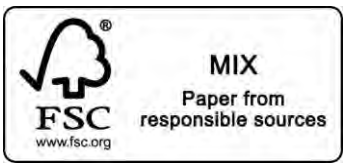
Navigating through complexity

NAVIGATING THROUGH COMPLEXITY

PROCESSES AND MECHANISMS UNDERLYING THE DEVELOPMENT OF PSYCHOSIS



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DISSERTATION

to obtain the degree of Doctor at Maastricht University and Katholieke Universiteit Leuven on the authority of the Rector Magnifici prof. dr. Rianne Letschert and prof. dr. Luc Sels in accordance with the decision of the Board of Deans, to be defended in public on Wednesday 21st of March 2018, at 16:00 hours in Maastricht

by

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CONTENTS

CHAPTER ONE

General introduction

THE PSYCHOSIS CONTINUUM

Psychosis is a mental state characterized by a distorted contact with reality. Individuals with psychosis often have hallucinatory experiences or delusions – so called positive symptoms. For instance, someone may be convinced that he is being stalked or followed by the police and everything that happens or occurs may be interpreted with this idea in mind. On the other hand, individuals may suffer from negative symptoms, such as flat affect, poverty of speech, or avolition. Furthermore, they may experience symptoms of thought disorder, as evidenced by disorganized speech, and may exhibit alterations in social functioning.

The psychosis phenotype has long been thought of as a dichotomous entity where individuals are either psychotic or not. Although breaking it down into two categories seems attractive in theory, this notion does not match the true nature of psychotic experiences and what has been observed in practice. Not everyone who suffers from psychotic experiences fulfills criteria of a mental disorder according to the ICD (International Classification of Diseases) or the DSM (Diagnostic and Statistical Manual of Mental Disorders). Psychotic experiences are prevalent in the general population [1]. Over the last two decades, the psychosis phenotype has therefore been characterized as a continuum of severity and persistence of psychotic experiences [1,2]. Although in most cases, subclinical psychotic symptoms are transient in nature, in some individuals psychotic experiences may be predictive of the development of a psychotic disorder [3]. In these individuals, experiences persist and get more severe, and the probability of developing clinically significant psychotic symptoms or a psychotic disorder increases. To identify this risk for developing clinically significant symptoms, the 'at-risk mental state' (ARMS) criteria have been introduced around the end of the 1990s [4]. Individuals that score positive on these criteria have a chance between 10 and 40% of making a transition to psychosis [5-7]. Beyond the threshold of clinically significant symptoms, at the severe end of the psychosis continuum, individuals fulfill criteria for a psychotic disorder. Although the lifetime prevalence of developing a full-blown psychotic disorder is relatively low with a mere 3-4% [8], it is often described as one of the most disabling mental conditions and associated with substantial economic and societal burden [9]. Recently, findings in favor of the continuum notion of psychosis are accumulating. However, the mechanisms and psychological processes involved in the complex etiology of symptoms and transitions along this continuum need to be elucidated further.

STRESS-REACTIVITY

Stress is inevitable and a constant companion in life. For several decades, stress has been suggested to be an important factor in the etiology of psychotic experiences, and studies have reported findings supporting this notion [10]. Victimization and childhood trauma [11-16], stressful life events [17-19] and daily hassles [20-23] have repeatedly been associated with the development of psychotic experiences (Figure 1). In particular, these studies agree on one fact – environmental stress is an important risk factor for psychosis. But how does environmental stress eventually lead to the formation of psychotic experiences, and what are processes and mechanisms involved? One putative psychological mechanism through which these knots may tie together, may be reactivity to daily stress, characterized by intense emotional reactions to small daily, stressful events [24,25] (Figure 1d). These events, also often called daily hassles, could take many shapes and forms, such as getting stuck in traffic, missing the bus, walking through the rain without an umbrella, or having an unpleasant social interaction with someone – the list is endless. To date, stress-reactivity is probably one of the most widely studied mechanisms in daily life.

Reactivity to stress has been studied in the realm of daily life, using ecological momentary assessment strategies, such as the Experience Sampling Method (ESM) [26]. The ESM is a structured diary method, where individuals are asked to rate their experiences (e.g., mood and symptoms) as well as the context they are in throughout their daily life (e.g., activity they are doing, company they are in, and their location). Usually, this is done up to 10 times a day on several consecutive days. This sampling strategy is especially designed to capture momentary ratings of experiences throughout the day. Therefore, it is perfectly suited to study concepts that are subject to change due to time, interpersonal and environmental influences – as is the case with reactivity to daily stress. This assessment strategy may, furthermore, provide insights into the dynamic associations of affect and psychotic symptoms and examine differences in populations with varying levels of vulnerability.

Several studies with samples at different levels of familial vulnerability to psychosis have looked into their differential response to stress in daily life. These studies have shown that patients with a psychotic disorder and unaffected first-degree relatives, react with increased levels of psychotic experiences and negative affect to daily life stress [23,27,28]. Another study showed significant associations between reactivity to stress in one twin and presence of subclinical or residual psychotic symptoms in the other twin [29]. Taken together, these

findings point towards a familial association between the psychosis phenotype and increased reactivity to daily stress, thereby adding evidence for stress reactivity as a mechanism underlying psychosis.

Meanwhile, several studies have investigated how stress reactivity may be influenced by risk factors that have been suggested by epidemiological findings. These studies have shown that increased emotional and psychotic reactivity to daily life stress, is linked to environmental adversity and events such as life events [30] and childhood trauma [31-33]. In line with the continuum idea of psychosis, studies have suggested similar patterns in general population samples [34,35], experiences of childhood trauma were associated with an increased reactivity to daily life stress. Previous research has proposed that behavioral sensitization may be underlying the link between environmental adversity and stress-reactivity [36,37]. Behavioral sensitization refers to a process in which (repeated) exposure to environmental risk factors results in increased behavioral responses to daily life stress later in life. Exposure to adverse experiences early in life may therefore shape later patterns of emotional reactivity, which, in turn have been linked to psychotic experiences [30].

Besides ecological assessment strategies, experimental approaches to study stress may be valuable, to obtain a better insight into the determinants of stress reactivity and to elucidate the link between environmental adversities and stress-reactivity. One example is the recently developed digi-SPEE [38], a novel task where participants are exposed to peer evaluation, one form of social stress. Combined with a twin design, it can then be studied to what extent reactivity to social stress is influenced by (interacting) environmental and genetic factors.

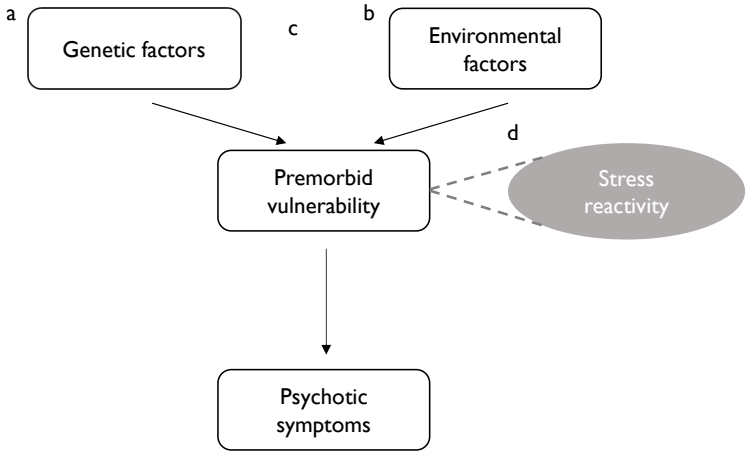

Figure 1. Schematic display of etiology of psychotic symptoms. Genetic (a) and environmental factors (e.g., childhood trauma, prenatal stress) (b) as well as gene × environment interactions (c) contributing to a vulnerability of developing psychotic symptoms. Stress reactivity (d) as an expression of premorbid vulnerability, one possible underlying mechanism linking genetic factors and environmental factors to psychotic symptoms.

NAVIGATING THROUGH COMPLEXITY: NEED FOR NOVEL METHODS AND INTERVENTIONS

Methods

So far, the ESM has proven particularly valuable for studying subtle fluctuations of symptoms as a function of changing experiences and context in the realm of daily life, and thereby helped gaining more insight into putative mechanisms underlying the development of psychosis. However, the interplay between daily stress, affect, and psychotic experiences or symptoms may be extremely complex and dynamic and therefore require analytic strategies that move beyond a classic predictor-response approach.

Recently, a network approach to psychopathology has been proposed to assess the complex associations between multitudes of aspects [39]. This approach posits that mental disorders may be best understood as dynamic networks of smaller entities (e.g., symptoms or affective states are displayed as nodes) that cluster together and interact with each other over time. This is in line with the well-observed fact that specific symptoms often co-occur and are highly inter-correlated. Applying the network approach to longitudinal data from ESM studies may provide insights into the dynamic interrelations between momentary affective states (e.g., feeling anxious or relaxed). Different recent studies have visualized the dynamic associations between momentary affective states, suggesting that the activation of one affective state simultaneously activates other affective states [40-42]. It has also been hypothesized that when

affective states repeatedly reinforce each other over time, vicious cycles may ensue from which it gets increasingly difficult to escape [42,43]. Experiences of daily stress are hypothesized to put those cycles in motion. From a network point of view, a small stressor may trigger a whole cascade of experiences or behavioral changes relevant to the eventual development of psychotic experiences.

Furthermore, recent advances in mediation analyses have opened up new possibilities to tackle complex research questions in daily life [44,45]. Multilevel moderated mediation models can be applied to ESM data to systematically test how different aspect in daily life combine to increase psychotic experiences. With this approach, in addition to direct effects of, for instance, minor daily stress on psychotic experiences, indirect effects of other aspects, such as, negative affect can be tested. As mentioned above, ESM studies provide extensive data from different moments throughout the day and week. Recently proposed adaptations of cross-lagged panel models to intensive longitudinal data, as from ESM studies, may give a better insight into the complex interplay of aspects over time [44] .

Interventions

Eventually, gaining insights into associations of momentary stress, psychological processes, and psychotic experiences in daily life may be very valuable for the development of prevention, treatment and rehabilitation strategies patients can benefit from. This knowledge is especially relevant for interventions provided in daily life of patients – Ecological Momentary Interventions (EMI) [46,47]. These real-world and real-life interventions, leveraged by mobile devices such as smartphones, enable the delivery of treatment at any time, and in almost any location – there where complaints occur.

AIMS AND OUTLINE OF THE THESIS

The overall aim of the work in this thesis was to investigate potential psychological mechanisms and processes underlying the development of psychosis. In particular, the studies presented in this thesis aimed at:

I) Elucidating the link between genetic and (adverse) environmental factors with increased stress-reactivity. In **chapter two,** we studied the determinants of differential reactivity to stress, whether these are genetic or environmental factors or a combination of

both. In this particular case, we focused on the reactivity to peer evaluation, which can be seen as one possible social stressor. Using a novel task, we exposed adolescent and young adult twins to peer evaluation comparable to what they may experience daily in online social interactions (Figure 2a). We then estimated the proportion of the variance in reactivity to peer evaluation due to genetic and environmental factors, as well as the association with specific a priori environmental risk factors (e.g., childhood trauma, bullying experiences).

II) Examining reactivity to daily stress in the context of complex micro-level dynamics. In **chapter three,** we examined reactivity to stressful experiences further, studying it this time by zooming in on micro-level dynamics. We studied reactivity to minor daily stress in daily life in three different samples varying on the continuum of psychosis; healthy controls, relatives of individuals with a psychotic disorder with a certain genetic liability for developing the disorder as well, and patients with a psychotic disorder. We analyzed the experience sampling data with the network approach to psychopathology to get a better insight into the mechanisms at the level of micro-dynamic moment-to-moment effects between stress, other daily experiences and symptomatology (Figure 2b).

In recent years, several integrated models of psychosis have suggested that experiences of stress contribute to the development of psychotic experiences via pathways through negative affect, cognitive biases, and anomalous experiences. In **chapter four,** we systematically tested comprehensive models of these pathways in individuals with a first-episode psychosis, individuals with an at-risk mental state for psychosis, and healthy control subjects. We fitted multilevel moderated mediation models to the experiences sampling data to investigate how stress, enhanced threat anticipation, and experiences of aberrant salience combine to increase psychotic experiences in daily life (Figure 2c). In **chapter five,** we investigated whether findings of chapter four replicate in another sample; a sample of individuals with a psychotic disorder, relatives of individuals with a psychotic disorder, and healthy control subjects. In a second step, we investigated how minor daily stress combines with negative affect to increase psychotic experiences longitudinally from one moment to the next.

III) Investigating real-life delivered treatment options for psychosis. As evidence on the micro-level dynamics of momentary experiences, affect and symptomatology is accumulating, real-world delivery of treatment seems to be a promising prospect for patients and individuals with an increased risk for developing a disorder. **Chapter six** of this thesis

provides a concise review on the feasibility, content and efficacy of currently available ecological momentary interventions in psychiatry.

