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# The role of stress and novel gene-environment interactions in the extended psychosis phenotype

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DOCTORAL THESIS

# The role of stress and novel gene-environment interactions in the extended psychosis phenotype

by

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*Para ti, Pepus.*

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# CONTENTS

# 1. INTRODUCTION

Schizophrenia and related psychotic disorders rank among the most severe and debilitating mental conditions, affecting approximately 3% of the population (Perälä et al., 2007; Van Os, 2015; Moreno-Küstner et al., 2018). Although considered 'low-prevalence' disorders (Baxter et al., 2013), they imply profound personal distress and burden, with enormous costs for patients, their families, and society at large (Van Os & Kapur, 2009). In addition, psychotic disorders emerge between late adolescence and early adulthood, disrupting a critical developmental period in terms of education, professional and social achievements and thus, provoking great disability at a young age.

Although traditional medical models have considered psychosis as a dichotomous entity (present versus absent), the reality is that psychotic-like experiences are common not only in individuals with a psychotic disorder, but also in the general population (Van Os & Reininghaus, 2016). Thus, compelling evidence suggests that psychotic disorders are expressed across a broad continuum of individual differences in personality, symptoms and impairment, ranging from nonclinical and minimal dysfunction to clinical and full-blown manifestations (e.g., schizophrenia). This extended psychosis-proneness phenotype has been referred to as schizotypy (Claridge et al., 1997; Kwapil & Barrantes-Vidal, 2015; Barrantes-Vidal et al., 2015) or the extended psychosis phenotype (Kaymaz & van Os, 2010; Van Os & Reininghaus, 2016; Guloksuz & van Os, 2018; 2021). The causes underlying the transition across this continuum are still not well understood; however, it is well accepted that both genetic and environmental factors are involved.

Contrary to traditional etiological models that considered schizophrenia a 'highly-heritable' disorder, currently it is acknowledged that mental disorders in general, and psychotic in particular, are multifactorial disorders with a substantial environmental

component in which hundreds of thousands of genetic variants interact (Van Os et al., 2008; Wermter et al., 2010; Uher & Zwicker, 2017). One of the main environmental factors involved is psychosocial stress, particularly at the earliest developmental periods (e.g., childhood and adolescence). Stressful experiences impact our stress-regulatory systems, such as the Hypothalamic-Pituitary-Adrenal (HPA) axis, leading to an increased stress-sensitivity that is suggested to be involved in the onset and exacerbation of psychotic symptoms (Read et al., 2001; 2014: Yuii et al., 2007: Belda et al., 2015; Walker et al., 2008: Pruessner et al., 2017). Understanding the biological markers of the HPA axis activity (e.g., cortisol) can help to disentangle the underlying mechanisms in the relationship between stress and psychopathology.

Regarding the interplay between genes and environment, research has been usually guided by the classic diathesis-stress model (Monroe & Simons, 1991; Walker & Diforio, 1997). This model has exclusively focused on the negative effects of adverse environments, which are considered merely triggers of an individuals' genetic predisposition. This has led to a damaging pessimism in terms of resilience and recovery possibilities in psychosis. In contrast, novel evolutionary-based thinking suggests that some individuals differ in their sensitivity to the environment, '*for better and for worse'* (Ellis et al., 2011). That is, that the same individual differences (e.g., genetic factors) involved in adverse risk-promoting environments, can also benefit from positive and supportive contexts, conferring resilience to the development of poor mental outcomes. This framework is referred to as the Differential Susceptibility (DS) model (Belsky et al., 2007; Ellis et al., 2011; Belsky & Pluess, 2013). However, this model has been mostly examined across depression and anxiety phenotypes, but not psychosis, where particularly the influence of positive and supportive environments has been largely neglected.

The empirical work of this thesis is embedded in the *Barcelona Longitudinal Investigation of Schizotypy Study (BLISS)*, a longitudinal study examining risk and resilience factors across the extended psychosis phenotype (Barrantes-Vidal et al., 2013a). The present thesis aims at a) understanding biological mechanisms linking stress and the nonclinical end of the psychosis extended phenotype, that is, schizotypy variation (**Section 1**); and b) testing novel gene-by-environment interactions from a novel DS approach (**Section 2**). To meet these objectives, this research employed the analysis of a biomarker of the HPA axis (i.e., cortisol), polygenic risk scores (PRS) and the assessment of a wide range of environmental and subclinical phenotypes, captured retrospectively and in daily-life using Experience Sampling Methodology (ESM). The samples of the studies reported in this thesis are comprised by nonclinical young adults with normative and elevated scores on schizotypy traits and psychotic-like experiences. Nonclinical samples enable the study of the potential underlying etiological mechanisms of psychosis without the confounding consequences associated to clinical status, such as hospitalization or medication (Barrantes-Vidal et al., 2015).

Findings derived from this thesis may contribute to a growing body of research that challenges current narrow conceptualizations of psychosis and to increase our knowledge about critical causative factors and mechanisms underlying risk and resilience of the extended psychosis phenotype. Furthermore, findings may inform to enhance prevention, detection and intervention abilities to reduce risk, disability and associated stigma, but also to increase the well-being of individuals at-risk or with established psychosis.

# 2. BACKGROUND

## 2.1.The Extended Psychosis-Proneness Phenotype

### *2.1.1. From Categories to Dimensions: The Construct of Schizotypy*

The medical model of psychosis has traditionally assumed a categorical view of the psychosis phenotype, considered a dichotomous entity that can be ascertained by applying discrete clinically-observed criteria to differentiate ill from non-ill individuals, as guided by predominating systems of diagnostic classification (e.g., Diagnostic and Statistical Manual of Mental Disorders [DSM] or International Classification of Diseases [ICD]; Van Os, 2003; Kaymaz & van Os, 2010). Schizophrenia, main 'category' among the psychosis illnesses, has for a long time been referred to as a "chronic brain disorder", a "debilitating neurological disorder" or a "devastating, highly heritable brain disorder" (Van Os, 2016). This 'medical model' involves a very narrow focus on biological phenomena and genetic heritability, dismissing the social context in which our genes and brain operate (Read et al., 2009). More importantly, this ideology has led to damaging pessimism about the potential for recovery possibilities and resilience in the context of risk to psychosis in general, and schizophrenia in particular.

This model has come under some pressure in the last two decades due to advances in the conceptualization of the psychosis phenotype. A large body of evidence has increasingly supported a dimensional view of the phenotype suggesting that psychosis is expressed across a broad dynamic continuum of individual differences in personality, symptoms and impairment, that ranges from nonclinical (e.g., psychotic-like traits or experiences) to full-blown clinical manifestations (e.g., schizophrenia-spectrum disorders) (Claridge, 1997; Guloksuz & van Os, 2018; 2021). This extended psychosis-proneness phenotype has been referred to as schizotypy (Barrantes-Vidal et al., 2015; Kwapil & Barrantes-Vidal, 2015; Grant et al., 2018). The schizotypy model suggests that

the same etiological genetic and environmental factors are shared across individuals at different levels of the continuum and that the expression of psychotic features differs in terms of degree of severity and dysfunction, but not qualitatively (Barrantes-Vidal et al., 2015). Thus, schizotypy is not considered to be a separate entity from schizophrenia, rather, schizophrenia would represent the extreme poor outcome fraction of this complex and much broader phenotype (Guloksuz & van Os, 2018). Whereas strong evidence indicates that milder forms of psychotic symptoms, namely psychotic-like experiences (PLE), are present in the general population (i.e., prevalence of ~7%), in most of the cases (~80%), experiences will be attenuated and transient, and a small proportion (~20%) may become persistent over time with eventually a minority developing a psychotic disorder (Linscott & van Os, 2013; Kaymaz et al., 2012; Zammit et al., 2013; Van Os & Reininghaus, 2016). Therefore, schizotypy offers a useful and unifying construct for understanding mechanisms involved in the transition from predisposition to disorder (Barrantes-Vidal et al., 2015; Kwapil & Barrantes-Vidal, 2015). Of note, phenotypic continuity across nonclinical and clinical manifestations has shown to be reflected by etiological continuity too, in which some genetic (Mistry et al., 2018; Legge et al., 2019) and environmental (Van Os & Rutten, 2010; Pignon et al., 2021) factors associated to schizophrenia have been associated to psychotic experiences in the general population.

Importantly, the heterogeneity of schizotypy has shown to be represented by a three-dimensional structure of positive, negative and disorganized schizotypy (Kwapil & Barrantes-Vidal, 2015; Kwapil et al., 2018; Kemp et al., 2021), replicating the most supported model of positive, negative and disorganized symptomatology in schizophrenia (Lenzenweger & Dworkin, 1996; Liddle, 1987).

Overall, the recognition of an extended psychosis-proneness phenotype enables the study of subclinical and nonclinical manifestations to potentially enhance the

identification of biological, social and psychological processes involved in the etiology and development of psychosis while minimizing the confounding consequences of fully-established clinical disorders, such as hospitalization and medication (McGorry et al., 2010).

### *2.1.2. The Psychosis Phenotype as a Transdiagnostic Dimension*

There is growing evidence supporting the notion of the extended psychosis phenotype as a transdiagnostic phenomenon. Research shows that many individuals with psychotic experiences have a diagnosis of a non-psychotic disorder (Varghese et al., 2011; Kelleher et al., 2012; Jeppesen et al., 2015; Kelleher & Cannon, 2021), primarily of depression or anxiety disorder, where psychotic experiences have been reported to be two times prevalent than in individuals without these diagnoses (Wigman et al., 2012). The concurrent presence of psychotic experiences and an affective or anxiety disorder has been shown to reflect clinical severity and poor response to treatment (Wigman et al., 2012; Wigman et al., 2014; Kelleher et al., 2013; Kelleher & Cannon, 2021). At the same time, experiencing subclinical psychotic experiences has shown to be causally associated to psychological disturbances, including anxiety, depressive and hypomanic symptoms (Armando et al., 2010; Kelleher & Cannon, 2016; Van Os & Reininghaus, 2016; Lindgren et al., 2022). Particularly at the earliest stages, psychopathology expression is highly heterogeneous and unstable, and a mixture of different symptom dimensions dynamically interact with each other (McGorry et al., 2018).

Whereas this multidimensional continuity is still not recognized by current diagnostic classification systems (e.g., DSM-V), this transdiagnostic conceptualization is recognized, particularly for research purposes, by models that cut across discrete diagnostics such as the Research Domain of Criteria (RDoC; Insel et al., 2010), the

Hierarchical Taxonomy of Psychopathology (HiTOP; Kotov et al., 2017) or the p-factor construct (Caspi et al., 2014).

Notably, this phenotypic non-specificity across psychopathology in general, and psychosis in particular, also seems to be supported by non-specific genetic (Nivard et al., 2017; Van Os et al., 2017; Richardson et al., 2019; Grotzinger et al., 2022) and environmental (Guloksuz et al., 2015; Pries et al., 2018; Radhakrishnan et al., 2018; Van Os et al., 2020) etiological factors influencing not only psychosis-spectrum phenotypes, but diverse psychopathology outcomes (Lahey et al., 2021; Lynch et al., 2021).

### 2.2. Current Approaches in Psychosis Etiology Research

Psychotic disorders, and particularly schizophrenia, have been defined as highly heritable disorders for many years, or at least, before the era of genome-wide association studies (GWAS), with little or no consideration of environmental influences. Nowadays, advances on molecular techniques as well as compelling epidemiological evidence on the impact of environmental factors on psychosis, has led to an increasing acknowledgement that mental disorders, including psychosis, are multifactorial diseases that result from the complex combination of genetic and environmental factors as well as their interplay (Van Os et al., 2008; Wermter et al., 2010; Uher & Zwicker, 2017). Nonetheless, the prevailing model guiding gene-environment research in psychosis continues to be the diathesis-stress model, which establishes that individuals carrying genetic-risk variants are more vulnerable to the effect of environmental adversity and thus, more prone to develop psychosis.

#### *2.2.1. Genetic Factors: From Candidate Genes to Genome Wide Approach*

Schizophrenia is considered a highly heritable disorder with heritability estimates around 70-80% based on family studies (i.e., twin studies or familial aggregation; Legge

et al., 2021). During the last two decades, psychiatric genetics has attempted to identify the specific genetic variants underlying susceptibility to psychosis focusing on candidate-gene research strategies. The candidate-gene approach aims at identifying allelic variants in different genes coding for proteins involved in neurobiological pathways that are believed to be disrupted in the phenotype of interest. Specifically in psychosis, variants related to lower efficacy of the dopaminergic, serotoninergic or glutamatergic systems as well as to pathways related with the neurodevelopment, have been of particular interest: the catechol-O-methyltransferase (COMT), the brain-derived neurotrophic factor (BDNF), or the zinc-finger protein 804A (ZNF804A), among others (Castro-Català, 2017; DeRosse et al., 2012; Modinos et al., 2013). However, there is little evidence to support almost none of the 'traditional' schizophrenia genes (Sullivan et al., 2017). In psychiatric genomics in general, but psychosis in, particular, candidate-gene approaches have been facing several challenges. Primarily, because of the lack of replicability caused, in part, by the very low effect sizes of these putative psychosis-susceptibility genes that hardly explain a few percent of the phenotypic variance (also referred to as, SNP-based heritability). In addition, these studies have been at times criticized for not integrating the information given by multiple candidate genes.

Conversely, and in an attempt to tackle such limitations, advances in genotyping techniques over the recent years have allowed large-scale studies analyzing up to a few million polymorphisms across the human genome in hundreds to thousands of samples, such as genome-wide association studies (GWAS). GWAS are hypothesis-free association studies aimed at identifying genetic variants associated with a given phenotype/disease. To date, large GWAS have identified numerous genome-wide significant loci for several psychiatric disorders, including more than 100 loci for schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium,

2014; 2022; Pardinas et al., 2018) and, overall, highlighting the polygenic architecture of such complex psychiatric traits. GWAS enable the creation of a single measure of common genetic liability for a phenotype, referred to as Polygenic Risk Score (PRS). A PRS is obtained by summing the number of alleles associated to the trait and weighting the sum by the effect size reported in the GWAS of reference. Thus, a PRS indexes the additive effect of multiple SNPs, where higher scores indicate greater genetic predisposition toward the phenotype of interest (Lewis & Vassos, 2020). Although PRSs give a much better representation of the genetic risk profile than a single candidate gene and have demonstrated to show larger cumulative effect sizes and predictive power (Halldorsdottir & binder, 2017; Bulik-Sullivan et al., 2015), PRS for schizophrenia (PRS-SCZ), one of the best powered mental disorder related GWAS, can currently explain around 7.7% of the variance in case-control status (International Schizophrenia Consortium et al., 2009; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2020). This represents a much lower amount of phenotypic variance explained by PRS than the variance estimated across twin studies, leading to a considerably 'heritability gap'. This phenomenon, also named as "missing heritability", has been suggested to be accounted by environmental effects, gene-gene interactions (i.e., epistasis), other rare genetic variants contributing to the complex polygenic architecture of mental disorders, and most importantly, the interplay between genes and environments, including gene-environment interactions (GxE) as well as epigenetic effects (Maher, 2008; Young, 2019; Marsman et al., 2020). Furthermore, studies employing PRSs have mostly focused on diagnosis-specific models, whereas studies aiming at identifying direct associations between PRS-SCZ and quantitative psychotic manifestations across the extended psychosis phenotype (and not only at the extreme end, that is, schizophrenia) have yielded controversial results, reporting positive (Isvoranu et al., 2020; Velthorst et

al., 2018; Hatzimanolis et al., 2018) and negative (Zammit et al., 2014; Van Os et al. 2020; Nenadić et al., 2020; Smigielski et al., 2021; Mas-Bermejo et al., *submitted*) findings. Also, in general population-based studies, PRS-SCZ seems to account for very low variance explained as a risk factor of mental health (Marsman et al., 2020). In addition, molecular studies indicate that most common genetic variants are non-specifically associated with a range of psychopathology manifestations (Cross-Disorder group of the Psychiatric Genomics Consortium et al., 2019; Marsman et al., 2020). In particular, PRS-SCZ has shown to genetically overlap with other 'major psychiatric disorders' such as bipolar disorder or major depression disorder (Cross-Disorder group of the Psychiatric Genomics Consortium et al., 2019; Nivard et al., 2017; Van Os et al., 2017; Richardson et al., 2019; Grotzinger et al., 2022; Mistry et al., 2018; Brainstorm Consortium et al., 2018), as well as neurodevelopmental outcomes (Hatzimanolis et al., 2015; Riglin et al., 2017), thus, adding support at a genetic level to the notion of the psychosis phenotype as a transdiagnostic dimension.

The 'missing heritability' problem, frustrating genotype-phenotype associations, and the genetic overlap across mental disorders, highlight the extremely complex polygenic architecture of psychosis in particular, and psychopathology in general but, most importantly, have led to an increasing attention and compelling evidence on the influence of environmental factors and their interplay with genetic factors in psychosis research.

### *2.2.2. Environmental Factors: The Role of Early and Recent Psychosocial Stress*

Epidemiological studies reporting associations between multiple environmental exposures and psychosis (Van Os et al., 2010) started to suggest that environment may played a more prominent role in the etiology of psychosis than traditionally accounted. Particularly, converging evidence has revealed associations between psychosocial factors, at both macro (e.g., urbanicity, poverty, minority status) and micro (e.g. family

environment, childhood adversity, cannabis use) levels, and nonclinical, subclinical and clinical expressions of the extended psychosis phenotype (Sheinbaum & Barrantes-Vidal, 2015; Radua et al., 2018; Williams et al., 2018; Stilo & Murray, 2019; Cullen et al., 2023). These include several psychosocial stressors that may take place at different developmental periods (Zwicker et al., 2018).

A critical developmental period in which psychosocial stress may exert a strong impact on the later development of psychopathology manifestations is childhood and adolescence (Dean & Murray, 2005; Zwicker et al., 2018). Particularly, one of the most extensively studied forms of early-life stress is childhood adversity, which encompasses a range of experiences such as emotional, physical, and sexual abuse, emotional and physical neglect, as well as other adverse experiences that might occur during childhood such as the death of a parent. Childhood adversity has been consistently associated with risk for clinical and subclinical psychosis, with studies usually reporting a 2 to 4 times increased likelihood of exhibiting psychotic manifestations (Van Winkel et al., 2013; Velikonja et al., 2015; Morgan & Gayer-Anderson, 2016; Rosenfield et al., 2022). More so, research has shown that early adversity not only impacts the onset, but the course and outcome of psychosis (Trotta et al., 2015; McGrath et al., 2017), by showing a dose-response effect between number and severity of such experiences and psychosis risk, severity and chronicity (Morgan & Gayer-Anderson, 2016; Li et al., 2015).

Exposure to childhood adversity has been predominantly associated with the positive dimension of psychosis (Gizdic et al., *submitted to publication*; Sheinbaum et al., *submitted for publication*; Gibson et al., 2016; Velikonja et al., 2015). However, recent meta-analytic work (Alameda et al., 2021) shows that general childhood adversity is associated with all psychotic dimensions, whereas results differ when examining abuse versus neglect forms of adversity. Abuse seems to be more strongly associated to the

positive dimension of psychosis, whilst neglect is associated with the negative one (Alameda et al., 2021; Bailey et al., 2018; Cristóbal-Narváez et al., 2016).

On the other hand, psychosocial stress in adulthood has also shown to impact the extended psychosis phenotype (Begemann et al., 2017). For instance, exposure to stressful life events has been strongly associated with the onset, exacerbation, or relapse of psychotic illness (Ira et al., 2014; Beards et al., 2020; Martland et al., 2020; Colizzi et al., 2023), and also to subclinical psychotic symptoms (Pignon et al., 2021; Lachowicz et al., 2022) and high levels of schizotypy (Kocsis-Bogár et al., 2013; Juan & Rosenfarb, 2022). Notably, the effect of life events seems to impact positive, negative, and disorganized dimensions (Donaldson et al., 2022). More so, the impact of minor daily hassles on psychosis risk has also been increasingly supported (Kwapil et al., 2012; Barrantes-Vidal et al., 2013b; Cristóbal-Narváez et al., 2016a,b; 2017; 2020; Kwapil et al., 2020; Monsonet et al., 2022a,b; 2023; Reininghaus et al., 2016; Rauschenberg et al., 2022; Juan & Rosenfarb, 2022; Kemp et al., 2023).

Finally, accumulating evidence indicates that the effects of most environmental factors on psychosis liability are also pleiotropic (Guloksuz et al., 2018), that is, that the same environmental exposures seem to confer risk for a diverse set of psychopathology outcomes, including psychosis and affective dysregulation (Guloksuz et al., 2015; Pries et al., 2018; Radhakrishnan et al., 2019; Conway et al., 2018; Van Os et al., 2020; McLaughlin et al., 2020; Hogg et al., 2022).

#### 2.2.2.1. *Mechanisms Linking Stress and Psychosis: The Hypothalamic-Pituitary-Adrenal Axis*

One way in which early and recent stress might interact increasing the risk to psychosis is through a process of stress sensitization. As posited by the traumagenic

neurodevelopment model of psychosis (Read et al., 2001; 2014: Yuii et al., 2007; Belda et al., 2015), prolonged and/or severe stressful experiences in highly sensitive developmental periods (i.e., childhood) might result in a process of behavioral and biological sensitization by which the development of enhanced stress sensitivity to subsequent minor adversities in adulthood, may contribute to an increasing liability for the onset and persistence of psychotic symptoms (Sheinbaum & Barrantes-Vidal, 2015). In order to examine the behavioral component of stress sensitization, research has advocated for the combined study of early and recent stressful exposures (Begeman et al., 2017). Increasing evidence has examined the interplay between childhood adversity and stressful life events or daily hassles in psychotic phenomena, supporting a mechanism of behavioral sensitization (Cristóbal-Narváez et al., 2016a, b; Lataster et al., 2012; Rauschenberg et al., 2017; Paetzold et al., 2021). On the other hand, biological sensitization involves the disruption of stress-regulatory systems such as the Hypothalamic Pituitary Adrenal (HPA) axis. As proposed by the neural diathesis-stress model of psychosis (Walker et al., 2008: Pruessner et al., 2017), the HPA axis plays a role as a mediator of the effects of stress on triggering and exacerbating psychosis symptoms. This axis acts in response to stressors by activating a hormonal cascade that starts with the release of the corticotropin-releasing hormone (CRH) from the hypothalamus, followed by the release of adrenocorticotropic hormone (ACTH) from the pituitary that finally, induces the secretion of adrenal cortisol. Cortisol binds to glucocorticoid receptors (GR) and promotes systemic physiological and behavioral responses to stress. This response is suppressed by a negative feedback loop once stressors are absent. Therefore, cortisol has received particular attention as a measure to study HPA axis dysfunction in psychopathology in general, and psychosis in particular. However, studies examining the association of cortisol levels and psychosis have

produced mixed findings, mostly due to methodological constraints. Cortisol concentrations can be analyzed from blood serum, saliva or urine. However, these measurements have only been capable of reflecting acute or short-term responses to stress but fail to measure stable long-term levels (Russell et al., 2012). In contrast, hair cortisol concentrations (HCC) have been proposed as a feasible and promising measure to retrospectively examine the long-term activity of the HPA axis (Herane Vives et al., 2015). However, very few studies have examined HCC across the psychosis spectrum, reporting elevated levels in clinical samples of schizophrenia (Aas et al., 2019; Streit et al., 2016), First Episode of Psychosis (FEP; Andrade et al., 2016) and populations at clinical risk for psychosis (Söder et al., 2019).

#### 2.2.3. *The Interplay Between Genes and Environment: From Diathesis-Stress to Differential Susceptibility*

Unsuccessful attempts to discover main genetic effects and increasing evidence supporting the substantial environmental component of psychosis, has led to the incorporation of gene-by-environment interactions (GxE) in psychosis research (Van Os et al., 2008; McGrath et al., 2013; Wahbeh & Avramopoulos, 2021).

Several theoretical models have been proposed to describe GxE. Among the most prominently used is the classic Diathesis-Stress Model (Gottesman & Shields, 1967; Monroe & Simons, 1991), which posits that genetic vulnerability predisposes an individual to psychopathology when exposed to negative environmental factors. That is, adversity has been considered as a merely trigger of a psychopathological condition in genetically susceptible individuals. GxE studies across the psychosis continuum have been mainly focusing on candidate-genes related to specific pathogenic factors in psychosis (e.g. dopaminergic striatal dysfunction, neurodevelopment) in interaction with

adverse environments (Modinos et al., 2013; Zwicker et al., 2018; Misiak et al., 2018), and more recently, also employing genome-wide PRS (Woolway et al., 2022).

Converging evidence supporting the pleiotropic and transdiagnostic effects of common genetic and environmental factors, calls for the exploration of the genetics of mental disorders as unspecific factors influencing individuals' sensitivity to environmental cues (Fox & Beevers, 2016; Assary et al., 2020; Zhang & Belsky, 2020). Moreover, increasing support to the role of positive environmental factors in relation to psychosis expression and outcome (Coughlan et al., 2019; McMahon et al., 2021; Ruiz-Yu et al., 2022; Donaldson et al., 2022) suggests that novel views should be applied to GxE research.

#### *2.2.3.1. A Novel Approach to Conceptualize Risk and Resilience for Psychosis: Differential Susceptibility (DS) to the Environment*

From an evolutionary-based perspective, it is implausible to think that natural selection would have favored genetic variants only to increase individuals' vulnerability for dysregulation and disorders. Alternatively, novel thinking based on evolutionary theory suggests that individuals may differ in their sensitivity (referred to as susceptibility) to the full spectrum of contextual factors, adverse and supportive. As a promising model to describe GxE, Belsky et al. (2007) defined the differential-susceptibility (DS) hypothesis, which proposes that individuals traditionally considered to carry greater vulnerability may be better conceptualized as being more plastic, sensitive or malleable to the environment (Belsky et al., 2007; Belsky & Pluess, 2009; Ellis et al., 2011; Belsky & Pluess, 2013). That is, that the same genetic variants, temperamental traits or physiological mechanisms involved in increasing the negative effects of adverse experiences could also be involved in enhancing the likelihood of benefiting from the positive ones ("*for better and for worse*"; Ellis et al., 2011). Although the DS model

partially integrates views from the classic diathesis-stress framework, as it contemplates the negative effects of adverse environments, the models are fundamentally different; the DS models implies that the traditional 'risk' genes must actually be called "susceptibility" genes (Bakermans-Kranenburg, 2015; Fox & Beevers, 2016), and that these would confer risk and resilience to both, supportive and adverse environments. Thus, for instance, from a family offspring, some children would have greater plasticity and sensitivity to environment, whereas others would display more fixed and stable features, and parents would safeguard part of their offspring against potential misfit to future environmental conditions and thereby, ensure reproductive fitness and survival of the family genes (Ellis et al., 2011; Belsky & Pluess, 2013). Another model derived from the DS reasoning is the vantage sensitivity model (Pluess & Belsky, 2013; Pluess et al., 2017). It is considered the mirror image of the diathesis-stress model as it poses that some individuals would disproportionally benefit from positive exposures, without also implying an increase in the susceptibility to negative exposures. However, this model seems to lack a strong theoretical and evolutionary background (Bakermans-Kranenburg & van IJzendoorn, 2015).

Candidate-gene studies have shown that genes involved in the serotoninergic (e.g., 5-HTTPLR; Van IJzendoorn et al., 2012) and dopaminergic systems (e.g., DRD4; Bakermans-Kranenburg & van IJzendoorn, 2011) seem to be more open to both, positive and negative environments. For instance, the short (S) allele of the 5-HTTLPR has shown to increase the levels of antisocial behavior, neuroticism, or depressive symptoms under negative contexts, but also to benefit more from positive environments.DS research has also benefited from the GWAS era. Keers et al. (2016) developed for the first time a PRS of environmental sensitivity (PRS-ES) from SNPs associated to within-pair variability in emotional problems in 1,026 monozygotic twin pairs. The observed within- pair

discordance was attributable to non-shared environmental effects, thus obtaining a PRS that differentiated between individuals more or less sensitive to environmental influences. PRS-ES has shown to moderate the effects of a cognitive-behavioral intervention (Keers et al., 2016) and a family-based intervention (Lemery-Chalfant et al., 2018) on children's internalizing symptoms, *for better and for worse*.

Of note, the DS model has mostly been examined in developmental research (Bakermans-Kranenburg & van Ijzendoorn, 2006; Bakermans-Kranenburg & Van Ijzendoorn, 2011) and more in the conceptualization and study of the anxiety and depression spectrums (Bogdan et al., 2014; Chen et al., 2015; Dalton et al., 2014), where the importance of psychosocial factors and malleability of the underlying neurobiology has been widely recognized. However, this novel theorization has been rarely invoked in psychosis. Only one study has shown that genetic variability related to the HPA axis (i.e., FKBP5 gene) moderated the effects of recent life events on neuroticism in a nonclinical sample with high schizotypy (Pérez-Pérez et al., 2018).

From a statistical viewpoint, a GxE interaction consistent with a DS model is disordinal in form. To distinguish disordinal from ordinal (i.e., consistent with diathesis-stress) interactions, two statistical approaches have been proposed. The exploratory approach (Roisman et al., 2012) involves a post hoc evaluation of initially exploratory tests of regression models that require significant GxE effects to probe the form of the interaction. Then, the Regions of Significance (RoS) determine the range of values of the environment where the environment-predicting outcome regression lines (slopes) significantly differ from each other. However, it was observed that the slopes under a diathesis-stress model might be identical to those under DS, and that what differed was the placement of the crossover point in the interaction. Following the theoretical significance of the crossover point, the competitive-confirmatory approach (Widaman et

al., 2012; Belsky, Pluess & Widaman, 2013) uses a priori testing method in which the regression model is reparametrized to estimate the crossover point according to the different models (diathesis-stress, DS, vantage sensitivity) and fit-indices criteria are used to determine which alternative model fits the data best. Claims by Belsky and Widaman (2018) advocate for using a mixed model in which data is first fit in a regression model under a traditional exploratory approach to assess interaction effects and, then, the form of the interaction is probed by using the competitive-confirmatory approach. Leading experts in DS have recently demonstrated a better performance and accuracy of the competitive-confirmatory approach in distinguishing the different interaction models compared to the exploratory (Jolicoeur-Martineau et al., 2020).

### 2.3. Enhancing the Study of GxE Interactions: Experience Sampling Methodology

One of the main criticisms of GxE studies has been the poor assessment of the environment, mostly relying on retrospective self-reports. In addition, most research focuses on major environmental inputs in terms of impact, such as stressful life events, although everyday minor situations, both positive and stressful, are more frequent in people's lives. Ambulatory assessment techniques such as Experience Sampling Methodology (ESM; Delespaul, 1995), also referred to as Ecological Momentary Assessment, allow the within-day examination of individuals' psychological state and contextual factors in real time and in their real-life settings. This offers several advantages as compared to traditional assessment techniques, including ecological validity, as individuals are assessed in their real environments and minimizing retrospective bias, as experiences are captured in real time (Myin-Germeys et al., 2009). Particularly relevant to the DS theorization, ESM allows to examine both momentary positive and negative experiences. More so, employing repeated high-quality measurement of the environment

has been suggested to substantially reduce the large sample size requirements of GxE studies, another one of the main criticisms of GxE research, and enhance the detection of subtle interaction effects (Rutter et al., 2006: van Os et al., 2008).

In fact, studies using ESM have already shown the impact of daily-stress appraisals in schizotypy traits, subclinical and clinical experiences (e.g., Myin-Germeys et al., 2003; Oorschot et al., 2009; Myin-Germeys & van Os, 2007; Kwapil et al., 2012; Barrantes-Vidal et al., 2013b; Cristobal-Narvaez et al., 2016a; 2020; Chun et al., 2017; Kwapil et al., 2020; Monsonet et al., 2022a,b; Kemp et al., 2023). Increasing GxE evidence has also supported the impact of day-to-day experiences across the extended psychosis phenotype (e.g., van Winkel et al., 2008; 2014; Cristobal-Narvaez et al., 2017; 2020; Pries et al., 2020; Schick et al., 2022).

# 3. AIMS AND OUTLINE OF THIS THESIS

The work presented in this thesis is embedded in the *Barcelona Longitudinal Investigation of Schizotypy Study* (BLISS), a longitudinal study examining risk and resilience factors across the extended psychosis phenotype (Barrantes-Vidal et al., 2013a). The present thesis aims at increasing knowledge about the biological mechanisms linking stress and the nonclinical end of the psychosis extended phenotype (that is, schizotypy) as well as testing for the first-time gene-by-environment interactions from the novel Differential Susceptibility (DS) approach in the psychosis phenotype.

The specific goals that derive from the overarching goal are the following:

1) To investigate the association between hair cortisol with a broad range of psychosocial stressors and stress-related phenotypes (including schizotypy, paranoia and psychotic-like experiences) as well as subjective self-reported levels of stress.
2) To examine the moderating role of hair cortisol in the association between early and recent psychosocial stressors with the expression of several stress-related phenotypes, including schizotypy, paranoia and psychotic-like experiences
3) To test whether genetic sensitivity to the environment moderated the association of adverse childhood experiences with subclinical expressions of anxiety, depression and psychosis in a DS manner.
4) To test whether genetic variability associated to psychotic-like experiences moderated the impact of adverse childhood experiences on subclinical phenotypes following the DS model.

5) To examine whether DS to the environment can be captured in the realm of daily life using Experience Sampling Methodology.
6) To investigate whether stress-related genetic variability moderates emotional reactivity in daily life following the DS model.

These specific goals were addressed by five empirical studies organized in two main sections.

The **first section** comprises the studies addressing goals 1 and 2, and examines stress as measured objectively with levels of hair cortisol and its relationship with stress-related phenotypes in the nonclinical end of the extended psychosis continuum. In particular, **chapter 1** presents a cross-sectional study on the direct association between hair cortisol concentrations (HCC) and subjective measures of stress as well as other stress-related phenotypes such as schizotypy traits, depressive and anxiety manifestations. A general pattern of associations between HCC with the stress-related measures and the different subclinical spectra in the nonclinical sample was expected. **Chapter 2**, examined cortisol as a moderator of both early and recent experiences in the expression of stress-related phenotypes. It was expected that the moderating role of the biological indicator of stress-sensitization, cortisol, would be involved in the associations between early and recent stress on all the phenotypes that have been robustly associated to stress, that is, the paranoid, positive schizotypy, depression and anxiety dimensions, as well as levels of perceived stress, but not with negative schizotypy.

The **second section**, pursuing goals 3-6, was dedicated to examining the goodness of fit of GxE interactions into the novel DS model to the expression of schizotypy in nonclinical young adults. Chapter 3 included the first GxE empirical work wh testing whether polygenic individual differences in sensitivity to the environment moderated the association of different childhood experiences with subclinical expressions of psychosis,

anxiety and depression in a DS manner. As an exploratory goal, the moderating role of a PRS related to PLE was also tested. It was expected that highly genetically sensitive individuals would show increased subclinical symptoms (positive, but not negative, psychotic-like manifestations, depression and anxiety) if they experienced childhood adversity and, at the same time, lower levels of symptoms if exposed to low or no adversity compared to those genetically less sensitive to the environment. **Chapter 4**, aimed at extending work conducted in chapter 3 by examining whether differential sensitivity to the environment was also captured in daily-life, employing ESM. It was expected that highly genetically susceptible individuals would also display greater PLE, paranoia, negative affect and lower positive affect when exposed to highly stressful or not positive daily situations, as compared to those low genetically susceptible, but also, they would show lower symptoms and greater positive affect in low stressful or high positive everyday contexts. Finally, **chapter 5** shows a second ESM study testing the role of a stress-related polygenic score as a moderator of daily emotional reactivity and whether individuals are also differentially affected by positive and negative daily contexts in a way consistent with the DS model. It was hypothesized that polygenic variability of the HPA axis would moderate the impact of perceiving situations as stressful on increases on negative affect (that is, negative emotional reactivity).

