. (*SE*)	Group: early-psychosis vs nonclinical γ_{12} (*df* = 316) Coeff. (*SE*)	*FKBP5* haplotype × group[b] γ_{13} (*df* = 315) Coeff. (*SE*)
ESM psychosis	Negative appraisals				
Psychotic experiences index	Situation stressful	0.042 (0.007)***	0.007 (0.007)	0.080 (0.011)***	0.013 (0.015)
	Alone b/c not wanted	0.104 (0.032)**	0.016 (0.029)	0.041 (0.040)	−0.005 (0.059)
	Positive appraisals				
	Situation positive	−0.059 (0.008)***	0.005 (0.008)	−0.059 (0.013)***	0.035 (0.018)*
	Others care about me	−0.034 (0.008)***	0.002 (0.008)	−0.045 (0.013)***	0.040 (0.018)*
ESM affect	Negative appraisals				
Negative affect index	Situation stressful	0.216 (0.015)***	0.004 (0.014)	0.065 (0.023)**	0.013 (0.033)
	Alone b/c not wanted	0.156 (0.050)**	0.086 (0.046)	0.001 (0.060)	−0.025 (0.092)
	Positive appraisals				
	Situation positive	−0.277 (0.018)***	0.021 (0.017)	−0.001 (0.026)	0.075 (0.037)*
	Others care about me	−0.133 (0.015)***	0.009 (0.014)	−0.009 (0.023)	0.078 (0.032)*

*$p < 0.050$.
**$p < 0.010$.
***$p < 0.001$.
[a]The table reports the coefficient of the association of the level 1 predictor and criterion for the analyses of *FKBP5* and group variables entered simultaneously.
[b]The effect of *FKBP5* × group interaction term was examined over and above the main effects.

NA. Group status moderated the associations of situational stress with PEs and NA (Table 2). Analysis of simple slopes showed that the associations were greater in the incipient psychosis group (PEs: 0.126, *SE* = 0.013, *p* < 0.001; NA: 0.285, *SE* = 0.023, *p* < 0.001) compared with the nonclinical group (PEs: 0.046, *SE* = 0.04, *p* < 0.001; NA: 0.218, *SE* = 0.011, *p* < 0.001). The group status also moderated the associations of the two positive appraisals with PEs, but not NA, in the moment. That is, as positive experiences increased, incipient psychosis participants experienced greater decreases in symptoms (positive situation: −0.114, *SE* = 0.014, *p* < 0.001; others care about me: −0.078, *SE* = 0.017, *p* < 0.001) than their nonclinical counterparts (positive situation: −0.055, *SE* = 0.005, *p* < 0.001; others care about me: −0.032, *SE* = 0.004, *p* < 0.001).

The *FKBP5* haplotype by group interaction moderated all the associations of positive, but not negative, experiences with decreased PEs and NA in daily-life (Table 2). As shown in Figure 1, simple slope analyses indicated that, among protective haplotype carriers (i.e., AGCC/−), the positive appraisal of the situation was associated with decreased PEs in the incipient psychosis group compared with the nonclinical group (PEs: −0.087, *SE* = 0.018, *p* < 0.001; NA: −0.043, *SE* = 0.038, ns). In addition, among protective haplotype carriers, the positive experience of feeling cared for by others was associated with decreased PEs, as well as NA, in the incipient psychosis group compared with the nonclinical group (PEs: −0.096, *SE* = 0.017, *p* < 0.001; NA: −0.066, *SE* = 0.033, *p* < 0.050; see Figure 2). Furthermore, among the mixed haplotype (i.e., one protective and one risk haplotype carriers; AGCC/CATT), the experience of a positive situation was associated with diminished PEs in incipient psychosis in comparison to nonclinical group (situation positive—PEs: −0.040, *SE* = 0.020, *p* < 0.050; NA: 0.002, *SE* = 0.040, ns; others care about me—PEs: −0.004, *SE* = 0.022, ns; NA: 0.014, *SE* = 0.036, ns).