Chapter seven contains a general discussion on processes and mechanisms in the development of psychosis. Here, we elaborate on a variety of topics covered in this thesis, and furthermore discuss the development of novel methods for research and treatment of psychotic disorders as envisioned in future directions for psychosis research.

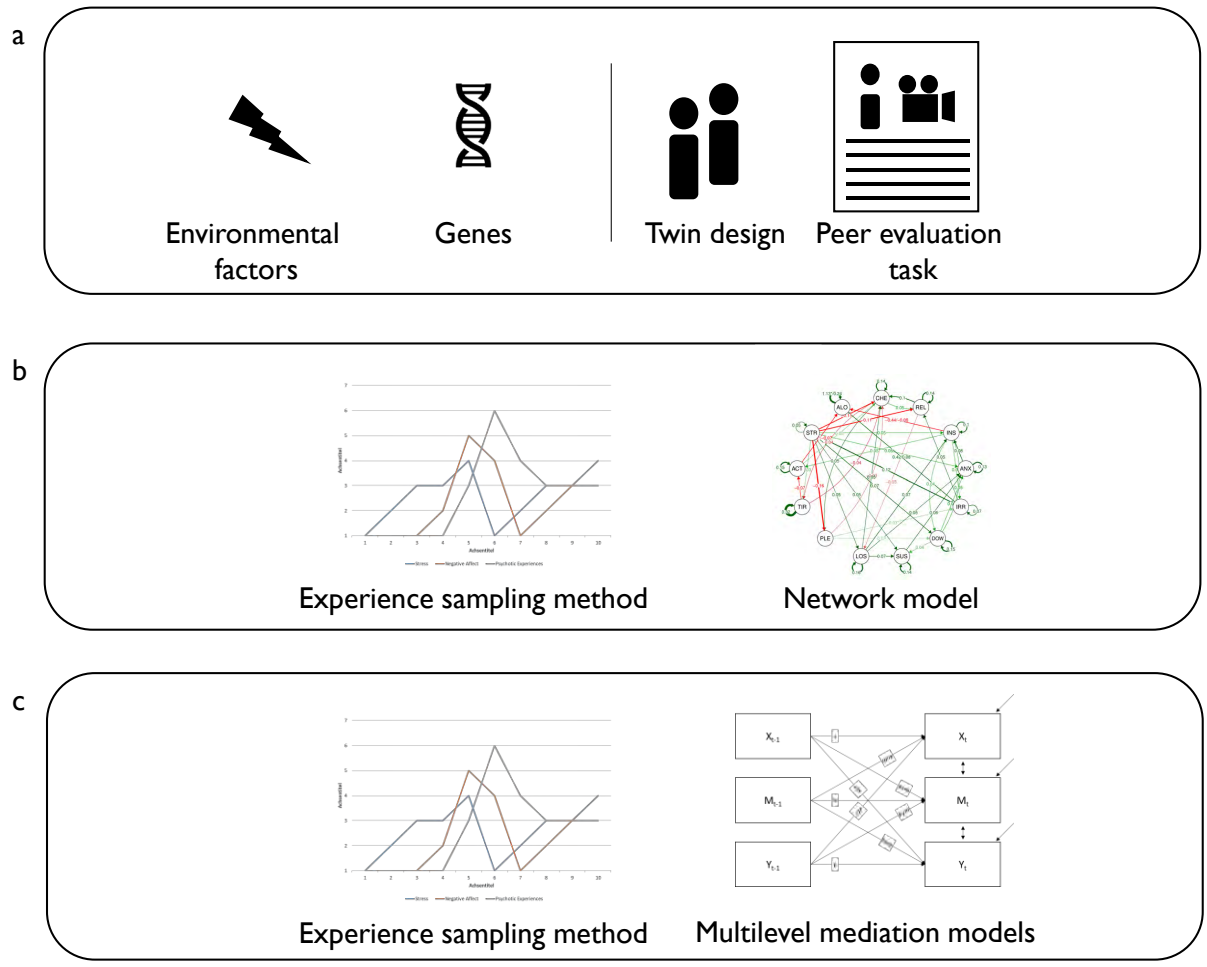

Figure 2. Schematic display of methods employed in this thesis.
Combination of twin design with novel task (a); application of network approach to ESM data (b); and application of multilevel mediation models to ESM data (c).

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CHAPTER TWO

Sensitivity to peer evaluation and its genetic and environmental determinants: findings from a population-based twin study

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ABSTRACT

Background. Adolescents and young adults are highly focused on peer evaluation, but little is known about sources of their differential sensitivity. We examined to what extent sensitivity to peer evaluation is influenced by interacting environmental and genetic factors.

Methods. A sample of 354 healthy adolescent twin pairs (n=708) took part in a structured, laboratory task in which they were exposed to peer evaluation. The proportion of the variance in sensitivity to peer evaluation due to genetic and environmental factors was estimated, as was the association with specific *a priori* environmental risk factors.

Results. Differences in sensitivity to peer evaluation between adolescents were explained mainly by non-shared environmental influences. The results on shared environmental influences were not conclusive. No impact of latent genetic factors or gene-environment interactions was found. Adolescents with lower self-rated positions on the social ladder or who reported to have been bullied more severely showed significantly stronger responses to peer evaluation.

Conclusions. Not genes, but subjective social status and past experience of being bullied seem to impact sensitivity to peer evaluation. This suggests that altered response to peer evaluation is the outcome of cumulative sensitization to social interactions.

INTRODUCTION

Humans have an inherent desire to belong to a group and to be accepted by their peers [1]. Feeling rejected by peers may induce significant stress and may negatively impact psychological, physical, and interpersonal well-being [2-7]. Negative social interactions with peers may threaten the social self in a subtle way, particularly in adolescents and young adults. When compared with children, adolescents show heightened levels of sensitivity and emotional responsiveness to peer evaluation [8]. Elevated sensitivity to peer evaluation during adolescence can in general be considered adaptive, as peer interactions become increasingly salient, and complex social cognitive skills and underlying neural correlates develop [8-12]. However, mental disorders often have their onset during adolescence and early adulthood [13], suggesting that increased sensitivity and reactivity to social interactions may contribute to dysregulation of stress responses and later psychopathology [8,14,15].

A considerable amount of peer interactions takes place on the internet, with individuals aged 18-25 being the most active group to use social media. Especially adolescents and young adults use social media extensively for their social interactions [16-18]. This may have many advantages, such as being able to connect with people from all over the world and staying in touch with friends on the go [17,18]. However, it may just as well be harmful for this young age group, since it is rather common to be evaluated and criticized based on an online personal profile. Receiving online evaluations by peers is prevalent among high school and college students and has been found to be at the least as impactful as the real life equivalent [19-21]. Given their frequent exposure to online peer evaluation and its potential detrimental effects on mental health, it is important to study the determinants of sensitivity to peer evaluation in adolescents.

Findings from previous research suggest that exposure to prenatal stress, childhood trauma, and bullying are specific risk factors that may sensitize the individual, contributing to enhanced reactivity to socially stressful events later in life [22-25]. In a study of young adult males, prenatal stress was associated with an altered cortisol response to social-evaluative stress [22]. Experiences of childhood trauma and childhood emotional maltreatment in particular were associated with an increase in sensitivity to social exclusion in a sample of young adults [25]. Also, experiences of bullying have been linked to an altered stress response to social-evaluative stress in adolescents [26] and young adult males [27]. Another *a priori* risk factor for sensitivity to peer evaluation may be a perceived lower social standing within one's

peer group, or 'subjective social status'. Subjective social status has repeatedly been associated with general and mental health outcomes [28,29] as well as greater reactivity to social evaluation [30]. This subjective measure of social status captures a broad range of different aspects and weighs income, education, and occupation in proportion to how important the individual finds each aspect in his/her own social context. From an evolutionary perspective, it is plausible that subjective social status may have an impact on sensitivity to evaluation by others. For example, an individual lower in hierarchy may be particularly aware of evaluation by others in order to reduce the risk of exclusion by his/her social group [31].

Previous studies have shown that early environmental exposures may result in 'behavioral sensitization', thus contributing to inter-individual differences in sensitivity to social stress, such as peer evaluation [14,32-34]. Behavioral sensitization refers to a process in which (repeated) exposure to environmental risk factors results in increased biological and behavioral responses to minor stress later in life. Exposure to a range of social adverse experiences early in life may shape later patterns of emotional reactivity, including reactivity to social stressors, such as evaluation by peers. Emotional reactivity to stress has been linked to the development of psychopathology [32,35,36]. Individual differences in emotional reactivity to peer evaluation may therefore represent an intermediary phenotype of later psychological symptoms, including psychotic and depressive symptoms [14,15,37,38].

In addition to environmental factors, there is some evidence that an individual's response to psychosocial stress may be influenced by genetic factors. In particular, there are findings from twin and candidate gene studies that genetic factors may play a role in differences in Hypothalamic-pituitary-adrenal axis (HPA) reactivity to social stressors [39-42]. To date, little attention has been paid to the role of genetic factors on behavioral outcome measures regarding social evaluative stress. Also, environmental and other contextual factors may increase risk in individuals with a susceptible genotype [14,43-48]. Individuals with a certain genotype may be more susceptible to the effects of, for instance childhood trauma, may respond with dysregulations in HPA axis activity and, in turn, show altered stress reactivity later in life [49]. In other words, it is important not only to examine environmental, contextual and genetic factors in isolation, but also their potential interactions.

The main purpose of this study was to examine the extent to which environmental and genetic factors predict sensitivity to peer evaluation. Using data from a large adolescent and young adult twin study, recruited from a population-based twin register in East-Flanders,

Belgium, we aimed to investigate the extent to which environmental and genetic factors, or their interaction, influence sensitivity to evaluation by peers, operationalized as change in negative and positive affect and implicit self-esteem following a structured exposure to online peer evaluation. In this study, we examined the influence of environment as a whole, but also specific environmental risk factors hypothesized to impact stress-sensitization or stress response. These include prenatal stress, childhood trauma, experiences of bullying, and the individual's subjective position on the social ladder. We tested the following hypotheses: An increase in sensitivity to peer evaluation is associated with (i) environmental risk factors; (ii) genetic factors; (iii) an interaction of genetic and environmental factors.

METHODS

Sample

The study sample consisted of adolescent and young adult twins that were recruited from the East Flanders Prospective Twin Survey (EFPTS). This population-based twin register has prospectively recorded multiple births in the province of East Flanders from 1964 onwards [50]. Zygosity was determined by sequential analysis based on sex, chorion type, umbilical cord blood groups, and in some cases DNA fingerprints. Starting in 2010, individuals of this register between the age of 15 and 34 were invited via a newsletter to take part in a longitudinal study to investigate the role of gene-environment interactions for vulnerability to mental disorders. In order to oversample twins between 15 and 18 years, additional invitational letters were sent to individuals meeting this age criterion. To date, 808 individuals were included in the study. Forty of the individuals were non-twin siblings and 18 were part of a triplet. These individuals were excluded from the current analyses. Of the resulting sample of 750 individuals, 708 took part in the structured peer evaluation task. The project was approved by the local ethics committee and all participants provided written informed consent before study inclusion. For participants under the age of 18 years additional informed consent was obtained from their parents.

The digital social peer evaluation experiment (d*igi-*SPEE)

At its core, communicating online with peers and receiving negative evaluations by peers may be different than receiving it face-to-face [19,51]. Digi-SPEE is a validated task developed to assess the effects of structured exposure to online peer evaluation similar to what adolescents

experience in their daily life (see Fig. 1) [52]. This task was designed to mimic online social network interactions as adolescents and young adults may experience on a regular basis. Peer evaluations as experienced in online social interactions are characterized by a greater level of psychological distance than real-life social encounters, are mostly based on personal traits visible in the individual's social media profile, and include feedback by their peers. The task was designed to expose participants to subtle negative evaluation of some fundamental personal characteristics (intelligence, stance in life, and appearance).

Participants were told that the general aim of the task was to examine reasons why people like or dislike each other based on online information regarding personal characteristics. During the first session, participants were asked to generate a written profile and short video introducing themselves and to rate five profiles and videos regarding appearance, intelligence, and congeniality using a 7-point scale (higher scores more positive). Participants were led to believe that they rated videos of other participants, when in reality they were presented with videos from five volunteers, which were matched according to age (±1 year) and gender (three of the same and two of the opposite gender). Participants were then told that peers would evaluate their own profile and video.

The second session took place several days later (mean=15.5 days; SD=7.7). Before receiving the evaluation, participants were asked to rate two more profiles, watch their own video and read their own written profile. The evaluation consisted of two filled vertical bars, with one bar stating 'your evaluation' and the other 'average evaluation for all individuals within the study' (higher fills more positive). For each of the three rated characteristics (intelligence, appearance, and congeniality), the participant's bar was filled up to approximately halfway, whereas the average bar filled up to approximately 80%. Alongside this general feedback, participants received evaluations (on the three rated characteristics) by five sham participants, of which seven were neutral or positive (e.g., 'seems friendly') and eight were mildly negative (e.g., 'strange nose').