*Note*. Please, note that all studies included in this thesis are presented in article format (that is, structured in abstract, introduction, methods, results and discussion sections) as they are articles published (study from chapter 1), submitted (studies from chapters 2 and 3) or to be submitted (studies from chapters 4 and 5) in scientific journals. Thus, the reference style of the articles varies according to the journal's requirements where they were or are going to be submitted.

# SECTION 1

# CORTISOL AND SCHIZOTYPY

# Chapter 1

# Examining the Relationship Between Hair Cortisol with Stress-related and Transdiagnostic Subclinical Measures

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**Abstract**

*Background*: Hair cortisol concentrations (HCC) provide a retrospective examination of long-term cortisol production as a measure of the hypothalamic-pituitary-adrenal (HPA) axis functioning, one of the major neural systems implicated in mediating the effects of stress on mental illness. However, evidence about the relationship between HCC with stressors and symptoms is scattered. In the present study, we aimed to examine the association between HCC and a wide range of stress-related and transdiagnostic subclinical measures in a sample of nonclinical young adults with a wide distribution of schizotypy.

*Methods*: A total sample of 132 nonclinical young adults recruited at college and technical schools oversampled for schizotypy scores were assessed on distal and proximal stressful experiences, appraisals of stress, traits and symptoms of the affective, psychosis and dissociation spectrums, as well as stress-buffering measures, and provided 3 cm-hair samples.

*Results*: No significant associations were found between HCC and any of the stress-related and subclinical measures. Only suspiciousness and disorganization showed a trend for a positive association with HCC but the magnitude was small.

*Conclusions*: The present findings support previous studies indicating an overall lack of concordance between a broad range of stress-related and (sub)clinical phenotypic measures with hair cortisol. This study examined for the first time the relationship of HCC with the nonclinical expression of the psychosis spectrum, that is, schizotypy, which complements previous studies on clinical high risk and established psychosis and offers a promising strategy for studying possible HPA dysfunctions characterizing the subclinical psychosis continuum without the confounds associated to clinical psychosis.

## 1. Introduction

The Hypothalamic-pituitary-adrenal (HPA) axis is one of the major neural systems implicated in mediating the effects of stress on mental illness. This axis acts in response to stressors by releasing glucocorticoid cortisol, thereby affecting brain function and facilitating physiological and behavioral responses to threats. The normal functioning of the HPA axis involves not only its activation under high stressful situations, but also the activation of a negative feedback-loop that stops cortisol secretion in the absence of stressors (1). However, both the activation and inactivation of the HPA axis can be susceptible of dysregulation, which has been widely connected with the development of mental disorders (2).

Cortisol concentrations have been widely analyzed from blood serum, saliva or urine. However, these measurements have only been capable of reflecting acute or short-term responses to stress, with remarkable intra- and inter-individual variability and day fluctuations. In contrast, hair cortisol, which enables a retrospective examination of long-term cortisol production, has recently been proposed as a more accurate measure of chronic stress (3). As hair grows approximately 1 cm per month (4), a 3 cm-sample of hair has been considered a reliable and usable segment to reflect the cortisol production of the last three months from the strand collection. Moreover, it is a non-invasive technique that avoids any further stress associated to the sampling procedure and can be easily stored and transported. Although hair cortisol has been found to be subject to developmental and seasonal variations (5), a considerable degree of intraindividual stability has been assumed and validated so far (6), thus constituting a promising method for the retrospective and stable assessment of cortisol functioning.

Research has provided emerging evidence on hair cortisol concentrations (HCC) alterations in clinical populations, mostly in affective and anxiety disorders and, to a

lesser extent, in psychosis. However, the direction of these alterations is yet to be elucidated and there is some inconsistency across studies (7). Depression has been associated with HPA axis hyperactivity (8) and elevated short-term cortisol response (9). Nonetheless, when examining the long-term activity of the HPA axis assessing HCC in depressed patients, results are unclear. A recent meta-analysis by Psarraki and colleagues (10) shows that most studies found no significant differences in HCC between Major Depression Disorder (MDD) patients and controls (11-13), although one study (14) showed higher HCC and two studies (15, 16) found lower HCC in MDD patients. Nonetheless, higher levels of HCC were found in first episode compared to recurrent depression (17, 18) or when there is comorbidity between MDD and an anxiety disorder (19). Bipolar Disorder patients seem to present higher HCC compared to controls (20-22) as reported in the meta-analysis by Koumantarou Malisiova and colleagues (7), and again, HCC were higher for those with psychiatric comorbidities (23). In contrast, decreased HCC have been found in patients with Generalized Anxiety Disorder (GAD) (24) or other anxiety disorders such as Post Traumatic Stress Disorder (PTSD) (25), although other studies have failed to find an association (16, 19). Results regarding stress-related symptoms in nonclinical populations are scant and have yielded mixed findings. HCC in adolescents (26, 27) or adult workers (28) have been positively associated with depressive symptoms, but lower HCC (29) or no association (30, 31) have also been reported. Studies examining the relationship between hair cortisol and anxiety in nonclinical participants did not find any significant association (29, 31).

Consistent with the current focus on a broader transdiagnostic approach to etiological research in psychopathology (e.g., 32, 33), studies on phenotypes that have been traditionally less associated to stress-sensitivity, such as the psychosis spectrum, are starting to emerge. There is robust evidence that psychotic-spectrum disorders are

associated to childhood adversity (34-37), heightened stress-sensitivity (38-40), and elevated HPA activity (1, 41), suggesting the HPA axis as a relevant mediator of the effects of stress on psychotic symptoms (42, 43). Specifically, elevated HCC has been found in clinical samples of schizophrenia (20, 21), First Episode of Psychosis (FEP) individuals (44) and populations at clinical risk for psychosis (45). However, no studies have examined yet the association of HCC with the nonclinical manifestations of the extended psychosis phenotype, that is, schizotypy traits. Schizotypy is a multidimensional construct that represents the underlying liability for psychosis-spectrum psychopathology expressed across a broad range of personality, subclinical and clinical psychotic features (46).

Exposure to early life adversity has been associated to HPA axis dysregulation, which, in turn, has been found to be robustly associated to elevated risk for developing mental illness. Thus, most current etiological models support that prolonged and/or severe stress exposure in highly sensitive developmental periods (i.e., childhood) disrupts psychobiological stress regulation mechanisms resulting in a process of behavioral and biological sensitization by which the individual manifests an enhanced stress sensitivity to subsequent minor adversities in adulthood (47, 48). Early adversity has been associated to HCC in clinical populations with a psychotic, affective, personality and/or anxiety disorder (20, 49), in individuals clinically at-risk for psychosis (45) and also in nonclinical populations (50-53). However, the last meta-analysis from Khoury and colleagues (54) assessing the strength and direction of the relationship between adverse experiences and HCC (including clinical and nonclinical samples) found two classes of studies: a first one including a majority of studies (N=24) showing a positive association between adversity and HCC, and a second minor group of studies (N=4) showing lower levels of hair cortisol in those exposed to adverse experiences. All studies in the latter group were assessing

childhood maltreatment and showed a moderate effect size; in contrast, the first class of studies included a variety of adversities other than childhood maltreatment (e.g., exposure to natural disasters or domestic violence) and showed a small effect size. This pattern of mixed results might be consistent with theories positing both types of HPA axis alteration following adversity; hyper-activity in the short-term and hypo-activity in the long-term (55). It also indicates the need of differentiating among types of adversities and populations when studying the effects of adversity on the HPA axis.

Another critical question is the association between proximal psychosocial stressors and HPA axis function. A major issue is that the relationship between subjective (i.e., perceived stress, subjective impact of life events) and objective (i.e., cortisol, number of life events) measures of stress has not been coherent across studies and yielded mixed findings. The meta-analysis by Stalder and colleagues (25) indicated no association between subjective perceived stress and HCC across populations exposed to different levels of chronic stress. More recent studies have also failed to find significant associations (30, 56-59), except for Ling and colleagues (60), who found a negative relationship between perceived stress and HCC in African nonclinical mothers (with a quite reduced sample size), and Xu and colleagues (29), who reported, in contrast, a positive association in a Chinese sample of healthy adolescents differing in stress exposure (incarcerated versus attending regular high school). On the other hand, another widely used measure to assess "objective" stress is the quantification of recent life events. This has been mostly studied in adolescent samples, and mixed results have been found. Shapero and colleagues (26) did not find any association between HCC and number of life events, whereas Xu's (27) and Karlén's (61) studies reported a positive association and Sierau's (31) a negative one. Finally, Cullen and colleagues (62) reviewed the literature examining the concordance between naturally-occurring psychosocial stressors,

both distal (trauma) and proximal (perceived stress and life events), with cortisol across clinical and at-risk psychosis populations. Although all types of cortisol measurements were included in the meta-analysis, a poor correlation [r=0.05 (95% CI: -0.00 to 0.10), p=0.059] was found between stressors and cortisol measures (including HCC).

Research so far has only studied the relationship between HCC and the occurrence of stressful life events, but any of those studies has reached to study the whole spectrum of life events, comprising both adverse as well as positive ones (e.g., getting married). Additionally, there is no research on the association between the HCC and the degree of subjective impact (positive or negative) of these life events on the individual. Given large individual differences in stress-related genetic make-up (e.g., BDNF, FKBP5, COMT, 5-HTTLPR), temperamental traits (e.g., neuroticism, harm avoidance), gene-environment interactions, and idiographic contextual factors, it is expected that the same amount of life events can impact very differently on individuals' appraisals (e.g., 63), and, therefore, on levels of HPA axis dysregulation.

The association between neuroticism, a temperamental trait defined by heightened stress reactivity (64), and HCC has only been examined in a twin study, showing no significant correlation (30). Similarly, little is known about the association of HCC with protective factors related to coping with stress. The buffering hypothesis poses that the presence of social support might help buffering the potential deleterious effects of stressful situations (65). However, the biological impact of the effects of social support on stress and, thus, on the HPA axis, has been scarcely investigated. Stalder and colleagues (25) did not find any significant association between HCC and social support in their meta-analysis, whereas Iob and colleagues (66) reported that low social support was associated to high levels of hair cortisol. In contrast, a recent study from Yang and colleagues (67) found a positive association between HCC and the amount of social

support in a sample of schizophrenia patients; however, social support moderated the relationship between stressful life events and HCC by attenuating the effects of life events on cortisol response, thus providing biological support to the buffering hypothesis.

In summary, there is a major concern about the lack of "psychoendocrine covariance" between subjective and objective measures of stress. As referred in Stalder's meta-analysis (25), no consistent associations between HCC and self-reports of perceived stress, social support and depression symptoms emerged in the most recent literature. Moreover, this literature is very scattered in terms of the types of constructs, measures and samples used. Importantly, most studies have examined a very narrow range of stress-related and/or phenotypic variables presumed to be associated to HCC within the same sample—in fact, only meta-analytic studies have offered an integrated perspective of the association of stress and psychopathology measures with HCC. Therefore, the present study aimed to investigate the association between HCC with a broad range of psychosocial stressors (childhood adversity, recent life events) and stress-related measures (perceived stress). Importantly, the stress-related measures used covered both the "objective" report of threatening and stressful life events as well as the "subjective" appraisal of stress impact. In addition, and consistent with current evidence on the relevance of heightened stress-sensitivity as a relevant transdiagnostic mechanism, the association of traits and symptoms of the affective (neuroticism, depression, anxiety), psychosis (suspiciousness, schizotypy) and dissociation spectrums with HCC was examined. Finally, stress-buffering factors (social support) were also examined in a nonclinical sample of young adults oversampled for high levels of schizotypy (i.e., the behavioral liability to psychosis). Examining nonclinical participants with a wide distribution of behavioral risk for psychosis ensures including a representation of individuals with a phenotype that has been consistently associated with high stress

exposures (36, 37) and heightened stress-sensitivity (1, 38, 39, 68), which should enrich the variability in the constructs of interest (stress exposures, HCC and stress-related phenotypic features). Consistent with evidence supporting the dimensional conceptualization of psychopathology and the transdiagnostic relevance of the HPA-axis dysregulation, we expected a general pattern of associations between HCC with the stress-related measures and the different subclinical spectra in a nonclinical sample.

## 2. Methods

### 2.1. Participants

The sample of this study consisted of 132 nonclinical young adults (mean age=27.86, SD= 3.07, range=26.07) belonging to the ongoing Barcelona Longitudinal Investigation of Schizotypy Study (BLISS) (68-70).

At T1, a large pool of 547 unselected college students and 261 technical school students were initially screened with self-report questionnaires (please see details in Barrantes-Vidal et al., 2013a,b). A subsample oversampled with elevated scores on both positive and negative schizotypy factors (to ensure enough variance in the measures of interest) from the Wisconsin Schizotypy Scales (WSS-S) (78, 79), the Schizotypal Personality Questionnaire (SPQ) (77) and the Community Assessment of Psychotic Experiences (CAPE) (106) was selected to conduct in-depth examinations comprising a wide range of interview, questionnaire, and experience sampling methodology measurements. At T2, 214 college and 39 technical school students were reassessed (1.7 and 0.4 years later, respectively). At T3, due to funding constraints, we invited to participate a reduced subsample that retained the original distribution of scores; 103 college and 31 technical school participants were reassessed (1.4 and 1.7 years later, respectively). Of these, 89 college participants were re-assessed at T4 (1.3 years later). Finally, at T5 we were able to successfully reassess 168 (79%) of the college students

assessed at T2 7.8 years later (and 3.2 years after T4). In addition, we reassessed 26 (77%) of the technical school participants at T3 2.4 years later. Therefore, a total of 194 participants were assessed at T5, the study phase when hair samples were collected.

At T5, 132 out of the 194 participants (112 were college students and 20 technical school students) were included in the present cross-sectional study. Participants completed self-report questionnaires (except for childhood adversity, which was available from T1) and provided 3 cm-hair samples . Sample size varies for some measures given that three of the participants who provided hair samples did not complete the questionnaire assessment (N=129). All participants provided written informed consent to participate.

2.2. Materials and Procedure

2.2.1. Stress-related measures

The Perceived Stress Scale (PSS) (71) enquires about the level of stress perceived by participants during the last month. It is a self-reported questionnaire of 14 items that provides a total score of perceived stress (Cronbach alpha = 0.86).

Two complementary measures of life events were used. The List of Threatening Events (LTE) (72) consists of 20 items (YES/NO) asking about adverse life events that might have occurred during the last year. In contrast, the Life Events Survey (LES) (105) includes 57 life events comprising a full range of experiences from negative to positive plus three blank spaces for other events. Forty-seven of them refer to general life events and 10 of them are academic-related. We removed one academic-related item ("Academic probation") given that there is not an equivalent of it in the Spanish education system. Participants rate both the occurrence (YES/NO) of the event and the impact it caused on them, capturing both a negative as well as a positive valence by using a Likert scale

ranging from -3 (very negative) to +3 (very positive). In the present study, only the subjective mean impact of life events was included (Cronbach alpha = 0.78).

The Childhood Trauma Questionnaire Brief (CTQ-B) (73) data was available for participants from the baseline data (T1) collection of the BLISS study. It is a self-reported measure covering 28 items rating the severity of emotional abuse and neglect, physical abuse and neglect and sexual abuse. A total score of childhood trauma comprising all the subscales is used in the present study (Cronbach alpha = 0.85).

### 2.2.2. Affective symptoms and personality

The Beck Depression Inventory-II (BDI-II) (74) was used to assess depressive symptoms. It has 21 items including a range of affective, behavioral, cognitive and somatic symptoms (Cronbach alpha = 0.88). Anxiety was measured with the Anxiety scale of the Symptom Checklist-90-Revised (SCL-90-R) (75). This scale consists of 10 items that can be answered with a Likert-scale from 0 to 4 (Cronbach alpha = 0.82).

Neuroticism was measured using the 8-item neuroticism subscale of the Big Five Inventory (BFI) (76), a 44-item inventory that measures five predominant dimensions of personality (extraversion, convenience, consciousness, neuroticism and openness) through 5-point Likert scales ranged from “strongly disagree” to “strongly agree” (Cronbach alpha = 0.83).

### 2.2.3. Psychosis and dissociation spectrum personality traits and experiences

In terms of paranoid personality, the Suspiciousness Scale of the Schizotypal Personality Questionnaire (SPQ) (77) was used (Cronbach alpha = 0.70). Schizotypy personality traits were assessed with the short forms of the Wisconsin Schizotypy Scales (WSS-S) (78, 79), from which participants were assigned positive and negative schizotypy factor scores (68, 69) and the Multidimensional Schizotypy Scales Brief

(MSS-B) (80), a 39-item measure which provides positive, negative and disorganized scores of schizotypy. The MSS-B was introduced in the protocol assessment once the sampling had already started, so only 59 (40 college and 19 technical school students) participants have data for the MSS-B. Of note, the MSS-B has demonstrated to overcome limitations associated with existing measures of schizotypy such as unclear conceptual framework, outdated items, ethnical/sex differences, or exclusion of disorganized schizotypy and to show good internal reliability and construct validity (81, 82). Data of the MSS-B for the disorganized dimension (Cronbach alpha = 0.75) and the factorially-derived dimensional scores based on the WSS for the positive and negative dimensions were used.

Dissociation was assessed using the Dissociative Experiences Scale (DES–II) (83), a 28-item instrument where participants are prompted to answer from a range of 0% (never) to 100% (all the time) the frequency of each of the dissociative experiences presented (Cronbach alpha = 0.82).

#### 2.2.4. Stress-buffering factors

The Multidimensional Scale of Perceived Social Support (MSPSS) (84) is a 12-item scale designed to measure perceived social support from three sources: Family, Friends, and a Significant Other. The total sum of perceived social support has been used in this study (Cronbach alpha = 0.92).

#### 2.2.5. Hair cortisol[a]

Hair strands were cut as close as possible from the posterior vertex area of the head. Specifically, cortisol concentrations were determined from the 3 cm hair segment most proximal to the scalp. As hair grows in average 1 cm per month (4), the samples represented the cortisol mean levels from the last three months. All samples were stored

in aluminum foil at room temperature until the extraction procedure. Then, the samples were washed twice for 1 minute with 10 ml of isopropanol and completely air dried at room temperature. After that, samples were further cut into fragments of approximately 2-3 mm and mixed with 1.6 methanol overnight with continuous rotation. All hair samples weighted within the recommended range required for immunoassay analyses (i.e. 5-50 mg; Kirschbaum et al., 2009; 61). Methanol was recovered in a new clean glass tube. The extraction was repeated, and the recovered methanol was pooled and dried up under a nitrogen stream. Extracted cortisol was re-suspended in 200 µl of PBS and assayed for cortisol. HCC were then determined by a radioimmunoassay procedure. Also, participants were prompted to answer whether they have ever dyed their hair and how many times do they wash their hair in a week.

#### 2.2.6. Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), Version 22.0 software (IBM Corp Released, 2013). ANOVA was used to test differences in hair cortisol concentrations for academic group, sex, age and hair dye, and Pearson correlations were used to test associations between hair cortisol and hair wash frequency as well as the different environmental, clinical and psychosocial measures.

## 3. Results

One out of 132 participants was excluded because of abnormally increased HCC (244.6 pg/mg) compared to the rest of the sample. As shown in Table 1, mean cortisol levels of the final sample of 131 participants were 6.22 pg/mg (s.d. 4.93), ranging from 1.30 to 39.70 pg/mg. Males (N= 22) showed mean cortisol levels of 8.20 pg/mg (s.d. 8.31)

[a] Please note that an erratum of this section is presented in Annex 1 of this chapter.

And females (N= 109) 5.81 pg/mg (s.d. 3.86), with no significant differences (p=0.20). No differences between college students and technical school students were found on HCC (p= 0.22). Therefore, the two samples were combined to perform the correlational analyses of HCC with the measures of interest. HCC were not affected by hair dye (p= 0.542) or frequency of washing (p= 0.146).

Correlational analyses (Table 2) showed no significant associations between HCC and any of the psychosocial or phenotypic measures. Only suspiciousness and disorganization showed a trend for an association with HCC with a positive correlation of r= 0.149 (p< 0.10) and r=0.220 (p<0.10), respectively.

## 4. Discussion

To the best of our knowledge, this is the first study examining a wide range of stress-related variables including both risk and protective factors, subjective and objective measurements, and employing a transdiagnostic perspective of stress-related phenotypes in a sample of nonclinical young adults. Moreover, this is the first study examining the relationship of HCC with the nonclinical expression of the psychosis spectrum, that is, schizotypy and paranoid personality traits along with other stress-related phenotypes.

Results showed no significant associations between HCC and the different psychosocial stress measures. Contrary to the hypothesis, but consistent with previous studies, depression, anxiety and neuroticism were not associated with HCC. In contrast, suspiciousness and disorganization, both strongly related to affective symptoms, showed a trend towards a significant association with HCC, although the magnitude was small in both cases. Suspiciousness consistently shows a large association with depression, low self-esteem, and neuroticism (87-89). Similarly, the disorganized dimension of schizotypy shows the strongest association with negative affect, depression and anxiety

compared to positive and negative schizotypy (90, 91). Interestingly, the disorganization dimension measured by the MSS scale does not include items that explicitly assess affect, but disrupted affect (e.g., excessive negative affect and inappropriate affect) is possibly equally relevant to this dimension as disruptions of thought, speech and behavior (91). It is likely that the fact that participants were oversampled for schizotypy to ensure sufficient variability in these traits allowed to capture this trend for an association—something that might be missed given the skewed nature of these traits in nonclinical samples. Finally, from a transdiagnostic psychopathology perspective, it is attractive to speculate that weak trends only emerged for the most severe traits of mental the disorder spectrum. Both suspiciousness and disorganization traits entail an intense and enduring disruption of a broad range of cognitive, affective and behavioral aspects, usually associated to mental suffering and impairment. Nonetheless, the weak associations of these constructs with hair cortisol calls for further examination of the association of HCC with a broad transdiagnostic range of psychopathology dimensions across non-clinical schizotypy and clinical high-risk populations.

Overall, the present findings add to previous studies showing a lack of psychoendocrine covariance between the long-term hair cortisol measurement with psychosocial stressors, symptomatology and other stress-related phenotypes in nonclinical samples. It has been suggested that this unexpected finding might be related to the fact that samples from studies assessing stress and cortisol usually comprise individuals that have been exposed to either very high (clinical) or very low ("super normal" controls) levels of stress (25). However, the present study aimed to avoid this limitation by employing a nonclinical sample encompassing a wide range of variance along schizotypy dimensions in order to ensure the presence of sufficient variability in the constructs of interest (i.e., stress-related measures, traits and subclinical symptoms).

Another hypothesis that has been raised to account for this poor concordance is that a significant hair cortisol elevation might require an intense and persistent exposure to stress (25). Cross-sectional studies might not be the most adequate to observe persistent or repeated exposure to stress. In that sense, further research based on longitudinal assessments is needed to examine whether a notable HPA axis dysfunction is observable after persistent exposure to stressful situations. Also, inconclusive findings between HCC and stress-related measures have been attributed to some methodological aspects. For instance, the use of different analytic methods to obtain HCC. Whilst most studies have been using traditional immunoassay methods and exhibiting great sensitivity, liquid chromatography-mass spectrometry (LCMS) based-assays are also employed, which might be yielding heterogeneous results in meta-analytic work including both techniques (7, 92). Another methodological limitation has been attributed to the discrepancy between timeframes captured by hair cortisol and self-reported stress-related measures (7, 93). However, there is no consensus as to whether this is actually a limitation, as hair cortisol is considered to be a "long-term", "stable" or even a "chronic" biological indicator of stress. Compared to previous "short-term" techniques such as saliva, blood serum or urine, HCC represent a long-term measurement of cortisol levels as 3-cm hair samples provide mean cortisol levels from the last three months. Importantly, intraindividual stability has been demonstrated in most studies assessing the correlation between repeated hair cortisol assessments (usually two to three time points) across periods of one (94), two (95), three (96, 97), four (95), six (5, 6) and twelve (95) months in adult populations. Nonetheless, all those studies employed nonclinical populations, usually healthy adults or unselected college students, and only two of them (96, 97) focused on individuals explicitly exposed to certain levels of stress (e.g., postpartum period or high-risk community). Findings in depression on higher HCC in the first but not in the recurrent

episodes (17, 18) and the inconsistent association of HCC and childhood trauma (54, 55), raise concerns about the validity of hair cortisol as a measure of chronic stress levels.

Of note, a major concern has been the degree of association between subjective and objective psychosocial stressors with biological markers of stress such as HCC. It has been suggested that exposure to early adversities in life predisposes individuals to overreact to subsequent stressful experiences in adulthood due to a biological and behavioral stress sensitization process that, in turn, contributes to the risk of mental illness in general, and psychosis in particular (39, 40, 98, 99). Moreover, the neural diathesis stress model poses that the HPA axis plays a major role as a mediator of the effects of stress on the development of, for instance, depression (100) and psychosis (1, 101). As hair cortisol has been considered a reliable biomarker to capture the HPA function, it is expected to find disrupted HCC in those individuals that have experienced higher levels of psychosocial stress. Nonetheless, only scarce research has found an association between early adversity, life events or perceived stress and hair cortisol, and the direction of the associations has been contradictory among studies. Cullen and colleagues (62) reviewed studies examining the concordance between psychosocial stressors and cortisol measures in healthy controls, individuals at clinical high-risk for psychosis and with clinical psychosis, and only weak correlations were found. The present study complements the studies reviewed (62) by focusing on nonclinical individuals with psychometric high risk, although more research on the psychoendocrine covariance across the psychosis continuum is needed. Furthermore, the present study included a critical measure not included in previous studies on HCC: the subjective appraisal of the impact of stressful life events. It has been suggested that the effect of a life event on an individual may result more from the appraisal of the perceived impact than the life event itself (102, 103), and most likely, the biological impact of such event on the stress system

depends on whether individuals do perceive that event as stressful However, no association was found with either the "objective" number of life events or the "subjective" appraisal. A possible explanation for this lack of associations might be the large individual variation in stress-sensitivity. Stress-sensitivity has been defined as a developmental phenomenon in which individuals tend to be highly reactive to both low and extremal levels of stress that emerges from relations between genetic, temperamental and contextual factors (48, 104). Thus, further gene – environment and person – environment interaction studies are needed to better understand the complexity of stress-sensitivity and to integrate individual differences in this trait in designs mostly based on group-level associations.

In conclusion, this study supports previous studies indicating an overall lack of concordance between a broad range of stress-related and (sub)clinical symptom measures with hair cortisol. This study examined HCC in individuals oversampled for schizotypy traits (i.e., psychometric high risk) for the first time, which complements studies on clinical high risk for psychosis and offers a promising strategy for studying possible HPA dysfunctions characterizing the subclinical psychosis continuum without the confounds associated to clinical status and medication. Further studies examining hair cortisol and its relationship with stress-related symptoms, phenotypes and psychosocial stressors in nonclinical samples exposed to different levels of stress are needed. Also, longitudinal studies might help to study stress persistence as a possible essential feature for HPA axis disruption. As posed by the RdoC framework (32), an integrated and translational approach from an endocrine, genetic and psychological level, as well as the study of their interaction with environmental influences, is needed to completely understand the mechanisms underlying HPA axis dysfunction and its relationship with mental health.

**Tables and Figures**

**Table 1.** Descriptive data of the sample and hair cortisol concentrations (HCC).

| | | HCC differences | |
|---|---|---|---|
| | | Statistic test | p value |
| **HCC (M, SD)** | 6.22 pg/mg, 4.93 | - | - |
| **Demographics** | | | |
| **Age (M, SD)** | 27.84, 3.08 | - | - |
| **Sex (N)** | | [a]t= 2.09 | 0.038* |
| **Male** | 22 | | |
| **Female** | 109 | | |
| **Hair-related variables** | | | |
| **Hair dye (N)** | | t= 0.612 | 0.542 |
| **Yes** | 22 | | |
| **No** | 109 | | |
| **Washing frequency (M, SD)** | 3.05, 1.76 | [b]r= 0.128 | 0.146 |

*[a] T-Test [b] Pearson Correlations. * p < .05. M=Mean, SD=Standard Deviation*.

**Table 2**. Correlational analyses between stress-related and subclinical measures with HCC.

| | **M, SD** | ***r*** | ***p value*** |
|---|---|---|---|
| **Psychosocial stress** | | | |
| **Distal** | | | |
| **Childhood Trauma** | 33.91, 8.03 | 0.094 | 0.287 |
| **Proximal** | | | |
| **Perceived Stress Scale** | 20.19, 7.63 | -0.006 | 0.949 |
| **Life Events** | | | |
| **List of Threatening Events (LTE)** | 2.28, 1.97 | 0.040 | 0.656 |
| **Subjective Impact of Life Events (LES)** | 0.51, 1.04 | -0.026 | 0.772 |
| **Affective, psychosis and dissociation spectrum traits and symptoms** | | | |
| **Neuroticism** | 2.69, 0.61 | -0.097 | 0.276 |
| **Depression** | 5.70, 6.66 | -0.046 | 0.607 |
| **Anxiety** | 5.41, 4.75 | 0.004 | 0.964 |
| **Suspiciousness** | 1.57, 1.67 | 0.149 | 0.094+ |
| **Positive Schizotypy** | 0.93, 1.5 | 0.130 | 0.326 |
| **Negative Schizotypy** | 2.13, 2.04 | -0.027 | 0.839 |
| **Disorganized Schizotypy** | 0.78, 1.45 | 0.220 | 0.094+ |
| **Dissociation** | 7.89, 7.19 | 0.043 | 0.630 |
| **Stress-buffering measures** | | | |
| **Social Support** | 71.97, 13 | -0.010 | 0.909 |

* p < .05. + p < .10. M=Mean, SD=Standard Deviation. Note: data was available for N=131 participants for the Childhood Trauma Questionnaire (CTQ) assessed at T1, whereas three participants that provided hair samples at T5 did not complete the questionnaire assessment at T5 (N=129).

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**Annex 1**

2.2.5. Hair cortisol

To determine HCC, 3 cm of hair were cut from the base of the scalp. Considering average hair growth of 1 cm per month (5), the samples represented the cortisol mean levels from the last three months. Subsequently, 40 mg of hair were weighed and washed twice with 4 ml of 2-propanol (SIGMA, Ref: 335639-2.5L-M). Three overnight extractions were performed with 1.6 ml of methanol (SIGMA, Ref: 34860-2.5L-M), that was evaporated in the Speed Vac. Samples were reconstituted with 200 µl of 0.1 M phosphate buffer and then processed in the assay (25 µl in duplicate).

After the extraction, HCC was determned using the Salivary cortisol enzyme immunoassay kit, Expanded Range High Sensitivity (Salimetrics, Ref: 1-3002-5, UK). Briefly, cortisol in standards and samples competes with cortisol conjugated to horseradish peroxidase for the cortisol antibody binding sites on a microtiter plate. Bound cortisol-enzyme conjugate is measured by the reaction of the horseradish peroxidase enzyme with the substrate tetramethylbenzidine (blue color), resulting in a yellow color whose optical density is read at 450 nm. Dilution of samples showed good parallelism with the standard curve and recovery of spiking samples was around 100%. All samples to be statistically compared were run in the same assay to avoid inter-assay variability. The intra-assay coefficient of variation was less than 7% and the inter-assay was 11%.

# Chapter 2

# The Moderating Role of Hair Cortisol in the Association of Early and Recent Stress with Stress-related Phenotypes

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*Submitted*

**Abstract**

*Background*: Increased hair cortisol concentrations (HCC) have been found in clinical samples of schizophrenia, first episode psychosis and clinical risk for psychosis, but evidence of such is scarce in schizotypy. High HCC are supposed to reflect elevated chronic stress. However, HCC were not directly associated with adversity measures and stress-related phenotypes in previous research. This study tested whether HCC moderated the association between a comprehensive range of psychosocial stressors with several stress-related phenotypes in a sample of nonclinical young adults. It was expected that stressors, either distal (i.e., early-life) or recent, would be associated with to subclinical features in the context of elevated biological sensitization to stress (i.e., elevated HCC).

*Methods***:** The sample comprised 132 nonclinical young adults belonging to the Barcelona Longitudinal Investigation of Schizotypy Study (BLISS). Participants completed a questionnaire of childhood adversity and two complementary measures of recent life events, tapping threatening *versus* more general life events. Both the frequency and subjective impact (positive *versus* negative) of general life events were also assessed. Psychotic (i.e., schizotypy, suspiciousness) and non-psychotic (i.e., depression, anxiety) subclinical features as well as appraisals of perceived stress were examined. Hierarchical linear regressions and simple slope analyses were computed.

*Results*: HCC moderated the effects of both early and recent stress on suspiciousness as well as the effects of recent life events on perceived stress, such that those with higher HCC presented increased suspiciousness and perceived stress at higher levels of stress exposure. Positive, but not negative, recent life events were associated with decreased perceived stress and depression, and these associations were moderated by low HCC, indicating a buffering effect for those with a non-impaired HPA axis.

*Conclusions*: In line with the neural diathesis-stress model, results highlight the role of the interplay between the HPA axis and exposure to stressful experiences in exacerbating psychosis features and extend evidence to the nonclinical expression of the psychosis continuum. In addition, findings support the protective effect of positive experiences in decreasing stress appraisals and affective disturbances, which is consistent with emerging research about the relevance of positive factors in reducing the likelihood of psychopathological outcomes.

## Introduction

The classic neural diathesis-stress model focuses on the role of the hypothalamic-pituitary-adrenal (HPA) axis as a mediator of the effects of stress on triggering and exacerbating psychosis symptoms (1-3). The HPA axis acts in response to stressful situations or threats by activating a hormonal cascade that culminates in the release of the glucocorticoid cortisol to facilitate physiological and behavioral responses to threats. This response is suppressed by a negative feedback loop once stressors are absent. Cortisol is the most frequently used measure to study the HPA axis function and its implication in mental disorders as it can be easily assayed in blood, urine, saliva and hair. Whereas samples of blood serum and saliva have been extensively used to analyze acute single point cortisol responses to stress and urine to obtain short term levels (i.e., 24 hour), hair cortisol concentrations (HCC) have been proposed as a more accurate measure of chronic stress enabling retrospective and long-term examination of cortisol production (4). As hair grows approximately 1 cm per month (5), a 3 cm-hair sample for instance allows to retrospectively assess hair cortisol from the last three months from the strand collection providing a valid, reliable, non-invasive, and easily transported and stored long-term measurement of the stress glucocorticoid (6). However, very few studies have examined HCC across the psychosis spectrum, reporting elevated levels in clinical samples of schizophrenia (7, 8), First Episode of Psychosis (FEP) (9) and populations at clinical risk for psychosis (10). To the best of our knowledge only one study (11) has examined HCC at the nonclinical end of the extended psychosis phenotype, that is, schizotypy, failing to find any significant association between HCC and a wide range of stress-related phenotypes. Schizotypy is conceptualized as a multidimensional construct indexing liability for psychosis-spectrum psychopathology that is expressed across a broad range of personality, subclinical and clinical psychotic features (12-14). Investigating HCC in

nonclinical individuals with schizotypy traits allows examining the role of HPA axis in the etiology of psychosis without the confounds associated with clinical status and medication, which have commonly been related to inconsistent replication findings when examining baseline cortisol levels in psychosis populations (3).