Finally, among risk haplotype carriers (i.e., CATT/−), no group differences were found in the association of both positive appraisals with symptoms (situation positive—PEs: −0.017, *SE* = 0.035, ns; NA: 0.135, *SE* = 0.079, ns; others care about me—PEs: −0.035, *SE* = 0.027, ns; NA: 0.088, *SE* = 0.055, ns).

Discussion

Main findings

The present work investigated whether the interplay between *FKBP5* variation and contextual factors is not limited to adverse experiences, but expands into the full spectrum of positive and negative experiences in real-life contexts. The study raised a novel finding indicating that the interaction of *FKBP5* variation with positive experiences is associated with diminished PEs and NA, in incipient psychosis compared with nonclinical group. Another relevant finding from the current study was that individuals with incipient psychosis, in comparison to their nonclinical counterparts, reported greater psychotic reactivity to negative, but also to positive, experiences in daily-life. Notably, the incipient psychosis group differed from the nonclinical group in terms of symptomatic reactivity to positive, but not negative, appraisals in the interpersonal domain, suggesting that positive interpersonal appraisals may act as a relevant coping mechanism for help-seeking individuals, ameliorating the intensity of symptom expression in the realm of daily-life.

The interpretation of these findings appears relevant at both basic and applied levels. At a basic science level, they seem to concur with numerous studies showing that environmental enrichment induces dramatic changes on brain and behavior in animal models
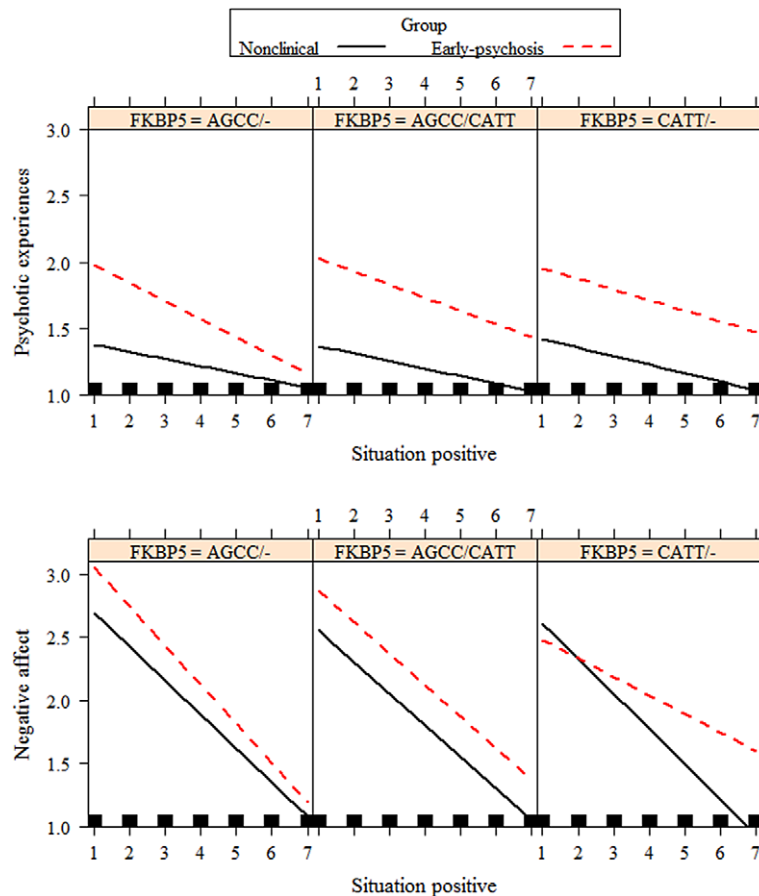
Figure 1. Group differences between nonclinical and early psychosis groups in the interaction of situation positive with *FKBP5* haplotype on psychotic experiences and negative affect.