This structured task consisted of two sessions which were both held in the participants' homes and were conducted by the same researcher. At the end of the second session, participants were debriefed about the true nature of the task. Menne-Lothmann and colleagues reported in their recently published paper that the majority of participants believed that they were in fact being evaluated by peers [52].

Design

In order to assess the effects of the Digi-SPEE, a within-subject (pre-post stressor) design was used (see Fig. 1). Implicit self-esteem, positive and negative affect were measured both before and right after the peer evaluation task during the second session [53]. Questionnaires on specific environmental factors were administered at baseline.

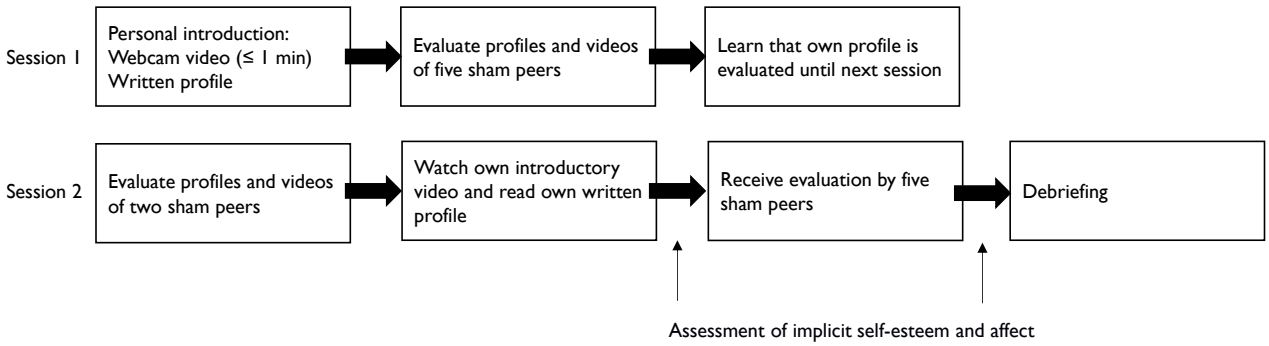

Figure 1. Display of experimental design. The experiment comprised two sessions. During the first session, participants were asked to create a personal profile and rate the profiles of 5 other individuals. A few days later, during the second session, participants had to rate two more profiles, review their own profile, and subsequently received evaluations of five sham participants on their personal profile. Lastly, participants were debriefed about the true nature of the experiment.

Outcome measures

Stress sensitivity was operationalized as change in positive and negative affect as well as change in implicit self-esteem from before to after the peer evaluation task.

Implicit self-esteem. Implicit self-esteem was measured using the Single Category Implicit Association Task (SC-IAT) [54,55]. Participants were asked to categorize personalized self-words (e.g., their first name) with either positive or negative words. The task comprised two blocks. In the first, self-words have to be sorted in the same category as positive. In the second, self-words have to be sorted into the same category as negative words. The data of this task were prepared in accordance with analysis recommendations from previously published literature on this task [52,56]. The faster people categorize self-words with positive words relatively to negative words, the higher their implicit self-esteem is (i.e., $RT_{\_self\ +neg.\ words} - RT_{\_self\ +\ pos.\ words}$ in ms). Change scores from before to after the Digi-SPEE were computed (change in implicit self-esteem = implicit $self\text{-}esteem_{after}$ – implicit $self\text{-}esteem_{before}$), so that negative values

correspond to a decrease in implicit self-esteem. The psychometric properties of the SC-IAT have been reported by Greenwald and colleagues [54].

Positive and negative affect. Current positive and negative affect before and after the evaluation were measured using the Positive and Negative Affect Scales (PANAS) [57]. This self-report inventory consists of a positive and a negative affect subscale, each comprising 10 items. For each affect characteristic (e.g., distressed, content, irritated), participants were asked to indicate on a visual analogue scale (VAS) of 105 mm length (with the outer ends labelled 'not' and 'very much') to what extent they were experiencing this affective state at the moment. Raw ratings (in mm) for positive and negative affect were averaged per person and per assessment. Change scores from before to after the digi-SPEE were computed (change in negative affect = negative $affect_{after}$ – negative $affect_{before}$; change in positive affect = positive $affect_{after}$ – positive $affect_{before}$), so that negative values correspond to a decrease in positive affect/negative affect. VAS-type instruments have been used widely to assess mood [58-60]. Using a VAS version of the PANAS enabled us to detect small changes from before to after the peer evaluation task. Besides showing higher levels of resolution and thereby providing sensitivity to detect subtle changes, visual analogue scales to assess mood have been shown to be valid and reliable [61]. The internal consistency of positive and negative affect before the peer evaluation task was alpha=0.79 and alpha=0.82, respectively. After the peer evaluation task, the internal consistency of positive and negative affect was alpha=0.87 and alpha=0.91, respectively.

Predictor measures

Prenatal stress. Birth weight (in gram) was used to estimate prenatal stress [62], with lower birth weight indicating more prenatal stress. Analyses using this estimation for prenatal stress were controlled for gestational age by including gestational age as a predictor to the models [63]. Perinatal data were registered prospectively at birth [64,65]. Gestational age (number of completed weeks of pregnancy) was based on routine gestational dating, combining last menstrual period and real time ultrasonography in early pregnancy.

Childhood trauma. Childhood trauma was measured using the Dutch shortened version of the Childhood Trauma Questionnaire [66]. This self-report inventory consists of 28 items and covers the following early experiences: emotional, physical, and sexual abuse, as well as

emotional and physical neglect. Participants were asked to rate statements such as 'There was not enough food' and 'I was abused' on a scale ranging from 1 (‘never true’) to 5 (‘very often’). For the analyses a sum score of all subscales was used. The internal consistency of this scale was alpha=0.89.

Experiences of bullying. An amended questionnaire version of the Retrospective Bullying Interview [48] was used to measure experiences of bullying. This inventory consists of 84 items covering physical, verbal, and indirect forms of bullying during primary school and high school. Furthermore, it contains items measuring the frequency and subjective severity of bullying as well as individual coping strategies. In this study, only the subscales measuring the frequency and subjective severity of bullying were included. The latter subscale consisted of six items measuring the subjective severity of bullying during different life stages on scales ranging from 1 (‘not bullied’) to 5 (‘extremely severe’), giving a maximal score of 30. The Frequency subscale comprised seven items measuring the frequency of bullying during different life stages using scales from 1 (‘not bullied’) to 4 (‘frequently’), giving a maximal score of 28. The internal consistency of the severity and frequency subscales were alpha=0.80 and alpha=0.75, respectively.

Subjective social status. Subjective social status was measured with an amended version of the MacArthur Scale of Subjective Social Status [28]. Participants were presented with an image of a 10-rung ladder with the following description: “See this ladder as a representation of people’s positions in their communities. This may be different for everyone. Choose the community that is of greatest importance to you. At the top of the ladder are the people with the highest position in this community, at the bottom those with the lowest.” Participants were then asked to mark the position on the ladder which best described where they felt they stood relative to other people in their community. This scale has previously been validated in both adolescents [67] and adults [68]. We used a visual analogue scale for this measure, since its degree of resolution offers options of very fine nuance in judgement. Scores could range between 0 and 100 mm. Raw score were used in the current study, with higher scores on this measure indicating higher subjective social status.

Analyses

First, we estimated the within-twin-pair similarity of change in implicit self-esteem and affect. Second, the main effects of the specific environmental risk factors on the change scores were examined. Third, we estimated the proportion of variance in implicit self-esteem and affect change scores that was attributable to genetic factors, latent shared environmental factors, and non-shared environmental factors. Last, we investigated whether the impact of adverse environmental factors on sensitivity to peer evaluation is modified by genetic factors. All analyses were carried out using Stata 13.1 (Stata Corporation, College Station, TX, USA) and were controlled for age and gender.

Part 1: Within-twin-pair similarity of change in implicit self-esteem and affect. Within-twin-pair similarity in the outcomes was assessed by estimating intraclass correlation coefficients (ICC) for twin pairs. For each outcome measure, an overall ICC for MZ and DZ twin pairs combined was computed. These ICCs were estimated (based on the ratio of the intercept variance to the sum of the intercept and error variances) using linear mixed-effects models with random intercepts for twin pairs [67].

Part 2: Main effects of environmental factors on change in implicit self-esteem and affect. The main effects of the specific risk factors on the outcome measures were assessed by adding the specific environmental risk factors as predictors to the aforementioned models. Again, random intercepts for twin pairs were included in these models.

Part 3: Latent genetic and environmental influences. First, a specific ICC for MZ pairs and a specific ICC for DZ pairs were computed for each outcome measure. This was done analogous to analyses performed in part 2 using linear mixed-effects models with random intercepts for twin pairs.

Second, using Falconer's formula [68], the proportion of variance in change in implicit self-esteem, positive affect, and negative affect in response to peer evaluation that is due to genetic factors was estimated. This proportion was defined in terms of heritability h^2, where $h^2 = 2(r_{MZ} - r_{DZ})$, and r_{MZ} and r_{DZ} are the ICCs of a particular outcome for monozygotic (MZ) and dizygotic (DZ) twin pairs, respectively. In addition, the contribution of a shared environment (c^2) was estimated by deducting the heritability value from the ICC of MZ twin pairs: $c^2 = (r_{MZ} - h^2)$.

Finally, non-shared environment (e^2) is a reflection of the degree to which identical twins raised together are dissimilar and was calculated as follows: $e^2 = (1-r_{MZ})$ [69].

To estimate the ICCs, linear mixed-effects models with random intercepts for twin pairs were used once again. Now, the intercept and error variances were allowed to differ for MZ and DZ pairs, so that the ICCs could be computed per zygosity. Models were fitted for each outcome variable (change in implicit self-esteem, positive affect, and negative affect) separately. Wald-type tests were used to examine whether the ICC of DZ pairs differed significantly from the ICC of MZ pairs (in case ICCs do not differ significantly, then this would imply the absence of evidence for a genetic component).

Part 4: Associations of genetic and specific risk factors with change in implicit self-esteem and affect. To test the effect of specific environmental risk factors and the latent genetic risk on change in implicit self-esteem and affect, the following four groups were created for each specific risk factor (prenatal stress, childhood trauma, frequency and severity of bullying, and subjective social status): (1) DZ high-score individuals, (2) DZ low-score individuals, (3) MZ high-score individuals, and (4) MZ low-score individuals. The division into high- and low-score groups was done using a median split procedure. Next, we fitted mixed-effects models with random intercepts for twin pairs, but now allowing intercept and error variances to differ for the four different groups mentioned above. Based on these analyses, an ICC for each group was computed. Using these ICCs, h^2 was calculated separately for high- and low-scoring individuals. To examine whether the specific environmental risk factors interact with (latent) genetic risk, we tested if h^2 of high-scoring individuals differed significantly from h^2 of low scoring individuals using Wald-type tests. This was done for each specific environmental risk factor separately.

RESULTS

Basic sample characteristics. Demographic information for the sample is presented in Table 1. The sample consisted of 708 subjects of whom 256 were MZ and 426 were DZ. The zygosity of 13 twin pairs could not be determined; these pairs were excluded from the genetic analyses (Part 1 and Part 3). The mean age of the participants was 17.8 years (SD=3.4, range 15-34).

Table 1. Characteristics of study population (N=708)

Age (years), mean (SD, range)		17.8 (3.4,15-34)
Gender, n (%)		
	Men	294 (41.5)
	Women	414 (58.5)
Gender combination of twin pairs, n (%)		
	Same sex female DZ	134 (18.9)
	Same sex female MZ	158 (22.3)
	Same sex female missing zygosity	14 (2.0)
	Same sex male DZ	76 (10.7)
	Same sex male MZ	98 (13.8)
	Same sex male missing zygosity	12 (1.7)
	Opposite-sex	216 (30.5)
Level of education, n (%)		
	Elementary school	1 (0.1)
	Intermediary vocational education	88 (12.4)
	High school	379 (53.5)
	Bachelor's degree	99 (14.0)
	Master's degree	81 (11.4)
	Missing	60 (8.5)
Employment status, n (%)		
	Homemaker	2 (0.3)
	Student	603 (85.2)
	Employed	56 (7.9)
	Missing	48 (6.8)
Zygosity, n (%)		
	MZ	256 (36.2)
	DZ	426 (60.2)
	Missing	26 (3.7)
Outcome measures, Mean (SD)		
	Change in implicit self-esteem	-.145 (.451)
	Change in positive affect	-17.9 (40.0)
	Change in negative affect	22.0 (48.0)
Predictor measures, Mean (SD)		
	Birth weight in g	2498 (501.8)
	Gestational age in weeks	36.4 (2.0)
	Childhood trauma	34.3 (9.0)
	Severity of bullying	9.9 (4.4)
	Frequency of bullying	10.7 (3.5)
	Subjective social status	38.3 (27.9)

Note: n Indicates the number of individual twins. MZ = monozygotic, DZ = dizygotic

Part 1: Within-twin-pair similarity of change in implicit self-esteem and affect. Table 2 shows the within twin pair ICCs for all three outcome measures. The correlations suggested that change in implicit self-esteem (ICC=.126; p=.025) as well as change in positive affect (ICC=.111; p=.046) were significantly associated between co-twins.