It is well established that psychotic spectrum disorders are associated with childhood adversity (15, 16) and heightened stress-sensitivity (17-20). A stress sensitization mechanism seems to underlie this association; prolonged and/or severe stressful experiences in highly sensitive developmental periods (i.e., childhood) might result in a process of behavioral and biological sensitization to stress through the disruption of stress regulation systems such as the HPA axis (21-23). This would enhance stress sensitivity to subsequent minor adversities in adulthood, which has been associated to a broad range of phenotypes (24-26), including psychosis (27, 28). Although some evidence of an association between early adversity and altered HCC has been found in clinical psychosis (7, 29) and clinical at-risk individuals (10), recent meta-analytic work by Cullen and colleagues (30) found poor concordance between psychosocial stressors (including both early adversity and recent stressful events) and cortisol levels (including studies using all types of measurements) in psychosis and high-risk individuals. In previous work, we also failed to find a direct association between HCC and early adversity as well as frequency and subjective appraisals of recent life events in nonclinical young adults with a wide distribution of schizotypy (11).

The lack of overall group-level association between HCC, stress-related phenotypes, and exposure to early and recent stress in our previous study might be influenced by limited statistical power as well as the fact that nonclinical samples do not generally present very high or persistent levels of stress (11). However, drawing from the stress sensitization framework, we propose that this may also be because of the association

between both early and recent experiences of stress with subclinical psychopathology would be moderated by HCC. Support for the moderating role of HCC on the relationship between stressful experiences and stress-related phenotypes has been found, for instance, in nonclinical samples of children (31), adolescents (32, 33) and in clinical depression (34), but little work has been conducted across the extended psychosis spectrum phenotype despite of considerable research linking psychosis vulnerability to HPA axis hyperactivation. Of note, there is a notable lack of research examining the psychobiological effects of exposure to stress transphenomically, even though recent claims from transdiagnostic approaches recognize the multidimensionality and evolving nature not only of a single diagnostic spectra (e.g., psychosis) but also across the whole psychopathology spectrum -including nonclinical manifestations- (35, 36), and ample evidence suggests that HPA axis disruption is present in many psychopathology phenotypes (37-39).

The goal of the present study was to examine whether HCC moderate the association between a comprehensive range of psychosocial stressors, including both early and recent stressful experiences, with the expression of several stress-related phenotypes in a sample of nonclinical young adults. It was hypothesized that the association between early-life and recent stressors with subclinical features would be greater for those with elevated HCC, that is, for individuals with a biological sensitization to stress. Specifically, we expected that the moderating role of the biological indicator of stress-sensitization (i.e., HCC) would be relevant for all the phenotypes that have been robustly associated to stress, that is, the paranoid, positive schizotypy, depression and anxiety dimensions, as well as levels of perceived stress (e.g., 40-42, 26), but not with negative schizotypy. Furthermore, we expected that among recent life events the measure of threatening events would show a greater effect compared to that of general life events given their clear

negative or even devastating nature. For the measure of recent general life events, we hypothesized that the subjectively rated impact of life events would yield more interaction effects than the raw number of events endorsed. Thus, subjective ratings of negative life events were supposed to increase the presence of subclinical phenotypes in those with higher levels of HCC, whereas those experiencing a greater positive impact from life events were expected to show a buffering effect by decreasing levels of subclinical features.

Several features of this study overcome limitations reported in previous work that have been suggested as possible sources of conflicting results. We investigated the effects of different time frames (early vs. recent), types (common vs. uncommon) and not only frequency but also subjective appraisals (positive vs negative) of stressors in the same sample. Furthermore, unlike most previous studies, we tested the hypothesis across psychosis and non-psychosis dimensions.

## Methods

### Participants

The present sample consisted of 132 nonclinical young adults (mean age=27.86, SD= 3.07, range=26.07, 83% women) belonging to the ongoing Barcelona Longitudinal Investigation of Schizotypy Study (BLISS; 43,44).

At Time 1 (T1), a large pool of 547 unselected college students and 261 technical school students were initially screened with self-report questionnaires. As described in detail elsewhere (43, 44, 11), a subgroup oversampled for schizotypy scores continued regular follow-ups (from T1 to T5). At T5, 168 (79% of 214 candidate participants) college students and 26 (77% of 31 candidate participants) technical school students were reassessed. Therefore, a total of 194 participants were assessed at T5, when hair samples

were collected. From these, 132 participants (112 college students and 20 technical school students) successfully provided 3 cm-hair samples and were included in the present study. Note that sample size may vary for some measures given that three of the participants who provided hair samples did not complete questionnaires at T5 (N=129). All participants provided written informed consent to participate.

Materials and Procedure

*Measures of adversity and stressful events*

To examine early adversity, the Childhood Trauma Questionnaire Short Form (45) was assessed at T1. CTQ-SF is a self-reported measure including 28 items rating the severity of emotional abuse and neglect, physical abuse and neglect and sexual abuse. A total score of childhood trauma comprising all the subscales is used in the present study.

Two complementary recent life events measures were used. As a measure of specifically threatening life events, we used The List of Threatening Events (LTE; 46). It consists of 20 items (YES/NO) asking about adverse life events that might have occurred during the last year. As a measure of more general and frequent life events we employed the Life Events Survey (LES; 47), which includes 57 life events that might have occurred during the last year comprising a full range of experiences from negative to positive plus three blank spaces for other events. Forty-seven of them refer to general life events and 10 of them are academic-related. We removed one academic-related item ("Academic probation") given that there is not an equivalent of it in the Spanish education system. Participants were asked to rate the occurrence (YES/NO) of each life event and the total sum of events endorsed was used. Additionally, the LES also allows to rate the subjective impact of each endorsed life event by using a Likert scale ranging from -3 (extremely negative) to +3 (extremely positive). The sum of ratings from -3 to -1 (negative spectrum) of endorsed life events was used as the amount of negative impact, whereas the sum of

ratings from 1 to 3 (positive spectrum) was used as the amount of positive impact. To ease interpretation of results, negative ratings (-3 to -1) were inversely recoded (3 to 1).

*Current appraisals of stress*

The Perceived Stress Scale (PSS; 48) is a self-reported questionnaire of 14 items enquiring about the level of stress perceived by participants during the last month that provides a total score of perceived stress.

*Hair cortisol*

To determine cortisol levels, 3 cm of hair strands were cut from the base of the scalp. Considering average hair growth of 1 cm per month (5), the samples represented the cortisol mean levels from the last three months. 40 mg of hair were weighed and washed twice with 4 ml of 2-propanol (SIGMA, Ref: 335639-2.5L-M) and three extractions were performed overnight with 1.6 ml of methanol (SIGMA, Ref: 34860-2.5L-M). Then methanol was evaporated in the Speed Vac. The samples were reconstituted with 200 µl of 0.1 M phosphate buffer and then processed in the assay (25 µl in duplicate).

HCC were determined after the above extraction using the Salivary cortisol enzyme immunoassay kit, Expanded Range High Sensitivity (Salimetrics, Ref: 1-3002-5, UK). In brief, cortisol in standards and samples competes with cortisol conjugated to horseradish peroxidase for the cortisol antibody binding sites on a microtiter plate. Bound cortisol-enzyme conjugate is measured by the reaction of the horseradish peroxidase enzyme with the substrate tetramethylbenzidine (blue color), resulting in a yellow color whose optical density is read at 450 nm. Dilution of samples showed good parallelism with the standard curve and recovery of spiking samples was around 100%. All samples to be statistically compared were run in the same assay to avoid inter-assay variability. The intra-assay coefficient of variation was less than 7% and the inter-assay was 11%. Participants

reported whether they have ever dyed their hair and how many times do they wash their hair weekly.

*Phenotype measures*

Paranoia was assessed using the Suspiciousness scale of the Schizotypal Personality Questionnaire (SPQ: 49) and schizotypy was assessed with the short forms of the Wisconsin Schizotypy Scales (WSS-S; 50), from which participants were assigned positive and negative schizotypy factor scores (see 43, 44).

Depressive symptoms were assessed with the Beck Depression Inventory-II (BDI-II; 51) and Anxiety was assessed with the Anxiety subscale of the Symptom Checklist-90-Revised (SCL-90-R; 52).

Statistical analyses

ANOVA was used to test differences in hair cortisol concentrations for academic group, sex, age, and hair dye. Hierarchical linear regressions were computed to examine direct and interaction effects of HCC with early and recent exposures on subclinical experiences. HCC and environmental measures were entered at first step and the interaction of HCC with the different environmental measures was entered at the second step. The standardized regression coefficient (β), change in R2, and effect size f2 were reported for each predictor in the regressions. Following Cohen (53), f2 values above 0.15 are medium and above 0.35 are large effect sizes. Finally, simple slope analyses using PROCESS (54) were computed to decompose significant interactions (p-value<0.05). Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), Version 22.0 software (55).

Ethical approval was granted by the Ethics Committee of the Universitat Autònoma de Barcelona. The study was developed in accordance with the Declaration of Helsinki for ethical conduct in research.

**Results**

One out of 132 participants was excluded because of abnormally increased HCC (244.6 pg/mg) compared to the rest of the sample. There were not significant differences in mean HCC ($p=0.20$) among men ($M=8.20$ pg/mg, $SD=8.31$) and women ($M=5.81$ pg/mg, $SD=3.86$), nor between college ($M=6.45$, $SD=5.17$) and technical school ($M=4.98$, $SD=3.15$) students ($p=0.22$). HCC were not affected by hair dye ($p=0.542$) or frequency of washing ($p=0.146$).

Table 1 shows descriptive statistics and Pearson correlations among study variables. Hierarchical linear regressions results are shown in tables 2-6. As shown in previous work (11), no significant main effects for HCC on any of the stress-related outcomes were detected. Early adversity (Table 2) showed a main effect on all stress-related phenotypes except for negative schizotypy, as well as an interaction with HCC in predicting levels of suspiciousness—a trend-level interaction was found for positive schizotypy. Simple slopes analysis of the significant interaction on suspiciousness (Figure 1) revealed that childhood adversity increased levels of suspiciousness only at high ($\beta=0.43$, $p<0.01$) and moderate ($\beta=0.28$, $p<0.01$) levels of HCC.

The number of recent threatening life events was directly associated with positive schizotypy (Table 3) and showed an interaction with HCC for predicting suspiciousness (also for appraisals of perceived stress at a trend level). Simple slopes analysis of the significant interaction on suspiciousness (Figure 2) revealed that threatening life events predicted higher levels of suspiciousness only at high levels of HCC ($\beta=0.24$, $p<0.05$). A

similar pattern was found for the measure of general life events (Table 4), showing direct effects on positive schizotypy and statistically significant interactions with HCC for both suspiciousness and perceived stress. Subsequent simple slopes showed that the general life events increased suspiciousness (Figure 3) only at high levels of HCC ($\beta$=0.24, $p<0.05$), whereas none of the slopes of HCC (low, moderate, high) were significant in the association between HCC and perceived stress.

Regarding the subjective impact of general life events, positive appraisals (Table 5) were associated with lower levels of perceived stress and depression, but to greater levels of positive schizotypy. In contrast, negative (Table 6) appraisals were associated with greater perceived stress and depression. Interaction effects between HCC and a positive impact of life events (Table 5) were only found for perceived stress and depression. Both associations (Figure 4a; 4b) were significant for low ($\beta$=-0.49, $p<0.001$ for perceived stress; $\beta$=-0.43, $p<001$ for depression) and moderate ($\beta$=-0.30, $p<0.001$ for perceived stress; $\beta$=-0.26, $p>0.01$ for depression) levels of HCC, indicating that those with lower levels of HCC reported decreased perceived stress and depressive symptoms when they had experienced more positive life events compared to individuals with high HCC who were not affected by the number of positive events. In contrast, no interaction effects between HCC and negative impact of life events were found (Table 6).

**Discussion**

This is the first study to examine the moderating role of hair cortisol as a proxy of HPA dysfunction in the association between early and recent stress with a range of stress-related subclinical phenotypes in young adults. HCC consistently moderated the effects of both early and recent life stress on suspiciousness and the effects of recent life events on perceived appraisals of stress. The subjectively rated positive impact of life events was associated with decreases in perceived stress and depression, and these relationships were

also moderated by HCC, such that this buffering effect only occurred for participants with low and moderate levels of HCC. These findings overall confirm the hypothesis that individuals with biological sensitization to stress present a stronger association between stressors and a variety of subclinical phenotypes robustly associated to stress.

Consistent with evidence suggesting that the positive dimension of psychosis is more strongly associated with childhood trauma (40, 41), early adversity predicted increased positive, but not negative, psychotic-like features, as well as depression, anxiety and increased appraisals of current stress, thus supporting the role of early negative environmental influences on the development of a variety of subclinical psychopathology manifestations (56, 57). HCC moderated the effects of childhood adversity and recent stressful life events (both general and threatening life events) on suspiciousness. In all cases, experiencing greater levels of early or recent life stress increased levels of suspiciousness specifically in those presenting elevated HCC. These findings are consistent with previous evidence linking childhood trauma as well as recent stress with the HPA axis function, psychiatric illness in general (58) and psychosis in particular (7, 59, 38). More so, results provide further support for the neural diathesis-stress model (2) and extend findings to nonclinical expressions of psychosis liability. The fact that suspiciousness was associated with all forms of stress aligns with cognitive theories suggesting that paranoid thoughts develop as a defensive self-protection mechanism that may arise as a psychological response to threatening or stressful experiences (60). This response was particularly evident in nonclinical individuals whose HPA axis might be disrupted. Of note, HCC also moderated the association between early adversity and positive schizotypy, although only at a trend level. The fact that HCC and childhood trauma only showed interaction effects on psychosis-spectrum features suggests an increased sensitivity of the HPA axis to the effects of early environmental influences for

the psychosis spectrum, which supports notions of a general psychopathology severity continuum in which psychotic expressions might index a greater level of severity (61, 62).

Results showed a similar pattern of results for threatening and general recent life events. Both predicted increased levels of positive, but not negative, schizotypy, which is consistent with previous evidence supporting the link between increased stress-sensitivity and positive features of psychosis liability (19, 63, 64). HCC moderated the effects of threatening and general life events on suspiciousness and current appraisals of perceived stress, although the latter only reached a trend level for the effects of threatening life events. This slight difference of the effects of threatening events (LTE) compared to general life events (LES) on perceived stress might be related to the greater skewness of the LTE measure in the present sample. As would be expected, most participants may have not encountered, or not as frequently, the severe and threatening experiences (e.g., "Serious illness, injury or assault to self" or "Parent, child or spouse died") asked in the LTE (M=2.27, SD=1.98). In contrast, the broader and more generally occurring life events appearing in the LES (e.g., "Major change in sleeping habits", "Outstanding personal achievement") are more frequently endorsed by young adults (M=10.33, SD=4.91) and thus increase the likelihood of detecting possible interaction effects. Of note, this finding also indicates that minor adversities or life-changes are also associated to subclinical features in those with a hyperactivated HPA axis, and suggests the relevance of taking into consideration the developmental phase of study populations when assessing stressful experiences for further research.

Contrary to our expectation, life events subjectively rated as negative did not show any significant interaction effects. In contrast, life events whose impact was rated as positive interacted with HCC to predict levels of perceived stress and depression.

Importantly, results showed that experiencing more positive life events significantly decreased appraisals of stress and depressive symptoms, specifically in those with lower levels of HCC, suggesting that positive life events may only exert a protective effect in those who are not biologically sensitized (i.e., showing low HCC). This finding highlights the importance of examining the combined effect of both early and recent experiences of stress as theorized by the stress sensitization hypothesis. Still, though, findings are consistent with emerging literature on the effect of positive environmental influences (65) as well as positive psychology interventions (66, 67) in reducing (the likelihood of) psychopathological outcomes. Interestingly, experiencing positive life events showed a main effect predicting increased positive schizotypy, which resonates with the notion of "happy schizotypes" (68). It has been shown that a proportion of nonclinical individuals with high levels of positive schizotypy (and low in negative and disorganized dimensions) also present hypomanic traits (69) and might reflect "benign schizotypy", in which psychotic-like experiences are not distressing and might even be rewarding. In fact, as reported in a previous study (70), "happy schizotypes" experience psychotic-like experiences in association to momentary happiness.

Lack of significant interactions with the negative impact of life events does not necessarily indicate that experiencing negative stressful situations do not affect the association between the HPA axis function and psychopathology but that probably the effects are not as devastating as we would expect them to be in a clinical or functionally impaired sample, whereas stronger or persistent negative experiences might be needed to capture the effects in a nonclinical sample of functional young adults (6, 11).

Several strengths characterize the present study. A major advantage compared to the extant literature is the examination of a comprehensive range of psychosocial stressors. We examined both early (i.e., childhood) and recent (i.e., past 12 months) indicators of

stress and two complementary measures of recent life events were employed to capture the objective frequency of threatening or uncommon experiences (LTE) as well as more general and commonly faced situations (LES). In addition, we assessed the positive versus negative subjectively rated impact of general life events in order to better understand individual differences in response to stress (71), which has been suggested to result from the individual's subjective interpretation and appraisal of it rather than the event itself (72, 73). Moreover, we employed a transphenomic approach by assessing traits and subclinical symptoms belonging to the psychotic, affective and anxiety spectrums. This is consistent with the developmental psychopathology notion of multifinality; that is, that the same risk factors can yield differential outcomes according to dynamic transactions with the environment and endogenous factors (74), and with recent claims about the need to investigate the etiological factors from a multidimensional psychopathology framework to provide further insights on common risk and protective factors across diagnostic spectra (75). Studying a nonclinical sample may have limited the ability to detect the expected effects as nonclinical individuals have probably not been exposed to very high or extreme levels of stress. However, employing a nonclinical sample with significant variance along schizotypy dimensions offers a promising strategy for studying the possible HPA axis dysfunctions as the many confounds associated with clinical status and medication are avoided. Our sample size was limited, and this possibly decreased the ability of detecting interaction effects, but the study tested a set of a priori and theory-grounded defined hypotheses. The available sample size prevented us from testing a three-way interaction of early and recent stress with cortisol as a moderator to examine how individuals with elevated early-life stress currently facing stressful life events presented with greater subclinical symptoms if biologically sensitized to stress (i.e., with elevated HCC). Future studies with greater sample sizes will be able to test this

and provide further insights on the biological manifestation of the stress sensitization hypothesis and its implications in several psychopathology outcomes. Finally, current dimensional models of early adversity suggest that different dimensions of adversity might have differential effects on psychopathology (76); however, due to limited statistical power, the present study only examined a general total score of trauma. Further studies employing bigger sample sizes will be able to examine differences across subtypes and co-occurrence of adverse experiences.

To conclude, the present findings support the moderating role of retrospective long-term levels of cortisol (i.e., HCC) on the association with both early and recent stressful experiences for a wide range of subclinical measures. Also, the buffering effects of recent positive experiences contribute to reduce pessimism around subclinical psychological manifestations and supports the importance of further focusing on positive resilience-building early interventions.

## Tables and Figures

**Table 1. Descriptive statistics and Pearson correlations of the study variables.**

| | *Descriptive statistics* | | | *Pearson correlations* | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | M (SD) | Range | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
| **1.** HCC | 131 | 1.30(4.94) | 1.3-39.7 | .094 | .089 | .102 | .045 | .120 | .089 | .096 | .149 | -.006 | -.046 | .004 |
| **2.** Early adversity | 131 | 33.91(8.03) | 25-67 | | .166 | .203* | .057 | .229** | 195* | .119 | .348** | .263** | .279** | .284** |
| **3.** Threatening life events | 128 | 2.27(1.98) | 0-9 | | | .371** | .228** | .207* | .262** | -.070 | .142 | -.012 | .005 | .072 |
| **4.** General life events | 129 | 10.33(4.91) | 2-24 | | | | .685** | .574** | .254** | -.064 | .172 | .074 | .064 | .114 |
| **5.** Positive impact events | 129 | 12.89(9.14) | 0-50 | | | | | -.056 | .326** | -.096 | .063 | -.236** | -.214* | -.067 |
| **6.** Negative impact events | 129 | 7.57 (5.9) | 0-27 | | | | | | -.001 | -.060 | .123 | .295** | .305** | .217* |
| **7.** Positive schizotypy | 128 | -0.66(0.45) | -1.17-1.32 | | | | | | | .207* | .473** | .181* | .214* | .262** |
| **8.** Negative schizotypy | 128 | -0.06(0.92) | -1.03-3.26 | | | | | | | | .331** | .243** | .334** | .124 |
| **9.** Suspiciousness | 128 | 1.58(1.68) | 0-8 | | | | | | | | | .492** | .511** | .546** |
| **10.** Perceived Stress | 128 | 20.19(7.63) | 5-43 | | | | | | | | | | .736** | .663** |
| **11.** Depression | 128 | 5.70 (6.66) | 0-35 | | | | | | | | | | | .631** |
| **12.** Anxiety | 128 | 5.41 (4.75) | 0-19 | | | | | | | | | | | |

HCC: Hair Cortisol Concentrations

Note. Sample size may vary for some measures given that three of the participants who provided hair samples (N=132) did not fully complete the questionnaire assessment at T5 and one participant was excluded for abnormally increased HCC.

**Table 2. Main effects of HCC, early adversity, and their interaction on stress-related outcomes.**

| | *Step 1* | | | | | | *Step 2* | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Hair cortisol concentrations (HCC)** | | | **Early adversity** | | | **HCC x Childhood trauma** | | |
| | $\beta$ | $\Delta R^2$ | $f^2$ | $\beta$ | $\Delta R^2$ | $f^2$ | $\beta$ | $\Delta R^2$ | $f^2$ |
| **Positive Schizotypy** | .073 | .005 | .005 | .189* | .035 | .036 | .164$^{+}$ | .027 | .029 |
| **Negative Schizotypy** | .086 | .007 | .008 | .112 | .012 | .013 | .040 | .002 | .001 |
| **Suspiciousness** | .120 | .014 | .016 | .337*** | .113 | .130 | .191* | .036 | .043 |
| **Perceived Stress** | .-028 | .001 | .001 | .266** | .070 | .075 | .003 | .000 | .000 |
| **Depression** | -.070 | .005 | .005 | .285** | .081 | .088 | -.099 | .010 | .011 |
| **Anxiety** | -.020 | .000 | .001 | .285** | .081 | .088 | .020 | .000 | .000 |

$^{+}$ p<.10; * p<.05; ** p<.01; *** p<.001

**Table 3. Main effects of HCC, recent threatening life events, and their interaction on stress-related outcomes.**

| | *Step 1* | | | | | | *Step 2* | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Hair cortisol concentrations (HCC)** | | | **Threatening life events** | | | **HCC x Threatening life events** | | |
| | $\beta$ | $\Delta R^2$ | $f^2$ | $\beta$ | $\Delta R^2$ | $f^2$ | $\beta$ | $\Delta R^2$ | $f^2$ |
| **Positive Schizotypy** | .067 | .004 | .004 | .256** | .065 | .070 | .083 | .007 | .007 |
| **Negative Schizotypy** | .103 | .011 | .010 | -.079 | .006 | .006 | .137 | .018 | .019 |
| **Suspiciousness** | .137 | .019 | .019 | .130 | .017 | .017 | .241** | .058 | .063 |
| **Perceived Stress** | -.005 | .000 | .000 | -.011 | .000 | .000 | .152$^{+}$ | .023 | .023 |
| **Depression** | -.047 | .002 | .001 | .009 | .000 | .000 | .125 | .016 | .016 |
| **Anxiety** | -.002 | .000 | .000 | .072 | .005 | .004 | .118 | .014 | .014 |

$^{+}$ p<.10; * p<.05; ** p<.01; *** p<.001

**Table 4. Main effects of HCC, recent general life events, and their interaction on stress-related outcomes.**

| | *Step 1* | | | | | | *Step 2* | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Hair cortisol concentrations (HCC)** | | | **General life events** | | | **HCC x General life events** | | |
| | $\beta$ | $\Delta R^2$ | $f^2$ | $\beta$ | $\Delta R^2$ | $f^2$ | $\beta$ | $\Delta R^2$ | $f^2$ |
| **Positive Schizotypy** | .064 | .004 | .004 | .248** | .061 | .065 | .070 | .005 | .005 |
| **Negative Schizotypy** | .104 | .011 | .011 | -.075 | .006 | .006 | -.064 | .004 | .004 |
| **Suspiciousness** | .132 | .017 | .017 | 159+ | .025 | .026 | .209* | .043 | .047 |
| **Perceived Stress** | -.019 | .000 | .001 | .075 | .006 | .005 | .180* | .032 | .033 |
| **Depression** | -.054 | .003 | .003 | .075 | .006 | .006 | .129 | .016 | .016 |
| **Anxiety** | -.008 | .000 | .000 | .115 | .013 | .013 | .154+ | .023 | .023 |

+ p<.10; * p<.05; ** p<.01; *** p<.001

**Table 5. Main effects of HCC, positive impact of life events, and their interaction on stress-related outcomes.**

| | *Step 1* | | | | | | *Step 2* | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Hair cortisol concentrations (HCC)** | | | **Positive impact of life events** | | | **HCC x Positive impact of life events** | | |
| | $\beta$ | $\Delta R^2$ | $f^2$ | $\beta$ | $\Delta R^2$ | $f^2$ | $\beta$ | $\Delta R^2$ | $f^2$ |
| **Positive Schizotypy** | .075 | .006 | .006 | .323*** | .104 | .117 | .123 | .013 | .014 |
| **Negative Schizotypy** | .100 | .010 | .010 | -.100 | .010 | .010 | -.092 | .007 | .007 |
| **Suspiciousness** | .146 | .021 | .021 | .056 | .003 | .003 | .075 | .005 | .005 |
| **Perceived Stress** | .005 | .000 | .000 | -.236** | .056 | .059 | 266** | .060 | .067 |
| **Depression** | -.036 | .001 | .001 | -.212* | .045 | .047 | .229* | .045 | .049 |
| **Anxiety** | .007 | .000 | .001 | -.067 | .005 | .005 | .133 | .015 | .015 |

+ p<.10; * p<.05; ** p<.01; *** p<.001

**Table 6. Main effects of HCC, negative impact of life events, and their interaction on stress-related outcomes.**

| | *Step 1* | | | | | | *Step 2* | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Hair cortisol concentrations (HCC)** | | | **Negative impact of life events** | | | **HCC x Negative impact of life events** | | |
| | $\beta$ | $\Delta R^2$ | $f^2$ | $\beta$ | $\Delta R^2$ | $f^2$ | $\beta$ | $\Delta R^2$ | $f^2$ |
| **Positive Schizotypy** | .091 | .008 | .007 | -.012 | .000 | .000 | .015 | .000 | .000 |
| **Negative Schizotypy** | .105 | .011 | .010 | -.073 | .005 | .005 | -.071 | .005 | .005 |
| **Suspiciousness** | .136 | .018 | .018 | .106 | .011 | .011 | .110 | .011 | .011 |
| **Perceived Stress** | -.042 | .002 | .002 | .300*** | .088 | .097 | .013 | .000 | .000 |
| **Depression** | -.084 | .007 | .007 | .315*** | .098 | .108 | -.001 | .000 | .000 |
| **Anxiety** | -.022 | .000 | .001 | .220* | .048 | .050 | .065 | .004 | .003 |

+ p<.10; * p<.05; ** p<.01; *** p<.001

**Figure 1. Significant interaction between HCC and early adversity on suspiciousness.**

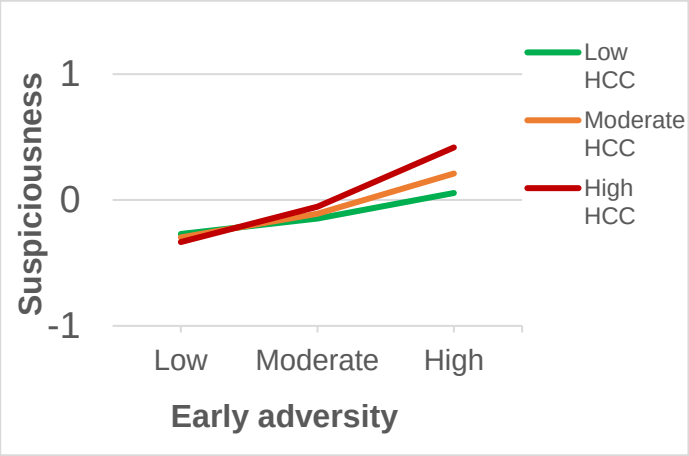

**Figure 2. Significant interaction between HCC and recent threatening life events on suspiciousness.**


**Figure 3. Significant interactions between HCC and recent general life events on suspiciousness.**

**Figure 4. Significant interactions between HCC and recent positive life events on a) perceived stress and b) depression.**

**a)**


**b)**

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# SECTION 2

# TESTING NOVEL GxE INTERACTIONS IN SCHIZOTYPY FROM A DIFFERENTIAL SUSCEPTIBILITY APPROACH

# Chapter 3

# Genetic Susceptibility to the Environment Moderates the Impact of Childhood Experiences on Psychotic, Depressive and Anxiety Dimensions

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**Abstract**

*Background*: Gene-by-environment (GxE) studies in psychosis have exclusively focused on negative exposures. However, evidence supports the resilience-enhancing effect of positive factors on psychosis outcome. The Differential Susceptibility (DS) model proposes that common genetic variants may confer not only disproportionate responsiveness to negative environments, but also greater sensitivity to positive, resilience-enhancing conditions. This study is the first to apply the DS model to the expression of subclinical psychosis, employing polygenic risk scores of environmental sensitivity (PRS-ES). PRS-ES were hypothesized to moderate, in a DS manner, associations between childhood adversity and psychosis, affective, and anxiety dimensions in young adults. An exploratory goal examined whether PRS for psychotic-like experiences (PRS-PLE) also showed DS patterns.

*Methods*: PRS, schizotypy, PLE, depression, anxiety, and childhood adversity ratings were obtained for 197 nonclinical young adults. LEGIT software for testing competitive-confirmatory GxE models was employed.

*Results*: Results largely supported DS: Individuals high on PRS-ES showed increased subclinical psychosis, depression and anxiety if they had experienced elevated childhood adversity, and lower symptoms if exposed to low levels of adversity as compared to those with low PRS-ES. Similarly, PRS-PLE moderated the effect of adversity on PLE, positive schizotypy, and depression following the DS model, but only PRS-ES moderation on PLE survived statistical correction.

*Conclusions*: Our results suggest that genetic DS to the environment is relevant to psychosis, depression, and anxiety. Current debates on reconceptualization of genetic 'risk' and resilience may benefit from this insight that support optimistic views on preventative efforts for early detection and intervention.

## Introduction

The psychosis phenotype is expressed across a dynamic continuum where schizophrenia represents the most extreme of a broad distributed behavioral expression of psychosis liability expressed as schizotypy traits and psychotic-like experiences (PLE) in the general population[1-7]. This extended phenotype ranges from adaptation or minimal dysfunction to frank psychosis and seems to reflect genetic and non-genetic etiological continuity—even if there is discontinuity in terms of impairment and need for care[8-10].

The presence of PLE not only in the psychosis spectrum but also within traditionally non-psychotic disorders such as anxiety or depression, supports the notion of psychosis as transdiagnostic[11,12]. Transdiagnostic research has acknowledged the multidimensionality and evolving nature of mental disorders not only within a single diagnostic spectrum, but across the whole psychopathology spectrum (including non-clinical populations), thus enabling research in risk and protective factors that could be common across diagnostic spectra[13]. There is phenotypic evidence of this commonality and non-specificity underlying psychopathology as shown by models that cut across discrete diagnostics such as the Research Domain of Criteria (RDoC)[14] or the Hierarchical Taxonomy of Psychopathology (HiTOP)[15], among others[16-19].

Correspondingly, recent cross-diagnostic genetic studies using Polygenic Risk Scores (PRS) also indicate that a substantial portion of common genetic variants associated with disorder risk are non-specifically associated with a range of mental disorders, thus representing transdiagnostic risk for mental suffering[20-23]. Moreover, similar psychosocial factors appear relevant for both psychosis and affective spectra[24-26]. The limited specificity of genetic and environmental factors along with studies reporting affective dysregulation in the earliest expression of psychosis[27,28] support the notion of a mental health severity spectrum, with neurodevelopmental impairment driving nonaffective

psychosis (e.g., schizophrenia), which indexes the most severe endpoint of this continuum[21]. Gene-by-environment interaction (GxE) studies suggested that "genetic-risk" variants may confer more sensitivity to general psychopathological effects of adverse environmental risk factors[29-32], and that the genetic architecture of mental disorders might, in fact, partly reflect the genetics of differential susceptibility to the environment.

Genetic vulnerability to the environment has traditionally been examined within diathesis-stress frameworks[33,34], which propose that individuals carrying genetic-risk variants are more vulnerable to the effects of adversity and more prone to develop psychopathology. Therefore, most GxE research has exclusively focused on negative environmental factors. However, recent studies indicate the impact of positive environmental factors on attenuated psychosis expressions and outcomes. For instance, secure attachment relationships or parental support seem protective against PLE among individuals who had experienced adversity[35,36], and social support decreased PLE among discriminated-against individuals[37]. This suggests that GxE models should consider *both* negative and positive environmental factors, as suggested by the Differential Susceptibility (DS) model[38-40]. This framework poses that individuals differ in their sensitivity (referred to as susceptibility) to both negative and positive environments, an evolutionarily-conserved feature documented also in other species. Thus, individuals traditionally considered to carry greater vulnerability may be better conceptualized as having a greater susceptibility to environmental influences (i.e., being more plastic or malleable). It suggests that the same genetic variants and biological or temperamental traits involved in increasing negative effects of risk-promoting experiences also enhance the likelihood of benefiting from positive ones ("for better and for worse")[39]. Candidate-gene studies have confirmed that genes involved in serotoninergic and dopaminergic

systems are likely more open to both supportive and adverse environments[41,42]. For example, carriers of the short allele ("S") of the 5-HTTLPR gene have shown to be more affected by negative contexts on antisocial behavior[43], neuroticism[44] or depressive symptoms[45] but, crucially, to also benefit more from positive environments and therapeutic interventions as compared to those without S alleles[46]. Finally, and mirroring the traditional diathesis-stress image, the vantage sensitivity model[47] poses that certain genetic variants may enhance the likelihood of benefiting from positive exposures without also implying an increase in the susceptibility to negative ones.

DS emerged within developmental psychopathology and has been mostly examined in relation to child psychopathology. This is the first study to examine whether DS applies to the expression of schizotypy and PLE in nonclinically-ascertained young adults. The main goal was to test whether Environmental Sensitivity PRS (PRS-ES)[48] moderated the association of different types of childhood adversity with subclinical expressions of anxiety, depression and psychosis in a DS manner. It was expected that highly genetically-sensitive individuals would show increased subclinical symptoms if they experienced childhood adversity and, at the same time, would report *lower* levels of symptoms if exposed to low or no adversity compared to those genetically less sensitive to the environment. As an exploratory goal, we tested whether a PRS specifically related to PLE in nonclinical samples (PRS-PLE)[49] also moderated the impact of adversity on transdiagnostic phenotypes following the DS model. Consistent with the notion that sensitivity to the environment is a key transdiagnostic causative factor of mental disorders, and with evidence that PRS-SZ indexes transdiagnostic risk for mental suffering[21], we hypothesized that some variance of the PRS-PLE captures this heightened sensitivity to the environment and would yield a DS pattern. Finally, we hypothesized that the positive dimension of schizotypy (unusual experiences and odd beliefs), but not

the negative (flattened affect and disinterest in others and the world), would show a DS pattern for both PRS-ES and PRS-PLE given that the positive dimension of psychosis is more strongly, consistently related to childhood adversity across subclinical and clinical expressions[50].

## Methods

### Participants

This sample was part of the ongoing Barcelona Longitudinal Investigation of Schizotypy Study (BLISS)[51-53].

At T1 of BLISS, 547 unselected college students were screened with self-report questionnaires. A subsample of 214 participants oversampled for schizotypy scores to ensure enough variance in the construct of interest was selected to conduct in-depth examinations comprising a wide range of interview, questionnaire, and experience sampling methodology measurements (T2). This study uses self-report, interview and genotype data collected at T2. After genetic quality control, the sample with usable genetic data comprised 197 nonclinical young adults (mean age=21.90, SD=2.37).