[31]. It has been shown that environmental enrichment improves behavioral impairment in animal models of schizophrenia. Importantly, environmental enrichment diminishes the long-term negative effects of stress on altered HPA function [32]. A specific effect of environmental enrichment on this reversal role of HPA dysregulation is seen in animal models of transgenerational and multigenerational prenatal stress [33]. In addition, it has been shown that the exposure to environmental enrichment remarkably reduced the stress-sensitive phenotype induced by ancestral stress and also improved several levels of HPA axis function.

From a clinical stance, the present findings support increasing evidence indicating that environmental factors in general [34], and daily-life experiences in particular [35], are potent factors in terms of influencing psychotic reactivity and expression. Research has been predominantly guided by diathesis-stress model, and there is a growing criticism regarding the disproportionate focus on stressors and negative life events and the negligence of positive environments. New conceptual frameworks, such as the diathesis-stress-support model [36], suggest that social support can boost skills and competences, prevent risk accumulation, and are essential for an individual's progress toward recovery. In this sense, the recent growing impact of Positive Psychology [37,38] and Positive Psychiatry [39] has demonstrated that persons with psychosis can experience positive psychological features [40]. Regarding ESM research, one study revealed that individuals with persistent PEs showed more social reward sensitivity than individuals without persistent PEs [41]. This realization has recently encouraged interest in developing momentary clinical interventions with

ecologically valid tools [42], providing new opportunities for treatment. The development of recent positive psychological interventions [43] and the new upsurge of real world interventions in mental health [44] may be particularly important in psychosis field.

Clinical relevance of individual genetic differences in the response to positive experiences

Although to the best of our knowledge there are no previous studies investigating whether the *FKBP5* haplotype moderates the association of positive experiences with symptom expression in daily-life, findings seem to resonate with recent work in the context of responsiveness to psychotherapy in Posttraumatic stress disorder (PTSD) [45]. The study examined whether improvement in PTSD symptoms after exposure-based therapy differed as a function of *FKBP5* (rs1360780) variability. They found that, although no genetic differences on symptoms emerged between baseline and a 4-month follow-up, individuals homozygous for the protective rs1360780 C-allele continued to show a reduction in symptoms in the 10-month follow-up, whereas this was not found for carriers of the risk T-allele [45]. According to Pluess [15], these results suggest that the C-allele may enhance vantage sensitivity in the context of exposure-based therapy in this population. Given that in the present study, the protective haplotype was associated with diminished symptoms in the context of positive experiences for incipient psychosis participants (but not increased symptoms in the context of negative ones), our findings would seem to be in line with a vantage sensitivity interpretation for incipient psychosis as
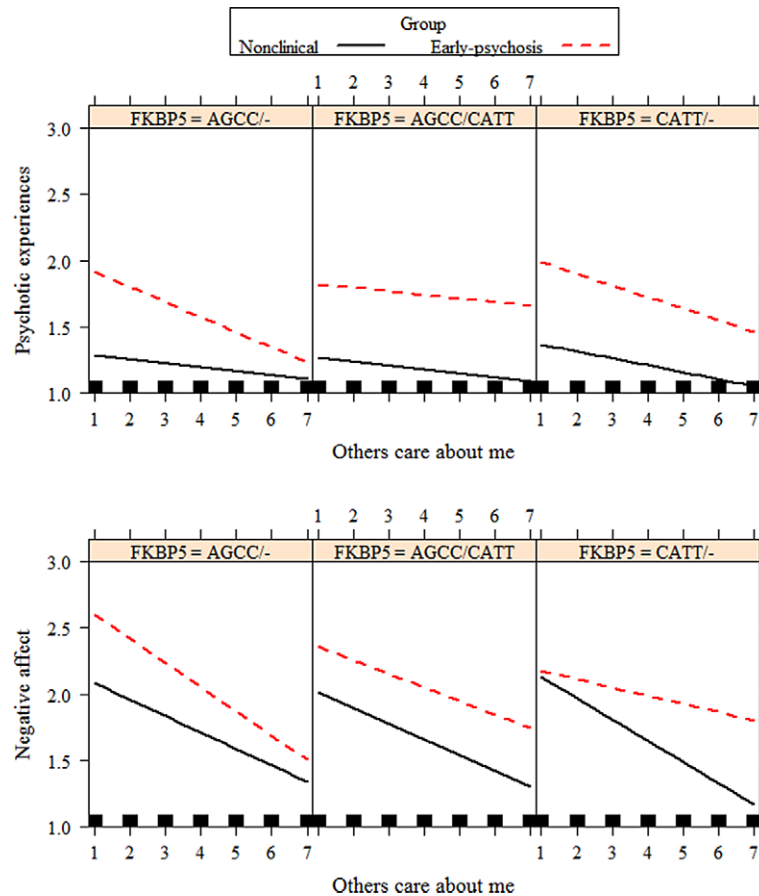
Figure 2. Group differences between nonclinical and early psychosis groups in the interaction of feeling cared for by others with *FKBP5* haplotype on psychotic experiences and negative affect.