Table 2. Within twin pair intra-class correlation coefficients of outcome measures

	Monozygotic n = 256		Dizygotic n = 426		all n = 682	
	ICC	p	ICC	p	ICC	p
Change in implicit self-esteem[1]	.138	.133	.118	.095	.126	.025
Change in positive affect[2]	.094	.296	.126	.077	.111	.046
Change in negative affect[2]	.113	.222	.026	.714	.058	.306

Note. n Indicates the number of individual twins. Missing values on change scores [1] n=63; [2] n=52; ICCs of monozygotic and dizygotic twins did not differ significantly from each other

Part 2: Main effects of environmental factors on change in implicit self-esteem and affect. Table 3 shows findings on the main effects of the specific environmental risk factors on sensitivity to peer evaluation. Severity of bullying was significantly associated with change in negative affect (b=.787, p=.033): The higher the level of subjective severity of bullying, the larger the increase in negative affect after the task. Individuals with a lower subjective social status showed a stronger decrease in implicit self-esteem (b=.002, p=.022) and in positive affect at trend level (b=.108, p=.066). None of the other risk factors were significantly associated with sensitivity to peer evaluation.

Table 3. Analysis of main effects of specific environmental factors on outcome variables (n=708)

	Change in implicit self-esteem[1]			Change in positive affect[2]			Change in negative affect[2]		
	b	p	95% C.I.	b	p	95% C.I.	b	p	95% C.I.
Birth weight	.000	.995	-.000 - .000	-.002	.581	-.010 - .006	.007	.156	-.004 - .016
Childhood trauma	.002	.440	-.002 - .006	.132	.498	-.249 - .513	-.080	.727	-.526 - .366
Bullying severity	.001	.845	-.007 - .009	-.026	.944	-.736 - .685	.836	.050	-.001 - 1.67
Bullying frequency	.007	.201	-.004 - .017	.210	.657	-.715 - 1.13	.847	.127	-.242 - 1.94
Subjective social status	.002	.016	.000 - .003	.114	.046	-.002 - .227	-.004	.648	-.136 - .128

Note. n Indicates the number of individual twins. Missing values on change scores [1] n=63; [2] n=52

Part 3: Latent genetic and environmental influences. Table 2 presents specific ICCs for MZ and specific ICCs DZ twin pairs for each outcome measure. Twin pair correlations appeared similar between MZ (change in implicit self-esteem and positive affect: ICC=.138, p=.133 and ICC=.094, p=.296, respectively) and DZ pairs (change in implicit self-esteem and positive affect:

ICC=.118, p=.095 and ICC=.126, p=.077, respectively), suggesting that the observed twin-pair correlations are driven by shared environmental factors rather than genetic influences.

The proportion of variance explained by additive genetic latent factors was not significant for all three outcome measures (respectively; implicit self-esteem, positive affect, and negative affect: 4.0%, p=.863; 0%; p=.789; 17.3%; p=.458). Shared environment explained 9.8% (p=.560) of the variance in change in implicit self-esteem, 15.7% (p=.353) of the variance in change in positive affect, and 0% (p=.723) of the variance in change in negative affect. For all three outcome measures, the largest proportion of variance was accounted for by the non-shared environment component.

All analyses were performed including different as well as same sex DZ twin pairs. However, a sensitivity analysis including only same-sex twins led to the same conclusions.

Table 4. Gene-environment interactions and their association with change in implicit self-esteem, positive affect and negative affect (n=682)

	Change in implicit self-esteem[1]				Change in positive affect[2]				Change in negative affect[2]			
	ICC	h^2	p^a	p^b	ICC	h^2	p^a	p^b	ICC	h^2	p^a	p^b
Birth weight												
High MZ	.000	-.309	*n.e.*	*n.e.*	.268	-.043	.912	.709	.151	-.079	.875	*n.e.*
DZ	.154				.289				.191			
Low MZ	.270	.403	.266		.097	.173	.688		.171	.343	*n.e.*	
DZ	.068				.010				.000			
Childhood trauma												
High MZ	.070	-.241	.596	.269	.318	.605	.109	.241	.184	.303	.468	*n.e.*
DZ	.191				.015				.032			
Low MZ	.258	.435	.285		.077	-.057	.893		.251	.502	*n.e.*	
DZ	.041				.106				.000			
Bullying severity												
High MZ	.161	.029	.951	.803	.183	.234	.570	.676	.025	-.084	.848	*n.e.*
DZ	.147				.067				.067			
Low MZ	.216	.180	.634		.013	-.009	.982		.354	.708	*n.e.*	
DZ	.126				.017				.000			
Bullying frequency												
High MZ	*n.e.*	*n.e.*	*n.e.*	*n.e.*	.077	.057	.909	*n.e.*	.000	-.325	*n.e.*	*n.e.*
DZ	.119				.048				.163			
Low MZ	.195	.023	.951		.000	-.426	*n.e.*		.359	.718	*n.e.*	
DZ	.182				.213				.000			
Subjective social status												
High MZ	.339	.191	.657	*n.e.*	*n.e.*	*n.e.*	*n.e.*	*n.e.*	.000	.000	*n.e.*	*n.e.*
DZ	.243				*n.e.*				.000			
Low MZ	.000	.000	*n.e.*		*n.e.*	*n.e.*	*n.e.*		.069	-.233	*n.e.*	
DZ	.000				*n.e.*				.186			

Note. n Indicates the number of individual twins. High = high scores on specific environmental factor. Low = low scores on specific environmental factor. MZ = monozygotic, DZ = dizygotic, *n.e.* = could not be estimated due to model conversion problems. [a] Significance of heritability (h^2). [b] Significance of differences in h^2 of two different groups (high, low). Missing values on change scores [1] n=63; [2] n=52.

Part 4: Associations of genetic and specific risk factors with change in implicit self-esteem and affect. Table 4 summarizes the results of the analyses examining whether the variation in sensitivity is attributable to the interaction between genetic and specific risk factors. There was no significant association of genetic and specific risk factors with sensitivity to peer evaluation.

DISCUSSION

To our knowledge, this study is the first to examine the determinants of sensitivity to peer evaluation in a young general population sample combining a twin design with a novel structured task. We found evidence that people reporting to be more severely bullied in the past are more sensitive to peer evaluation as indicated by a stronger increase in negative affect response following exposure. Furthermore, people who rated themselves lower on the social ladder showed a stronger decrease in positive affect and implicit self-esteem in reaction to the task. The impact of shared environmental factors remained inconclusive as intraclass correlations suggested an effect but the estimation of variance components did not. We did not find evidence that genetic factors explained a significant proportion of variance in sensitivity to peer evaluation nor that the impact of latent environmental and specific risk factors on sensitivity was modified by genetic factors.

Our findings are in line with earlier work in healthy participants suggesting that bullying [27] and subjective social status [30] impact on sensitivity to evaluative stress as measured with the Trier Social Stress Test (TSST; [53]). However, studies using the TSST also found prenatal stress [22] and childhood trauma [70,71] to be associated with sensitivity to evaluative stress. This may be due to the nature of the task. In the TSST, people are led to believe that they will be evaluated based on their performance in front of a professional panel, rather than on their personal characteristics by peers as is the case in the digi-SPEE. Based on the current results, we can hypothesize that there may be a certain degree of specificity of the link between quality of prior environmental exposures (i.e., bullying, subjective social status) and the quality of current stressors in the task. Only those specific environmental factors that involved an element of evaluation by peers were associated with an affective response following the digi-SPEE exposure.

There is an extensive body of work on determinants of endocrine and sympathetic responses to experimentally induced evaluative stress. Although the current study focused primarily on affective outcome measures, our findings complement those by Hamilton and

colleagues [27] who reported altered sympathetic responses to evaluative stress in men exposed to bullying. In line with recently published work by Chen and colleagues [72], we measured *severity* and *frequency* of bullying in order to capture different perspectives of these bullying experiences. While we did find an association between *severity* of bullying and sensitivity to peer evaluation, *frequency* was unrelated to the response to the digi-SPEE. This may be due to the fact that *frequency* of bullying likely also reflects bullying situations that were not serious enough to exert its detrimental effects on individuals. *Severity*, in contrast, reflects a subjective evaluative component and may provide insight into the psychological impact of bullying incidents.

Our findings concerning the association between subjective social status and sensitivity to peer evaluation are in agreement with a recent study conducted by Derry and colleagues [30]. They found that individuals who see themselves lower on the social ladder show a greater reactivity to brief social-evaluative stress as induced with the TSST. Particularly, the social evaluative component of a stressor may be a crucial aspect in explaining the differences in stress response by individuals with high and low subjective social status [73]. According to earlier work, subjective social status is closely associated with levels of optimism, perceived control, as well as sense of belonging and acceptance [29,74]. All these aspects may be related to how an individual perceives, and behaves in social interactions with peers. In particular, it may be plausible that through a sense of belonging and acceptance higher subjective social status may create a buffer against social stressors [75].

The findings in the light of sensitization to social stress

The findings of the current study are in line with the hypothesis that social stress sensitivity may be the result of sensitization processes initiated by specific environmental exposures. According to the theory of sensitization, stressors of similar magnitude result in progressively stronger stress responses over time [14,32,76]. These processes may finally result in heightened sensitivity to the exposure of social stressors in adulthood, such as negative evaluation by others. It is striking that, in the current study, the two risk factors that are explicitly peer-related in nature (bullying and subjective social status) are the ones that were associated with sensitivity to peer evaluation. With this in mind, we may speculate that the sensitization processes responsible for this effect are specific rather than global in nature. Only previous exposures to *social (peer) evaluative* stressors may have the potential to sensitize

people to novel and subtle *social (peer) evaluation* stress encounters, such as those that subjects were exposed to in this structured task. This may also explain why we did not find any associations between other frequently reported environmental stressors, like low birth weight or childhood trauma. However, in the current study, sensitivity to peer evaluation was operationalized in terms of a response in affect and implicit self-esteem. It could very well be that other mechanisms need to be considered in the context of sensitivity to peer evaluation, like threat anticipation, for instance. Further work is needed to provide additional evidence of this specificity for other mechanisms.

Methodological considerations

The findings of the current study must be viewed in the light of some methodological considerations. First, the sample of the current study is with a mean age of 17.8 rather young. The findings of our analyses thus cannot be generalized to other age groups. However, as stated above, understanding sources of differences in sensitivity to peer evaluation in this particular group is essential. Individuals of this age show a peak in number of social interactions, as well as elevated levels of sensitivity and emotional responsiveness to these interactions [17,11,16].

Second, based on our findings we cannot exclude the possibility that shared environmental factors were associated with the response to peer evaluation. The findings from the ICC analysis provide crude support that there is a certain similarity within twin pairs that cannot be explained by genetic factors and therefore may be related to socio-environmental factors that were shared within pairs which would be in support of a purely socio-environmental pathway to psychopathology [77,78]. However, this is at variance with contemporary work that suggests several pathways (e.g., environmental and genetic) combine and interact with each other in the development of complaints [79,80].

We cannot exclude the possibility that unmeasured confounders account for some of the retrospective appraisal, or even bias recall of bullying events and potentially explain some of the variance in the stress response to peer evaluation. Furthermore, it is possible that personality characteristics or other unmeasured factors had an influence on sensitivity to peer evaluation. The role of personality characteristics should be investigated in future research.

The variance components analyses did not suggest any effect of gene-environment interactions on sensitivity to peer evaluation. However, we cannot exclude the possibility that gene-environmental interactions do play an important role. As unaccounted gene-environment

interactions may be summarized in the non-shared environment component [81], and the biggest proportion of variance in sensitivity to peer evaluation was explained by this component, it may be that gene-environment interactions or epigenetic processes [82] are involved in the development of sensitivity to peer evaluation. Nonetheless, our analyses on specific risk factors did not show evidence for gene-environment interactions. This may be due to the complexity of the models employed as well as the use of binary risk factors, which may imply a reduction in power (however, in the context of the models we fitted, there is no straight forward method of letting h^2 be a function of a continuous covariate).

The current study did not investigate timing effects of bullying, as to what extent experiences during primary school are differently associated with sensitivity to peer evaluation than more recent events during secondary school. It has been suggested by recent studies that bullying experiences during both primary and secondary school are associated with alterations in health and mental health [83-85]. However, the phases of primary and secondary school may each be marked by different critical developmental processes [86,87], and therefore experiences of bullying may have different *consequences* for the personal development. Future studies should therefore investigate further, whether experiences of bullying during these distinct developmental stages have a differential impact on sensitivity to peer evaluation.