### Materials and Procedure

#### *Calculation of Polygenic Risk Scores (PRS)*

DNA was extracted from saliva or cotton swabs. See details on the genotyping, quality control and imputation procedures in supplementary materials.

PRS were computed by summing the number of risk alleles that individuals carried multiplied by their effect sizes, as reported in a Genome Wide Association Study (GWAS) of reference. We created a PRS-ES based on Keers and colleagues' GWAS[48] conducted with a monozygotic twin sample to capture genetic variants associated to intra-

pair differences in emotional (internalizing) symptoms. The unique nature of a twin sample genetically identical and sharing basically the same family environment allows to attribute symptom differences to genetic susceptibility to potentially subtle non-shared environmental factors and, thus, to capture environmental sensitivity as a moderator. PRS-PLE was created in the usual way following Legge and colleagues GWAS[49].

We applied the classical Clumping + Thresholding (C+T) method with PLINK v1.9. Independent variants were selected by clumping (r2<0.1 within a 1000kb window for PRS-ES and r2<.02 within a 1000 kb window for PRS-PLE) using the 1000 Genomes Project phase 3[54] as a European linkage disequilibrium (LD) reference panel. 93,494 and 104,891 SNPs for PRS-ES and PRS-PLE, respectively, survived clumping. Consistent with previous evidence using PRS-ES[55], we obtained scores with *p*-value thresholds of 0.001, 0.01, 0.05 and 0.1. For the sake of consistency, and given the lack of previous GxE studies with PRS-PLE, the same thresholds were employed for the secondary exploratory analyses with PRS-PLE. The PRS-ES was computed based on 369 SNPs for $p<.001$; 2,819 SNPs for $p<.01$; 11,244 SNPs for $p<.05$; and 19,895 SNPs for $p<.10$. PRS-PLE included 1,428 SNPs for $p<.001$; 8,815 SNPs for $p<.01$; 26,831 SNPs for $p<.05$; and 40,372 SNPs for $p<.10$.

*Early adversity*

Three complementary measures were used to assess early adversity. The Childhood Trauma Questionnaire-Short Form (CTQ-SF)[56] is a self-report measure capturing subjective reports of sexual abuse, physical abuse, emotional abuse, emotional neglect, and physical neglect. The Interview for Traumatic Events in Childhood (ITEC)[57] is a semi-structured interview also assessing sexual abuse, physical abuse, emotional abuse, emotional neglect, and physical neglect with follow-up questions assessing age of onset,

perpetrator(s), duration, and frequency to calculate composite severity scores for each maltreatment subtype. The semi-structured Childhood Experience of Care and Abuse (CECA)[58] interview focuses on more objective aspects of childhood experiences. Specifically, parental antipathy, role reversal, parental discord, violence between parents, and bullying subscales were used.

We computed factor scores based on CTQ, CECA and ITEC using principal component analysis with an oblique rotation (Gizdic et al., *submitted*). Four factors labeled Intrafamilial Adversity, Deprivation, Threat, and Sexual Abuse explained 63% of the total variance. Given the highly skewed distribution of the Sexual Abuse factor, it was excluded from further analyses.

*Phenotypic measures*

*Psychosis spectrum*. Schizotypy traits were assessed with the Wisconsin Schizotypy Scales short form (WSS-S)[59] from which participants were assigned positive and negative schizotypy factor scores[60]. Positive schizotypy taps magical thinking (α=0.86) and abnormal perceptual experiences (α=0.84), whereas negative schizotypy captures social (α=0.88) and physical (α=0.80) anhedonia. Subclinical positive PLE were assessed using the Positive subscale (e.g., "Do you ever feel as if there is a conspiracy against you?") of the Community Assessment of Psychic Experiences (CAPE)[61], which showed a reliability of α=0.76 in this sample.

*Affective and anxiety spectrums*. Anxiety (α=0.81) and Depression (α=0.85) subscales of the Symptom Checklist-90-Revised (SCL-90-R)[62] were used.

Statistical Analysis

To fit GxE models and test for DS interactions, we used Version 3.6.3 of the LEGIT package[63] in R[64]. In a first exploratory phase, main and interaction effects of the PRS and early adversity on the phenotypic outcome measures were analyzed. In the second phase, interactions yielding significant effects (*p*-values<0.05) were examined with the competitive-confirmatory approach[65,66] to determine the type of GxE interaction. The competitive-confirmatory approach envisions weak and strong versions of each model; thus, we fitted a total of six GxE models. The model showing lowest Akaike Information Criterion (AIC) represents the best fit. An interaction is classified as "DS" if a) reporting lowest AIC and b) the 95% interval of its estimated crossover point is within observable bounds of the environmental score. In addition, to find a balance between possible fitting ill-conditioned models with near-zero interaction effect and minimize the presence of false positives, LEGIT also examines four models excluding the GxE interaction term: (a) Intercept only, (b) gene(s) only, (c) environment(s) only, and (d) gene(s) and environment(s) only. If any of the four models without an interaction shows the lowest AIC, the interaction is classified as "no evidence of GxE". Importantly, this confirmatory approach has been shown to be more powerful than the classic Regions of Significance method[67] in classifying the type of interaction, especially in smaller samples[63].

All analyses included the first two ancestry-informative principal components from the MDS, Principal Component 1 (PC1) and 2 (PC2), as covariates in the first exploratory phase and were trimmed from the second competitive-confirmatory test phase if they were nonsignificant. We used False Discovery Rate (FDR)[68] to correct for multiple testing across thresholds of PRS-ES and PRS-PLE for each of the outcome measures.

**Results**

Descriptive statistics and Pearson correlations among study variables are presented in supplementary materials (supplementary table 1). One of the criteria to examine the fit

of the DS model is that the susceptibility factor (i.e., PRS) should not be correlated with the environmental factor (i.e., early adversity) or outcomes. PRSs did not correlate with other measures—except for two correlations, PRS-ES at threshold $p<.001$ with Intrafamilial Adversity ($r=.18$) and PRS-ES threshold $p<.05$ with Threat ($r=.14$), both small effect sizes. Main effects of covariates PC1 and PC2 are not reported as they did not show any significant association with outcome variables.

*PRS-ES as a moderating susceptibility factor*

As shown in in Table 1, PRS-ES moderated the association between Intrafamilial Adversity and PLE (thresholds $p<.001$; .05; .10) and between Intrafamilial Adversity and anxiety (thresholds $p<.05$; .10). Subsequent competitive-confirmatory analyses classified the interactions as fitting a DS model, indicating that participants with high PRS-ES showed more PLE and anxiety if they experienced high levels of Intrafamilial Adversity, but also lower PLE and anxiety if not exposed to Intrafamilial Adversity. Only threshold $p<.10$ was best fitted in a diathesis-stress model for anxiety, indicating that individuals with high PRS-ES showed greater anxiety when exposed to high levels of Intrafamilial Adversity. Those with low PRS-ES were relatively unaffected by Intrafamilial Adversity. Significant interactions were also found with Threat for positive schizotypy (threshold $p<.10$) and depression (threshold $p<.01$) consistent with DS.

Only significant interactions between PRS-ES and Intrafamilial adversity on PLE survived a subsequent FDR correction (please see graphic representation for one of the three significant thresholds in Figure 1).

*PRS-PLE as a moderating susceptibility factor*

Regarding exploratory analyses for PRS-PLE**,** Table 2 shows that the interaction of PRS-PLE and Intrafamilial Adversity on PLE (threshold $p<.10$) was consistent with a

model of strong DS, and that the interaction of PRS-PLE and Threat on positive schizotypy (threshold $p<.001$) and depression (thresholds $p<.05$; .10) were consistent with a model of weak DS −except for threshold $p<.05$ on depression for which competitive-confirmatory tests could not fit the interaction in any of the GxE models and classified the effect as "Environment only". PRS-PLE moderated the association between Intrafamilial Adversity and Anxiety (threshold $p<.05$) fitting a diathesis-stress model; however, those with lower PRS-PLE were more affected by the environmental effects. PRS-PLE (threshold $p<.01$) moderated the association between Deprivation and positive psychotic-like experiences, positive schizotypy and depression, all showing models of both weak DS and diathesis-stress; however, those with low PRS-PLE were more affected by Deprivation. None of the interactions with PRS-PLE survived FDR correction.

## Discussion

To our knowledge, this is the first study examining DS along the psychosis spectrum. Findings partly supported the DS model as individuals with high environmental genetic sensitivity showed increased levels of subclinical psychosis, depression and anxiety expressions if they experienced high levels of childhood adversity and fewer symptoms if they reported low or no levels of adversity, compared to those with low PRS-ES. Secondarily, the PRS-PLE also moderated associations between childhood adversity and later symptomatology following a DS pattern, most notably for psychosis and, to a lesser extent, depression dimensions but these moderations did not survive FDR.

As hypothesized, most GxE interactions using PRS-ES were consistent with DS (excepting negative schizotypy), supporting the idea that sensitivity to the environment and psychosocial exposures are relevant causative factors to myriad psychopathological expressions—even if some factors would be more relevant for specific dimensions. Stronger DS effects were found for PLE and positive schizotypy, and results remained significant for PLE and suggestive for positive schizotypy after FDR correction. This result supports the suggested continuum of mental disorders severity[28], in which psychotic-like manifestations index greater deviance; thus, greater environmental sensitivity in combination with greater adversity may contribute to stronger effects for such phenotypes. However, here variability related to PRS-ES moderated the impact of adversity on PLE in a 'for better and for worse' manner, suggesting that genetics of DS to the environment are relevant to anxiety and depression, as well as behavioral psychosis risk expression. This supports the idea that the genetic bases of mental disorders may (partly) reflect genetic variability in environmental sensitivity.

Consistent with the role of adverse psychosocial influences in risk for developing positive symptoms[50,69], their severity[70], and impact on outcome and course[71], we found

that DS models predicted positive, but not negative, psychosis dimensions. This finding supports the hypothesis that a heightened affective/stress-sensitivity pathway is relevant to the positive dimension[72,73]. As hypothesized, we found no significant interactions between PRS-ES and adversity to negative schizotypy**.** Given that this dimension is characterized by diminished motivation and low openness to experience[52,74], we did not expect that a proxy genetic score of environmental sensitivity would moderate variability in negative schizotypy expression.

Research has recently examined whether *positive* psychosocial factors could also impact psychosis risk and outcome. Findings about the protective effect of an absence of adverse childhood experiences in genetically sensitive individuals are consistent with recent epidemiological studies showing the protective role of positive experiences[35] and studies indicating that positive psychology interventions lower psychosis expression[75,76].

Regarding the second exploratory goal, we examined DS using PRS-PLE for the first time. Similar to PRS-ES, PRS-PLE moderated the impact of maltreatment on PLE and positive (but not negative) schizotypy, and depression, in a DS pattern. However, the interactions with PRS-PLE did not survive FDR correction. Belsky & Widaman[65], however, advocated for eschewing the use of strict *p* values in the exploratory phase and using other less restrictive parameters, which suggests that the subsequent model testing phase may be feasible. The use of the conventional low-powered manner of testing interaction significance may be responsible for the failure to detect more subtle GxE effects in previous research[77] but could have led to false positives. Given the exploratory nature of the present study along with limited sample size, a more conservative statistical approach based on the conventional $p<0.05$ threshold was employed. Additionally, unlike some GxE studies using a single PRS and environmental predictor[78-81], this study examined several models by testing two PRS at four different evidence-based thresholds

and three types of adversity, which required applying multiple testing correction procedures based on conventional *p*-values. Although not significant after correction, the effect sizes we found may indicate that genetic variants related to PLE index transdiagnostic risk and resilience for mental suffering as shown with PRS-SCZ[21] and thus suggest that part of the variance of PRS-PLE may also capture environmental sensitivity.

The pattern of findings with PRS-PLE partially mirror those obtained with PRS-ES, although PRS-PLE yields a more mixed picture. As expected, PRS-ES detected DS effects across several symptom dimensions, whereas PRS-PLE yielded DS effects for PLE and positive schizotypy, with depression showing a weak DS model and no effects for anxiety. This pattern seems consistent with the psychopathology severity continuum hypothesis, in which non-affective psychosis manifestations index the extreme end of a severity continuum[28]. Within the psychosis-spectrum, strong DS was supported for positive PLE, while weak DS was detected for positive schizotypy. This likely reflects that PLE was the phenotype used to develop the PRS-PLE, which focuses on symptom-like experiences of delusions and hallucinations[49] rather than milder perceptual abnormalities and magical ideation characterizing schizotypy. Altogether, this picture of findings is consistent with the possibility that PRS-PLE captures both specific disorder-related factors as well as sensitivity to environment.

Regarding the impact of different types of adversity, most interactions were driven by Intrafamilial Adversity and Threat. This is not surprising considering that emotional abuse loaded on both factors as subscales were not forced to load on a single factor (Gizdic et al., *submitted*)−consistent with evidence of substantial co-occurrence of different adversity subtypes[82,83], also referred to as polyvictimization[84]. Intrafamilial Adversity included threatening experiences that primarily pertained to the family domain

(e.g., parental discord, role reversal, parental violence, and parental antipathy), while the Threat factor also included physical abuse and bullying. In contrast, Deprivation did not yield significant interactions with PRS-ES.

Our findings support claims that genetic liability for psychosis is partially driven by DS to environmental psychosocial insults that affect brain functioning[85], and extend them by highlighting the need for integration of positive exposure impact. Homberg and Jagiellowicz[86] recently pointed out that studying outcomes in both negative and positive environments *simultaneously* may explain some inconclusive findings in GxE research, and advanced models of neural mechanisms involved in DS. Specifically, sensitive individuals exhibit hyperactivity in brain regions involved in the salience network (i.e., increased bottom-up processing of exogenous stimuli) and less-efficient inhibition in the central executive network (i.e., decreased top-down control over stimuli) which may lead to a more 'permissive' neural state to both negative and positive environmental influences[86].

This model may resonate with experimental evidence that the schizotypic nervous system is characterized by weak regulatory or inhibitory control, manifesting as fluctuations in arousal and responsivity at 'lower' levels of information processing and as loosened or flexible cognitive processing at 'high' levels[87], a feature that likely is involved in the association of psychotic (and affective) temperaments-syndromes with enhanced creativity[88-92]. It has been suggested that life experiences stored in long-term memory as mental products would 'leak' more easily from preconscious to conscious levels. Such unexpected inputs may either disrupt mental processes and become cognitive-perceptual psychotic experiences or fuel unusual associations facilitating creativity[87]. Relevant to these ideas, PRS-SCZ[93] and PRS-Bipolar Disorder[93,94] show

associations with creativity, and a recent GWAS reported a positive association of PRS-creativity with PRS-SCZ and PRS-Depression in a Chinese population[95].

*Strengths and Limitations*

Most previous studies testing DS employed sets of dopaminergic and serotoninergic candidate genes[97]. In contrast, this study used a PRS-ES indexing plasticity to environment. Recent evidence suggests that PRS show larger cumulative effect sizes and have greater predictive power[97,98]. Another critical strength of the current study is the combination of self-report with intensive and validated interviews of complementary aspects of childhood experiences. These interviews allowed for contextualized in-depth information that is difficult to tap with self-reports. It contributes to minimizing biases related to subjective responding as ratings rely on objective aspects of experience rather than individual subjective attitudes. However, these high-quality intensive measurements limited our sample size, and thus the ability to detect replicable interaction effects. Nonetheless, the competitive-confirmatory approach used in LEGIT has shown an accuracy of around 70-85% in similar sample sizes in simulation studies[63], compared to 40-70% with the classic Regions of Significance approach used with similar sample sizes.

Further, the use of a predominantly female university student sample limits generalizability. Thus, replication in community samples with more representative distributions of gender and age would enhance generalizability. Also, absence of adverse childhood experiences was used as a proxy for "positive" environment as employed in previous DS research[101,102] rather than assessments of specifically positive exposures. Despite this, a notable strength of this sample is that the measurements of PLE and schizotypy dimensions have shown construct[51], ecological[52,100] and predictive validity over 3[53] and 10 years[100].

*Conclusions and Implications*

This study showed for the first time that environmental genetic susceptibility moderates the association between childhood adversity and psychosis, affective and anxiety subclinical experiences consistent with the DS model. That is, participants with high PRS-ES were more reactive to the environment by showing more subclinical symptoms following high levels of adversity but fewer symptoms if not, compared to those with low PRS-ES. Results from the secondary exploratory goal with PRS-PLE, though not surviving statistical correction, depicted a similar pattern. These preliminary findings, if replicated, may support the notion that environmental sensitivity is a key transdiagnostic causative factor of mental suffering. One may speculate that part of this heightened sensitivity could also be captured by specific psychosis-related genetic variants. Although limited statistical power and the exploratory nature of the present study call for replication in larger independent samples, accumulating support for the DS model entails a paradigm shift in schizotypy theory and research. These findings challenge traditional assumptions about vulnerability guided by the diathesis-stress model and call for further consideration of individuals' environmental susceptibility heterogeneity in etiological research. This should reduce the damaging pessimism surrounding the traditional "heritable broken brain" model in psychopathology, particularly present for psychosis, stressing the potential value of positive exposures, positive psychology interventions and prevention strategies to decrease the likelihood of poor outcomes in highly sensitive individuals.

## Tables and Figures

**Table 1. Effects of PRS-ES, childhood adversity and their interaction on subclinical psychosis-spectrum, anxiety and depression.**

| | | PRS | | Childhood adversity | | PRS x Childhood adversity | | $R^2$ | Best GxE model[b] |
|---|---|---|---|---|---|---|---|---|---|
| | | Est. (S.E.) | *p* | Est. (S.E.) | *p* | Est. (S.E.)[a] | *p* ($p_{FDR}$) | | |
| ***Psychosis spectrum*** | | | | | | | | | |
| *Positive Psychotic-like Experiences (CAPE)* | | | | | | | | | |
| PRS-ES (*p*<.001) | Intrafamilial adversity | -0.315 (0.336) | 0.348 | 0.168 (0.511) | 0.742 | 0.857 (0.328) | 0.010 (0.038) | 0.088 | DS S |
| | Deprivation | -0.148 (0.333) | 0.658 | 1.024 (0.522) | 0.051 | 0.27 (0.375) | 0.457 | 0.075 | |
| | Threat | -0.245 (0.331) | 0.460 | 1.390 (0.532) | 0.010 | 0.199 (0.353) | 0.573 | 0.112 | |
| PRS-ES (*p*<.01) | Intrafamilial adversity | -0.040 (0.151) | 0.791 | -0.198 (0.818) | 0.809 | 0.277 (0.157) | 0.080 | 0.068 | |
| | Deprivation | -0.004 (0.151) | 0.978 | 0.248 (0.911) | 0.786 | 0.237 (0.188) | 0.208 | 0.079 | |
| | Threat | -0.059 (0.147) | 0.688 | 0.369 (0.813) | 0.651 | 0.292 (0.173) | 0.094 | 0.121 | |
| PRS-ES (*p*<.05) | Intrafamilial adversity | 0.021 (0.072) | 0.770 | -0.454 (0.617) | 0.462 | 0.206 (0.069) | 0.003 (0.026) | 0.096 | DS S |
| | Deprivation | 0.039 (0.072) | 0.594 | 0.796 (0.704) | 0.259 | 0.069 (0.084) | 0.417 | 0.076 | |
| | Threat | 0.025 (0.072) | 0.731 | 0.607 (0.694) | 0.383 | 0.130 (0.082) | 0.108 | 0.119 | |
| PRS-ES (*p*<.10) | Intrafamilial adversity | 0.029 (0.058) | 0.619 | -0.504 (0.649) | 0.438 | 0.167 (0.058) | 0.004 (0.026) | 0.094 | DS S |
| | Deprivation | 0.032 (0.059) | 0.593 | 1.053 (0.726) | 0.149 | 0.027 (0.070) | 0.701 | 0.073 | |
| | Threat | 0.010 (0.058) | 0.863 | 1.031 (0.703) | 0.144 | 0.059 (0.065) | 0.369 | 0.111 | |
| *Positive Schizotypy (WSS)* | | | | | | | | | |
| PRS-ES (*p*<.001) | Intrafamilial adversity | 0.034 (0.060) | 0.572 | 0.066 (0.092) | 0.477 | 0.090 (0.059) | 0.133 | 0.059 | |
| | Deprivation | 0.055 (0.059) | 0.355 | 0.230 (0.093) | 0.014 | -0.005 (0.067) | 0.944 | 0.076 | |
| | Threat | 0.049 (0.059) | 0.408 | 0.159 (0.095) | 0.095 | 0.080 (0.063) | 0.204 | 0.101 | |
| PRS-ES (*p*<.01) | Intrafamilial adversity | 0.013 (0.027) | 0.635 | -0.002 (0.147) | 0.987 | 0.037 (0.028) | 0.193 | 0.055 | |
| | Deprivation | 0.014 (0.027) | 0.594 | 0.197 (0.163) | 0.227 | 0.006 (0.006) | 0.853 | 0.073 | |
| | Threat | 0.011 (0.026) | 0.661 | -0.090 (0.144) | 0.534 | 0.081 (0.031) | 0.010 (0.115) | 0.123 | DS S |
| PRS-ES (*p*<.05) | Intrafamilial adversity | 0.017 (0.013) | 0.186 | 0.046 (0.112) | 0.682 | 0.017 (0.012) | 0.185 | 0.065 | |
| | Deprivation | 0.018 (0.013) | 0.171 | 0.247 (0.125) | 0.049 | -0.004 (0.015) | 0.812 | 0.081 | |
| | Threat | 0.017 (0.013) | 0.185 | 0.035 (0.124) | 0.778 | 0.028 (0.014) | 0.052 | 0.115 | |
| PRS-ES (*p*<.10) | Intrafamilial adversity | 0.015 (0.011) | 0.152 | 0.087 (0.118) | 0.463 | 0.009 (0.010) | 0.392 | 0.060 | |
| | Deprivation | 0.014 (0.010) | 0.172 | 0.310 (0.129) | 0.017 | -0.009 (0.012) | 0.444 | 0.084 | |
| | Threat | 0.012 (0.010) | 0.255 | 0.089 (0.125) | 0.477 | 0.017 (0.012) | 0.151 | 0.107 | |
| *Negative Schizotypy (WSS)* | | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PRS-ES ($p$<.001) | Intrafamilial adversity | 0.050 (0.074) | 0.498 | 0.023 (0.113) | 0.836 | -0.056 (0.072) | 0.440 | 0.028 | |
| | Deprivation | 0.034 (0.071) | 0.634 | 0.198 (0.113) | 0.081 | 0.012 (0.081) | 0.882 | 0.062 | |
| | Threat | 0.012 (0.071) | 0.868 | 0.316 (0.115) | 0.007 | -0.055 (0.076) | 0.470 | 0.082 | |
| PRS-ES ($p$<.01) | Intrafamilial adversity | -0.025 (0.033) | 0.451 | -0.190 (0.178) | 0.288 | 0.035 (0.034) | 0.303 | 0.032 | |
| | Deprivation | -0.042 (0.032) | 0.198 | 0.500 (0.195) | 0.011 | -0.063 (0.040) | 0.120 | 0.078 | |
| | Threat | -0.042 (0.032) | 0.186 | 0.420 (0.177) | 0.019 | -0.036 (0.038) | 0.338 | 0.092 | |
| PRS-ES ($p$<.05) | Intrafamilial adversity | 0.020 (0.016) | 0.204 | -0.068 (0.137) | 0.621 | 0.004 (0.015) | 0.787 | 0.032 | |
| | Deprivation | 0.017 (0.016) | 0.275 | 0.279 (0.151) | 0.066 | -0.010 (0.018) | 0.575 | 0.068 | |
| | Threat | 0.013 (0.016) | 0.423 | 0.300 (0.152) | 0.049 | -0.007 (0.018) | 0.679 | 0.084 | |
| PRS-ES ($p$<.10) | Intrafamilial adversity | 0.017 (0.013) | 0.183 | -0.067 (0.143) | 0.641 | 0.003 (0.013) | 0.785 | 0.033 | |
| | Deprivation | 0.016 (0.013) | 0.220 | 0.249 (0.156) | 0.112 | -0.005 (0.015) | 0.761 | 0.069 | |
| | Threat | 0.013 (0.013) | 0.319 | 0.159 (0.152) | 0.299 | 0.009 (0.014) | 0.518 | 0.086 | |
| *Anxiety (SCL-90-R)* | | | | | | | | | |
| PRS-ES ($p$<.001) | Intrafamilial adversity | 0.032 (0.391) | 0.934 | 0.785 (0.595) | 0.188 | 0.431 (0.381) | 0.260 | 0.061 | |
| | Deprivation | 0.207 (0.388) | 0.595 | 1.276 (0.607) | 0.037 | -0.043 (0.436) | 0.922 | 0.052 | |
| | Threat | 0.098 (0.381) | 0.797 | 1.564 (0.609) | 0.011 | 0.184 (0.405) | 0.650 | 0.104 | |
| PRS-ES ($p$<.01) | Intrafamilial adversity | -0.014 (0.174) | 0.935 | -0.092 (0.938) | 0.922 | 0.294 (0.181) | 0.105 | 0.068 | |
| | Deprivation | 0.015 (0.176) | 0.934 | 0.997 (1.062) | 0.349 | 0.054 (0.219) | 0.805 | 0.051 | |
| | Threat | -0.038 (0.170) | 0.822 | 0.947 (0.939) | 0.314 | 0.200 (0.201) | 0.320 | 0.108 | |
| PRS-ES ($p$<.05) | Intrafamilial adversity | 0.062 (0.083) | 0.451 | -0.357 (0.708) | 0.614 | 0.217 (0.079) | 0.007 (0.079) | 0.096 | DS S |
| | Deprivation | 0.083 (0.084) | 0.327 | 1.286 (0.817) | 0.117 | -0.010 (0.098) | 0.917 | 0.055 | |
| | Threat | 0.052 (0.083) | 0.533 | 1.688 (0.803) | 0.037 | 0.008 (0.094) | 0.928 | 0.105 | |
| PRS-ES ($p$<.10) | Intrafamilial adversity | 0.058 (0.068) | 0.392 | 0.001 (0.751) | 0.999 | 0.134 (0.067) | 0.047 (0.283) | 0.078 | Diathesis-stress S |
| | Deprivation | 0.058 (0.069) | 0.399 | 1.824 (0.841) | 0.031 | -0.066 (0.081) | 0.417 | 0.057 | |
| | Threat | 0.033 (0.067 | 0.629 | 2.145 (0.810) | 0.009 | -0.041 (0.076) | 0.589 | 0.105 | |
| *Depression (SCL-90-R)* | | | | | | | | | |
| PRS-ES ($p$<.001) | Intrafamilial adversity | 0.161 (0.550) | 0.770 | 1.438 (0.836) | 0.087 | 0.572 (0.536) | 0.287 | 0.090 | |
| | Deprivation | 0.440 (0.548) | 0.423 | 2.240 (0.857) | 0.010 | -0.369 (0.615) | 0.550 | 0.073 | |
| | Threat | 0.172 (0.518) | 0.740 | 3.537 (0.829) | 0.000 | -0.183 (0.551) | 0.741 | 0.188 | |
| PRS-ES ($p$<.01) | Intrafamilial adversity | -0.162 (0.245) | 0.508 | 0.802 (1.323) | 0.545 | 0.292 (0.255) | 0.253 | 0.093 | |
| | Deprivation | -0.079 (0.248) | 0.752 | 0.506 (1.498) | 0.736 | 0.311 (0.308) | 0.314 | 0.074 | |
| | Threat | -0.210 (0.228) | 0.359 | 0.648 (1.258) | 0.607 | 0.651 (0.269) | 0.016 (0.197) | 0.215 | DS S |
| PRS-ES ($p$<.05) | Intrafamilial adversity | -0.038 (0.118) | 0.749 | 0.585 (1.009) | 0.563 | 0.207 (0.112) | 0.068 | 0.100 | |
| | Deprivation | -0.019 (0.119) | 0.876 | 1.928 (1.159) | 0.098 | -0.006 (0.139) | 0.967 | 0.068 | |
| | Threat | -0.066 (0.112) | 0.558 | 1.860 (1.084) | 0.088 | 0.206 (0.126) | 0.104 | 0.201 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| PRS-ES ($p$<.10) | Intrafamilial adversity | 0.037 (0.096) | 0.697 | 0.782 (1.062) | 0.462 | 0.140 (0.095) | 0.141 | 0.096 |
| | Deprivation | 0.037 (0.097) | 0.703 | 2.071 (1.193) | 0.084 | -0.022 (0.114) | 0.848 | 0.069 |
| | Threat | -0.009 (0.091) | 0.919 | 1.697 (1.095) | 0.123 | 0.177 (0.102) | 0.085 | 0.200 |

[a] Adjusted for ancestry PC1 and PC2.

[b] Complete outputs of the LEGIT competitive-confirmatory analyses are shown in supplementary tables 2-5.

Note. PRS-ES=Polygenic Risk Score of Environmental Sensitivity; CAPE=Community Assessment of Psychic Experiences; WSS=Wisconsin Schizotypy Scales; SCL-9-R=Symptom Checklist-90-Revised; Est=Estimate; S.E=Standard Error; GxE=Gene-by-environment interaction; DS=Differential Susceptibility; S=Strong; W=Weak.

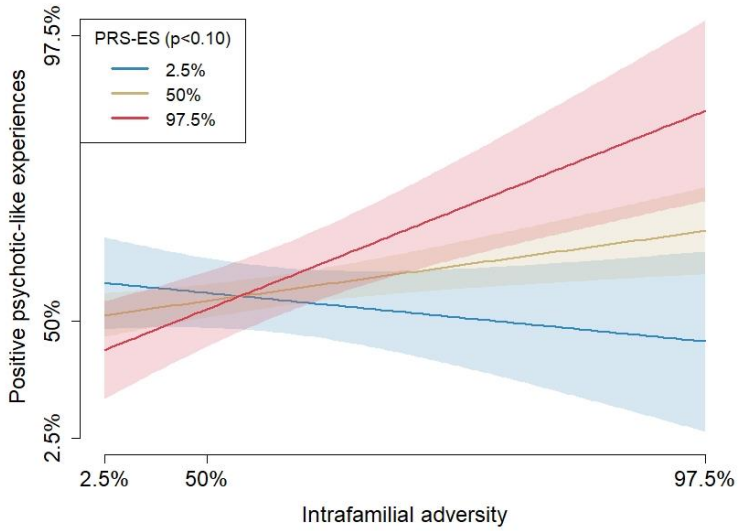
**Table 2. Effects of PRS-PLE, childhood adversity and their interaction on subclinical psychosis-spectrum, anxiety and depression.**