compared with nonclinical group. It must be noted, although, that we did not employ specific statistical tests [46] to formally investigate such pattern of G × E interactions.

Recent etiological evidence that advocates for positive and negative effects of genetic and environment factors on the developmental trajectories of psychosis has not yet been embodied into preventive interventions. In this regard, it is imperative to devise new real-world targeted strategies based on knowledge about the individual capacity of people at-risk or with psychotic symptoms in showing differential reactivity to negative and positive factors. This is a critical issue, as many clinicians, even those with knowledge and sensitivity toward psychological factors in incipient psychosis services with a preventive framework, continue to treat persons with any degree of psychosis expression in a very different manner to that employed with persons presenting with risk for or overt non-psychotic disorders. Most likely, decades of a narrow conceptualization of psychosis as the straightforward product of a genetically determined brain disease, the historically engraved "broken brain" view of schizophrenia [47] and the youth of a developing agreed upon conceptual framework in which to integrate the dynamic, malleable, and reactive nature of psychosis experiences, partly account for this situation.

Strengths and limitations

The present study has a number of strengths, including the estimation of a haplotype that increases the power to detect genetic associations [48] and the use of valid ecological measures that are considered to increase the power and reliability of G × E research [49]. In this sense, the design of the study offers a useful model for researchers wanting to examine complex G × E effects in the real world. As regards to limitations, these include gender differences in the composition of nonclinical and clinical samples, which may limit the generalizability of findings; and the fact that causal inferences of the effects of momentary positive and negative experiences cannot be definitively drawn given that ESM predictor and criterion variables were measured concurrently. Future G × E longitudinal studies should also examine the association of PE and NA interactions over time in large samples allowing examination of potential differences in affective versus nonaffective psychosis diagnoses. This would shed light on the complex relationship between affect and psychosis and potential similarities and differences in phenotypes with a predominance of each component.

Conclusions

Overall, the study provides evidence of individual differences in the interaction of genetic variation with proximal environmental factors in nonclinical and incipient psychosis groups. Future studies should employ ambulatory assessments to investigate potential mechanisms involved in the interplay of positive momentary exposures with protective individual variation in relevant genes for the homeostasis of the HPA axis, which may result in an adaptive response to stress in the realm of daily-life. Moreover, empirical evidence from research examining patterns of reactivity to the

environment could encourage real-world targeted strategies based on the knowledge of individual differences in the reactivity from negative to positive factors in the field of psychosis. This is a critical issue given that, despite intense efforts in the early intervention paradigm [50], there continues to be a great amount of therapeutic helplessness associated with psychosis risk outcomes.

Conflict of Interest. The authors declare no conflict of interest.

Supplementary Materials. To view supplementary material for this article, please visit http://dx.doi.org/10.1192/j.eurpsy.2019.4.

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