Finally, our bullying measure focused on aspects of 'traditional' bullying rather than 'cyberbullying'. Although similar in various ways, recent findings suggest that these two forms of bullying are two distinct concepts [88,89]. In this era of increased social media use and internet communication — especially among adolescents and young adults [16-18] — it would therefore be worthwhile to study the differential effects of (early) cyberbullying experiences on online peer evaluation in future research.

CONCLUSION

In conclusion, we found support for the hypothesis that sensitivity to peer evaluation may be the result of specific sensitization processes initiated by adverse experiences. The findings of the current study provide first evidence that subjective social status as well as bullying are among potential risks associated with sensitivity to peer evaluation. Evidence on the determinants of differential sensitivity to peer evaluation in such a young sample of adolescents and young adults is vital for gaining a better understanding of when and how to intervene best. Assessment and monitoring of subjective social status provides useful information on future

health risk [90]. Interventions targeting feelings of social belonging may decrease this risk, as individuals that feel confident in their belonging may experience the social world in a way that it may be self-reinforcing. As a consequence, they may initiate more relationships and obtain opportunities for growth and belonging, which in turn promote well-being [91].

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CHAPTER THREE

The cascade of stress: a network approach to explore differential dynamics in populations varying in risk for psychosis

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ABSTRACT

Stress plays a central role in the development and persistence of psychosis. Network analysis may help to reveal mechanisms at the level of the micro-dynamic effects between stress, other daily experiences and symptomatology. This is the first study to examine time-lagged networks of the relations between minor daily stress, momentary affect/thoughts, psychotic experiences, and other potentially relevant daily life contexts in individuals varying in risk for psychosis. Intensive longitudinal data were obtained through 6 studies. The combined sample consisted of 654 individuals varying in risk for psychosis: healthy control subjects (n = 244), first-degree relatives of psychotic patients (n = 165), and psychotic patients (n = 245). Using multilevel models combined with permutation testing, group-specific time-lagged network connections between daily experiences were compared between groups. Specifically, the role of stress was examined. Risk for psychosis was related to a higher number of significant network connections. In all populations, stress had a central position in the network and showed direct and significant connections with subsequent psychotic experiences. Furthermore, the higher the risk for psychosis, the more variables "loss of control" and "suspicious" were susceptible to influences by other network nodes. These findings support the idea that minor daily stress may play an important role in inducing a cascade of effects that may lead to psychotic experiences.

INTRODUCTION

Minor daily stress and psychosis

Stress plays a central role in the development and persistence of psychosis [1-5]. Recently, studies have focused on minor stressors in the realm of daily life and their dynamic associations with affect and psychotic experiences [6], using ecological assessment strategies such as the Experience Sampling Method (ESM) [7]. These ESM studies found minor daily stress to be associated with an increase in both negative affect and momentary psychotic experiences in patients with psychosis, and in individuals with a familial or psychometric risk for developing a psychosis [8-10]. Increased sensitivity to minor daily stress has been proposed to be a vulnerability marker for the development of psychotic symptoms [11]. To date, it has remained relatively unclear, if stress acts directly upon experiences or if the association relies on more complex dynamics. According to the "affective pathway" theory, minor daily stress possibly impacts on psychosis through altered affective responses [11]. Indeed, increases in anxiety have been found to precede the increase of paranoia [12], and such dynamic interplay of momentary affect and paranoia was also found to be associated with the development and course of psychotic experiences [13]. Furthermore, Reininghaus and colleagues found elevated emotional reactivity to minor stress to be associated with more intense psychotic experiences in daily life [14]. Overall, it is apparent that the interplay between minor daily stress, affect, and psychosis is complex and dynamic and requires analytic strategies that move beyond a classic predictor-response approach.

The network approach

Recently, a network approach to psychopathology has been proposed as a valuable alternative to the more traditional latent construct perspective [15-18]. It posits that mental disorders are best understood as dynamic networks of smaller entities (e.g., symptoms or affective states displayed as nodes) that cluster together and interact with each other over time [19,20].

Applying the network approach to fine-grained ESM data may provide a better understanding of dynamic interrelations between momentary affective states (e.g., feeling anxious or cheerful). A number of recent studies have visualized the dynamic associations between momentary affective states [20-22] suggesting that the activation of one affective state can simultaneously activate other affective states. Furthermore, individuals with a mental disorder showed more direct connections between momentary affective states compared to

healthy controls [22,23]. It can be speculated that when affective states repeatedly reinforce each other over time, vicious cycles may ensue, from which it gets increasingly difficult to escape [23,24]. Experiences of minor daily stress are hypothesized to put in motion or maintain such vicious cycles. From a network point of view, a stressor may be able to trigger a whole cascade of other experiences or behavioral changes [15,24] relevant to the eventual development of psychotic experiences by activating one of the strongly connected nodes in the network.

In order to examine these relationships, we first require temporal data to estimate networks in which we can visualize which experiences precede other experiences over time. ESM data are very suitable for this purpose. Second, to examine whether the proposed micro-level dynamics play a role in psychosis, comparisons need to be made between groups with different levels of risk for psychosis. Third, as stress and other relevant contextual factors may play an important role in these dynamics, we need to create networks incorporating not only affective and psychotic experiences, but also incorporate measurements representing stress, current thoughts, as well as various situational characteristics.

In the current study, we aim to examine the dynamic interplay between minor daily stress, momentary affect/thoughts, psychotic experiences, and other potentially relevant daily life contexts. For this purpose, we created dynamic networks using combined data from 6 ESM studies in controls, first-degree relatives of patients with psychotic disorder, and patients with psychotic disorder. Permutation testing procedures (comparable to the Network Comparison Test [25] were then used to test for differences in the network connections between these 3 groups.

METHODS

Samples

We used data from 6 different studies [10,26-29] (see supplementary Table S1 for inclusion and exclusion criteria of these studies) that used a similar ESM protocol. Participants were classified either as (1) "healthy" control individuals (i.e., neither a personal diagnosis nor a family history of psychotic disorder/symptoms), (2) first-degree relatives of individuals with a psychotic disorder, or (3) individuals with a psychotic disorder.

All studies included in this paper were approved by the local medical ethics committee. All further procedures and analyses were performed according to the ethical standards formulated by this committee.

Experience sampling method

In all studies, ESM (a structured diary technique) was used to study minor stress in everyday life (Table 1). Individuals received a diary and a wristwatch which was programmed to beep 10 times a day (between 7:30 AM and 10:30 PM) for 5 (Aripiprazol study [27]) or 6 days (remaining studies) at semi-random intervals (random within 90-min time frames). Thus, the time lag between the measurements was, on average, approximately 90 minutes. Information on the ESM can be found elsewhere [30,31].

ESM measures

We selected 13 ESM items for our analyses based on the following criteria: (1) all variables had to be assessed in all 6 ESM studies, (2) the selected variables needed to capture different aspects relevant to psychosis, and (3) the variables had to have a considerable within-person variability over measuring points. This resulted in the following variables: "minor daily stress" (hereafter called "stress"), "cheerful," "relaxed," "insecure," "anxious," "irritated," "down," "suspicious," "loss of control," "pleasant thoughts," "tired," "active," and "alone". "Stress" was assessed with the item "Think about the most important event since the last beep. This event was…" This item was rated on a 7-point bipolar scale (−3 "very unpleasant," 0 "neutral," 3 "very pleasant"). Positive scores (0, 1, 2 and 3) were coded as 0 "neutral" and all negative scores were recoded (−3 = 3, −2 = 2, −1 = 1) so that high scores reflect stress. This item has been used widely to assess minor daily stress [8,9,32] and its convergent validity [32] as well as its association with physiological stress response has been reported previously [33]. More information on the included variables is presented in Table 1.

Table 1. ESM procedure[a] and measures[b] of stress, affect, psychotic experiences, and context

	Variable name	ESM measures[b]	Rating
Minor daily stress	Stress	'Think about the most important event since the last beep. This event was…'	Rated on a 7-point bipolar scale (-3 'very unpleasant', 0 'neutral', 3 'very pleasant'). Positive scores indicated the absence of an unpleasant event since the last beep, which means that there was no stressor present. Therefore these scores (0, 1, 2 and 3) were coded as 0 `neutral´. Negative scores implicated the presence of an unpleasant event, which means that there was a stressor present. To let high scores reflect more stress, these negative scores were recoded (-3=3, -2=2, -1=1).
Affect	Cheerful Relaxed Insecure Anxious Irritated Down	'I am cheerful' 'I feel relaxed' 'I feel insecure' 'I feel anxious' 'I feel irritated' 'I feel down'	Rated on a 7-point Likert scale ranging from 1 ('not at all') to 7 ('very').
Psychotic experiences	Suspicious Loss of control	'I feel suspicious' 'I am afraid to lose control'	Rated on a 7-point Likert scale ranging from 1 ('not at all') to 7 ('very').
Cognitive, physical, and contextual aspects	Pleasant thoughts Tired	'I have pleasant thoughts' 'I am tired'	Rated on a 7-point Likert scale ranging from 1 ('not at all') to 7 ('very').
	Active	'I am currently doing […]. I am actively engaged in this activity'	Choice of different of activities that is followed by a question on how actively engaged the individual is in this particular activity. This item is rated on a 7-point Likert scale ranging from 1 ('not at all') to 7 ('very'). Only the rating of engagement was included in the current analyses.
Alone	Alone	'Who am I with'	Choice of different categories for social company (e.g. with partner, with friend, etc.). Based on answer, dichotomous variable 'alone' was generated with 0 'not alone' and 1 'alone'.

[a]ESM procedure: Individuals received a diary and a wristwatch which was programmed to beep 10 times (from 7:30 AM to 10:30 PM) a day for five (Aripiprazol study [27]) or six days (remaining studies) at semi-random intervals (random within 90-minute time blocks). At each prompt, participants were asked to stop their activity and to fill in a short questionnaire including the above items. Prior to the assessment period, participants were provided with detailed instructions during a short training session. The ESM assessment period started on any day of the week, usually one day after the training session. Participants were at least contacted once during the assessment period, to assess instruction adherence, identify concerns or problems with the method and in order to maximize the number of observations. Participants had to provide valid responses to at least one-third of the beep signals to be included in the analyses of the current study.

Range of variables

To make model coefficients more directly comparable, all variables (with the exception of "alone") were transformed to range between 0 and 1 before the analyses (with $z_{ij} = \frac{x_{ij} - \min(x)}{\max(x) - \min(x)}$, where x_{ij} is the jth observation of the ith individual and $\min(x)$ and $\max(x)$ are the theoretically lowest and highest possible scores on the variable, so that 0 corresponding to the lowest possible score on the variable and 1 corresponding to the highest possible score). Since "alone" was assessed on a dichotomous scale, a transformation of this variable was not necessary.

Analyses

Given the hierarchical structure of ESM data (with multiple observations nested within individuals), multi-level (mixed-effects) regression models were used. In line with previous work, we used VAR-specified multilevel models to obtain regression coefficients that would serve as estimates for network connection strengths between nodes (e.g., momentary experiences) [21]. This means that for each group of participants, 13 models were fitted, where each variable once served as the dependent variable in turn. The time-lagged values of all 13 variables (e.g., lag one, at one beep earlier) served as covariates/predictors in the model, so that each variable at time t was predicted by all 13 variables at t−1 simultaneously [21]. The lags in the current study had an average distance of 90 minutes. The predictor variables were person-mean centered prior to the analyses. Since we were interested in the temporal relationships of the variables within a day, the first beep on each day was excluded from the analyses. To account for any time trends in the outcome variables, time was included as a covariate. All analyses were controlled for age and gender.

To allow observations from the same individual to be correlated, random intercepts at the individual level were included. Moreover, time trends in ESM data are assumed to differ systematically per individual, and we therefore allowed slopes of the time variable to differ randomly across individuals (with random intercepts and slopes allowed to be correlated). For reasons to be outlined further below, we did not model random slopes for the remaining predictors.

Since "alone" was assessed dichotomously, we used logistic mixed-effects regression models when this variable served as the outcome variable. For the 12 remaining variables, we used standard linear mixed-effects models. The analyses were carried out using R, version 3.2.1

using the nlme [34] and lme4 [35] packages for the standard and logistic mixed-effects models, respectively.

Significant network connections. Group networks were generated based on significant regression coefficients (fixed effects with a corresponding 2-side P-value < .05) [36]. Since the associations between predictors and outcomes are likely to differ across individuals, it would have been preferable to add random effects for all regression coefficients. Since this would result in models that are too complex for our dataset, we opted for models with random intercepts and random slopes only for the time variable. While regression coefficients themselves are then still unbiased estimates, the standard errors of the coefficients (and hence P-values) from the models are not trustworthy. To obtain accurate P-values and thus identify significant network connections, we used a permutation procedure [37] with 10 000 iterations to conduct the tests of the coefficients (supplementary text S1).

Variable "alone". Using logistic regression multilevel models for the outcome variable "alone" would result in networks containing coefficients which are not directly comparable in magnitude. Since linear models for this outcome yielded similar P-values (and identical conclusions) as the logistic models, the linear coefficients from these models were the ones used in the computation of network measures.