| | | PRS | | Childhood adversity | | PRS x Childhood adversity | | $R^2$ | Best GxE model[b] |
|---|---|---|---|---|---|---|---|---|---|
| | | Est. (S.E.) | *p* | Est. (S.E.) | *p* | Est. (S.E.)[a] | *p* ($p_{FDR}$) | | |
| ***Psychosis spectrum*** | | | | | | | | | |
| *Positive Psychotic-like Experiences (CAPE)* | | | | | | | | | |
| PRS-PLE (*p*<.001) | Intrafamilial adversity | 0.934 (0.965) | 0.335 | 1.213 (0.381) | 0.002 | 0.931 (1.147) | 0.418 | 0.058 | |
| | Deprivation | 0.329 (0.953) | 0.730 | 1.283 (0.356) | 0.003 | -0.170 (1.139) | 0.882 | 0.072 | |
| | Threat | 0.857 (0.916) | 0.351 | 1.906 (0.383) | 0.000 | 1.834 (1.047) | 0.081 | 0.124 | |
| PRS-PLE (*p*<.01) | Intrafamilial adversity | 0.584 (0.487) | 0.232 | 0.854 (0.403) | 0.036 | 0.613 (0.589) | 0.291 | 0.063 | |
| | Deprivation | 0.303 (0.475) | 0.524 | 1.851 (0.442) | 0.000 | -1.195 (0.564) | 0.035 (0.212) | 0.096 | DS W |
| | Threat | 0.505 (0.471) | 0.285 | 1.624 (0.367) | 0.000 | -0.185 (0.613) | 0.764 | 0.114 | |
| PRS-PLE (*p*<.05) | Intrafamilial adversity | 0.006 (0.317) | 0.984 | 0.599 (0.510) | 0.241 | 0.530 (0.391) | 0.177 | 0.061 | |
| | Deprivation | -0.057 (0.307) | 0.853 | 2.011 (0.509) | 0.000 | -0.639 (0.337) | 0.060 | 0.089 | |
| | Threat | 0.087 (0.308) | 0.777 | 1.570 (0.420) | 0.000 | 0.041 (0.410) | 0.920 | 0.108 | |
| PRS-PLE (*p*<.10) | Intrafamilial adversity | 0.326 (0.284) | 0.253 | 0.312 (0.498) | 0.531 | 0.734 (0.344) | 0.034 (0.212) | 0.077 | DS S |
| | Deprivation | 0.138 (0.281) | 0.624 | 1.931 (0.595) | 0.001 | -0.522 (0.391) | 0.184 | 0.082 | |
| | Threat | 0.301 (0.276) | 0.277 | 1.411 (0.458) | 0.002 | 0.221 (0.373) | 0.555 | 0.114 | |
| *Positive Schizotypy (WSS)* | | | | | | | | | |
| PRS-PLE (*p*<.001) | Intrafamilial adversity | 0.041 (0.173) | 0.810 | 0.204 (0.068) | 0.003 | 0.223 (0.205) | 0.278 | 0.052 | |
| | Deprivation | -0.080 (0.169) | 0.637 | 0.229 (0.063) | 0.000 | -0.060 (0.203) | 0.769 | 0.073 | |
| | Threat | 0.033 (0.163) | 0.841 | 0.334 (0.068) | 0.000 | 0.444 (0.187) | 0.019 (0.203) | 0.118 | DS W |
| PRS-PLE (*p*<.01) | Intrafamilial adversity | -0.046 (0.087) | 0.599 | 0.112 (0.072) | 0.120 | 0.189 (0.103) | 0.068 | 0.066 | |
| | Deprivation | -0.109 (0.084) | 0.196 | 0.335 (0.079) | 0.000 | -0.208 (0.100) | 0.040 (0.203) | 0.098 | Diathesis-stress W |
| | Threat | -0.059 (0.085) | 0.483 | 0.241 (0.66) | 0.000 | 0.066 (0.110) | 0.550 | 0.096 | |
| PRS-PLE (*p*<.05) | Intrafamilial adversity | -0.048 (0.056) | 0.400 | 0.080 (0.091) | 0.377 | 0.107 (0.070) | 0.124 | 0.064 | |
| | Deprivation | -0.062 (0.054) | 0.255 | 0.359 (0.090) | 0.000 | -0.116 (0.060) | 0.054 | 0.095 | |
| | Threat | -0.036 (0.055) | 0.517 | 0.244 (0.075) | 0.001 | 0.016 (0.073) | 0.829 | 0.094 | |
| PRS-PLE (*p*<.10) | Intrafamilial adversity | 0.004 (0.051) | 0.935 | 0.069 (0.089) | 0.442 | 0.102 (0.062) | 0.099 | 0.060 | |
| | Deprivation | -0.026 (0.050) | 0.609 | 0.348 (0.106) | 0.001 | -0.097 (0.070) | 0.166 | 0.082 | |
| | Threat | 0.003 (0.050) | 0.952 | 0.228 (0.082) | 0.006 | 0.033 (0.067) | 0.625 | 0.093 | |
| *Negative Schizotypy (WSS)* | | | | | | | | | |
| PRS-PLE (*p*<.001) | Intrafamilial adversity | 0.122 (0.210) | 0.561 | -0.036 (0.083) | 0.663 | -0.031 (0.250) | 0.902 | 0.025 | |
| | Deprivation | 0.008 (0.203) | 0.969 | 0.195 (0.076) | 0.011 | -0.412 (0.243) | 0.091 | 0.075 | |
| | Threat | 0.100 (0.200) | 0.618 | 0.239 (0.084) | 0.005 | -0.080 (0.229) | 0.727 | 0.082 | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PRS-PLE ($p$<.01) | Intrafamilial adversity | -0.018 (0.106) | 0.865 | -0.007 (0.088) | 0.933 | -0.068 (0.126) | 0.592 | 0.025 | |
| | Deprivation | -0.060 (0.103) | 0.562 | 0.316 (0.096) | 0.001 | -0.208 (0.089) | 0.089 | 0.076 | |
| | Threat | -0.027 (0.103) | 0.795 | 0.267 (0.080) | 0.001 | -0.052 (0.134) | 0.698 | 0.081 | |
| PRS-PLE ($p$<.05) | Intrafamilial adversity | -0.070 (0.069) | 0.307 | 0.032 (0.111) | 0.776 | -0.059 (0.085) | 0.488 | 0.030 | |
| | Deprivation | -0.077 (0.066) | 0.243 | 0.353 (0.109) | 0.001 | -0.124 (0.073) | 0.088 | 0.081 | |
| | Threat | -0.058 (0.067) | 0.387 | 0.269 (0.091) | 0.004 | -0.029 (0.089) | 0.743 | 0.083 | |
| PRS-PLE ($p$<.10) | Intrafamilial adversity | -0.022 (0.062) | 0.721 | 0.047 (0.109) | 0.669 | -0.075 (0.076) | 0.325 | 0.028 | |
| | Deprivation | -0.035 (0.061) | 0.566 | 0.351 (0.128) | 0.007 | -0.111 (0.084) | 0.188 | 0.070 | |
| | Threat | -0.013 (0.060) | 0.834 | 0.275 (0.100) | 0.006 | -0.026 (0.081) | 0.751 | 0.080 | |
| *Anxiety (SCL-90-R)* | | | | | | | | | |
| PRS-PLE ($p$<.001) | Intrafamilial adversity | 0.927 (1.103) | 0.402 | 1.100 (0.436) | 0.012 | -1.322 (1.311) | 0.315 | 0.066 | |
| | Deprivation | 0.661 (1.100) | 0.548 | 1.162 (0.412) | 0.005 | -1.185 (1.318) | 0.370 | 0.057 | |
| | Threat | 1.287 (1.051) | 0.223 | 2.124 (0.440) | 0.000 | 1.987 (1.202) | 0.100 | 0.121 | |
| PRS-PLE ($p$<.01) | Intrafamilial adversity | -0.381 (0.560) | 0.497 | 1.527 (0.463) | 0.001 | -0.660 (0.665) | 0.322 | 0.061 | |
| | Deprivation | -0.428 (0.555) | 0.441 | 1.748 (0.516) | 0.001 | -0.995 (0.659) | 0.133 | 0.063 | |
| | Threat | -0.183 (0.543) | 0.737 | 1.705 (0.424) | 0.000 | 0.355 (0.708) | 0.617 | 0.105 | |
| PRS-PLE ($p$<.05) | Intrafamilial adversity | -0.863 (0.357) | 0.017 | 2.279 (0.574) | 0.000 | -0.965 (0.440) | 0.030 (0.356) | 0.097 | Diathesis-stress W |
| | Deprivation | -0.648 (0.354) | 0.069 | 1.584 (0.590) | 0.008 | -0.278 (0.391) | 0.478 | 0.069 | |
| | Threat | -0.458 (0.351) | 0.194 | 1.520 (0.479) | 0.002 | 0.399 (0.468) | 0.395 | 0.117 | |
| PRS-PLE ($p$<.10) | Intrafamilial adversity | -0.542 (0.327) | 0.099 | 2.040 (0.571) | 0.000 | -0.694 (0.394) | 0.080 | 0.078 | |
| | Deprivation | -0.418 (0.327) | 0.202 | 1.255 (0.691) | 0.071 | 0.017 (0.455) | 0.971 | 0.059 | |
| | Threat | -0.283 (0.317) | 0.373 | 1.380 (0.525) | 0.009 | 0.484 (0.260) | 0.260 | 0.114 | |
| *Depression (SCL-90-R)* | | | | | | | | | |
| PRS-PLE ($p$<.001) | Intrafamilial adversity | 1.895 (1.551) | 0.223 | 2.015 (0.614) | 0.001 | -0.722 (1.845) | 0.696 | 0.094 | |
| | Deprivation | 1.402 (1.559) | 0.370 | 1.786 (0.583) | 0.003 | -0.629 (1.866) | 0.736 | 0.073 | |
| | Threat | 2.027 (1.434) | 0.159 | 3.614 (0.601) | 0.000 | 1.615 (1.640) | 0.326 | 0.198 | |
| PRS-PLE ($p$<.01) | Intrafamilial adversity | 0.220 (0.787) | 0.780 | 2.452 (0.652) | 0.000 | -0.999 (0.935) | 0.287 | 0.091 | |
| | Deprivation | 0.126 (0.780) | 0.872 | 2.832 (0.726) | 0.000 | -2.022 (0.927) | 0.030 (0.162) | 0.092 | DS W |
| | Threat | 0.548 (0.737) | 0.459 | 3.138 (0.575) | 0.000 | 0.852 (0.960) | 0.376 | 0.192 | |
| PRS-PLE ($p$<.05) | Intrafamilial adversity | -0.529 (0.512) | 0.303 | 2.680 (0.822) | 0.001 | -0.535 (0.397) | 0.397 | 0.091 | |
| | Deprivation | -0.343 (0.505) | 0.497 | 2.459 (0.841) | 0.004 | -0.509 (0.557) | 0.362 | 0.074 | |
| | Threat | 0.073 (0.476) | 0.879 | 2.554 (0.476) | 0.000 | 1.308 (0.634) | 0.040 (0.162) | 0.205 | E only |
| PRS-PLE ($p$<.10) | Intrafamilial adversity | 0.039 (0.465) | 0.934 | 2.329 (0.812) | 0.005 | -0.205 (0.561) | 0.715 | 0.085 | |
| | Deprivation | 0.091 (0.465) | 0.845 | 1.883 (0.982) | 0.057 | -0.009 (0.647) | 0.989 | 0.069 | |
| | Threat | 0.367 (0.429) | 0.393 | 2.295 (0.709) | 0.001 | 1.273 (0.578) | 0.029 (0.162) | 0.208 | DS W |

[a]Adjusted for ancestry PC1 and PC2.
[b] Complete outputs of the LEGIT competitive-confirmatory analyses are shown in supplementary tables 6-9.
Note. PRS-PLE=Polygenic Risk Score of Psychotic-like Experiences; CAPE=Community Assessment of Psychic Experiences; WSS=Wisconsin Schizotypy Scales; SCL-9-R=Symptom Checklist-90-Revised; Est=Estimate; S.E=Standard Error; GxE=Gene-by-environment interaction; DS=Differential Susceptibility; S=Strong; W=Weak.

**Figure 1. Graphic representation of the best-fitted GxE model for PRS-ES and Intrafamilial Adversity on positive PLE.**




Note: PRS-ES=Polygenic Risk Score Environmental Sensitivity.

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**Supplementary Materials**

*Genotyping, Quality Control and Imputation*

DNA was extracted from saliva or cotton swabs using the following extraction kits: i) the prepIT-L2P kit (DNA Genotek Inc., Ottawa, Ontario, Canada) for saliva samples and ii) the RealPure Genomic DNA Extraction Kit (Durviz S.L.U., Valencia, Spain) for cotton swab samples. DNA samples were genotyped at the "Centro Nacional de Genotipado" (CEGEN-PRB3-ISCIII; CNIO-Madrid) using the Illumina Infinium Global Screening Array-24 v2.0 (GSA) BeadChip. Genotype calls were generated with GenomeStudio v2.0.4 (Illumina Inc., San Diego, CA, USA). The quality control (QC) was performed using PLINK v1.9 (www.cog-genomics.org/plink/1.9/)[1]. During QC, SNPs were excluded when: had a missing call rate >2%; had a Minor Allele Frequency (MAF) <0.1%; or deviated from Hardy-Weinberg equilibrium with a P-value <0.001. Subjects were excluded when they had a missing call rate >2%; were genetically related to other participants or duplicated samples according to the pairwise identity by descent method (PI_HAT >0.25); or had non-European ancestry according to a Multidimensional Scaling (MDS) analysis, which was carried out with PLINK v1.9 to obtain a representation of genetic ancestry in our study, extracting the first 10 ancestry components. Seventeen subjects were excluded during QC leaving a sample of 197 subjects. MDS components were recalculated in this final sample and the two first components were used in all models including PRS as independent variables. Imputation was performed using the Haplotype Reference Consortium panel (www.haplotype-reference-consortium.org)[2] in the Michigan Imputation Server[3]. A post-imputation QC was carried out to exclude SNPs that had an imputation quality score of R2 <0.3; or had a MAF <1%. A total of 7,755,414 SNPs passed post-imputation QC.

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## Table 1. Descriptive statistics and Pearson correlations for study variables (N=197).

| | *Descriptive statistics* | | *Pearson correlations* | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M (SD) | Range | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** |
| **1.**PRS ES (p<0.001) | 0.91 (1.02) | -2.04 - 3.89 | - | .41*** | .39*** | .37*** | -.050 | -.12 | -.04 | -.05 | .18* | .05 | .10 | -.02 | .08 | .05 | .05 | .08 |
| **2.**PRS ES (p<0.01) | 4.11 (2.27) | -1.55 - 10.76 | | | .68*** | .60*** | -.02 | -.04 | -.02 | -.03 | .12 | .08 | .13 | .00 | .05 | -.06 | .02 | -.02 |
| **3.**PRS ES (p<0.05) | 6.83 (4.69) | -5.39 - 20.08 | | | | .89** | -.02 | .01 | -.01 | -.02 | .05 | .08 | .14* | .05 | .11 | .11 | .08 | .01 |
| **4.**PRS ES (p<0.10) | 9.11 (5.73) | -3.31 - 25.15 | | | | | .03 | .05 | .01 | .00 | .02 | .05 | .12 | .05 | .11 | .11 | .07 | .05 |
| **5.**PRS PLE (p<0.001) | -0.14 (0.36) | -1.18 - 0.78 | | | | | | .49*** | .36*** | .35*** | .01 | .13 | .03 | .06 | .01 | .05 | .08 | .10 |
| **6.**PRS PLE (p<0.01) | 0.26 (0.71) | -1.54 - 2.16 | | | | | | | .72*** | .66*** | .07 | .11 | .03 | .09 | -.04 | .01 | -.02 | .06 |
| **7.**PRS PLE (p<0.05) | 0.83 (1.10) | -2.35 - 3.74 | | | | | | | | .90*** | .11 | .06 | -.04 | .01 | -.05 | -.05 | -.11 | -.02 |
| **8.**PRS PLE (p<0.10) | 1.00 (1.22) | -2.54 - 4.20 | | | | | | | | | .07 | .08 | -.01 | .07 | .01 | .01 | -.07 | .04 |
| **9.** Intrafamilial maltreat. | -0.02 (0.97) | -1.15 - 3.01 | | | | | | | | | | .38*** | .32*** | .22** | .20** | -.03 | .23** | .27*** |
| **10.** Deprivation | -0.3 (0.96) | -1.19 - 5.35 | | | | | | | | | | | .45*** | .26*** | .25*** | .21** | .22** | .24*** |
| **11.** Threat | -0.04 (0.97) | -1.54 – 5.38 | | | | | | | | | | | | .32*** | .28*** | .24** | .31*** | .41*** |
| **12.**CAPE Positive PLE | 8.23 (4.82) | 0 - 23 | | | | | | | | | | | | | .75*** | .09 | .52*** | .45*** |
| **13.**WSS Pos schizotypy | -0.34 (0.86) | -1.56 - 2.24 | | | | | | | | | | | | | | .09 | .54*** | .49** |
| **14.**WSS Neg schizotypy | -0.02 (1.03) | -1.57 - 4.27 | | | | | | | | | | | | | | | .13 | .20** |
| **15.**SCL-R-90 Anxiety | 6.67 (5.53) | 0 - 29 | | | | | | | | | | | | | | | | .60** |
| **16.**SCL-R-90 Dep | 11.78 (7.90) | 0 -4 3 | | | | | | | | | | | | | | | | |

∗p < 0.05. ∗∗ p < 0.01. ∗∗∗ p < 0.001

r>0.30 are medium effect sizes and r>0.50 are large effect sizes.

## Table 2. LEGIT competitive-confirmatory tests for PRS-ES on Positive psychotic-like experiences significant (p<0.05) interactions.

| ***Outcome:*** | | **PRS ES (p<.001) x Intrafamilial adversity** | | **PRS ES (p<.05) x Intrafamilial adversity** | | **PRS ES (p<.10) x Intrafamilial adversity** | |
|---|---|---|---|---|---|---|---|
| ***Positive psychotic experiences (CAPE)*** | | AIC | Crossover point (95%) | AIC | Crossover point (95%) | AIC | Crossover point (95%) |
| **GxE models** | DS STRONG | **1161.92** | **-0.3 (-0.59 / -0.01)** | **1160.77** | **-0.52 (-0.81 / -0.23)** | **1161.38** | **-0.56 (-0.86 / -0.26)** |
| | DS WEAK | 1163.82 | -0.29 (-0.57 / 0) | 1162.27 | -0.5 (-0.79 / -0.21) | 1162.8 | -0.53 (-0.83 / -0.24) |
| | Diathesis STRONG | 1169.22 | -1 | 1162.39 | -1 | 1162.34 | -1 |
| | Diathesis WEAK | 1168.29 | -1 | 1163.99 | -1 | 1164.06 | -1 |
| | Vantage STRONG | 1173.04 | 1 | 1174.79 | 1 | 1174.78 | 1 |
| | Vantage WEAK | 1166.95 | 1 | 1169.39 | 1 | 1169.46 | 1 |
| **Non-GxE models** | Intercept only | 1175.5 | NA | 1175.5 | NA | 1175.5 | NA |
| | G only | 1177.46 | NA | 1176.92 | NA | 1177.02 | NA |
| | E only | 1167.55 | NA | 1167.55 | NA | 1167.55 | NA |
| | G+E only | 1168.92 | NA | 1169.17 | NA | 1169.14 | NA |

*Note: Best model indicated by lowest AIC is **highlighted**.*

**Table 3. LEGIT competitive-confirmatory tests for PRS-ES on Positive schizotypy significant (p<0.05) interactions.**

| ***Outcome:*** | | **PRS ES (p<.01) x Threat** | |
|---|---|---|---|
| ***Positive schizotypy (WSS)*** | | AIC | Crossover point (95%) |
| **GxE models** | DS STRONG | **481.74** | **-0.58 (-0.82 / -0.35)** |
| | DS WEAK | 483.21 | -0.58 (-0.82 / -0.35) |
| | Diathesis STRONG | 487.05 | -1 |
| | Diathesis WEAK | 486.5 | -1 |
| | Vantage STRONG | 502.59 | 1 |
| | Vantage WEAK | 488.65 | 1 |
| **Non-GxE models** | Intercept only | 501.73 | NA |
| | G only | 503.28 | NA |
| | E only | 486.71 | NA |
| | G+E only | 488.68 | NA |

*Note: Best model indicated by lowest AIC is **highlighted**.*

**Table 4. LEGIT competitive-confirmatory tests for PRS-ES on Anxiety significant (p<0.05) interactions.**

| ***Outcome:*** | | **PRS ES (p<.05) x Intrafamilial adversity** | | **PRS ES (p<.10) x Intrafamilial adversity** | |
|---|---|---|---|---|---|
| ***Anxiety (SCL-R-90)*** | | AIC | Crossover point (95%) | AIC | Crossover point (95%) |
| **GxE models** | DS STRONG | **1214.71** | **-0.61 (-0.91 / -0.31)** | 1218.15 | -0.66 (-0.99 / -0.32) |
| | DS WEAK | 1216.48 | -0.58 (-0.88 / -0.29) | 1220.15 | -0.66 (-0.99 / -0.33) |
| | Diathesis STRONG | 1214.98 | -1 | **1217.64** | -1 |
| | Diathesis WEAK | 1216.66 | -1 | 1218.98 | -1 |
| | Vantage STRONG | 1229.98 | 1 | 1230.16 | 1 |
| | Vantage WEAK | 1223.08 | 1 | 1223.01 | 1 |
| **Non-GxE models** | Intercept only | 1229.55 | NA | 1229.55 | NA |
| | G only | 1230.17 | NA | 1230.54 | NA |
| | E only | 1221.09 | NA | 1221.09 | NA |
| | G+E only | 1222.02 | NA | 1222.16 | NA |

*Note: Best model indicated by lowest AIC is **highlighted**.*

**Table 5. LEGIT competitive-confirmatory tests for PRS-ES on Depression significant (p<0.05) interactions.**

| ***Outcome:*** | | **PRS ES (p<.01) x Threat** | |
|---|---|---|---|
| ***Depression (SCL-R-90)*** | | AIC | Crossover point (95%) |
| **GxE models** | DS STRONG | **1328.95** | **-0.47 (-0.64 / -0.3)** |
| | DS WEAK | 1330.83 | -0.46 (-0.63 / -0.29) |
| | Diathesis STRONG | 1349.37 | -1 |
| | Diathesis WEAK | 1336.96 | -1 |
| | Vantage STRONG | 1364.88 | 1 |
| | Vantage WEAK | 1334.68 | 1 |
| **Non-GxE models** | Intercept only | 1369.4 | NA |
| | G only | 1371.32 | NA |
| | E only | 1335.03 | NA |
| | G+E only | 1335.72 | NA |

*Note: Best model indicated by lowest AIC is **highlighted**.*

**Table 6. LEGIT competitive-confirmatory tests for PRS-PLE on Positive psychotic-like experiences significant (p<0.05) interactions.**

| ***Outcome:*** | | **PRS PLE (p<.01) x Deprivation** | | **PRS PLE (p<.10) x Intrafamilial adversity** | |
|---|---|---|---|---|---|
| ***Positive psychotic experiences (CAPE)*** | | AIC | Crossover point (95%) | AIC | Crossover point (95%) |
| **GxE models** | DS STRONG | 1177.54 | -1.27 (-3.42 / 0.88) | **1164.61** | **-0.65 (-0.98 / -0.32)** |
| | DS WEAK | **1162.1** | **-0.56 (-0.88 / -0.23)** | 1166.2 | -0.67 (-1 / -0.35) |
| | Diathesis STRONG | 1175.67 | -1 | 1165.71 | -1 |
| | Diathesis WEAK | 1164.98 | -1 | 1165.56 | -1 |
| | Vantage STRONG | 1176.29 | 1 | 1177.39 | 1 |
| | Vantage WEAK | 1163.91 | 1 | 1169.49 | 1 |
| **Non-GxE models** | Intercept only | 1175.5 | NA | 1175.5 | NA |
| | G only | 1175.94 | NA | 1176.5 | NA |
| | E only | 1163.3 | NA | 1167.55 | NA |
| | G+E only | 1164.54 | NA | 1168.9 | NA |

*Note: Best model indicated by lowest AIC is **highlighted**.*

**Table 7. LEGIT competitive-confirmatory tests for PRS-PLE on Positive schizotypy significant (p<0.05) interactions.**

| ***Outcome:*** | | **PRS PLE (p<.01) x Deprivation** | | **PRS PLE (p<.001) x Threat** | |
|---|---|---|---|---|---|
| ***Positive schizotypy (WSS)*** | | AIC | Crossover point (95%) | AIC | Crossover point (95%) |
| **GxE models** | DS STRONG | 504.71 | -0.39 (-2.12 / 1.35) | 505.72 | -1.68 (-75.48 / 72.12) |
| | DS WEAK | 488.6 | -0.8 (-1.12 / -0.48) | **485.18** | **-0.58 (-0.83 / -0.33)** |
| | Diathesis STRONG | 503.72 | -1 | 503.72 | -1 |
| | Diathesis WEAK | **487.55** | **-1** | 487.35 | -1 |
| | Vantage STRONG | 503.14 | 1 | 503.72 | 1 |
| | Vantage WEAK | 491.32 | 1 | 488.53 | 1 |
| **Non-GxE models** | Intercept only | 501.73 | NA | 501.73 | NA |
| | G only | 503.34 | NA | 503.72 | NA |
| | E only | 489.9 | NA | 486.71 | NA |
| | G+E only | 490.74 | NA | 488.7 | NA |

*Note: Best model indicated by lowest AIC is **highlighted**.*

**Table 8. LEGIT competitive-confirmatory tests for PRS-PLE on Anxiety significant (p<0.05) interactions.**

| ***Outcome:*** | | **PRS PLE (p<.05) x Intrafamilial adversity** | |
|---|---|---|---|
| ***Anxiety (SCL-R-90)*** | | AIC | Crossover point (95%) |
| **GxE models** | DS STRONG | 1230.06 | 0.35 (-0.84 / 1.54) |
| | DS WEAK | 1216.62 | -0.88 (-1.19 / -0.56) |
| | Diathesis STRONG | 1231.46 | -1 |
| | Diathesis WEAK | **1214.82** | **-1** |
| | Vantage STRONG | 1228.25 | 1 |
| | Vantage WEAK | 1221.19 | 1 |
| **Non-GxE models** | Intercept only | 1229.55 | NA |
| | G only | 1229.14 | NA |
| | E only | 1221.09 | NA |
| | G+E only | 1219.26 | NA |

*Note: Best model indicated by lowest AIC is **highlighted**.*

**Table 9. LEGIT competitive-confirmatory tests for PRS-PLE on Depression significant (p<0.05) interactions.**

| ***Outcome:*** | | **PRS PLE (p<.01) x Deprivation** | | **PRS PLE (p<.05) x Threat** | | **PRS PLE (p<.10) x Threat** | |
|---|---|---|---|---|---|---|---|
| ***Depression (SCL-R-90)*** | | AIC | Crossover point (95%) | AIC | Crossover point (95%) | AIC | Crossover point (95%) |
| **GxE models** | DS STRONG | 1372.53 | -1.27 (-4.5 / 1.95) | 1349.32 | -0.59 (-0.83 / -0.34) | 1343.24 | -0.63 (-0.84 / -0.41) |
| | DS WEAK | **1359.13** | **-0.61 (-0.96 / -0.25)** | 1335.56 | -0.59 (-0.77 / -0.4) | **1334.38** | **-0.67 (-0.85 / -0.48)** |
| | Diathesis STRONG | 1370.58 | -1 | 1365.7 | -1 | 1358.59 | -1 |
| | Diathesis WEAK | 1361.05 | -1 | 1336.4 | -1 | 1334.56 | -1 |
| | Vantage STRONG | 1370.86 | 1 | 1370.21 | 1 | 1371.3 | 1 |
| | Vantage WEAK | 1361.22 | 1 | 1336.92 | 1 | 1336.83 | 1 |
| **Non-GxE models** | Intercept only | 1369.4 | NA | 1369.4 | NA | 1369.4 | NA |
| | G only | 1370.71 | NA | 1371.3 | NA | 1371.02 | NA |
| | E only | 1359.84 | NA | **1335.03** | **NA** | 1335.03 | NA |
| | G+E only | 1361.61 | NA | 1337.02 | NA | 1336.51 | NA |

*Note: Best model indicated by lowest AIC is **highlighted**.*

# Chapter 4

## Genetic Individual Differences in Reactivity to the Environment Impact Psychotic-Like and Affective Reactivity in Daily-Life

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**Abstract**

***Background and Hypothesis:*** Consistent with diathesis-stress models, psychosis research has focused on genetic moderation of *adverse* environmental exposures. In contrast, the Differential Susceptibility (DS) model suggests that the same genetic variants that increase risk-inducing effects of adverse experiences also enhance beneficial effects from positive experiences. This study examined whether individuals with high genetic susceptibility to the environment showed differential psychotic-like and affective reactivity in response to positive and negative events in daily-life.

***Study Design***: Experience sampling methodology assessed context (positive and stressful) and momentary levels of paranoia, psychotic-like experiences (PLE), and positive (PA) and negative affect (NA) in 217 nonclinical adults oversampled for schizotypy. Linear mixed models examined whether Polygenic Risk Scores of Environmental Sensitivity (PRS-ES) moderated the impact of current context on subsequent experiences.

***Study Results***: PRS-ES moderated positive, but not stressful, context on subsequent levels of momentary paranoia, NA, and PA, but not PLE. GxE interactions indicated diathesis-stress at lower thresholds of PRS-ES, but a DS model at the highest threshold of the PRS-ES. Participants with elevated PRS-ES showed increased paranoia and NA and decreased PA in subsequent assessments when reporting low positive situations, but also decreased paranoia and NA and increased PA when rating situations as positive.

***Conclusions***: Findings support that genetic sensitivity to the environment influences psychotic-like and affective reactivity in daily-life, particularly in response to positive contexts. This highlights the transdiagnostic protective role of positive experiences and informs ecological momentary interventions.

## Introduction

The extended psychosis-proneness phenotype, referred to as schizotypy, ranges in expression from minimal dysfunction (e.g., psychotic-like experiences; PLE) to full-blown psychosis (e.g., schizophrenia) (Claridge, 1997; Grant et al., 2018; Kwapil & Barrantes-Vidal, 2015). Evidence suggests that vulnerability factors to the psychosis-spectrum phenotype are shared across a broad range of psychotic and non-psychotic phenotypes (Barrantes-Vidal, Grant, and Kwapil, 2015) at both genetic (Nivard et al., 2017; Van Os et al., 2020; Marsman et al., 2020; Smigielski et al., 2021) and environmental (Binbay et al., 2012; Kounali et al., 2014; Guloksuz et al., 2015; Guloksuz et al., 2016; McLaughlin et al., 2020) levels.

The study of the interplay between genetic and environmental etiological factors (GxE) in psychosis has been mainly guided by the traditional diathesis-stress framework (Monroe & Simons, 1991; Walker & Diforio, 1997) that posits that individuals carrying genetic risk variants are more vulnerable to the effects of negative environments and more prone to develop psychopathology. This framework has neglected the role of positive experiences. In contrast, novel thinking based on evolutionary theory suggests that individuals may differ in their susceptibility to the environment across a broad range of exposures (not just negative) and, therefore, beneficial moderation effects by genetic variation should also be expected to positive contexts. The Differential Susceptibility (DS) model proposes that the same genetic variants and biological or temperamental traits that increase the negative effects of adverse experiences also enhance the likelihood of benefiting from positive experiences and, thus, that some individuals may be more plastic or malleable to the environment (Belsky et al., 2007; Ellis et al., 2011; Belsky & Pluess, 2013). Of note, the DS model integrates the classic diathesis-stress perspective, focused on the negative side of environment, as well as its mirror image, vantage sensitivity, a

model exclusively focused on the beneficial effects of positive environments. However, the latter seems not to be sustained by strong theoretical and evolutionary background (Bakermans-Kranenburg & van IJzendoorn, 2015).

Research has supported the DS model for several phenotypes (e.g., van IJzendoorn et al., 2012; Bakermans-Kranenburg & van IJzendoorn, 2011; Belsky & Pluess, 2016), but only one previous study has tested the validity of DS for schizotypy and PLE (Barrantes-Vidal et al., *submitted*). This is possibly related to the fact that psychosis research is only starting to attend to effects of positive environmental exposures (e.g., Coughlan et al., 2020; McMahon et al., 2021; Ruiz-Yu et al., 2022). Barrantes-Vidal et al. (*submitted*) showed that nonclinical young adults who are genetically sensitive to the environment displayed increased levels of positive schizotypy and PLEs, depression and anxiety if they reported high levels of childhood adversity but, at the same time, less severe symptoms if they reported low or no levels of adversity compared to those with low genetic sensitivity.

DS research has mostly focused on long-term developmental changes, that is, how early life experiences affect an individual's developmental trajectory. Another level of analysis that has received little empirical attention involves focusing on short-term changes, such as immediate effects of stimuli on behavior. This approach has been referred to as Differential Reactivity (Slagt et al., 2019). Differential reactivity involves more transient behavioral changes, which have also been referred to as 'activational' (Snell-Rood, 2013) or 'contextual' (Stamps, 2016) plasticity. Research on differential reactivity has mostly relied on experimental manipulations of the environment (Quas et al., 2004; Sasaki et al., 2013; Slagt et al., 2017), but it can also be explored in relation to immediate normally occurring stimuli or daily-life events (Slagt et al., 2019). In this regard, ambulatory assessment techniques such as experience sampling methodology

(ESM) may be optimal for the examination of dynamic, within-person environmental reactivity.

ESM is a within-day self-assessment technique used to capture cognition, affect, symptoms, and contextual factors (Delespaul, 1995). Repeatedly assessing participants' experiences in real-time and in the real-world minimizes retrospective bias and enhances ecological validity (Myin-Germeys et al., 2009; Ebner-Priemer & Trull, 2009). ESM has successfully been used to examine psychotic and affective reactivity to stress across clinical (Myin-Germeys & van Os, 2007; Reininghaus et al., 2016) and nonclinical (Barrantes-Vidal et al., 2013b; Cristóbal-Narváez et al., 2016a; Chun et al., 2017; Monsonet et al., 2022; Kemp et al., 2023) samples. More so, stress-related genes have shown to moderate such psychotic reactivity in the flow of daily-life (Cristóbal-Narváez et al., 2016b; 2017; 2020). However, to the best of our knowledge only one study has examined genetic differential reactivity to both positive and negative daily events (Sicorello et al., 2020). This study tested whether carriers of the short allele (S) of the 5-HTTLPR variant, one of the most studied variants as a proxy genetic indicator of plasticity and DS effects (Van IJzendoorn et al., 2012; Van IJzendoorn & Bakermans-Kranenburg, 2015), moderated the reactivity to both uplifts and stressors. Contrary to expectations, carriers of the S allele showed less reactivity than the homozygous carriers of the long allele (L/L), which was interpreted in the context of the unsuccessful replicability efforts of candidate-gene studies (and particularly, of variant 5-HTTLPR). In this regard, modern polygenic approaches have been suggested to greatly improve our understanding of the role of GxE in psychopathology (Bulik-Sullivan & Neale, 2015; Maier et al., 2015), and more so in combination with real-time measurement of individuals' context and mental state (Fox & Beevers, 2016; Pries et al., 2020).

The present study examined differential reactivity in daily-life by testing, for the first time, whether a Polygenic Risk Score of Environmental Sensitivity (PRS-ES; Keers et al., 2016) moderated the association of momentary appraisals of the current context (both positive and stressful) with subsequent momentary reports of subclinical psychotic experiences (of the positive, paranoid, negative dimensions) as well as affective (positive and negative affect) manifestations in a DS manner.

It was expected that highly genetically sensitive individuals who rated their current context as stressful or as not positive would show subsequent greater levels of PLE, paranoia, and negative affect, as well as lower positive affect, as compared to low genetically sensitive individuals. In contrast, those same highly genetically sensitive individuals were expected to show lower levels of subsequent symptoms and more positive affect when they rated their current context as minimally stressful or highly positive. Given that the positive and paranoid, but not the negative, dimensions of schizotypy and clinical psychosis have been associated with increased stress-induced psychotic reactivity (Kemp et al., 2023; Monsonet et al., 2022; Udachina et al., 2017; Chun et al., 2017; Cristóbal-Narváez et al., 2016a,b; Lataster et al., 2013; Barrantes-Vidal et al., 2013b; Kwapil et al., 2012), and that the negative dimension is characterized by diminished motivation and low openness to experience (Kwapil et al., 2008; Barrantes-Vidal et al., 2013), we hypothesized that this genetically moderated reactivity to context would not be observed for momentary negative PLE. Furthermore, findings from the previous study examining DS in relation to schizotypy and PLE using retrospective measures did not find an association with negative schizotypy (Barrantes-Vidal et al., *submitted*).

## Methods

### *Participants*

The sample of the present study consisted of 217 (mean age=21.92, SD=2.78; 75% female) non-clinical participants belonging to the Barcelona Longitudinal Investigation of Schizotypy Study (BLISS; Barrantes-Vidal et al., 2013a; b). At T1, a large pool of 547 unselected college students and 261 technical school students were initially screened with self-report questionnaires. At T2, a subsample 214 college and 39 technical school students oversampled for schizotypy scores was selected to conduct in depth examinations comprising a wide range of interview, questionnaire, and ESM measurements. Usable ESM data were available for a total of 206 college and 36 technical school students (see details in Racioppi et al., 2018). Participants at T2 were also genotyped. After genetic quality control, the sample with usable genetic and ESM data comprised a total of 217 nonclinical young adults (197 from college and 20 from technical schools). T-test for independent samples did not reveal any significant difference in PRS or ancestry covariates between these two samples.

### *Materials and Procedure*

#### *Calculation of Polygenic Risk Scores (PRS)*

DNA was extracted from saliva or cotton swabs. The details about the genotyping, quality control and imputation procedures can be found in supplementary materials. PRS were computed based on Genome Wide Association Study (GWAS) of reference by summing the number of risk alleles that participants carried multiplied by their effect sizes. We formed a PRS of environmental sensitivity (PRS-ES; Keers et al., 2016) based on a monozygotic twin study that captured genetic variants associated to intra-pair differences in emotional (internalizing) symptoms.

We applied the classical Clumping + Thresholding (C+T) method with PLINK v1.9. Independent variants were selected by clumping (r2 < 0.1 within a 1000 kb window for PRS-ES) using the 1000 Genomes Project phase 3 (The 1000 Genomes Project Consortium, 2015) as a European linkage disequilibrium (LD) reference panel and 93,494 SNPs survived clumping. We obtained scores with p-value thresholds of 0.001, 0.01, 0.05 and 0.1, based on previous GxE evidence using PRS-ES (Lemery-Chalfant et al., 2018; Barrantes-Vidal et al., submitted). The PRS-ES was computed based on 369 SNPs for $p<.001$; 2,819 SNPs for $p<.01$; 11,244 SNPs for $p<.05$; and 19,895 SNPs for $p<.10$.

*Experience Sampling Methodology*

ESM data were collected on personal digital assistants (PDAs) that signaled participants randomly 8 times a day (between 10 a.m. and 10 p.m.) for one week to complete short questionnaires enquiring about a variety of daily life experiences. Participants had 5 minutes to initiate responding to the questionnaire following the signal, after this period or completion of the questionnaire, the PDA was shut down until next signal. Consecutive survey notifications could range from 10 min to 170 min apart. The complete list of ESM items can be found in Barrantes-Vidal et al. (2013b). All items were rated on 7-point scales from "not at all" to "very much". In the present study, reports of momentary paranoia, PLE, diminished thoughts/emotions (as a proxy of negative psychotic symptoms), and negative (NA) and positive (PA) affect were employed as outcome measures. Ratings of how positive and how stressful the current situation was were used as indicators of current context. Details on indices, items, and reliabilities are presented in Table 1.

***Statistical Analysis***

ESM data have a hierarchical structure in which ESM ratings (level 1 data) are nested within participants (level 2 data). As the standard approach for the analysis of ESM data, linear mixed models were used to control for within-subject clustering of multiple observations using Version 3.6.3 of the LEGIT package (Jolicoeur-Martineau et al., 2020) in R (R Core Team, 2013). The present study examined 1) the time-lagged association between the preceding ratings of situations as (i) positive and (ii) stressful (*time t – 1*) on levels of criteria at the subsequent ESM assessment (*time t*), and 2) the cross-level interaction between level 2 genetic data (PRS-ES) and appraisals of the situation at *time t – 1* on criteria at *time t*. Time-lagged analyses were limited to examining within-day associations. Moreover, cases with missing data on relevant variables at *time t – 1* or *time t* were excluded from each analysis. Interactions yielding significant effects (p-values < 0.05) were examined based on the competitive-confirmatory approach (Belsky & Widaman, 2018; Widaman et al., 2012) to determine whether the GxE interaction fitted in a DS model. As detailed elsewhere (Barrantes-Vidal et al., *submitted*), the LEGIT package envisions weak and strong versions of three GxE models (DS, diathesis-stress and vantage sensitivity), and the model showing lowest Akaike Information Criterion (AIC) represents the best fit. To classify an interaction within the DS model, the 95% interval of its estimated crossover point needs to be within observable bounds of the environmental score.

All analyses included the first two ancestry-informative principal components from the MDS, Principal Component 1 (PC1) and 2 (PC2), as covariates in the mixed models examined and were trimmed from the competitive-confirmatory test phase if they were nonsignificant. We used False Discovery Rate (FDR; Benjamini & Hochberg, 1995) to correct for multiple testing across thresholds of PRS-ES for each of the outcome variables.

**Results**

Table 2 shows the descriptive statistics and the Pearson correlations of the study variables. PRS-ES (thresholds $p<.001$; .05; .10) showed small effect size correlations with positive appraisals of the current situation and PA (thresholds $p<.001$; .05) with values ranging from $r=-.10$ to $r=-.18$. The PRS-ES (threshold $p<.10$) also showed a small association with PLE (r=.15). Following Belsky et al. (2007) stepwise testing approach for DS, the potential susceptibility factor (here, PRS-ES) should not be associated with the environmental predictor or the outcome. However, the examination of the confidence intervals (see supplementary table 1) indicates that all the correlation values fall within the other correlations' confidence intervals--indicating that the six correlation values do not significantly differ (and can essentially be considered equivalent). Although the correlation values attained statistical significance, these are small effects indicating only 1% to 3% of shared variance shared, and minimal collinearity between the ESM item and the PRS-ES. Thus, such small effects and minimal collinearity should not preclude the examination of the interaction of the PRS-ES and ESM scores from a DS perspective.

As shown in Table 3, ratings of the current situation as positive were directly associated with subsequent levels of momentary paranoia, PLE, negative-like symptoms, NA, and PA. After adjusting for multiple testing, PRS-ES moderated the association between positive situation and subsequent momentary paranoia (thresholds $p<.01$; .05; .10), NA (thresholds $p<.01$; .05; .10) and PA (threshold $p<.01$; .05; .10). For the interactions on subsequent levels of paranoia, the competitive-confirmatory analyses revealed strong patterns of DS for the greater polygenic thresholds (thresholds $p<.05$ and .10) and diathesis-stress for the lower threshold $p<.01$. That is, participants with higher (specially more polygenic) PRS-ES scores showed increased levels of subsequent paranoia when in low positive contexts, but also less paranoia when the context was

positive (Figure 1a), whereas those with lower polygenic PRS-ES were only affected by low, not high, positive contexts, which increased their subsequent paranoia. In other words, only participants with high polygenic PRS-ES showed paranoid reactivity in the form of *both* increases and decreases in momentary paranoia in relation to the context (from low to high positive, respectively). Similarly, interactions on subsequent levels of negative as well as positive affect were classified as fitting a weak model of DS for the most polygenic threshold ($p<.10$), but a weak diathesis-stress pattern for lower thresholds ($p<.01$ and .05).Thus, participants with a more polygenic PRS-ES threshold showed reduced PA and increased NA if the situation was not positive, but increased PA and reduced NA if the situation was highly positive (Figures 1b, c). However, at lower thresholds of PRS-ES, participants were only affected by low positive contexts, showing subsequent reduced PA and increased NA.

Table 4 shows the results of the effects of stressful situations, which predicted subsequent levels of momentary paranoia, PLE, NA and PA, but not negative-like symptoms. After adjusting for multiple testing, PRS-ES only moderated the association between the current stressful situation with subsequent paranoia (threshold $p<0.001$) and the interaction was best fitted within a weak model of diathesis-stress, in this case for participants with low PRS-ES.

**Discussion**

The present study examined for the first time whether highly environmental genetic sensitive individuals showed differential psychotic-like and affective reactivity to positive and negative contexts in daily-life. We found that PRS-ES moderated the effects of positive, but not negative, contexts on subsequent momentary levels of paranoia, NA and PA. GxE interactions were consistent with a pattern of diathesis-stress at the lower

thresholds of PRS-ES, but results supported the DS model at the highest threshold of the PRS-ES ($p<0.10$). This indicates that participants with elevated scores (at more polygenic thresholds of) PRS-ES showed increased levels of momentary paranoia and NA as well as decreased PA in the subsequent assessment when reporting low positive situations, but also decreased paranoia and NA as well as increased PA when they had previously rated the situation as positive.

Overall, this study adds novel evidence regarding DS in schizotypy and PLE by showing that participants with high genetic sensitivity to environment are not only differentially affected by early-life experiences (Barrantes-Vidal et al., *submitted),* but also by normally occurring events in daily-life. Sensitivity might be related to developmental trajectories triggered by experiences that occurred in the past (that is, developmental plasticity; Snell-Rood, 2013; Stamps, 2015) and to the immediate effects of current environmental stimuli (that is, contextual plasticity; Snell-Rood, 2013; Stamps, 2015). Only a few studies have focused on short-term changes when examining DS, and most of them tended to rely on experimental manipulations of the environment (Quas et al., 2004; Sasaki et al., 2013; Slagt et al., 2017). For instance, at a temperamental level, a previous study by Slagt and colleagues (2019) examined the moderating effect of children's emotional reactivity, a potential susceptibility marker in infancy, on moment-to-moment interactions between parents and children (Slagt et al., 2019). They found evidence supporting differential reactivity as highly emotional reactive children were more likely to respond with increasingly negative emotions in response to their mother's negative emotions, but also more likely to show increasingly positive emotions in response to their mother's positive emotions (Slagt et al., 2019).

As hypothesized, significant interactions between PRS-ES and positive context ratings were associated with subsequent levels of paranoia, NA and PA. These

interactions were consistent with a GxE model of diathesis-stress at PRS-ES threshold $p<.01$, indicating that those with high levels of PRS-ES exposed to low positive situations showed increased momentary paranoia and NA, as well as decreased PA, at the subsequent assessment time point. However, when the PRS-ES *p*-value threshold increased (that is, more SNPs were included into the polygenic score), interactions fitted DS. At threshold $p<.05$, the interaction between PRS-ES and positive context on paranoia was consistent with DS, and at threshold $p<.10$ all three interactions (paranoia, NA and PA) were best fitted into DS models, indicating that participants with high (and more polygenic) PRS-ES were not only affected by less positive situations but, also, showed decreased levels of paranoia and NA, as well as increased PA, when the situation was highly positive, as compared to those with lower PRS-ES. Interestingly, these differential findings based on the *p*-value threshold of PRS-ES are in line with previous studies employing this polygenic score. Keers et al. (2016) and Lemery-Chalfant et al. (2018) also found that the thresholds $p<.05$ and $p<.10$, but not $p<.01$ or $p<.001$, of PRS-ES moderated the effects of a cognitive-behavioral intervention on children's anxiety (Keers et al., 2016) and the effects of a family-based intervention on children's internalizing symptoms (Lemery-Chalfant et al., 2018) in a '*for better and for worse*' pattern. Thus, the present study supports PRS-ES as a proxy DS factor, particularly at thresholds $p<.05$ and $p<.10$, indicating that sensitivity to the environment and daily-life (positive) experiences are relevant in the mechanistic pathway to a myriad of subclinical psychopathology expressions. In line with emerging evidence about the transdiagnostic protective role of positive experiences (Coughlan et al., 2020), we found that positive context ratings predicted lower paranoia and NA, as well as greater PA—this positive impact was only found for PLE at the level of direct effects, possibly related to a reduced ability to capture interaction effects given the more limited variance of these experiences

in our nonclinical sample. This finding is particularly relevant for the psychotic dimension, as research has traditionally focused on the detrimental effects of adversity, with scant attention to the potential impact of positive environmental factors. Furthermore, this may have important clinical implications for the design of ecological momentary interventions from a positive psychology perspective, aimed at promoting resilience-building and well-being rather than only focusing on diminishing risk for symptom expression and maintenance (Reininghaus et al., 2023).

As expected, and in line with previous evidence (Barrantes-Vidal et al., *submitted*), PRS-ES did not moderate the effects of positive context ratings on negative psychotic-like symptoms. In contrast, we did expect that PRS-ES moderated the effects of positive context on subsequent PLE, as we found a DS pattern when examining the PRS-ES moderation of childhood adversity on positive PLE retrospectively (Barrantes-Vidal et al., *submitted*). It is relevant to highlight that the assessment of PLEs can be challenging, especially in daily-life and in nonclinically-ascertained college-student samples (Kwapil et al., 2020). As compared to paranoia, one of the most prevalent psychotic manifestations reported in the general population (with prevalence ~10%; Sheffield et al., 2021; Johns et al., 2004) that can be ascertained by perceptions of suspiciousness and mistrust, PLEs are a diverse and heterogeneous phenomenon that can include unusual perceptual experiences (visual, olfactory, auditory, etc.) and odd beliefs. This possibly explains in part their low endorsement rates and variability, which impacts the power of detecting significant interaction effects.

Contrary to our hypothesis, the PRS-ES did not yield interactions with stressful contexts, except for one interaction with the lowest threshold of PRS-ES ($p<.001$) predicting paranoia. However, given the lack of consistency across thresholds and the fact that it was an isolated effect compared to the multiple consistent effects of PRS-ES on

the association between positive context and subclinical phenomena, this finding should be considered cautiously. Our ability to capture significant interaction effects might have been limited by the fact that the item '*My current situation is stressful*' showed a lower endorsement (M=2.15, SD=1.06) than '*My current situation is positive*; M=5.35, SD=0.96)−also, from the total amount of time points (N=7526), more than half (i.e., 57.1%) were endorsed as '1' ('Not at all'), indicating an absence of stress. Nevertheless, we did find main effects of stress on subsequent levels of momentary paranoia, PLE, NA and PA, consistent with previous evidence on psychotic and affective stress-reactivity in daily-life across the psychosis continuum (Myin-Germeys & van Os, 2007; Reininghaus et al., 2016; Barrantes-Vidal et al., 2013b; Cristóbal-Narváez et al., 2016a; Chun et al., 2017; Monsonet et al., 2022; Kemp et al., 2023). Of note, in another study using the same sample, we showed that a PRS indexing variability of the hypothalamic-pituitary-adrenal (HPA) axis function, one of the main neural systems involved in regulating the stress response, moderated the effects of momentary stressful appraisals on subsequent levels of NA in daily-life (Torrecilla et al., *to be submitted*). Thus, it might be speculated that the PRS-ES may not be as sensitive to moderate the impact of mild daily stressful situations as other genetic indicators more directly indexing biologically functional variability in stress-regulating systems.

The present study has several strengths and limitations. In order to overcome replicability limitations of candidate-gene research, the present study employed a polygenic approach based on a twin-based GWAS predicting pair-differences in emotional response (Keers et al., 2016). Thus, in contrast to traditional GWAS designs, characterized by essentially aggregating small genetic main effects, the PRS-ES is a combination of variants associated with the magnitude of response to twins' nonshared environments. The use of ecologically valid measures of context and subclinical

experiences across multiple time points over a week in real life is a notable strength of the present study. Specifically, the examination of ESM time-lagged associations between previous contextual appraisals and subsequent psychological states enables to estimate causal inferences of the effects of the predictor on the criterion. Finally, the use of real-time measurement in combination with polygenic approaches has been suggested to greatly advance our understanding of GxE in psychopathology and well-being as well as enhancing GxE reliability research (Fox & Beevers, 2016).

Findings of the present study should be interpreted with caution due to several limitations. First, the use of a high-quality intensive repeated assessment method over a week (ESM) conditioned a reduction of sample size. However, momentary assessment technologies have been suggested to substantially reduce sample size requirements and substantially enhance the detection of subtle GxE effects (Van Os et al., 2008). Furthermore, the use of a predominantly female university student sample limits generalizability Finally, it has been suggested that to adequately examine DS, a single environmental measure should cover both negative and positive aspects (Belsky et al., 2007; Widaman et al., 2012). Although previous research (Sicorello et al., 2020) combined two (positive and negative) environmental variables (i.e., number of daily uplifts and daily stressors) into one index, we decided not to combine positive and stressful contextual appraisals into a single score to avoid the inaccurate assumption that an overall positive situation is one where positive appraisals overweight stressful appraisals, and vice versa (Sicorello et al., 2020).

The present findings offer a promising initial examination of DS in schizotypy, but ultimately require replication in larger independent samples with more representative distributions of gender, age, and educational levels. Results are in line with the notion that environmental sensitivity may be a crucial transdiagnostic causative factor of diverse

psychopathology dimensions and highlight the potential value of protective factors such as minor daily positive experiences. Further support to this research would stress the value of positive intervention and prevention strategies focused on decreasing poor mental health outcomes and increasing well-being in highly sensitive people.

## Tables and Figures

### Table 1. ESM items used in this study.

| Domain | ESM items | Reliability |
|---|---|---|
| ***Outcomes*** | | |
| **Paranoia index** | Computed as the mean of 2 items:<br>Right now, I feel suspicious<br>Right now, I feel mistreated | Between α=0.75 |
| **Psychotic-like experiences index (PLE)** | Computed as the mean of 8 items:<br>Right now, I fear losing control<br>Right now, I feel weird<br>Right now, I have difficulty controlling my thoughts<br>Right now, my thoughts are strange or unusual<br>Right now, my sight or hearing seem strange or unusual<br>Since the last beep, I have heard or seen things others could not<br>Right now, I feel that someone or something is controlling my thoughts or actions<br>Right now, familiar things seem strange and unusual | Between α=0.79 |
| **Negative-like symptoms** | Right now, I have no thoughts or emotions | - |
| **Negative affect index (NA)** | Computed as the mean of 4 items:<br>Right now, I feel sad<br>Right now, I feel anxious (nervous)<br>Right now, I feel angry<br>Right now, I feel guilty or ashamed | Between α=0.81 |
| **Positive affect index (PA)** | Computed as the mean of 2 items:<br>Right now, I feel happy<br>Right now, I feel relaxed | Between α=0.81 |
| ***Contextual predictors*** | | |
| **Stressful situation** | My current situation is stressful | - |
| **Positive situation** | My current situation is positive | - |

**Table 2. Descriptive statistics and Pearson correlations for the study variables (*n* = 217).**

| | *Descriptive statistics* | | *Pearson correlations (r)* | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **M (SD)** | **Range** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** |
| **1. PRS-ES (*p*<.001)** | 0.88 (1.04) | -2.03-3.89 | - | .39*** | .40*** | .37*** | -.00 | -.14* | -.04 | -.00 | -.01 | .05 | -.15* |
| **2. PRS-ES (*p*<.01)** | 4.13 (2.25) | -1.55-10.76 | | - | .67*** | .61*** | -.02 | -.10 | .07 | .09 | -.05 | .04 | -.05 |
| **3. PRS-ES (*p*<.05)** | 6.70 (4.73) | -5.39-20.08 | | | - | .88*** | .03 | -.18** | .12 | .11 | .07 | .11 | -.14* |
| **4. PRS-ES (*p*<.10)** | 9.01 (5.64) | -3.31-25.15 | | | | - | -.02 | -.17* | .10 | .15* | .08 | .08 | -.08 |
| **5. ESM Stressful situation** | 2.15 (1.06) | 1 - 6.31 | | | | | - | -.39*** | .36*** | .39*** | .01 | .62*** | -.53*** |
| **6. ESM Positive situation** | 5.35 (0.96) | 1.91 - 7 | | | | | | - | -.36*** | -.29*** | -.10 | -.53*** | .81*** |
| **7. ESM Paranoia** | 1.21 (0.35) | 1 - 3.25 | | | | | | | - | .70*** | .18*** | .76*** | -.34*** |
| **8. ESM PLE** | 1.12 (0.18) | 1 - 2.63 | | | | | | | | - | .24*** | .58*** | -.28*** |
| **9. ESM Negative symptoms** | 1.35 (0.69) | 1 - 4.90 | | | | | | | | | - | .09 | -.01 |
| **10. ESM Negative Affect** | 1.51 (0.47) | 1 - 3.92 | | | | | | | | | | - | -.56*** |
| **11. ESM Positive Affect** | 4.70 (0.79) | 2.57 - 6.47 | | | | | | | | | | | - |

Note. Mean ESM scores for each participant are reported. *$p$<0.05. **$p$<0.01. ***$p$<0.001. r>0.30 are medium effect sizes and r>0.50 are large effect sizes.

**Table 3. Effects of PRS of Environmental Sensitivity (p=0.001, 0.01, 0.05, 0.10), positive situation and their interaction on predicting subsequent momentary psychotic-like and affective manifestations**.

| | PRS-ES | T-1 Positive situation | PRS-ES x T-1 Positive situation | Best GxE model[c] |
|---|---|---|---|---|
| | Est. (S.E.) | Est. (S.E.) | Est. (S.E.)[a, b] | |
| ***T1 ESM Psychosis spectrum*** | | | | |
| *T1 ESM Paranoia* | | | | |
| PRS-ES ($p$<.001) | -0.015 (0.022) | -0.167 (0.024)*** | -0.010 (0.018) | - |
| PRS-ES ($p$<.01) | 0.024 (0.011) | -0.020 (0.039)*** | -0.036 (0.008)*** | Diathesis-stress S |
| PRS-ES ($p$<.05) | 0.014 (0.005) | -0.037 (0.034)*** | -0.019 (0.004)*** | DS S |
| PRS-ES ($p$<.10) | 0.010 (0.004) | -0.027 (0.037)*** | -0.015 (0.003)*** | DS S |
| *T1 ESM PLE* | | | | |
| PRS-ES ($p$<.001) | 0.003 (0.012) | -0.040 (0.011)*** | -0.017 (0.008) | - |
| PRS-ES ($p$<.01) | 0.008 (0.006) | -0.034 (0.018)*** | -0.005 (0.004) | - |
| PRS-ES ($p$<.05) | 0.005 (0.003) | -0.022 (0.016)*** | -0.004 (0.002) | - |
| PRS-ES ($p$<.10) | 0.005 (0.002) | -0.035 (0.017)*** | -0.002 (0.002) | - |
| *T1 ESM Negative-Like Symptoms* | | | | |
| PRS-ES ($p$<.001) | 0.015 (0.048) | 0.111 (0.035)* | -0.056 (0.026) | - |
| PRS-ES ($p$<.01) | -0.010 (0.022) | 0.128 (0.058)* | -0.016 (0.012) | - |
| PRS-ES ($p$<.05) | 0.005 (0.11) | 0.034 (0.050)* | 0.004 (0.006) | - |
| PRS-ES ($p$<.10) | 0.003 (0.009) | -0.025 (0.055)* | 0.009 (0.005) | - |
| ***T1 ESM Affect*** | | | | |
| *T1 ESM Negative affect* | | | | |
| PRS-ES ($p$<.001) | 0.016 (0.030) | -0.365 (0.030)*** | -0.022 (0.022) | - |
| PRS-ES ($p$<.01) | 0.014 (0.014) | -0.255 (0.049)*** | -0.030 (0.010)** | Diathesis-stress W |
| PRS-ES ($p$<.05) | 0.017 (0.007) | -0.200 (0.042)*** | -0.025 (0.005)*** | Diathesis-stress W |
| PRS-ES ($p$<.10) | 0.011 (0.005) | -0.191 (0.046)*** | -0.020 (0.004)*** | DS W |
| *T1 ESM Positive affect* | | | | |
| PRS-ES ($p$<.001) | -0.069 (0.045) | 0.734 (0.049)*** | 0.016 (0.036) | - |
| PRS-ES ($p$<.01) | -0.032 (0.021) | 0.551 (0.080)*** | 0.046 (0.016)** | Diathesis-stress W |
| PRS-ES ($p$<.05) | -0.027 (0.010) | 0.511 (0.070)*** | 0.032 (0.008)*** | Diathesis-stress W |
| PRS-ES ($p$<.10) | -0.013 (0.008) | 0.479 (0.076)*** | 0.027 (0.007)*** | DS W |

Abbreviations: ESM=Experience Sampling Methodology; PRS-ES=Polygenic Risk Score; PLE=Psychotic-like experiences; GxE=Gene-by-environment interaction; DS=Differential Susceptibility; S=Strong, W=Weak. * $p$<.05. ** $p$<.01. *** $p$<.001 [a] Adjusted for ancestry PC1 and PC2.. [b] P values are indicated after FDR correction for multiple testing. [c] Complete outputs of the LEGIT competitive-confirmatory analyses are shown in supplementary tables 2-4.

**Table 4. Effects of PRS of Environmental Sensitivity (*p*=0.001, 0.01, 0.05, 0.10), stressful situation and their interaction on predicting subsequent momentary psychotic-like and affective manifestations.**

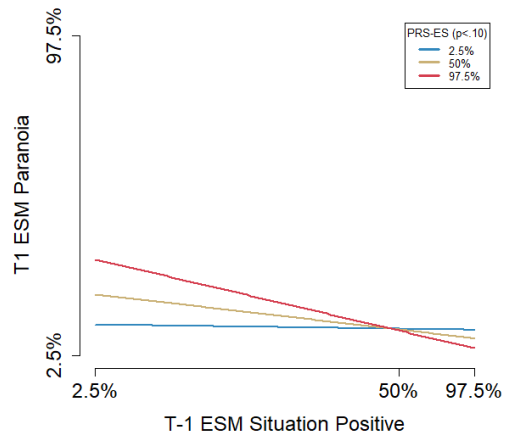
| | PRS-ES | T-1 Stressful situation | PRS-ES x T-1 Stressful situation | Best GxE model |
|---|---|---|---|---|
| | Est. (S.E.) | Est. (S.E.) | Est. (S.E.)[a, b] | |
| ***T1 ESM Psychosis spectrum*** | | | | |
| *T1 ESM Paranoia* | | | | |
| PRS-ES (*p*<.001) | -0.049 (0.024) | 0.192 (0.020)*** | -0.062 (0.015)*** | Diathesis-stress W |
| PRS-ES (*p*<.01) | 0.017 (0.011) | 0.106 (0.033)*** | 0.008 (0.007) | - |
| PRS-ES (*p*<.05) | 0.011 (0.005) | 0.107 (0.028)*** | 0.005 (0.003) | - |
| PRS-ES (*p*<.10) | 0.009 (0.004) | 0.088 (0.030)*** | 0.006 (0.003) | - |
| *T1 ESM PLE* | | | | |
| PRS-ES (*p*<.001) | -0.010 (0.012) | 0.064 (0.009)*** | -0.015 (0.007) | - |
| PRS-ES (*p*<.01) | 0.003 (0.006) | 0.074 (0.015)*** | -0.005 (0.003) | - |
| PRS-ES (*p*<.05) | 0.005 (0.003) | 0.044 (0.013)*** | 0.001 (0.002) | - |
| PRS-ES (*p*<.10) | 0.005 (0.002) | 0.045 (0.014)*** | 0.001 (0.001) | - |
| *T1 ESM Negative-Like Symptoms* | | | | |
| PRS-ES (*p*<.001) | -0.027 (0.049) | 0.015 (0.029) | -0.027 (0.022) | - |
| PRS-ES (*p*<.01) | -0.030 (0.022) | 0.067 (0.050) | -0.017 (0.011) | - |
| PRS-ES (*p*<.05) | 0.001 (0.011) | 0.056 (0.042) | -0.009 (0.005) | - |
| PRS-ES (*p*<.10) | 0.003 (0.009) | 0.042 (0.045) | -0.005 (0.004) | - |
| ***T1 ESM Affect*** | | | | |
| *T1 ESM Negative affect* | | | | |
| PRS-ES (*p*<.001) | 0.004 (0.030) | 0.355 (0.024)*** | -0.033 (0.019) | - |
| PRS-ES (*p*<.01) | 0.004 (0.014) | 0.355 (0.041)*** | -0.006 (0.009) | - |
| PRS-ES (*p*<.05) | 0.015 (0.006) | 0.290 (0.035)*** | 0.005 (0.004) | - |
| PRS-ES (*p*<.10) | 0.012 (0.005) | 0.270 (0.037)*** | 0.006 (0.003) | - |
| *T1 ESM Positive affect* | | | | |
| PRS-ES (*p*<.001) | -0.084 (0.053) | -0.478 (0.041)*** | 0.018 (0.032) | - |
| PRS-ES (*p*<.01) | -0.025 (0.025) | -0.468 (0.070)*** | 0.001 (0.015) | - |
| PRS-ES (*p*<.05) | -0.023 (0.011) | -0.469 (0.059)*** | 0.001 (0.007) | - |
| PRS-ES (*p*<.10) | -0.014 (0.010) | -0.420 (0.062)*** | -0.005 (0.006) | - |

Abbreviations: ESM=Experience Sampling Methodology; PRS-ES=Polygenic Risk Score; PLE=Psychotic-like experiences; GxE=Gene-by-environment interaction; DS=Differential Susceptibility; S=Strong, W=Weak. * *p*<.05. ** *p*<.01. *** *p*<.001.

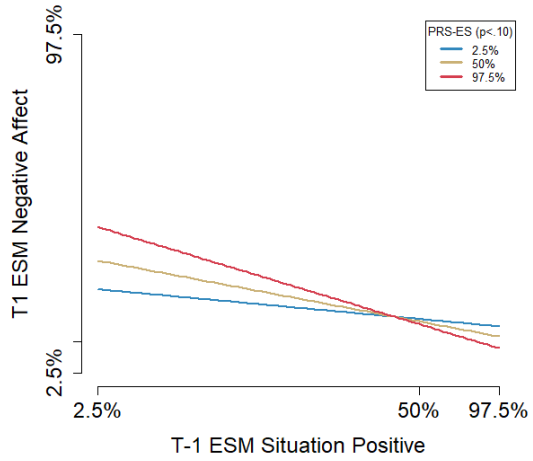
[a] Adjusted for ancestry PC1 and PC2. [b] P values are stated after FDR correction for multiple testing. [c] Complete outputs of the LEGIT competitive-confirmatory analyses are shown in supplementary table 5.

**Figure 1. Graphic representation of the significant predictive interactions of PRS-ES (*p*<.10) with previous ratings of positive situation on subsequent momentary a) paranoia, b) negative affect and c) positive affect.**

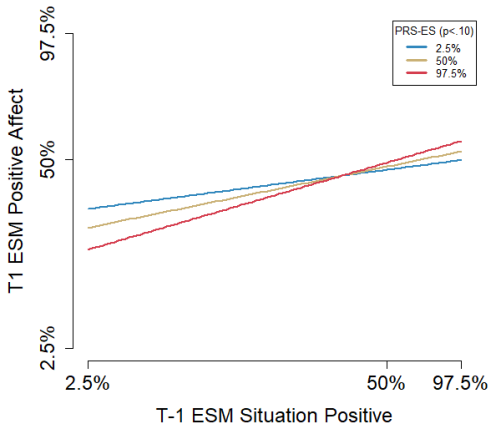
**a)**




**b)**



**c)**


PRS-ES (p<.10)
2.5%
50%
97.5%
T1 ESM Positive Affect
97.5%
50%
2.5%
2.5%
50%
97.5%
T-1 ESM Situation Positive

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**Supplementary Materials**

*Genotyping, Quality Control and Imputation*

DNA was extracted from saliva or cotton swabs using the following extraction kits: i) the prepIT-L2P kit (DNA Genotek Inc., Ottawa, Ontario, Canada) for saliva samples and ii) the RealPure Genomic DNA Extraction Kit (Durviz S.L.U., Valencia, Spain) for cotton swab samples. DNA samples were genotyped at the "Centro Nacional de Genotipado" (CEGEN-PRB3-ISCIII; CNIO-Madrid) using the Illumina Infinium Global Screening Array-24 v2.0 (GSA) BeadChip. Genotype calls were generated with GenomeStudio v2.0.4 (Illumina Inc., San Diego, CA, USA). The quality control (QC) was performed using PLINK v1.9 (www.cog-genomics.org/plink/1.9/; Chang et al., 2015). During QC, SNPs were excluded when: had a missing call rate >2%; had a Minor Allele Frequency (MAF) <0.1%; or deviated from Hardy-Weinberg equilibrium with a P-value <0.001. Subjects were excluded when they had a missing call rate >2%; were genetically related to other participants or duplicated samples according to the pairwise identity by descent method (PI_HAT >0.25); or had non-European ancestry according to a Multidimensional Scaling (MDS) analysis, which was carried out with PLINK v1.9 to obtain a representation of genetic ancestry in our study, extracting the first 10 ancestry components. From the total sample at Time 2 of 253 non-clinical individuals, 25 subjects were excluded during QC leaving a sample of 228 subjects. MDS components were recalculated in this final sample and the two first components were used in all models including PRS as independent variables. Imputation was performed using the Haplotype Reference Consortium panel (www.haplotype-reference-consortium.org; McCarthy et al., 2016) in the Michigan Imputation Server (Das et al., 2016). A post-imputation QC was carried out to exclude SNPs that had an imputation quality score of R2 <0.3; or had a MAF <1%. A total of 7,755,414 SNPs passed post-imputation QC.

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**Table 1. Bootstrapped Pearson correlations for the study variables (n=217).**

| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1. PRS-ES (*p*<.001)** | r | - | .39*** | .40*** | .37*** | -.00 | -.14* | -.04 | -.00 | -.01 | .05 | -.15* |
| | 95% CI[a] | | [.28, .51] | [.28, .51] | [24, .49] | [-.14, .13] | [-.25, -.02] | [-.19, .13] | [-.17, .18] | -.14, .12] | [-.09, .18] | [-.28, -.03] |
| **2. PRS-ES (*p*<.01)** | r | | - | .67*** | .61*** | -.02 | -.10 | .07 | .09 | -.05 | .04 | -.05 |
| | 95% CI | | | [.58, .73] | [.52, .68] | [-.16, .12] | [-.23, .03] | [-.05, .22] | [.00, .20] | [-.15, .06] | [-.10, .17] | [-.19, .08] |
| **3. PRS-ES (*p*<.05)** | r | | | - | .88*** | .03 | -.18** | .12 | .11 | .07 | .11 | -.14* |
| | 95% CI | | | | [.85, .91] | [-.10, .18] | [-.31, -.06] | [.00, .24] | [.00, .26] | [-.04, .17] | [-.01, .24] | [-.26, -.02] |
| **4. PRS-ES (*p*<.10)** | r | | | | - | -.02 | -.17* | .10 | .15* | .08 | .08 | -.08 |
| | 95% CI | | | | | [-.15, .12] | [-.31, -.04] | [-.01, .23] | [.07, .27] | [-.03, .17] | [-.03, .20] | [-.20, .05] |
| **5. ESM Stressful situation** | r | | | | | - | -.39*** | .36*** | .39*** | .01 | .62*** | -.53*** |
| | 95% CI | | | | | | [-.53, -.23] | [.23, .49] | [.27, .56] | [-.09, .12] | [.51, .71] | [-.63, -.42] |
| **6. ESM Positive situation** | r | | | | | | - | -.36*** | -.29*** | -.10 | -.53*** | .81*** |
| | 95% CI | | | | | | | [-.48, -.23] | [-.46, -.16] | [-.24, .03] | [-.62, .43] | [.75, .86] |
| **7. ESM Paranoia** | r | | | | | | | - | .70*** | .18*** | .76*** | -.34*** |
| | 95% CI | | | | | | | | [.60, .80] | [.02, .39] | [.67, .83] | [-.46, -.22] |
| **8. ESM PLE** | r | | | | | | | | - | .24*** | .58*** | -.28*** |
| | 95% CI | | | | | | | | | [.07, .39] | [.48, .74] | [-.47, -.15] |
| **9. ESM Negative symptoms** | r | | | | | | | | | - | .09 | -.01 |
| | 95% CI | | | | | | | | | | [-.07, .30] | [-.16, .14] |
| **10. ESM Negative Affect** | r | | | | | | | | | | - | -.56*** |
| | 95% CI | | | | | | | | | | | [-.64, -.48] |
| **11. ESM Positive Affect** | r | | | | | | | | | | | - |
| | 95% CI | | | | | | | | | | | |

∗p < 0.05. ∗∗ p < 0.01. ∗∗∗ p < 0.001. a Bootstrapped 95% confidence intervals for N=1000 samples.