Comparison of Group Networks

Specific paths differences. Significant differences in magnitude (P < .05) of specific paths (e.g., regression coefficients) between groups (supplementary materials) were tested with a permutation procedure.

Differences in average network connectivity. The average whole network connectivity was computed based on all absolute network connection strengths in a network. Network connectivity represents the ease with which the activation of nodes triggers the activation of other nodes in the network. A higher average whole network connectivity means that in the first network activation of nodes is more easily spread throughout the network producing a cascade of changes in the activity of all the network nodes. Furthermore, we also split the measure of whole network connectivity in average internode connectivity and average self-

loop strength. The first measure is based on all connection strengths that run between different nodes in the network. The second measure is based on all connection strengths that are present within each node. The latter connections are also called "self-loops" or "autocorrelations" [21,23].

Network centrality. Centrality characteristics are based on all network connections and were computed using the "qgraph" package [36]. Inward and outward strength were calculated by adding the absolute weights of all the respectively incoming and outgoing connections (not including self-loops) per node in the network. The higher the outward strength, the stronger the influence the node exerts directly on other nodes in the network. Therefore, hypothetically, alterations in the activity of a node with a high outward strength can thus easily lead to changes in the activity of the other nodes as well. The inward strength of a node gives insight into the extent that a node is influenced directly by other nodes. Finally, nodes with a high betweenness centrality are situated on a high number of shortest paths between other nodes. For example, it can be imagined that the shortest path for stress to influence a node representing a psychotic experience, is by first activating nodes of negative affective states. If many shortest paths run through the latter nodes then these are said to have a high betweenness centrality. In our particular case, connections with higher weights are shorter. Shortest paths are therefore determined by taking the inverse of absolute connection weights.

RESULTS

Basic sample characteristics

Demographic information and mean levels of ESM items are presented in Table 2. Patients differed significantly in their means from controls and relatives on all ESM measures (all $P < .05$), except for "pleasant thoughts" and "active". Controls and relatives did not show significant differences on ESM measures. Figure 1 shows network visualizations for controls, first-degree relatives, and patients.

Specific path differences

Minor Daily Stress. Compared to relatives and controls, patients showed a stronger connection from "stress" to feelings of "suspiciousness" and "loss of control" (Table 3). Relatives also showed a stronger connection than controls from "suspicious" to "stress". Controls showed a

stronger connection from "stress" to "active" than both patients and relatives. For them, when feeling more "stress" one moment they are more "active" the next. In contrast, in patients and relatives "stress" at t−1 was associated with being less "active" at t.

Negative experiences and symptomatology. Patients differed significantly from relatives in their connection from irritated to alone. Relatives were less often alone, whereas patients were more often alone the moment following feeling irritated. Patients showed a stronger positive connection from "insecure" to "down" than both controls and relatives. Furthermore, patients showed a significantly stronger negative association than controls in their connection from "relaxed" to "down" and from "relaxed" to "loss of control". Also, in controls feelings of "loss of control" were followed by increases in feeling "irritated," "stress," "tired" the next moment, which was not the case in relatives.

Table 2. Sample characteristics per group

	Controls	First-degree relatives	Patients with psychosis
N	244	165	245
Mean age (S.D.)	36.5 (12.3)	36.8 (12.6)	35.3 (10.8)
Age range	16-64	16-63	17-64
Gender			
Male (%)	111 (44)	68 (41)	111 (46)
Female (%)	132 (56)	97 (59)	132 (54)
Mean (S.D.) level of ESM measures			
Stress	0.21 (0.21)	0.21 (0.21)	0.27 (0.35)
Cheerful	5.10 (0.76)	5.08 (0.91)	4.28 (1.11)
Anxious	1.15 (0.29)	1.20 (0.50)	1.70 (0.91)
Irritated	1.49 (0.49)	1.51 (0.52)	1.91 (0.95)
Relaxed	5.23 (0.73)	5.17 (0.86)	4.56 (1.05)
Insecure	1.30 (0.44)	1.38 (0.63)	1.99 (0.99)
Down	1.30 (0.47)	1.35 (0.64)	1.94 (1.02)
Suspicious	1.08 (0.19)	1.07 (0.31)	1.65 (1.05)
Loss of control	1.06 (0.22)	1.05 (0.20)	1.56 (1.06)
Tired	2.51 (0.95)	2.51 (1.05)	2.86 (1.13)
Pleasant thoughts	4.30 (0.68)	4.42 (0.72)	4.36 (0.91)
Active	3.65 (1.07)	3.66 (1.05)	3.58 (1.20)
Alone	0.35 (0.17)	0.37 (0.18)	0.45 (0.24)

Note. ESM, Experiences Sampling Method; S.D, standard deviation; Patients differed significantly in their means from healthy controls and relatives on all ESM measures (all $P < .05$), except for 'pleasant thoughts' and 'active'. Healthy controls and relatives did not show significant differences on ESM measures.

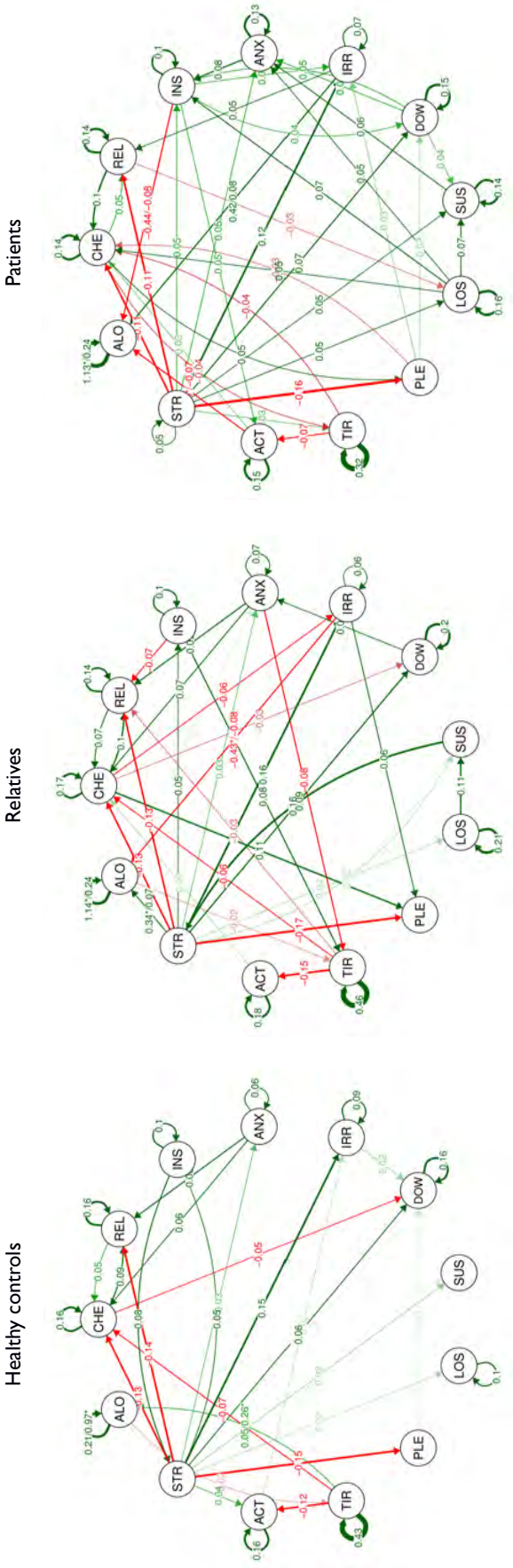

Figure 1. Graphic display of significant connections for healthy controls, first-degree relatives and patients. Arrows represent the strength of the connections between any two pairs of ESM measures (one measure at time $t-1$ and the other at time t, equal to a distance of approx. 90 min.). Solid colours represent stronger connections, the more faded the edges the weaker the connection. Connections marked with an asterisk (*) represent log-odd coefficients (corresponding linear coefficient is presented in line). CHE=cheerful, REL=relaxed, INS=insecure, ANX=anxious, IRR=irritated, DOW=down, SUS=suspicious, LOS=loss of control, PLE=pleasant thoughts, TIR=tired, ACT=active, STR=stress, ALO=alone.

Table 3. Significant path differences between controls and first-degree relatives, controls and patients, and first-degree relatives and patients.

Path	Differences					
	Controls vs. first-degree relatives		Controls vs. patients		First-degree relatives vs. patients	
	difference	P	difference	P	difference	P
$Stress_{t-1}$ → $active_t$	**0.057**	**0.025**	**0.060**	**0.009**	0.003	0.933
$Stress_{t-1}$ → $loss\ of\ control_t$	0.002	0.899	**-0.037**	**0.006**	**-0.035**	**0.018**
$Stress_{t-1}$ → $suspicious_t$	0.004	0.801	**-0.028**	**0.031**	**-0.032**	**0.026**
$Tired_{t-1}$ → $active_t$	0.032	0.305	-0.052	0.062	**-0.084**	**0.007**
$Tired_{t-1}$ → $tired_t$	-0.032	0.372	**0.103**	**0.001**	**0.136**	**0.000**
$Irritated_{t-1}$ → $alone_t$	0.405	0.152	-0.446	0.077	**-0.851**	**0.002**
$Relaxed_{t-1}$ → $cheerful_t$	-0.022	0.430	**-0.050**	**0.039**	-0.028	0.285
$Relaxed_{t-1}$ → $down_t$	0.019	0.327	**0.035**	**0.041**	0.016	0.393
$Relaxed_{t-1}$ → $loss\ of\ control_t$	-0.016	0.254	**0.026**	**0.031**	**0.041**	**0.003**
$Insecure_{t-1}$ → $down_t$	-0.031	0.275	**-0.054**	**0.033**	-0.024	0.400
$Loss\ of\ control_{t-1}$ → $irritated_t$	**-0.140**	**0.040**	-0.058	0.369	0.082	0.228
$Loss\ of\ control_{t-1}$ → $tired_t$	**-0.130**	**0.034**	-0.033	0.547	0.096	0.126
$Loss\ of\ control_{t-1}$ → $stress_t$	**-0.151**	**0.040**	-0.039	0.566	0.112	0.124
$Suspicious_{t-1}$ → $stress_t$	**-0.188**	**0.008**	-0.057	0.371	0.131	0.068
$Alone_{t-1}$ → $suspicious_t$	-0.007	0.055	**-0.008**	**0.018**	0.000	0.893

Note. Representation of significant (P<0.05) path differences between controls and first-degree relatives, controls and patients, and first-degree relatives and patients. Significant differences are presented in bold. Corresponding coefficients for above paths are presented below.

Path	Coefficients					
	Healthy controls		First-degree Relatives		Patients	
	b	P	b	P	b	P
$Stress_{t-1}$ → $active_t$	0.040	0.020	-0.018	0.398	-0.020	0.206
$Stress_{t-1}$ → $loss\ of\ control_t$	0.017	0.000	0.017	0.000	0.053	0.000
$Stress_{t-1}$ → $suspicious_t$	0.023	0.004	0.019	0.000	0.051	0.000
$Tired_{t-1}$ → $active_t$	-0.121	0.000	-0.153	0.000	-0.069	0.000
$Tired_{t-1}$ → $tired_t$	0.426	0.000	0.458	0.000	0.322	0.000
$Irritated_{t-1}$ → $alone_t$	-0.029	0.882	-0.435	0.031	0.416	0.011
$Relaxed_{t-1}$ → $cheerful_t$	0.046	0.001	0.068	0.000	0.096	0.000
$Relaxed_{t-1}$ → $down_t$	0.008	0.417	-0.011	0.412	-0.027	0.074
$Relaxed_{t-1}$ → $loss\ of\ control_t$	-0.004	0.253	0.011	0.076	-0.029	0.006
$Insecure_{t-1}$ → $down_t$	-0.013	0.425	0.017	0.433	0.041	0.021
$Loss\ of\ control_{t-1}$ → $irritated_t$	-0.083	0.070	0.057	0.349	-0.025	0.349
$Loss\ of\ control_{t-1}$ → $tired_t$	-0.053	0.343	0.077	0.277	-0.019	0.483
$Loss\ of\ control_{t-1}$ → $stress_t$	-0.053	0.425	0.099	0.281	-0.014	0.789
$Suspicious_{t-1}$ → $stress_t$	-0.032	0.498	0.156	0.048	0.025	0.466
$Alone_{t-1}$ → $suspicious_t$	-0.005	0.008	0.003	0.126	0.004	0.376

Positive experiences. In patients feeling relaxed was more strongly followed by feeling cheerful than in controls. Patients also had a stronger negative connection from tired to active than relatives. Feeling more tired one moment was associated with being less active the next moment. All 3 groups, however, showed similar self-loops of "cheerful" and "relaxed" as well as comparable connections from "active" to "cheerful" (Figure 1).

Centrality measures

The number of significant connections increased with higher risk for psychosis. The network of patients showed 49, the network of relatives 41, and the network of healthy controls 34 significant connections.

However, we did not find significant differences in average whole network connectivity (controls vs relatives: difference = 0.007, P = .106; controls vs patients: difference = 0.002, P = .457; relatives vs patients: difference = 0.005, P = .349). Also, the networks did not differ significantly in average internode connectivity (controls vs relatives: difference = 0.007, P = .158; controls vs patients: difference = 0.001, P = .564; relatives vs patients: difference = 0.005, P = .383), nor did they differ in average selfloop strength (controls vs relatives: difference = 0.018, P = .223; controls vs patients: difference = 0.010, P = .471; relatives vs patients: difference = 0.008, P = .567).

Minor daily stress. In all 3 networks, "stress" was the most central node in terms of outstrength when compared to the remaining nodes of the network, with an outstrength at least twice as large (Table 4). In controls and relatives "stress" had the highest betweenness centrality. The outstrength of "stress" exceeded the instrength in all 3 groups. The total outstrength of "stress" was similar for all 3 groups, while the instrength was highest in relatives.

Negative experiences and symptomatology. In controls and relatives, "loss of control" showed overall high levels of outstrength in comparison to other nodes. There was a positive dose-response association of risk for psychosis and instrength of "anxious," "suspicious" and "loss of control". "Down" was the most central node in terms of betweenness centrality in controls and relatives, but not in patients. In relatives and patients "alone" showed a much higher instrength than in controls.

Positive experiences. In all 3 groups, "cheerful," "relaxed," and "pleasant thoughts" showed high levels of instrength. Also, the level of instrength of these items exceeded the level of outstrength. There was a dose response association of increasing risk for psychosis with a lower instrength on "active". "Cheerful" was among the nodes with the highest betweenness centrality in all 3 groups.

Table 4. Centrality measures for each group

	Stress	Cheerful	Relaxed	Insecure	Anxious	Irritated	Down	Suspicious	Loss of control	Pleasant	Tired	Active	Alone
Controls													
Instrength	0.33	0.45	0.46	0.26	0.15	0.4	0.26	0.12	0.07	0.41	0.21	0.47	0.32
Outstrength	0.83	0.37	0.15	0.27	0.44	0.16	0.27	0.28	0.57	0.12	0.30	0.08	0.06
Betweenness	48	45	0	7	1	5	19	0	0	0	11	0	1
Self-loop	0	0.16	0.16	0.1	0.06	0.09	0.16	0.06	0.1	0.01	0.43	0.16	0.21
First-degree relatives													
Instrength	0.42	0.47	0.51	0.23	0.22	0.38	0.30	0.17	0.12	0.58	0.49	0.42	0.62
Outstrength	0.90	0.51	0.26	0.30	0.42	0.28	0.36	0.73	0.46	0.12	0.36	0.14	0.08
Betweenness	52	29	3	0	4	1	11	2	1	0	20	0	10
Self-loop	0.02	0.17	0.14	0.1	0.07	0.06	0.2	0.06	0.21	0.01	0.46	0.18	0.24
Patients													
Instrength	0.18	0.44	0.38	0.34	0.29	0.33	0.30	0.25	0.20	0.43	0.16	0.25	0.62
Outstrength	0.84	0.30	0.32	0.31	0.35	0.26	0.36	0.36	0.39	0.14	0.27	0.17	0.05
Betweenness	24	40	13	7	1	3	4	1	2	0	11	0	0
Self-loop	0.05	0.14	0.14	0.1	0.13	0.07	0.15	0.14	0.16	-0.01	0.32	0.15	0.24

DISCUSSION

This is the first study to use a dynamic network approach to examine the differences in moment-to-moment timelagged associations between minor daily stress, momentary affect/thoughts, psychotic experiences, and other potentially relevant daily life contexts in individuals belonging to 3 samples with varying risk for psychosis.

We found that groups with a higher risk for psychosis had networks in which more nodes were strongly connected with each other, as can be concluded from the number of significant network connections in these 3 groups. We further found that experiencing higher levels of minor daily stress led to a stronger increase in feeling "suspicious" and "loss of control" in patients compared to controls and relatives. Finally, the higher the risk for psychosis the more variables "anxious," "suspicious" and "loss of control" were likely to be activated by other network nodes.

Affective pathway to psychosis

The current findings provide further insight into the complex link between minor daily stress, affect, and psychotic experiences. Based on previous findings, showing that a higher risk for psychosis is associated with alterations in affect [10], increased stress-sensitivity [38], and affective dysregulation, an "affective pathway" to psychosis had been postulated [39]. The dynamic networks in the current study support this theory as the findings suggest that minor daily stress and psychotic experiences may be linked through a multitude of temporal network connections that pass through nodes representing common, frequently experienced, affective states. We observed that in all 3 groups daily stress has a central position and connects directly to many other mental states and contextual factors. Due to this position, changes in minor daily stress may go hand in hand with changes in the transfer between numerous other mental states. The 3 networks showed similar numbers of direct connections of minor daily stress with other mental states. However, the actual impact of minor daily stress on other nodes, including psychotic experiences, may be stronger in people with risk for psychosis as a higher number of connections may spread the impact of stress in the network further.

The theory regarding the affective pathway to psychosis suggests that minor daily stress impacts on psychotic experiences via feelings of anxiety [12] and negative affect [13,38,40]. In the network of patients, connections suggested that the negative affect item "down" had an intermediary position between minor daily stress, psychotic experiences, and other mental

states (such as "insecure" and "anxious"). Anxiety was not directly connected to psychotic experiences but based on the reported network connections that link anxiety with other negative affective experiences we can hypothesize that anxiety may be connected to psychotic experiences through moods such as "down" and "insecure".

This suggests that subclinical psychotic experiences may be activated by changes in affective states and that this may happen much more easily in some individuals than in others, depending on differences in network structure. It also generates the hypothesis that stress may not only directly influence psychotic experiences, but that stress-induced alterations in other nodes—such as affect states—may play a crucial role in propagating the impact of stress to psychotic experiences in those people at risk.

Network connectivity and risk

The finding that the number of significant network connections increased with risk for psychosis is in line with theories on the relationship between network connectivity and risk in the field of psychiatry. It may support the notion that the complex dynamical system theory can be applied to mental disorders. In complex dynamical system theory, networks with a large number of inter-node connections are hypothesized to be rather rigid and less resilient to effects of stressors [41,42]. This makes sense as in such a strongly connected network a single trigger (stressor) that activates a first node of the network will easily cause a cascade of changes in the system as the initial impact is easily transferred to other nodes in the network [20]. Recent empirical studies add to this hypothesis [22,43] by showing that higher levels of mental state network connectivity were indeed associated with higher levels of (risk for) psychopathology.

Our findings may therefore be compatible with the idea that vulnerability arises because mental states "infect" each other and to a stronger extent in individuals at risk for psychosis. However, we did not find a significant difference in the strength of the overall network connections between the 3 groups; only in the number.

Methodological issues

First, differing group variances in network nodes could create a problem when comparing the network connectivity between groups. As expected, means did not differ between relatives and controls. It therefore seems unlikely that differences in connection strengths between these

latter groups could be attributed to differences in variances. Some means, though, were higher in the patient group than in the other groups. This was unavoidable as patients score, of course, higher on certain symptom measures.

Permutation procedures were necessary to obtain reliable coefficients in these complex analyses. However, CIs are not provided in the current article as it is computationally extremely demanding to obtain those when using permutation procedures. Also, results should be interpreted with caution as we cannot exclude the presence of type I or II errors.

While it is an important strength that the current study used data from a large pooled dataset with ESM measurements of a total of 654 participants (total of 28 466 filled in time points), combining data from 6 different studies may also come with possible disadvantages. First, the above described variable selection only allowed for 2 psychosis items to be included in the current study. Second, medication status was not available for all included studies, and therefore, we cannot exclude the possibility that use of anti-psychotics obscured some of the network dynamics of patients. This would have likely resulted in a too conservative estimation of total network connectivity in the patient group.

Last, the current study used group average estimates. A natural progression of this work is to use the data to create personalized networks based on data of individual patients. This requires datasets with even more measurements per individual. Such personalized networks are an opportunity to derive personalized precision that may help in targeting specific individual needs.

CONCLUSION

Evidence that psychopathology can be described as a complex network of interacting nodes is accumulating. The current study provides novel support for this idea since we found a dose-response association between the number of significant network connections and risk for psychosis. Clinical interventions able to specifically target mental state cascades and reduce connection strengths in the network may prove valuable.

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SUPPLEMENTARY MATERIALS

Table S1. Overview of in- and exclusion criteria of merged studies

Study	N	
PREVENT [29]	N=26 Healthy controls	Inclusion criteria controls: (i) age between 18 and 45 Exclusion criteria controls: (i) current axis I disorder as assessed with the Structured Clinical Interview for DSM-IV [44] (ii) family history of psychotic disorder
MAPS [10]	N=139 Healthy controls (n=49); First-degree relative (n=47); Psychotic disorder (n=43)	Inclusion criteria for all participants: (i) age between 18 and 55 (ii) sufficient command of the Dutch language Exclusion criteria controls: (i) current use of psychotropic medication (ii) family or personal history of psychotic symptoms Inclusion criteria relatives: (iii) first-degree relatives with a lifetime occurrence of psychotic symptoms Exclusion criteria relatives: (i) lifetime occurrence of psychotic symptoms Inclusion criteria patients: (i) normal physical examination results (ii) lifetime occurrence of psychotic symptoms as assessed with the Life Chart , the Brief Psychiatric Rating Scale, the Positive and Negative Syndrome Scale (PANSS) [45], and the Operational Criteria Checklist for Psychotic illness (OPCRIT) [46] Exclusion criteria patients: (i) endocrine, cardiovascular, or brain disease (ii) excessive use of alcohol (≥5 standard units per day) (iii) weekly use of illicit drugs (iv) history of head injury with loss of consciousness (v) need for inpatient care
GROUP [26]	N=219 Healthy controls (n=83); First-degree relative (n=70); Psychotic disorder (n=66)	Inclusion criteria for all participants: (i) age between 16 and 55 (ii) sufficient command of the Dutch language Exclusion criteria controls: (i) first-degree relative with a psychotic disorder as assessed with the Family Interview for Genetic Studies [47] Inclusion criteria relatives: (ii) first-degree relatives with a lifetime occurrence of psychotic symptoms Exclusion criteria relatives: (i) use of steroid medication (ii) current axis I disorder (iii) lifetime history of psychotic disorder Inclusion criteria patients: (iii) DSM-IV diagnosis of nonaffective psychotic disorder as assessed with the Comprehensive Assessment of Symptoms and History [48] or Schedules for Clinical Assessment for Neuropsychiatry version 2.1 [49] Exclusion criteria patients: (i) brain disease (ii) history of head injury with loss of consciousness (iii) substance-related psychosis (iv) psychosis with a known organic cause
STRIP [26]	N=138 Healthy controls (n=48); First-degree relative (n=48); Psychotic disorder (n=42)	

(continued) **Table S1.** Overview of in- and exclusion criteria of merged studies

Study	N	
ZAPP [28,50]	N=113 Healthy controls (n=38); Psychotic disorder (n=75)	Inclusion criteria for all participants: (i) age between 18 and 65 (ii) sufficient command of the Dutch language Inclusion criteria controls: (i) average range score on symptom dimensions (between the 45th and 55th percentile) of the Community Assessment of Psychic Experiences (CAPE) [51] Exclusion criteria controls: (i) high scores on paranoid items (90th percentile) on the CAPE Inclusion criteria patients: (i) ICD-10 diagnosis of psychotic disorder as assessed with OPCRIT computer program [46], PANSS [45], and the Life Chart [52] (ii) current paranoid and/or positive psychotic symptoms or remitted psychotic symptoms as assessed with the PANSS [45] (items P1, P3, P5, P6, and G9)
Aripiprazole [27]	N=19 Psychotic disorder	Inclusion criteria patients: (i) age between 18 and 65 (ii) sufficient command of the Dutch language (iii) DSM-IV diagnosis of schizophrenia as generated with the OPCRIT computer program [46] (iv) insufficient therapeutic response to antipsychotic treatment (v) current use of a traditional dopamine antagonist antipsychotic Exclusion criteria patients: (i) hospitalization within 2 month prior to study (ii) endocrine, cardiovascular, or brain disease; history of neuroleptic malignant syndrome (iii) pregnancy or lactation (in women)

Text S1.

PERMUTATION PROCEDURE

Below we describe the permutation procedure that was used in the analyses of the data in the current study. This procedure was used to identify significant network connections, for the comparison of specific network paths of group networks (healthy controls vs. first-degree relatives, healthy controls vs. patients, first-degree relatives vs. patients) as well as for the comparison of average connectivity of group networks. Text files with the corresponding R code can also be found in the supplementary materials at schizophreniabulletin.oxford journals.org.