**Table 2. LEGIT competitive-confirmatory tests for PRS-ES and T-1 ESM Positive situation on T1 ESM Paranoia significant interactions.**

| *Outcome:* | | **PRS-ES (p=.01) x ESM Positive situation** | | **PRS-ES (p=.05) x ESM Positive situation** | | **PRS-ES (p=.10) x ESM Positive situation** | |
|---|---|---|---|---|---|---|---|
| *T1 ESM Paranoia* | | AIC | Crossover point (95%) | AIC | Crossover point (95%) | AIC | Crossover point (95%) |
| **GxE models** | DS STRONG | 8865.91 | 0.65 ( 0.57 / 0.74 ) | **8864.45** | **0.67 ( 0.59 / 0.75 )** | **8866.64** | **0.60 ( 0.51 / 0.68 )** |
| | DS WEAK | 8872.31 | 0.67 ( 0.58 / 0.75 ) | 8870.23 | 0.71 ( 0.63 / 0.8 ) | 8872.9 | 0.62 ( 0.54 / 0.7 ) |
| | Diathesis STRONG | **8865.82** | **1** | 8864.77 | 1 | 8867.55 | 1 |
| | Diathesis WEAK | 8872.31 | 1 | 8869.45 | 1 | 8872.74 | 1 |
| | Vantage STRONG | 8896.76 | -1 | 8906.68 | -1 | 8900.56 | -1 |
| | Vantage WEAK | 8886.55 | -1 | 8888.52 | -1 | 8888.42 | -1 |
| **Non-GxE models** | Intercept only | 16037.17 | NA | 16037.17 | NA | 16037.17 | NA |
| | G only | 16029.17 | NA | 16004.19 | NA | 16012.18 | NA |
| | E only | 10145.17 | NA | 10145.17 | NA | 10145.17 | NA |
| | G+E only | 10145.92 | NA | 10143.38 | NA | 10144.7 | NA |

*Note: Best model indicated by lowest AIC is **highlighted**.*

**Table 3. LEGIT competitive-confirmatory tests for PRS-ES and T-1 ESM Positive situation on T1 ESM Negative affect significant interactions.**

| *Outcome:* | | **PRS-ES (p=.01) x ESM Positive situation** | | **PRS-ES (p=.05) x ESM Positive situation** | | **PRS-ES (p=.10) x ESM Positive situation** | |
|---|---|---|---|---|---|---|---|
| *T1 ESM Negative affect* | | AIC | Crossover point (95%) | AIC | Crossover point (95%) | AIC | Crossover point (95%) |
| **GxE models** | DS STRONG | 11338.57 | 0.48 ( 0.43 / 0.54 ) | 11314.84 | 0.57 ( 0.52 / 0.62 ) | 11314.45 | 0.48 ( 0.43 / 0.53 ) |
| | DS WEAK | 11316.48 | 0.48 ( 0.43 / 0.53 ) | 11298.97 | 0.67 ( 0.62 / 0.72 ) | **11303.5** | **0.55 ( 0.5 / 0.6 )** |
| | Diathesis STRONG | 11344.94 | 1 | 11321.11 | 1 | 11322.68 | 1 |
| | Diathesis WEAK | **11315.85** | **1** | **11298.61** | **1** | 11304.02 | 1 |
| | Vantage STRONG | 11389.5 | -1 | 11395.21 | -1 | 11379.25 | -1 |
| | Vantage WEAK | 11320.46 | -1 | 11318.29 | -1 | 11318.28 | -1 |
| **Non-GxE models** | Intercept only | 20686.08 | NA | 20686.08 | NA | 20686.08 | NA |
| | G only | 20685.03 | NA | 20645.63 | NA | 20665.48 | NA |
| | E only | 12763.54 | NA | 12763.54 | NA | 12763.54 | NA |
| | G+E only | 12765.13 | NA | 12762.2 | NA | 12764.95 | NA |

*Note: Best model indicated by lowest AIC is **highlighted**.*

**Table 4. LEGIT competitive-confirmatory tests for PRS-ES and T-1 ESM Positive situation on T1 ESM Positive affect significant interactions.**

| *Outcome:* | | **PRS-ES (p=.01) x ESM Positive situation** | | **PRS-ES (p=.05) x ESM Positive situation** | | **PRS-ES (p=.10) x ESM Positive situation** | |
|---|---|---|---|---|---|---|---|
| *T1 ESM Positive affect* | | AIC | Crossover point (95%) | AIC | Crossover point (95%) | AIC | Crossover point (95%) |
| **GxE models** | DS STRONG | 17292.41 | 0.54 ( 0.49 / 0.58 ) | 17289.7 | 0.61 ( 0.56 / 0.66 ) | 17278.35 | 0.43 ( 0.38 / 0.47 ) |
| | DS WEAK | 17251.12 | 0.65 ( 0.61 / 0.7 ) | 17242.7 | 0.85 ( 0.81 / 0.89 ) | **17244.61** | **0.47 ( 0.43 / 0.51 )** |
| | Diathesis STRONG | 17300.07 | 1 | 17296.76 | 1 | 17293.15 | 1 |
| | Diathesis WEAK | **17249.84** | **1** | **17241** | **1** | 17245.44 | 1 |
| | Vantage STRONG | 17366.84 | -1 | 17392.23 | -1 | 17356.68 | -1 |
| | Vantage WEAK | 17256.08 | -1 | 17257.6 | -1 | 17254.36 | -1 |
| **Non-GxE models** | Intercept only | 29593.37 | NA | 29593.37 | NA | 29593.37 | NA |
| | G only | 29592.05 | NA | 29537.16 | NA | 29580.66 | NA |
| | E only | 18237.1 | NA | 18237.1 | NA | 18237.1 | NA |
| | G+E only | 18238.78 | NA | 18232.89 | NA | 18237.36 | NA |

*Note: Best model indicated by lowest AIC is **highlighted**.*

**Table 5. LEGIT competitive-confirmatory tests for PRS-ES and T-1 ESM Stressful situation on T1 ESM Psychotic-like experiences significant interactions.**

| *Outcome:* | | **PRS-ES (p=.01) x ESM Stressful situation** | |
|---|---|---|---|
| *ESM Psychotic-like experiences* | | AIC | Crossover point (95%) |
| **GxE models** | DS STRONG | -127.54 | -0.47 ( -0.89 / -0.05 ) |
| | DS WEAK | -167.27 | -0.75 ( -0.91 / -0.59 ) |
| | Diathesis STRONG | -129 | -1 |
| | Diathesis WEAK | **-169.13** | **-1** |
| | Vantage STRONG | -126.51 | 1 |
| | Vantage WEAK | -166.04 | 1 |
| **Non-GxE models** | Intercept only | 4001.27 | NA |
| | G only | 4002.38 | NA |
| | E only | 1968.37 | NA |
| | G+E only | 1968.78 | NA |

*Note: Best model indicated by lowest AIC is **highlighted**.*

# Chapter 5

# Genetic variation in HPA-axis moderates emotional reactivity in the flow of daily-life

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**Abstract**

***Background and Hypothesis:*** The contribution of genetic factors to individual differences in emotional reactivity has traditionally been examined in the context of diathesis-stress. However, the Differential Susceptibility (DS) model expands this approach by suggesting that the same genetic variants that increase the negative effects of stress, also enhance benefitting from positive contexts. This study tested for the first time 1) the moderating role of a stress-system related polygenic risk score (PRS-HPA) in the association between positive and stressful daily-life situations with momentary positive (PA) and negative (NA) affect, respectively, and 2) whether interaction patterns fitted DS or diathesis-stress.

***Study Design***: Experience Sampling Methodology was employed to assess how positive and stressful contexts as well as levels of PA and NA in 217 nonclinical young adults. PRS-HPA was developed based on genome-wide data on plasma cortisol levels. Cross-sectional and time-lagged associations between context and affect were explored using linear mixed models and fit of significant interactions to DS was tested with the *LEGIT* package.

***Study Results:*** PRS-HPA moderated time-lagged, but not cross-sectional, associations. Consistent with a DS pattern, participants with high PRS-HPA showed subsequent higher NA levels after stress, and lower NA after low stressful situations compared to those with low PRS-HPA. In contrast, although participants with high PRS-HPA also showed subsequent low PA after stressful situations, their PA was not predicted by positive situations, fitting a diathesis-stress model.

***Conclusions:*** Genetic variation relevant to HPA axis activity impacts positive and negative emotional reactivity in daily life. Understanding individual differences in real-life emotional reactivity informs the development of tailored ecological momentary interventions.

## 1. Introduction

Emotional reactivity is defined by the affective reactions that occur in response to an external emotion-inducing event (Thompson et al., 2012). In particular, the experience of increased negative affect (NA) following negatively appraised events has been referred to as 'negative emotional reactivity' or 'stress reactivity', whereas increases of positive affect (PA) in response to positively appraised situations are referred to as 'positive emotional reactivity' or 'reward experience' (Trull & Ebner-Priemer, 2013). The assessment of dynamic processes such as affect is a critical challenge. Self-report ambulatory assessment techniques, namely Experience Sampling Methodology (ESM) or Ecological Momentary Assessment (EMA), have shown to adequately capture affective dynamics, that is, the context-dependent fluctuations of affect, as compared to single measures of affect (Trull & Ebner-Priemer, 2013; Trull et al., 2015; Kemp et al., 2022). Thus, ESM provides a powerful approach to measure emotional reactivity to daily life events as it minimizes retrospective biases while collecting ecologically valid data from individual's real context in everyday life (Myin-Germeys et al., 2003; 2009; Ebner-Priemer, & Trull, 2009; Trull & Ebner-Priemer, 2013).

Consistent with the dimensional and transdiagnostic model of psychopathology defined by the Research Domain Criteria (RDoC; Insel et al., 2010), which includes emotional reactivity as a behavioral element of one of the five representative domains (i.e., Arousal and Regulatory Systems) underlying psychopathology, strong evidence supports that individual differences in emotional reactivity constitute a crucially important mechanism of risk and resilience for different psychopathology dimensions, including affective and anxiety symptoms (Geschwind et al., 2010; Lamer et al., 2018; Herres et al., 2018), psychosis (Myin-Germeys et al., 2003; Myin-Germeys & Van Os, 2007; Chun et al., 2017; Cristóbal-Narváez et al., 2016a; Monsonet et al., 2022; Kemp et al., 2023), attention deficit hyperactivity disorder (Skirrow et al., 2014) and borderline personality disorder (Hepp et al., 2020).

Genetic factors have shown to predict differences in emotional reactivity, particularly, variants involved in serotoninergic, dopaminergic (e.g., 5-HTTLPR, MAOA, COMT) and, to some extent, oxytocinergic (e.g., OXTR) pathways (Sturm et al., 2016; Weeland et al., 2015; Bajgarova, & Bajgar, 2020). Although most research has exclusively focused on laboratory settings and negative emotionality, some studies have used ambulatory techniques to examine emotional reactivity in daily-life (Trull & Ebner-Priemer, 2013). Although in a small proportion, genetic factors seem to contribute to variance in stress-reactivity (12%; Jacobs et al., 2006) and reward experience (15%; Menne-Lothmann et al., 2012). In particular, variability in 5-HTTLPR, BDNF or COMT polymorphisms (Oorschot et al., 2009; Finan et al., 2012; Van Winkel et al., 2014; Cristóbal-Narváez et al., 2016b; 2017; 2020), have shown to moderate daily-life stress-reactivity and impact on the expression of momentary depression, anxiety or psychosis symptoms in daily-life.

The dopaminergic and serotoninergic systems interact in a bidirectional way with the physiology of the hypothalamic–pituitary–adrenal (HPA) axis, one of the main neural systems involved in our response to environmental stimuli and stress coping (Packard et al., 2016; Heuser & Lammers, 2003). This may support the notion that genes coding monoamine metabolism influence the biological underpinnings of emotional reactivity (Weeland et al., 2015).

Most research in this area has been framed within the diathesis-stress model (Monroe & Simons, 1991), which exclusively focuses on how 'negative' features (e.g., high emotional reactivity) constitute a vulnerability factor for poor outcomes in interaction with negative environmental conditions. In contrast, the evolutionary-based theory of Biological Sensitivity to Context (BSC) proposes that stress-related physiological systems such as the HPA axis could be considered as indicators of the sensitivity to the environment '*for better and for worse*' (Boyce & Ellis, 2005; Ellis et al., 2011; Ellis & Del Guidice, 2019). That is, the same response

systems that increase vulnerability to dysfunctional outcomes in adversity conditions, would also facilitate positive outcomes in the presence of supportive environments. From an evolutionary perspective, it is plausible to think that natural selection would have not preserved features that exclusively contribute to individuals' vulnerability to contextual adversity, and thus, undermine reproductive fitness (Ellis et al., 2011; Belsky & Pluess, 2013). Instead, individuals traditionally considered to carry greater vulnerability may be better conceptualized as having a greater plasticity to both, positive and negative environments, in order to maximize their fit to an uncertain future. This theorization is now framed into the Differential Susceptibility (DS) model (Belsky et al., 2007; Ellis et al., 2011). Of note, the DS model integrates perspectives from the classic adversity-focused model of diathesis-stress and its mirror image, the vantage sensitivity model, a concept derived from the DS reasoning that focuses on the notion that some individuals would exclusively profit disproportionally from positive environments (Pluess & Belsky, 2013). However, the latter model has been suggested to lack a firm theoretical and evolutionary background (Bakermans-Kranenburg & Van IJzendoorn, 2015). To the best of our knowledge, only one study has examined the moderating role of the serotoninergic 5-HTTLPR polymorphism as a DS factor of emotional reactivity in the flow of daily-life (Sicorello et al., 2020).Contrary to findings suggesting that the S allele would confer greater plasticity (e.g., Van IJzendoorn & Bakermans-Kranenburg, 2015), individuals with the long allele (L) of the 5-HTTLPR showed increased negative and positive emotional reactivity when exposed to daily stressors and uplifts, respectively. Authors discussed this finding in the context of failured replications of studies conducted with a candidate-gene approach. Novel polygenic approaches based on Genome Wide Association Studies (GWAS) seem to provide larger effect sizes and predictive power, enhancing gene-by-environment (GxE) research (Bulik-Sullivan & Neale, 2015; Maier et al., 2015; Halldorsdottir

& Binder 2017), especially when combined with multiple, prospective, and real-time measurement of individuals' context and phenotypes (Fox & Beevers, 2016; Pries et al., 2020).

### *The present study*

This study examined for the first time whether a Polygenic Risk Score related to the HPA axis (PRS-HPA; Crawford et al., 2021) moderated the dynamics of positive and negative emotional reactivity in daily-life, and whether interaction effects were consistent with the evolutionary-based DS model. Negative emotional reactivity was determined by the association of ratings of situational stress with levels of NA, whereas positive emotional reactivity was defined by the association of ratings of positive context and levels of PA. Of note, we examined the moderating role of PRS-HPA on both, cross-sectional associations of stressful and positive situations with levels of NA and PA as well as the *prospective,* time-lagged, associations of the situation at the previous time point with *subsequent* levels of affect at the next time point. It was hypothesized that PRS-HPA would moderate the impact of stressful situations on increases on NA.

## 2. Methods

### *2.1.Participants*

The present study includes a sample of 217 non-clinical participants (mean age=21.92, SD=2.78; 75.1% female) belonging to the Barcelona Longitudinal Investigation of Schizotypy Study (BLISS; Barrantes-Vidal et al., 2013a,b). At Time 1, usable screening data was obtained from 547 unselected college students and 261 technical school students. At Time 2, a subset of 214 college and 39 technical school students were oversampled for both positive and negative schizotypy scores to ensure sufficient variability in this construct and to conduct in depth examinations comprising a wide range of interview, questionnaire, and ESM measurements. Participants at Time 2 were also genotyped. Usable ESM data were available for a total of 206

college and 36 technical school students. After genetic quality control, the sample with usable genetic and ESM data included a total of 217 (197 from college and 20 from technical schools) nonclinical young adults.

### *2.2.Materials and Procedure*

*Calculation of Polygenic Risk Scores (PRS)*

DNA was extracted from saliva or cotton swabs. Please see details on the genotyping, quality control and imputation procedures in supplementary materials. We created a PRS related to the HPA axis function (PRS-HPA) based on Crawford et al. (2021) Genome Wide Association Study (GWAS), in which genetic variants were associated with variation in morning plasma cortisol. PRS were computed as the sum of the number of relevant alleles that individuals carried multiplied by their effect sizes reported in GWAS.

We applied the classical Clumping + Thresholding (C+T) method with PLINK v1.9. Independent variants were selected by clumping (r2<.02 within a 1000 kb window) using the 1000 Genomes Project phase 3 (The 1000 Genomes Project Consortium, 2015) as a European linkage disequilibrium (LD) reference panel. 105631 SNPs for PRS-HPA survived clumping. Genome-wide significance threshold ($p<5\times10–8$) was employed for the present analyses.

*Experience Sampling Methodology*

ESM surveys were administered using personal digital assistants (PDAs). Participants were signaled randomly 8 times a day (between 10 a.m. and 10 p.m.) for one week to complete short questionnaires (∼2 minutes to complete). Consecutive survey notifications could then range from being 10 min apart to 170 min apart. For the present study, momentary reports of NA were defined by the mean score of items ‘Right now, I feel sad’, ‘Right now, I feel anxious (nervous)’, ‘Right now, I feel angry’ and ‘Right now, I feel guilty or ashamed’ (between $\alpha=0.81$), whereas reports of PA were defined by the mean of items ‘Right now, I feel happy’

and ‘Right now, I feel relaxed’ (between α=0.81). Both positive (‘My current situation is positive’) as well as stressful (‘My current situation is stressful’) ratings of momentary contexts were examined. All items were rated on 7-point scales from ‘not at all’ to ‘very much’. The complete list of the ESM questionnaire can be found in Barrantes-Vidal et al. (2013b).

### *2.3.Statistical Analysis*

To test hierarchical ESM data with ratings (level 1 data) nested within participants (level 2) we used linear mixed models to control for within-subject clustering of multiple observations using Version 3.6.3 of the LEGIT package (Jolicoeur-Martineau et al., 2020) in R Studio (R Core Team, 2013). First, we examined the cross-level interactions between PRS-HPA and positive/stressful ratings of the situation using cross-sectional reports of context and affect at the same time point (Figure 1a); secondly, we examined the time-lagged association between the preceding ratings of positive and stressful situation (*time t – 1*) on levels of affect at the subsequent (*time t*) ESM assessment (Figure 1b). Time-lagged analyses were limited to examining within-day associations and cases with missing data on relevant variables at *time t – 1* or *time t* were excluded from each analysis.

Interactions yielding significant effects (p-values < 0.05) were examined based on the competitive-confirmatory approach (Belsky & Widaman, 2018; Widaman et al., 2012) to determine whether the GxE interaction fitted in a DS model. As detailed elsewhere (Barrantes-Vidal et al., *submitted* a,b), the LEGIT package envisions weak and strong versions of three GxE models (DS, diathesis-stress and vantage sensitivity) and the model showing lowest Akaike Information Criterion (AIC) represents the best fit. To classify an interaction within the DS model, the 95% interval of its estimated crossover point needs to be within observable bounds of the environmental score.

The first two ancestry-informative principal components from the MDS, Principal Component 1 (PC1) and 2 (PC2), were included in all analyses as covariates in the mixed models and were trimmed from the competitive-confirmatory test phase if they were nonsignificant. Additionally, in subsequent time-lagged analyses we controlled for levels of the criteria at the preceding ESM assessment (*time t – 1*) to examine whether previous levels of affect accounted for variance in the levels of affect at *time t*.

## 3. Results

Table 1 presents descriptive statistics and Pearson correlations among study variables. PRS-HPA scores did not correlate with either the environmental predictors or the outcomes, fulfilling criteria to consider the PRS a susceptibility factor in subsequent analyses (Belsky et al., 2007). Aggregated mean scores of stressful situation correlated positively with NA and inversely with positive situation and PA. Mean for positive situation was associated with PA and inversely with NA, and the association between PA and NA was significantly negative.

### *3.1. Cross-sectional analyses of the PRS-HPA moderation of emotional reactivity*

Ratings of both positive and stressful situation were associated with concurrent NA and PA, respectively (see Table 2). The PRS-HPA did not interact with either stressful or positive situation to predict concurrent levels of affect.

### *3.2. Time-lagged analyses of the PRS-HPA moderation of emotional reactivity*

Table 3 shows the results of the time-lagged analyses examining whether ratings of the preceding ESM signal predicted levels of affect at the current time-point assessment. Situation stressful predicted NA at the subsequent assessment, *(* and positive situation predicted PA . In both cases, PRS-HPA moderated these associations. According to the competitive-confirmatory test, the interaction between PRS-HPA and stressful situation fitted a DS weak model, indicating that participants with high PRS-HPA showed increases in subsequent levels

of NA when exposed to high levels of momentary stress but, also, reduced NA if exposed to low stressful situations as compared to those with low PRS-HPA (Figure 2a). In contrast, the interaction between PRS-HPA and positive situation was best fitted in a weak diathesis-stress model, indicating that participants with high PRS-HPA were more affected by being exposed to low, but not high, positive contexts, showing decreased levels of subsequent PA (Figure 2b). We further tested whether these effects held even when partialing out the effects of NA and PA at the preceding signal−that is, the significant association of prior stress/positive situation with current NA/PA, respectively, were not simply the result of NA/PA at the prior signal. When controlling the effect of the previous levels of the corresponding criteria (NA and PA, respectively) on each time-lagged cross-level interactions, the interaction between PRS-HPA and situation stressful did not reach nominal significance (Est=1.03, SE=0.57, $p<0.10$), but still was consistent with a DS model. In contrast, the interaction between PRS-HPA and positive situation remained statistically significant (Est=2.38, SE=1.11, $p<0.05$), showing a pattern of diathesis-stress.

## 4. Discussion

The present study examined for the first time whether an HPA-related PRS moderated positive and negative emotional reactivity in daily-life and whether the GxE interactions fitted into the evolutionary-based DS model. Results showed that the PRS-HPA moderated prospective, but not cross-sectional, associations between positive and stressful situations with subsequent PA and NA, respectively. Specifically, and consistent with a DS pattern, participants with high PRS-HPA showed increased levels of NA if they had experienced higher levels of stress at the previous time-point and, at the same time, they showed decreased levels of NA if their previous ratings of contextual stress were low, as compared to those with low PRS-HPA. However, participants with high PRS-HPA were more affected by low, but not

high, positive situations at the previous time point by showing less subsequent PA, in line with the classic diathesis-stress model.

Although we captured positive and negative emotional reactivity when examined both as concurrent and predictive associations (between positive situations with PA and stress with NA, respectively), the moderating effect of PRS-HPA was significant for time-lagged but not cross-sectional associations. This may suggest that genetic variability in the HPA axis activity could be particularly relevant for the processing of emotional responses once the contextual stimulus is absent, and not so much for when stimuli are still present. In subsequent analyses, the interaction effects on positive emotional reactivity remined statistically significant after controlling for previous levels of PA, whereas the GxE effects on negative emotional reactivity reached only a trend association ($p<.10$). However, a reduction of the magnitude and statistical power is expected in time-lagged analyses when adding levels of the criteria as a covariate (Hartley et al., 2014; Monsonet et al., 2022).

The role of PRS-HPA in negative emotional reactivity or stress-reactivity was consistent with a model of DS, whereas results for positive emotional reactivity or reward experience showed a pattern of diathesis-stress. The fact that participants with high PRS-HPA were more affected by low and high levels of stress (following DS) as well as by absence of positive contexts (consistent with diathesis-stress), but not by highly positive situations, may reflect that the PRS-HPA is specifically related to variability in stress-reactivity, but not in reward experience. This is consistent with previous research (Utge et al., 2018) showing an association between PRS-HPA and physiological stress-reactivity (i.e., increased stress-induced salivary cortisol) in children. Of note, the PRS was developed with genetic variants associated at a genome-wide significance level to differences in morning plasma cortisol, as reported by Crawford et al. (2021) GWAS. Interestingly, only a single genetic locus was identified, as compared with hundreds and thousands of genetic variants usually identified in

large GWASs. This locus included the genes SERPINA6, which encodes corticosteroid-binding globulin (CBG), a protein that binds to cortisol to be transported through plasma, and SERPINA1, encoding α1-antitrypsin, which inhibits the cleavage of a reactive loop that releases cortisol from CBG; thus, both genes are involved in the transportation and availability of cortisol through plasma. Notably, increased levels of plasma cortisol have been associated with psychopathology phenotypes such as depression (Capponi et al., 2018; Zhou & Qiao, 2019), anxiety (Funke et al., 2017) and schizophrenia (Girshkin et al., 2014). However, the low SNP heritability of plasma cortisol (4-6%) may reflect the substantial impact of environmental and specially situational factors on cortisol measurement in blood (Neumann et al., 2017; Crawford et al., 2021). Alternatively, future genomic studies may consider more long-term and stable cortisol measures such as hair cortisol (Russell et al., 2012) to enhance the identification of variants involved in the HPA axis activity and its main downstream effector, cortisol (Neumann et al., 2017). Furthermore, other well-known biologically-meaningful variants might also be included in polygenic scores indexing HPA axis reactivity as suggested by Gene Set Enrichment Analysis techniques (Holden et al., 2008) or studies showing strong polygenic effects using stress-related aggregate polymorphisms (Feurer et al., 2017; Di Iorio et al., 2017; Starr et al., 2019a,b; Huang & Starr, 2019; McKenna et al., 2020; Chen et al., 2021). For instance, variation in glucocorticoid receptor genes (e.g., FKBP5), genes coding for the CRH receptor (e.g.,CRHR1), and mineralocorticoid receptor genes (e.g., NR3C1, NR3C2), have been mostly employed given their primary role in HPA axis activity, which in turn, may act as susceptibility factors for risk and resilience to a variety of mental health outcomes.

DS findings of the present study are in line with evolutionary-based thinking positing that individual differences in neurobiological traits, specifically variation in autonomic and adrenocortical reactivity to stress, confer susceptibility '*for better and for worse'* to the environment, as originally framed by the BSC model (Boyce & Ellis, 2005). To the best of our

knowledge, only one study examined positive and negative affect changes after exposure to daily uplifts and stressors from a DS perspective (Sicorello et al., 2020). In this study, they used a candidate-gene approach and showed that carriers of the L allele of the 5-HTTLPR were more reactive to both daily uplifts and stressors compared to carriers of the S allele. These results, however, were contrary to amassing evidence supporting the S allele as a DS factor as tested in research examining developmental changes (Van IJzendoorn et al., 2012; Van IJzendoorn & Bakermans-Kranenburg, 2015), but not short-term differential reactivity to contextual factors.

Several strengths characterize the present study. First, the use of ambulatory assessment, which allows to (i) prospectively collect repeated measurements over the day for a period of a week, (ii) assess contextual information and affective variation as they unfold, (iii) and examine their covariation and predictive ability in real-life settings. ESM enhances the detection of subtle GxE effects while adding ecological validity (Van Os et al., 2008; Trull & Ebner-Priemer, 2013). In addition, the examination of time-lagged associations helps to better understand the affective dynamics of emotional reactivity and disentangle the temporal sequence of stress, as shown in previous ESM studies (e.g., Barrantes-Vidal et al., 2013a; Monsonet et al., 2022; Kemp et al., 2022). Also, the use of a nonclinical sample with participants oversampled for schizotypy scores enriches variability in emotional reactivity. Schizotypy is a multidimensional construct including positive (i.e., unusual experiences and odd beliefs), negative (i.e., flattened affect and social disinterest) and disorganized features, that represents the underlying liability for psychosis-spectrum psychopathology expressed across a continuum of traits, subclinical and clinical symptoms (Barrantes-Vidal et al., 2015; Kwapil & Barrantes-Vidal, 2015).Our sample includes participants with low, average and high levels of both positive and negative schizotypy. Research shows that participants with high positive, but not negative, schizotypy display increased stress-reactivity (Kemp et al., 2023;

Monsonet et al., 2022; Chun et al., 2017; Cristóbal-Narváez et al., 2016a,b; Lataster et al., 2013; Barrantes-Vidal et al., 2013b).

This study employed a polygenic approach to overcome the drawbacks of candidate-gene studies. However, the PRS-HPA shows low polygenicity, which might be considered a limitation. Future replication studies may benefit from more comprehensive HPA axis-related polygenic scores in combination with ecological assessments in daily life in order to examine the evolutionary-based groundings of affective dynamics. Furthermore, research examining environmental and outcome variables comprising both positive and negative aspects are best equipped to test the DS model (Belsky et al., 2007). The present study employed separate ratings of the situation and affect. This allowed us to clearly differentiate between positive and negative emotional reactivity, for which the underlying mechanisms might differ. Although previous research has combined positive and negative context and affect variables into a single index (Sicorello et al., 2020), the assumption that two separate items represent opposite poles of the same construct might not be as accurate as using bipolar measures to assess context or affect.

To conclude, genetic variation related to HPA axis activity impacts positive and negative emotional reactivity in daily life. Moreover, this stress-system related PRS showed a pattern of DS to contextual factors, supporting the notion that the same stress-regulatory systems adversely affected by negative contexts are also likely to benefit from supportive ones. Increasing our knowledge on individual differences to positive and negative reactivity in real life has relevant clinical implications for the development of tailored ecological momentary interventions (Reininghaus et al., 2023; Myin-Germeys et al., 2016) for reducing risk and enhancing resilience in a fundamental transdiagnostic psychological mechanism.

## Tables and Figures

### Table 1. Descriptive statistics and Pearson correlations for study variables (n = 217).

| | *Descriptive statistics* | | *Pearson correlations (r)* | | | | |
|---|---|---|---|---|---|---|---|
| | **M (SD)** | **Range** | **1** | **2** | **3** | **4** | **5** |
| **1.** PRS-HPA | 0.04 (0.03) | 0.00-0.13 | - | -0.11 | -0.03 | -0.10 | 0.01 |
| **2.** ESM Stressful situation | 2.15 (1.06) | 1-6.31 | | - | -0.39*** | 0.62*** | -0.53*** |
| **3.** ESM Positive situation | 5.35 (0.96) | 1.91-7 | | | - | -0.53*** | 0.81*** |
| **4.** ESM Negative Affect | 1.51 (0.47) | 1-3.92 | | | | - | -0.56*** |
| **5.** ESM Positive Affect | 4.70 (0.79) | 2.57-6.47 | | | | | - |

Note. Mean ESM scores for each participant are reported. *p<0.05. **p<0.01. ***p<0.001. r>0.30 are medium effect sizes and r>0.50 are large effect sizes.

### Table 2. Cross-sectional analyses.

| | **PRS-HPA** | **ESM Situation** | **PRS-HPA x ESM Situation** | **Best GxE model fit** |
|---|---|---|---|---|
| | Est. (SE) | Est. (SE) | Est. (SE) | |
| **ESM NA** | | | | |
| ESM Situation stressful | -0.48 (0.83) | 0.63 (0.02)*** | 0.42 (0.46) | - |
| **ESM PA** | | | | |
| ESM Situation positive | 1.19 (1.05) | 1.66 (0.04)*** | -1.18 (0.78) | - |

*Note*. PRS-HPA = Polygenic Risk Score related to the Hypothalamic Pituitary Adrenal axis; ESM = Experience Sampling Methodology; NA = Negative affect; PA = Positive Affect; GxE = Gene-by-environment interaction; Est = Estimate; SE = Standard Error.
* p<0.05, ** p<0.01, *** p<0.001.

### Table 3. Time-lagged analyses.

| | **PRS-HPA** | **ESM T -1 Situation** | **PRS-HPA x ESM T -1 Situation** | **Best GxE model fit** |
|---|---|---|---|---|
| | Est. (SE) | Est. (SE) | Est. (SE) | |
| **ESM NA** | | | | |
| ESM T – 1 Situation stressful | 0.16 (0.95) | 0.27 (0.03)*** | 1.58 (0.62)*[a] | DS W |
| **ESM PA** | | | | |
| ESM T – 1 Situation positive | -1.01 (1.43) | 0.65 (0.06)*** | 2.44 (1.15)* | Diathesis-stress W |

[a] The interaction did not reach nominal significance level (p=0.06) when controlling for previous levels of negative affect.
*Note*. PRS-HPA = Polygenic Risk Score related to the Hypothalamic Pituitary Adrenal axis; ESM = Experience Sampling Methodology; NA = Negative affect; PA = Positive Affect; GxE = Gene-by-environment interaction; NA= Not Applicable; Est = Estimate; SE = Standard Error. W = weak.
* p<0.05, ** p<0.01, *** p<0.001.

**Figure 1. Graphic representation of the a) cross-sectional and b) time-lagged models examined.**

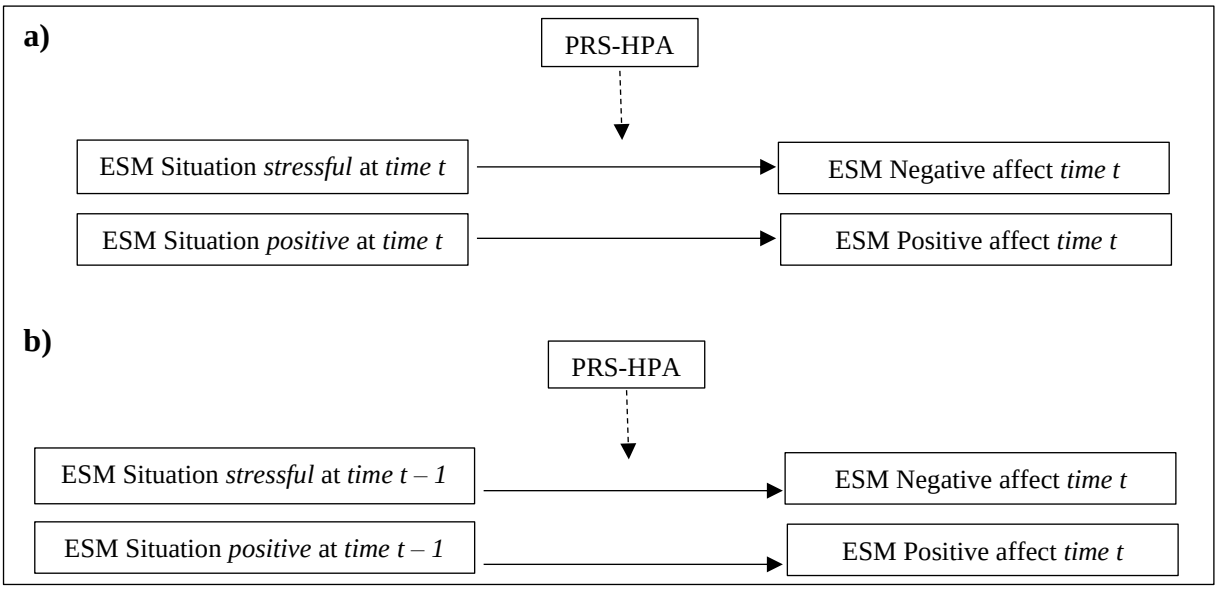
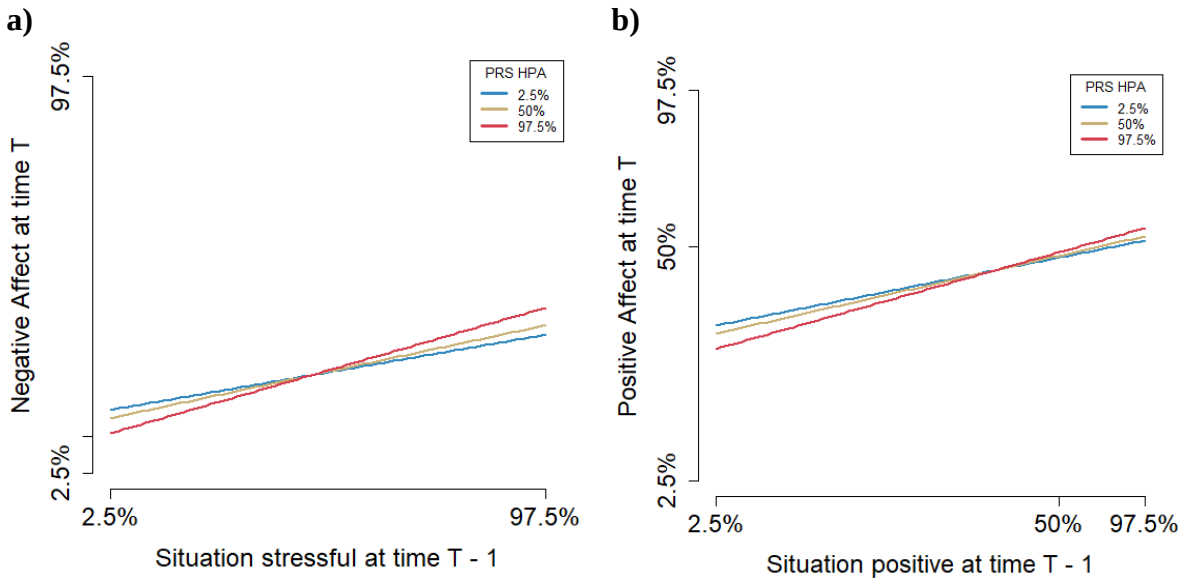



**Figure 2. Time-lagged cross-level interactions between a) PRS-HPA and stressful situation on subsequent levels of negative affect and b) between PRS-HPA and positive situation on subsequent levels of positive affect.**




*Note*. PRS-HPA = Polygenic Risk Score related to the Hypothalamic Pituitary Adrenal axis.

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**Supplementary Materials**

*Genotyping, Quality Control, and Imputation*

DNA was extracted from saliva or cotton swabs using the prepIT-L2P kit (DNA Genotek Inc., Ottawa, Ontario, Canada) and the RealPure Genomic DNA Extraction Kit (Durviz S.L.U., Valencia, Spain) for saliva samples and cotton swab samples, respectively. DNA samples were genotyped using the Illumina Infinium Global Screening Array-24 v2.0 (GSA) BeadChip at the "Centro Nacional de Genotipado" (CEGEN-PRB3-ISCIII; CNIO-Madrid). Genotype calls were generated with GenomeStudio v2.0.4 (Illumina Inc., San Diego, CA, USA). A quality control (QC) was carried out with PLINK v1.9 (www.cog-genomics.org/plink/1.9/; Chang et al., 2015) in order to exclude SNPs that: had a missing call rate >2%; had a Minor Allele Frequency (MAF) <0.1%; or deviated from Hardy-Weinberg equilibrium with a P-value <0.001. Subjects were excluded when: had a missing call rate >2%; were related with other participants or duplicated samples according to the pairwise identity by descent method (PI_HAT >0.25); or had non-European ancestry according to a Multidimensional Scaling (MDS) analysis. The MDS analysis was carried out with PLINK v1.9 to represent population admixture and the first 10 ancestry components were extracted. From the total sample at Time 2 of 253 non-clinical individuals, 25 subjects were excluded during QC leaving a sample of 228 subjects. MDS components were recalculated in this final sample and the first two components were used in all models including PRS as independent variable. Imputation was performed in the Michigan Imputation Server (Das et al., 2016) considering the Haplotype Reference Consortium panel (www.haplotype-reference-consortium.org; McCarthy et al., 2016). A post-imputation QC was performed to exclude SNPs that: had an imputation quality score of R2 <0.3; or had a MAF <1%. A total of 7,755,414 SNPs passed post-imputation QC.

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**Table S1. LEGIT output for the competitive-confirmatory test of significant GxE time-lagged interactions between PRS-HPA and ESM situation stressful at *t – 1* on subsequent ESM negative affect.**

| ***Outcome:*** | | **PRS-HPA x ESM stressful situation *t - 1*** | |
|---|---|---|---|
| ***ESM Negative Affect*** | | AIC | Crossover point (95%) |
| **GxE models** | DS STRONG | **11298.94** | **-0.11** |
| | DS WEAK | 11372.7 | -0.48 |
| | Diathesis-stress STRONG | 11381.74 | -1 |
| | Diathesis-stress WEAK | 11299.35 | -1 |
| | Vantage sensitivity STRONG | 11426.03 | 1 |
| | Vantage sensitivity WEAK | 11299.42 | 1 |
| **Non-GxE models** | Intercept only | 20686.08 | NA |
| | G only | 20657.3 | NA |
| | E only | 12667.53 | NA |
| | G+E only | 12662.58 | NA |

*Note: Best model indicated by lowest AIC is **highlighted**.*

**Table S2. LEGIT output for the competitive-confirmatory test of significant GxE time-lagged interactions between PRS-HPA and ESM situation positive at *t – 1* on subsequent ESM positive affect.**

| ***Outcome:*** | | **PRS-HPA x ESM positive situation *t - 1*** | |
|---|---|---|---|
| ***ESM Positive Affect*** | | AIC | Crossover point (95%) |
| **GxE models** | DS STRONG | 17352.48 | 0.43 |
| | DS WEAK | 17238.5 | 0.36 |
| | Diathesis-stress STRONG | 17370.54 | 1 |
| | Diathesis-stress WEAK | **17237.86** | **1** |
| | Vantage sensitivity STRONG | 17431.76 | -1 |
| | Vantage sensitivity WEAK | 17240.02 | -1 |
| **Non-GxE models** | Intercept only | 29593.37 | NA |
| | G only | 29595.31 | NA |
| | E only | 18228.3 | NA |
| | G+E only | 18230.11 | NA |

*Note: Best model indicated by lowest AIC is **highlighted**.*

# 5. GENERAL DISCUSSION

The main aim of this thesis was to study the relationship between cortisol, as a biomarker of stress, with psychosocial stress, schizotypy and stress-related phenotypes, as well as examining the fit of novel GxE interactions into the Differential Susceptibility (DS) model along the nonclinical expression of the psychosis phenotype.

The summary and integration of findings is presented below, followed by a consideration of the main clinical implications that may derive from this work, the strengths and limitations of the thesis and, finally, a discussion of future directions for further research and the final conclusions.

## 5.1.Summary of Findings

On the one hand, work presented in **section 1** showed that levels of cortisol in hair as an objective long-term measurement of stress were not associated with other subjective self-reported measurements of stress (early adversity, life events, perceived stress) and stress-related phenotypes (schizotypy, depression, anxiety; chapter 1), whereas hair cortisol seemed to play a moderating role in the association between stress and some psychotic and non-psychotic subclinical manifestations in a sample of nonclinical young adults (chapter 2). Particularly, hair cortisol moderated the effects of both early and recent life stress on suspiciousness and the effects of recent life events on perceived appraisals of stress. Positive life events were associated with decreases in perceived stress and depression, and these relationships were also moderated by HCC, such that this buffering effect only occurred for participants with low and moderate levels of HCC.

On the other hand, findings from **section 2** partly supported the model of differential susceptibility to the environment in the nonclinical end of the extended psychosis phenotype. Specifically, the work presented in chapter 3 showed that a polygenic score of sensitivity to the

environment (PRS-ES) moderated the effects of early adversity on subclinical psychotic (PLE and positive schizotypy), depressive and anxiety features. Although only the interaction between PRS-ES and childhood adversity on PLE survived multiple testing correction, interactions were fitted into a model of DS. That is, high genetically sensitive individuals showed increased levels of subclinical positive PLE, positive schizotypy, anxiety and depression when exposed to high levels of childhood adversity but also displayed lower levels of subclinical symptoms if they were exposed to low or absent levels of adversity. Secondary exploratory analyses employing a specific psychosis-related genetic score (PRS-PLE) moderated the effects of childhood adversity mainly on subclinical psychosis, and to a lesser extent, depression; however these interactions did not survive multiple testing correction. Next study (chapter 4) employed ESM to examine whether high genetically sensitive to environment individuals were also more affected by positive and negative contexts in the expression of psychotic and affective states in daily-life. Results showed that PRS-ES moderated the effects of positive, but not stressful, ratings of the current situation on subsequent levels of momentary paranoia, NA and PA. Of note, individuals with high PRS-ES not only were more affected by less positive situations increasing their levels of paranoia and NA, and reducing PA but, also, as the polygenicity of the PRS-ES increased, they also displayed decreased paranoia and NA, as well as increased PA, when exposed to highly positive contexts. Finally, an HPA-related PRS was shown to play a moderating role in positive and negative emotional reactivity in daily-life (chapter 5). Consistent with a DS pattern, participants with high PRS-HPA showed increased levels of NA when exposed to highly stressful contexts at the previous time point, whereas in low stressful situations, they showed subsequent decreased levels of NA as compared to those with low PRS-HPA. However, in terms of positive emotional reactivity, participants were only affected by lower levels of positive contexts showing reduced PA, but not by highly positive contexts, consistent with a diathesis-stress pattern.

## 5.2.Integration of findings and theoretical implications

Overall, the findings of this thesis contribute to increase our knowledge on some of the risk and resilience factors, as well as underlying mechanisms, involved in the expression of the extended psychosis-proneness phenotype. More so, they highlight the importance of environmental influences and how individuals' sensitivity to them may play a crucial role in both, the exacerbation as well as the mitigation of subclinical psychotic and affective manifestations in the nonclinical end of the psychosis phenotype.

Specifically, the lack of associations between HCC, considered a long-term biomarker of the HPA axis, and individuals' subjective appraisals of stress, stressful experiences, or other stress-related phenotypes as reported in chapter 1 is consistent with recent meta-analytic work (Cullen et al., 2020) reporting poor concordance between psychosocial stressors and different cortisol measurements, including hair, in clinical samples with established psychosis, at-risk individuals and healthy controls. It has been argued that this lack of psychoendocrine covariance might be related to the fact that studies assessing cortisol in nonclinical populations usually comprise individuals that have been exposed to very low levels of stress ("super normal" controls), as compared to studies with clinical individuals, who have potentially been exposed to very high levels of stress (Stalder et al., 2017). However, the present study tried to tackle this limitation by including individuals with normative and elevated scores on schizotypy dimensions, and thus, avoiding a complete usual control sample. Other aspects that have been associated to this poor concordance are related to the persistence of stress exposure (Stalder et al., 2017), and thus, the need to longitudinally examine the effects of psychosocial stressors, and methodological constraints associated to the timeframe captured by self-reported measures compared to hair cortisol measurement, that usually reflect the levels of cortisol from the last 3 months. Instead, HCC may play a moderating role in the association of psychosocial stress and stress-related phenotypes, as examined by chapter 2 of this thesis. Particularly, HCC

showed to be consistently involved in the associations between early childhood adversity as well as recent life events from the past year with suspiciousness. These findings align with the neural diathesis-stress model of psychosis (Walker & Diforio, 1997; Pruessner et al., 2017) which highlights the crucial role of stress and the HPA axis in the onset and exacerbation of psychotic disorders, a phenomenon that is also be captured in this study over the nonclinical end of the psychosis continuum. Also, cognitive theories support the close relationship between stress and suspiciousness, as individuals may develop paranoid thoughts as a defense mechanism in response to threats (Freeman & Fowler, 2009). Moreover, recent life events also seemed to interact with high levels of HCC to increase individuals' subjective appraisals of stress, indicating that a hyper-responsive HPA axis may also influence individuals' subjective perception of stress following high levels of life events. Although it was expected that those life events rated by the individuals as negative would interact with levels of cortisol, no significant interactions were found, which is suggested to be related with the low endorsement of negative/threatening life events reported by the study sample, comprised by nonclinical college students. Of note, positive life events reduced levels of stress appraisals and subclinical depressive symptoms, and the associations were reported to be particularly relevant to those with low levels of HCC, which suggests that positive experiences buffer against perceptions of stress and subclinical depression only if the HPA axis is not disrupted.

Furthermore, research from section 2 provided preliminary findings on DS in the psychosis phenotype. Results seemed to support the notion that sensitivity to the environment and psychosocial stress (e.g., childhood adversity) are relevant etiological factors associated, not only to the psychotic dimension, but also to the depressive and the anxiety ones, as consistent with emerging transdiagnostic perspectives of psychopathology (Cuthbert et al., 2021). The fact that the strongest effects were found for the positive psychotic dimensions (particularly, positive PLE and schizotypy), being the only ones surviving multiple testing correction at a

nominal or trend p value, is consistent with evidence showing that psychotic experiences, in co-occurrence with other psychopathology dimensions such as depression or anxiety, are associated to symptom severity and poor response to treatment (Kelleher et al., 2013; Kelleher & Cannon, 2021)—which is consistent and supports the notion of a severity continuum across psychopathology (McGorry & van Os, 2013). These findings may also suggest that genetic factors underlying psychopathology may partly be accounted for genetic variability in sensitivity to the environment. Of note, a similar pattern of interactions was yielded by a specific PRS related to subclinical psychotic experiences (PRS-PLE). Although PRS-PLE effects did not survive multiple testing correction, it is attractive to speculate that, similarly to the overlap between PRS-SCZ and genetic variability of multiple mental disorders (Nivard et al., 2017; Cross-Disorder group of the Psychiatric Genomics Consortium et al., 2019; Grotzinger et al., 2022), genetic variability linked to subclinical psychotic features may also index a transdiagnostic risk and resilience factor through differential sensitivity to environment.

The subsequent study (chapter 4) found initial support to the notion that DS to the environment can be captured not only at in a long-term temporal framework as a response to early-life exposures (an indicator of developmental plasticity; Stamps, 2016), but, also at short-term in response to daily-life stimuli (indexing contextual plasticity; Stamps, 2016). Similar to previous findings, the pleiotropic effect of PRS-ES on the psychotic and affective dimensions was also captured in response to minor daily situations. Finally, a proxy genetic score of the HPA axis functioning (PRS-HPA), also showed to be involved in daily emotional-reactivity as a DS factor. In particular, PRS-HPA was involved in individuals' reactivity to stress, 'for better and for worse', which is consistent with the biological compound of the DS theory originally proposed by Ellis et al. (2011), which posited that stress-sensitive physiological systems such as the HPA axis could be considered as indicators of the sensitivity to the environment. This is

particularly relevant in the context of stress-reactivity and psychosis: stress-reactivity has been considered an endophenotype of psychosis, that is, an underlying vulnerability substrate of the development of psychotic phenomena (Myin-Germeys & van Os, 2007). As such, patients with psychosis, individuals at-risk and subclinical phenotypes have shown elevated stress-reactivity in daily life (Myin-Germeys et al., 2003; Lataster et al., 2009; Reininghaus et al., 2016; Van der Steen et al., 2017). The present findings support the key role of the HPA axis, indexed by genetic variability in plasma cortisol, as one of the mechanisms involved in heightened stress-reactivity (Myin-Germeys & van Os, 2007; Walker & Diforio, 1997). More importantly, the study shows that those with high genetic HPA axis susceptibility, when exposed to low levels of stress, will display decreased levels of negative affect as compared to those with low genetic susceptibility. This adds further support to definitely abandon narrow 'bio-medical' perspectives that exclusively focus on genetic risk factors as fully responsible of vulnerability to psychosis in particular, and psychopathology in general (Read et al., 2009).

Overall, there are several aspects consistently supported across this thesis that align with previous empirical evidence or theoretical models. First, that both early and recent environmental exposures operate in shaping risk, but also resilience, to the nonclinical expression of psychosis (Begemann et al., 2017), and that the HPA axis functioning, as assessed with hair cortisol, plays a relevant role underlying these associations (Pruessner et al., 2017). Second, that the genetics of mental disorders may be better captured by the genetics of sensitivity to the environment conferring a key transdiagnostic causative factor of psychopathology (Van Os & Rutten, 2010). As such, highly environmental sensitive individuals may differ in their susceptibility '*for better and for worse'* to psychotic and affective manifestations, consistent with the DS model (Belsky et al., 2007; Belsky & Pluess, 2013). Finally, the buffering effect of positive environmental influences (or the absence of adverse ones) across studies is consistent with emerging evidence about the protective role of

positive experiences in the context of psychosis liability (Coughlan et al., 2020; McMahon et al., 2021; Ruiz-Yu et al., 2022).

### 5.3. Clinical Implications

Although further replication studies are needed in order to offer direct therapeutic insight, some clinical implications may be derived from the current thesis. Firstly, increasing our knowledge about individual differences in stress-sensitivity and its relationship with psychosis and other stress-related phenotypes can lead to the development of targeted interventions and assessment of their effectiveness (Pruessner et al., 2017; Cullen et al., 2023). Specifically, identifying reliable biomarkers of the HPA axis (dys)function (e.g., cortisol) may help targeting those individuals at an increased risk of being greatly impacted by stress exposures to and apply psychosocial prevention and intervention strategies focused on reducing stress appraisals and increasing resiliency towards stress. In fact, some stress-management intervention programs have already shown to alleviate not only subjective appraisals of stress in response to stress exposure, but also physiological levels of stress response (that is, decreased cortisol levels after intervention; Lupien et al., 2013).

Furthermore, findings across the studies of this thesis about the direct effects of positive experiences (e.g., positive recent life events or positive daily-life situations) on the reduction of schizotypy traits and affective manifestations are in line with emerging evidence supporting the potential efficacy of positive psychology interventions to reduce psychotic manifestations (Grant et al., 2018; Pina et al., 2021).

Importantly, preliminary findings supporting the DS model to the environment in the psychosis phenotype contribute to challenge current conceptualizations on "genetic risk" and how "at risk'" individuals are treated in the clinic. Indeed, these should be better conceptualized as being more plastic, sensitive, or malleable to (positive and negative) environmental

influences. Thus, far from being exclusively 'doomed' to pathology outcomes and in need to work hard to reduce symptoms, they also need to be offered tools that boost their actually greater capacity to respond strongly to positive experiences. Further validation of the DS model should stress the value of interventions focused on personal strengths and resilience-building (as claimed by positive psychology framework; Jeste et al., 2015; Seligman & Csikszentmihalyi, 2000; Vázquez, 2017), rather than only focusing on diminishing risk behaviors or symptoms. In turn, highlighting positive personal factors empower people to be active partners in prevention and intervention programs, thus increasing therapeutic adherence, and ultimately decreasing the likelihood of developing poor outcomes (Assary et al., 2023). This paradigm shift not only would benefit individuals attending clinical settings, but the clinicians themselves, by reducing the engraved pessimism around therapeutic gains attained in psychosis. Of note, adopting a "*for better and for worse*" perspective would also have an important repercussion at a societal level by decreasing the current associated stigma to "at risk" individuals.

Finally, increasing our knowledge on individual differences in reactivity to negative and positive daily-life factors would benefit the development of more personalized approaches in prevention and treatment. As such, Ecological Momentary Intervention (EMI) strategies offer a great opportunity to deliver tailored interventions toward individual's needs in a specific moment (Myin-Germeys et al., 2016), which at the same time, contribute to make primary prevention initiatives and interventions more widely available and inexpensive to the general population. For instance, a recent randomized control trial shows that a compassion-focused EMI significantly reduced momentary stress-reactivity and aberrant salience, but also, enhanced momentary resilience and quality of life in youth with early mental health problems (Reininghaus et al., 2023).

### 5.4. Strengths and Limitations

It is acknowledged across the empirical work presented in this thesis that the sample sizes of the studies were limited. However, a "quality over quantity' approach underlies this limitation: participants included in this thesis were part of a longitudinal data collection (BLISS; Barrantes-Vidal et al., 2013a; Racioppi et al., 2018) comprised by 5 time points of assessment across 7.8 years, recruited from college (Universitat Autònoma de Barcelona) and technical schools in the area of Barcelona, Spain. From a total of 808 unselected young adults assessed a T1, a subset of 252 individuals were oversampled based on scores of both positive and negative schizotypy dimensions to be assessed at T2, from which studies from section 2 are derived. This procedure reduced the size of the sample, but enabled an in-depth assessment that included clinical interview measures, self-reported measures, and an intensive one-week ambulatory assessment that prompted participants to respond questionnaires about their context and psychological state eight times a day over one week (ESM). Furthermore, the genotyping process was also enabled at this time point. At T3 and T4 assessments, the sample size was further reduced (134 and 89, respectively) due to funding constraints (related to the severe economic crisis) but maintained the original distribution of scores. At T5 of the longitudinal data collection, participants from T2 were re-contacted which permitted to increase again the sample size and successfully reassess a total of 194 participants, maintaining the variability in schizotypy scores. At this time point, hair samples were collected to analyze hair cortisol levels. Retaining a sample with significant variance along schizotypy dimensions across all time points is a notable strength of this longitudinal data collection, as it helped to ensure the presence of sufficient variability in the constructs of interest (i.e., stress-related measures, traits and subclinical symptoms). Also, manageable sample sizes allowed us to include a wide range of stress-related variables including both risk and protective factors, subjective and objective measurements, and employing a transdiagnostic perspective (including psychotic, affective and

anxiety spectrums) across all the studies, which is a notable strength of the present thesis. Nonetheless, it is undeniable that sample size might have limited our ability to detect significant interaction effects. This mostly applies to chapters 1, 2 and 3, whereas the use of multilevel data collected across multiple data points and nested within participants (ESM) in chapters 4 and 5, is suggested to improve the detection of subtle interaction effects (Van Os et al., 2008). Of note, a predominantly female sample may also limit the generalizability of the reported findings.

Furthermore, the use of a polygenic approach is a strength of this thesis given that PRS have shown to increase effect sizes and predictive power as compared to candidate-gene approaches. Particularly, PRS-ES employed in chapters 3 and 4 adds novel insights to conventional GWAS designs which consist essentially of aggregating small genetic effects derived from the direct associations between genetic variants and the phenotype of interest. In contrast, Keers et al. (2016) GWAS was based on a twin-based approach where within-pair differences in emotional problems were predicted as the outcome of the GWAS. This approach allowed capturing the magnitude of response to twins' non-shared environments and thus, identify genetic variants associated to sensitivity to environment whilst controlling for genetic and shared environmental effects.

Finally, the adequate testing of the DS model could be improved. As in previous studies examining DS (Belsky & Beaver, 2011; Bousman et al., 2017), the absence of adverse childhood experiences was used as an indicator of individuals' positive environment in chapter 3. Although chapters 4 and 5 included specific measurements of stressful and positive experiences, it is suggested that to confirm the role of a trait or genetic factor as a DS factor, a single environmental measure should cover both negative and positive aspects. Also, besides the diminution of risk as an outcome measure, the repercussion in positive mental health

outcomes and well-being should be further assessed to adequately test the DS hypothesis (Belsky et al., 2007; Widaman et al., 2012).

### 5.5. Future Directions

Future replication studies in nonclinical samples with an increased sample size and a wider distribution of gender and age, as well as a comprehensive assessment of environmental and outcome measures comprising both positive and negative aspects, are required. The increment of statistical power would allow to extend findings from chapter 2 by examining a three-way interaction between early and recent stress exposure and cortisol to capture the effects of stress in those individuals biologically and behaviorally sensitized to stress. This would provide further insights on the stress-sensitization hypothesis and its implications in several psychopathology outcomes. Also, recent review work advocates for large-scale multisite and prospective studies employing an integrative and multi-domain approach to the putative stress-related biomarkers combined with the collection of multiple measures of psychosocial stress exposure to determine their prognostic value in subclinical and at-risk samples (Cullen et al., 2023).

With respect to GxE studies, emerging evidence on the protective role of positive experiences and preliminary findings about the DS model in psychosis call for continuing this line of GxE research. To do so, high-quality assessments (e.g., ESM) of the environment considering the complete range of environmental exposures are required. At the same time, our efforts should be focused on identifying variants related to plasticity rather than, as in diathesis-stress work, the phenotype to be explained (Zhang & Belsky, 2020). In other words, moving the field forward from PRS to "Polygenic Sensitivity Scores" (PSS; Fox & Beevers, 2016) or "Polygenic Plasticity Scores" (PPS; Zhang & Belsky, 2020). Of note, the further development of PSS/PPS may not disregard the inclusion of biologically-meaningful variants indexing

variability in the biological pathways (e.g., the HPA axis) known to be functionally linked to phenotypes (Lemery-Chalfant et al., 2018).

More importantly, converging evidence supports that targeting genetic sensitivity to the environment applied to transdiagnostic psychopathology dimensions, as well as the intermediate phenotypes involved (e.g., emotional reactivity), will help us to understand the etiological pathway underlying a wide range of mental health outcomes rather than a specific phenotype and, therefore, potentially identify novel and effective prevention and intervention pathways (Assary et al., 2020).

### 5.6.Conclusions

The research presented in this thesis provided novel insights into the biological mechanisms underlying the association between stress and psychosis and, also, applied for the first time the DS model to the interplay between genetic and environmental factors along the extended psychosis-proneness phenotype. Overall, the main conclusions that can be derived from this thesis are:

1) There is a lack of psychoendocrine covariance between hair cortisol, considered a chronic biomarker of the HPA axis, and psychosocial stressors or stress-related phenotype in nonclinical young adults.
2) The HPA axis function, as measured by hair cortisol, plays a key moderating role in the effects of early and recent psychosocial stress on the manifestation of psychotic-like subclinical symptoms (i.e., suspiciousness), appraisals of stress, and to a lesser extent, depression symptoms.
3) The DS model may also apply to the extended psychosis phenotype; that is, individuals with high genetic sensitivity to the environment show more psychotic-like and affective

symptoms when in adverse situations, but also benefit more from low-adverse or positive environments than those less genetically sensitive to the environment.

4) This differential psychotic-like and affective reactivity to the environment can also be captured in daily life when individuals are exposed to low versus high levels of positive situations.
5) Genetic variation relevant to HPA axis activity also impacts positive and negative emotional reactivity in daily life and shows a pattern of DS to stressful situations, supporting the notion that the same stress-regulatory systems adversely affected by negative contexts are also likely to benefit from supportive ones.

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CURRICULUM VITAE

# Pilar Torrecilla González

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## 1. PERSONAL DETAILS

Date and place of birth: July 10th, 1995, Barcelona (Spain)

Nationality: Spanish

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Sex: F

## 2. PROFESSIONAL ADDRESS

Departament de Psicologia Clínica i de la Salut

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Universitat Autònoma de Barcelona

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## 3. EDUCATION

2019-Present Ph.D in Clinical and Health Psychology. Department of Clinical and Health Psychology, Universitat Autònoma de Barcelona. Supervisor: Prof. Neus Vidal Barrantes

2017-2018 MSc in Neuroscience. Institut de Neurociènies, Universitat Autònoma de Barcelona.

2013-2017 BSc in Psychology

***International Training***

| | |
|---|---|
| February 2023-May2023 | Predoctoral International Research Stay at Erasmus University of Rotterdam (The Netherlands), supervised by Prof. M.H. van IJzendoorn and co-supervised by Prof. M.J. Bakermans-Kranenburg. |
| February 2017-June 2017 | *Erasmus Program*. Faculty of Psychology, Universität Mannheim (Germany). |

## 4. RESEARCH EXPERIENCE

| | |
|---|---|
| 2019-2023 | Predoctoral fellow "Ayudas para la Formación de Personal Investigador (FPI)" funded by Ministerio de Ciencia, Innovación y Universidades (PRE2018-085299) associated to project PSI2017-87512-C2-1-R. Research group: "Person-Environment Interaction in Risk and Resilience for Mental Health", Department of Clinical and Health Psychology, Universitat Autònoma de Barcelona. PI: Prof. Neus Vidal Barrantes. |
| 2017-2018 | Internship at the research group "Animal and human models of mental disorders", Department of Psychiatry and Legal Medicine, Institute of Neuroscience (INc), Universitat Autònoma de Barcelona. PI: Alberto Fernández-Teruel. |

## 5. TEACHING EXPERIENCE

Department of Clinical and Health Psychology, Universitat Autònoma de Barcelona:

| | |
|---|---|
| 2019-2020 | Personality disorders, undergraduate course (Psychology) |
| 2020-2021 | Personality disorders, undergraduate course (Psychology) |
| 2022-2023 | Personality and Individual Differences, undergraduate course (Psychology) |
| | Personality disorders, undergraduate course (Psychology) |

## 6. PARTICIPATION IN FUNDED RESEARCH PROJECTS

1) **Recognition as a Consolidated Research Group: Person-Environment Interaction in Risk and Resilience for Mental Health - (SGR 2021)**

   Principal Investigator: Neus Barrantes-Vidal

   Project Reference: 2021SGR01010

   Funding Agency: Agencia de Gestió d'Ajuts Universitaris i de Recerca (AGAUR) - Generalitat de Catalunya

   Amount Funded: 40.000€

   Duration: 01/01/2022-31/12/2024

   Investigators UAB: Ballespí, S., Chanes, L., Gizdic, A., **Torrecilla, P**., Galiano, J., Icancovsky, T., Robles, M., Clusa, D. (Fundació Sanitària Sant Pere Claver), Pérez, A (Fundació Sanitària Sant Pere Claver), Villarreal, B. (Fundació Sanitària Sant Pere Claver), Ramos, I. (Fundació Mútua de Terrassa per a la Docència i Recerca Biomèdica i Social), Escarmís, D. (Fundació Sanitària Sant Pere Claver), Vallmajó, M. (Fundació Sanitària Sant Pere Claver), Massanet, M. (Fundació Sanitària Sant Pere Claver).

2) **Testing the Shift from a 'Disease Risk' to a 'Differential Susceptibility' Conceptualization of Person-Environment and Gene-Environment Interactions in the Psychosis Continuum**

   Principal Investigator: Neus Vidal Barrantes

   Project Reference: PID2020-119211RB-I00

   Funding Agency: Spanish Ministry of Science, Innovation and Universities, Plan Nacional de I+D+i (National Plan of R+D+i).

   Amount Funded: 145.200€ (120.000 direct costs) plus a 4-year predoctoral contract

   Duration: 1/9/2021 - 31/8/2024 (3 years)

   Teamwork: Clusa, D. (Fundació Sanitària Sant Pere Claver), Gizdic , A. (UAB), Massanet Forteza, M. (Fundació Sanitària Sant Pere Claver), Monsonet, M. (UAB), **Torrecilla, P**. (UAB), Bakermans-Kranenburg, Marian J (ISPA, Lisbon), Kwapil, T. (University of Illinois at Urbana-Champaign, USA), Vallmajó, M. (Fundació Sanitària Sant Pere Claver), van IJzendoorn, M. (Erasmus University Rotterdam), Rosa de la Cruz, A. (University of Barcelona), Escarmís, D. (Fundació Sanitària Sant Pere Claver),Vives, L. (Fundació Sanitària Sant Pere Claver), Herrera, S. (Fundació Sanitària Sant Pere Claver), Torices, I. (Fundació Sanitària Sant Pere Claver)

3) **Trajectories of Risk and Resilience to Psychosis: Integrative study of Gene-Person-Environment Interactions across the Extended Psychosis Phenotype**

Principal Investigator: Neus Barrantes-Vidal (Universitat Autònoma de Barcelona, UAB)

Funding Agency: Spanish Ministry of Economy and Competitiveness (MINECO), Plan Nacional de I+D+I (National Plan of R+D)

Project Reference: PSI2017-87512-C2-00

Duration: 1/1/2018 to 31/12/2021 (a 12-month extension included)

Total funding: 128.260€ plus a 4-year predoctoral contract (Formación de Personal Investigador) associated to the Project

Subproject 1: Developmental Trajectories of Risk and Resilience to Psychosis: Longitudinal Examination of the Psychological and Biological Stress Sensitization Hypothesis

Principal investigator: Neus Barrantes-Vidal (Faculty of Psychology, UAB)

Project Reference: PSI2017-87512-C2-1-R

Amount Funded: 99.220,00 € + A 4-year predoctoral contract (FPI)

Investigators: Ballespí, S. (UAB).

Teamwork: Cristóbal, P. (UAB)., Domínguez, T. (Instituto de Psiquiatría de Méjico), Herrera, S. (Fundació Sanitària Sant Pere Claver), Hinojosa, L. (UAB), Kwapil, T.R. (University of Illinois at Urbana-Champaign, USA), Monsonet, M. (UAB), Montoro, M. (Fundació Sanitària Sant Pere Claver), Myin-Germeys, I. (KU Leuven, Belgium), Racioppi, A. (UAB), Sheinbaum, T. (University of Southern California, USA), Torices, I. (Fundació Sanitària Sant Pere Claver), **Torrecilla, P**. (UAB), Gizdic, A. (UAB).

## 7. PUBLICATIONS

***Submitted***

**Torrecilla, P**., Barrantes-Vidal, N. (*Submitted*). The Moderating Role of Hair Cortisol in the Association of Early and Recent Stress with Stress-related Phenotypes.

Barrantes-Vidal, N., **Torrecilla, P**., Mas-Bermejo, P., Papiol, S., Bakermans-Kranenburg, M.J., van IJzendoorn, M.H., Jolicoeur-Martineau, A., Kwapil, T.R., Rosa, A. (*Submitted*).

Genetic Susceptibility to the Environment Moderates the Impact of Childhood Experiences on Psychotic, Depressive and Anxiety Dimensions.

Gizdic, A., **Torrecilla, P**., Laift, G., Myin-Germeys, I., Kwapil, T.R., Barrantes-vidal, N. (*Submitted*). A longitudinal study of the stability and trajectories of stress-sensitivity in young adults: retrospective and momentary daily-life assessments of stress appraisals.

Mas-Bermejo, P., Papiol, S., Via, M., Rovira, P., **Torrecilla, P**., Kwapil, T.R., Barrantes-Vidal, N., Rosa, A. (*Submitted*). Schizophrenia polygenic risk score in psychosis proneness.

Sampedro-Viana, D., Cañete, T., Sanna, F., Oliveras, I., Lavín, V., **Torrecilla, P**., Río-Álamos, C., Tapias-Espinosa, C., Sánchez-González, A., Tobeña, A., Fernández-Teruel, A. (*Submitted*). Atypical antipsychotics attenuate mk801-induced social withdrawal and hyperlocomotion in the rha rat model of schizophrenia-relevant features.

***Articles published in international journals***

**2022**

1. Hird, E. J., Ohmuro, N., Allen, P., Moseley, P., Kempton, M. J., Modinos, G., Sachs, G., van der Gaag, M., de Haan, L., Gadelha, A., Bressan, R., Barrantes-Vidal, N., Ruhrmann, S., Catalan, A., and the **EU-GEI High Risk Study**, & McGuire, P. (2022). Speech illusions in people at clinical high risk for psychosis linked to clinical outcome. Schizophrenia Bulletin, sbac163. https://doi.org/10.1093/schbul/sbac163.

**2021**

2. **Torrecilla, P**., & Barrantes-Vidal, N. (2021). Examining the Relationship Between Hair Cortisol With Stress-Related and Transdiagnostic Subclinical Measures. *Frontiers in psychiatry*, 12, 746155. https://doi.org/10.3389/fpsyt.2021.746155
3. Sampedro-Viana, D., Cañete, T., Sanna, F., Soley, B., Giorgi, O., Corda, M. G., **Torrecilla, P**., Oliveras, I., Tapias-Espinosa, C., Río-Álamos, C., Sánchez-González, A., Tobeña, A., & Fernández-Teruel, A. (2021). Decreased social interaction in the RHA rat model of schizophrenia-relevant features: Modulation by neonatal handling. Behavioural processes, 188, 104397. https://doi.org/10.1016/j.beproc.2021.104397.

## 8. SCIENTIFIC PRESENTATIONS

### a) Posters

1. Mas-Bermejo,P., Papiol, S., Via, M., **Torrecilla, P**., Sheinbaum, T., Racioppi, A., Peña, E., Azcona-Granada, N., Kwapil, T.R., Rovira, P., Barrantes-Vidal, N., & Rosa, A. (2021). Association of schizophrenia polygenic risk scores with schizotypy and psychotic-like experiences in non-clinical subjects. Presented as a poster communication at the XLII Congress of the Sociedad Española de Genética (SEG2021). June 14th -18th, 2021.
2. Mas-Bermejo, P., Papiol, S., Kwapil, T. R., Sheinbaum, T., **Torrecilla, P**., Via, M., Barrantes-Vidal, N., Rosa, A. (2021). Polygenic liability for environmental and stress sensitivity pathways, childhood trauma and psychosis-proneness. Presented virtually as a poster at the 2021 Congress of the Schizophrenia International Research Society (SIRS). April 17th - 21st, 2021.
3. **Torrecilla, P.,** Barrantes-Vidal., N. (2021). Lack of covariance of hair cortisol with stress-related measures and phenotypes in schizotypy. Presented virtually as a poster at the 2021 Congress of the Schizophrenia International Research Society (SIRS). April 17th - 21st, 2021.
4. **Torrecilla, P**., Gizdic, A., Barrantes-Vidal, N. (2021). Examining the association of hair cortisol levels with a comprehensive and longitudinally defined phenotype of persistent stress-exposure and stress-related symptoms in schizotypy. Presented virtually at the 2021 Congress of the Schizophrenia International Research Society (SIRS). April 17th - 21st, 2021.
5. **Torrecilla, P.,** Gizdic, A., Racioppi, A., Monsonet, M., Kwapil, T.R., & Barrantes-Vidal, N. (2020). Stress sensitization as the underlying mechanism linking childhood trauma and psychotic-like symptoms in nonclinical young adults. Presented as a poster in the virtual 2020 Congress of the Schizophrenia International Research Society (SIRS). Abstract published in Schizophrenia Bulletin, 46 (S1), S232. https://doi.org/10.1093/schbul/sbaa029.565

### b) Oral Communications

1. **Torrecilla, P**., Barrantes-Vidal., N. (2022). The role of distal and proximal stress in the association between hair cortisol and transdiagnostic stress-related phenotypes in schizotypy. Presented as oral communication at the International Consortium for Schizotypy Research (ICSR). June 2nd – 4th.

2. **Torrecilla, P**., Barrantes-Vidal., N. (2021). Examining the psychoendocrine covariance between hair cortisol and a wide range of stress-related measures in schizotypy. Presented virtually as an oral communication at the 8th European Conference on Schizophrenia Research (ECSR). September 23rd- 25th, Virtual Conference.
3. Gizdic, A., **Torrecilla, P**., Lafit, G., Myin-Germeys, I., Kwapil, T.R., Barrantes-Vidal, N. (2021). The association of a longitudinally defined stress-sensitivity phenotype with psychosis-proneness. Presented as an oral presentation in the virtual 8th European Conference on Schizophrenia Research (ECSR). September 23rd- 25th, Virtual Conference.
4. Gizdic, A., **Torrecilla, P**., Lafit, G., Myin-Germeys, I., Kwapil, T.R., Barrantes-Vidal, N. (2021). The association of a longitudinally defined stress-sensitivity phenotype with psychosis-proneness. Presented as an oral communication at the Congress of the Schizophrenia International Research Society (SIRS). April 17th - 21st, 2021.

### c) Other Dissemination Activities

Torrecilla, P. "L'efecte de les experiències estressants en el risc i la resiliència a la salut mental: quin paper hi juga el cortisol?" Online talk at "Cervella't" event as part of the Brain Awareness Week 2023, organized by Institut de Neurociències and CORE de Salut Mental, Universitat Autònoma de Barcelona. March 14$^{th}$ 2023, virtual.