Significant network connections

A model was fitted with the actual data and the regression coefficients were saved. Then, the outcome variable was randomly reshuffled within subjects and the model was fitted with the reshuffled data. By doing this, clustering of assessments within subjects and the correlation between predictor variables is preserved, while any associations between the predictors (at time t-1) and the outcome variable (at time t) is broken. By repeating this procedure 10,000 times, we obtained the permutation distributions of the regression coefficients under the null hypothesis. Finally, the observed coefficients as obtained from the model fitted with the actual data were compared with the permutation distributions of the estimated coefficients under the null hypothesis. For each coefficient, the (one-sided) p-value is then computed based on the proportion of times that the coefficient under the permutation distribution is as extreme or more extreme than the actually observed value (i.e., based on the area in the right or left tail of the permutation distribution, depending on whether the coefficient is positive or negative). The two-sided p-values were then obtained by doubling those proportions. Coefficients with a (two-sided) p-value below .05 were considered statistically significant. The R code for this test can be found supplementary materials at schizophrenia bulletin.oxfordjournals.org (R file name: 'R code significant connections').

Specific path differences

Models were again fitted with the actual data within each group. Then, group differences in the regression coefficients were calculated as follows: Coefficients of relatives were subtracted from coefficients of healthy controls, coefficients of patients were subtracted from coefficients

of relatives, and coefficients of patients were subtracted from coefficients of healthy controls. In the next step, group labels (healthy controls, relatives, and psychotic patients) were randomly reshuffled between subjects and models were fitted. Each time, group differences for each coefficient were computed. This was repeated a total of 10,000 times, leading to the permutation distributions of the size of the group differences under the null hypothesis. In order to determine the level of significance of the group differences, the size of the observed group differences for each coefficient as observed in the actual data was compared to the permutation distributions of the difference scores. We again computed (two-sided) p-values as twice the proportion of times that a group difference for a particular path under the permuted data was as large or larger than the one observed with the actual data. The results of this analysis therefore give an overview of the connections that differ significantly ($p < .05$) between groups as well as the difference in strengths of those connections. The R code for this test can be found in the supplementary materials at schizophreniabulletin.oxfordjournals.org (R file name: 'R code specific paths differences').

Differences in average network connectivity

Differences in average whole network connectivity, average internode connectivity, and average self-loop strength between the three groups were tested. Average whole network connectivity is computed based on all absolute network connections in a network (e.g., in a directed network with 3 nodes, there are a total of 9 network connections, i.e., 3 self-loops and 6 connections between nodes). Average internode connectivity is computed based on all absolute connection strengths between nodes and average self-loop strength is computed based on all absolute connections that nodes have with themselves.

Differences in these averages were then calculated; comparing healthy controls with relatives, relatives with patients, and healthy controls with patients. The permutation-based p-values are then computed as described above by permuting the group variable. The R code for these tests can be found elsewhere in the supplementary materials at schizophreniabulletin.oxfordjournals.org (R file name: 'R code network connectivity differences').

Computational details

Due to the complexity of the permutation testing procedures (requiring repeated fits of the mixed-effects regression models), the permutation-based tests were conducted on a cluster computer with 128 cores (8 AMD Opteron Processor 6276 CPUs each with 16 cores) and 512GB of RAM using parallel/multicore processing. Total computation time for the analyses was approximately 3000 core hours.

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CHAPTER FOUR

Modeling the interplay between psychological processes and adverse, stressful contexts and experiences in pathways to psychosis: an experience sampling study

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ABSTRACT

Several integrated models of psychosis have implicated adverse, stressful contexts and experiences, and affective and cognitive processes in the onset of psychosis. In these models, the effects of stress are posited to contribute to the development of psychotic experiences via pathways through affective disturbance, cognitive biases, and anomalous experiences. However, attempts to systematically test comprehensive models of these pathways remain sparse. Using the Experience Sampling Method in 51 individuals with first-episode psychosis (FEP), 46 individuals with an at-risk mental state (ARMS) for psychosis, and 53 controls, we investigated how stress, enhanced threat anticipation, and experiences of aberrant salience combine to increase the intensity of psychotic experiences. We fitted multilevel moderated mediation models to investigate indirect effects across these groups. We found that the effects of stress on psychotic experiences were mediated via pathways through affective disturbance in all 3 groups. The effect of stress on psychotic experiences was mediated by threat anticipation in FEP individuals and controls but not in ARMS individuals. There was only weak evidence of mediation via aberrant salience. However, aberrant salience retained a substantial direct effect on psychotic experiences, independently of stress, in all 3 groups. Our findings provide novel insights on the role of affective disturbance and threat anticipation in pathways through which stress impacts on the formation of psychotic experiences across different stages of early psychosis in daily life.

INTRODUCTION

There is now strong evidence that subclinical psychotic experiences are prevalent in the general population and phenomenologically and temporally continuous with clinical symptoms in psychotic disorders [1,2]. A number of psychological mechanisms have been implicated in the development of psychotic experiences (PE) across different stages of subclinical and clinical psychosis. Several integrated models of psychosis implicate adverse, stressful contexts and experiences, as well as affective and cognitive processes in the onset of psychosis [3-7]. These models propose that, in individuals with an increased premorbid vulnerability of biopsychosocial origin [4], the effects of stress on the development of PE are (in part) mediated through affective disturbances, cognitive biases, and anomalous experiences [3-5]. Unravelling the complex interplay between stress, affective and cognitive processes as basis for targeting these at an early stage, with the goal of preventing onset and achieving better outcomes of psychosis, is of public health importance [8-12].

Recently, the interplay between affective disturbances and stressful contexts and experiences in daily life (including stressful events, activities, and social situations) that may be underlying the development of PE has received much attention [12-16]. It has been repeatedly suggested that emotional reactivity to such routine daily hassles and minor socioenvironmental stressors may be an important mechanism [5,13]. Previous studies have found elevated emotional reactivity to minor stressors in individuals with psychotic disorder and increased familial or psychometric risk (i.e., a high score of sub-clinical PE) [12,16]. Similarly, a recent study reported elevated emotional reactivity in response to minor stressors in individuals with an at-risk mental state (ARMS) [17]. Previous research further suggest some degree of specificity, for example, of elevated emotional reactivity to social but not event-related stress as a putative mechanism underlying the association between childhood trauma and psychosis [18]. Affective disturbances, more generally, have been shown to be linked to PE across different stages along the psychosis continuum [19-25].

Cognitive models of psychosis provide a detailed specification of the cognitive processes associated with emotional responses to stress and consider cognitive biases, such as a hypervigilance for threat, to be involved in stress reactivity [4,26]. First, stressful experiences per se may alter cognitive interpretation and bias individuals toward hypervigilance for threat [3,12]. Further, cognitive models ascribe a prominent role to (stress-induced) affective disturbances, such as symptoms of anxiety, which are considered to drive individuals

into enhanced anticipation of threat [23,27]; enhanced threat anticipation, in turn, has been shown to be linked to the formation of PE [5,21,23,28].

Stress-induced emotional and cognitive changes may result in anomalous experiences such as experiences of aberrant novelty and salience in vulnerable individuals [4,29]. Cognitive models further posit, based on neurobiological approaches, that these experiences are closely linked to a sensitized dopaminergic system (secondary to variant genes, early neurological insults, and exposure to social adversity) [3,4,30], which in the event of further stressful experiences, even if minor, will be followed by dysregulated dopamine release, leading to the aberrant assignment of salience to otherwise irrelevant stimuli. As individuals seek to explain these experiences, biased cognitive processes (such as enhanced threat anticipation) then result in the appraisal of anomalous experiences as uncontrollable, threatening, externally caused or attributable, which, ultimately, lead to abnormal beliefs and hallucinations becoming symptomatic[3,4]. In this regard, PE may be seen as an attempt to make sense of these aberrant salient stimuli [3,30].

From the above, it becomes apparent that much attention has been paid to the association between stress and PE across different stages of psychosis. Several models have proposed that the formation of PE is complex and likely to be the result of the interplay between stress, cognitive, and affective processes. However, only a small number of studies have directly tested these specific pathways. Also, no study that we are aware of has tested these pathways in individuals' daily lives. However, in order to elucidate the multi-factorial nature of psychotic disorders further, the pathways to psychosis, as proposed by prior work, should be tested in one comprehensive model. The primary aim of the current study therefore was to examine how stressful contexts and experiences (event-related, activity-related, and social stress), affective disturbance (i.e., negative affect), cognitive bias (i.e., enhanced threat anticipation), and anomalous experiences (i.e., aberrant salience) combine to increase the intensity of PE in daily life. We used the Experience Sampling Method (ESM) [31], a structured diary technique, in a sample of individuals with a first-episode psychosis (FEP), individuals with ARMS, and controls to test the following hypotheses (Figure 1): within each group, (1) stressful contexts and experiences in daily life increase the intensity of PE via pathways through affective disturbance, enhanced threat anticipation, and aberrant salience; (2) affective disturbance increases the intensity of PE through enhanced threat anticipation and aberrant salience; and (3) enhanced threat anticipation increases intensity of PE through experiences of aberrant

salience. We furthermore hypothesized that the indirect effects of stressful contexts and experiences on PE through affective disturbance, anomalous experiences, and cognitive bias are greater in FEP than in controls, ARMS than in controls, and FEP than in ARMS.

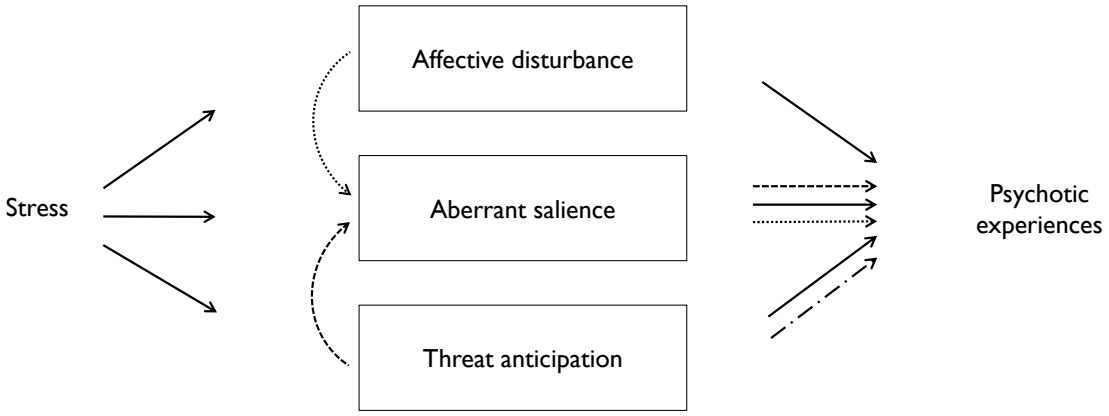

Figure 1. Schematic representation of pathways tested within each group: The following hypotheses were tested within each group: (1) stressful contexts and experiences in daily life increase the intensity of psychotic experiences through their impact on affective disturbance, enhanced threat anticipation, and aberrant salience (⟶); (2) affective disturbance increases the intensity of psychotic experiences through enhanced threat anticipation (—·—·→) and aberrant salience (·····→); and (3) enhanced threat anticipation increases intensity of psychotic experiences through their impact on experiences of aberrant salience (--------→), while controlling for adjusted for age, gender, ethnicity, level of education, employment status, area-related stress and outsider status as potential confounders.

METHODS

Sample

A sample of FEP individuals, ARMS individuals, and controls with no history of psychosis was recruited as part of the Childhood Adversity and Psychosis study and EU-GEI [32]. FEP individuals were recruited from mental health services in South-East London, UK. Inclusion criteria were: aged 18–64; resident in defined catchment area; diagnosis of FEP (ICD-10, F20-F29, F30-F33) [33]; command of the English language. Exclusion criteria were: transient psychotic symptoms resulting from intoxication; psychotic symptoms precipitated by an organic cause. Individuals with an ARMS were recruited from Outreach and Support in South London [34], the West London Mental Health NHS Trust, and a community survey of General Practitioner (GP) practices. Inclusion criteria were: aged 18–35; presence of an ARMS as assessed with the CAARMS [32,35]; command of the English language. Exclusion criteria were: prior experience of a psychotic episode for more than 1 week as determined by the CAARMS

and Structured Clinical Interview for DSM Disorders [36]; previous treatment with an antipsychotic for a psychotic episode; IQ <60 measured with an adapted version of the WAIS [32,37]. Controls were recruited through GP lists and the national postal address file. Inclusion criteria were: aged 18–64; resident within the same areas as FEP individuals, command of the English language. Exclusion criteria were: personal/family history of psychosis, presence of PE as measured with the Psychosis Screening Questionnaire; and presence of an ARMS based on the CAARMS or the Schizophrenia Proneness Instrument–Adult version.

Data collection

Basic sample characteristics. Data on basic sample characteristics were collected with the modified MRC sociodemographic schedule. ICD-10 diagnosis of FEP was determined using the OPCRIT system. Presence of an ARMS was based on the CAARMS and the SCID.

ESM measures. We used the ESM, a structured diary technique, to collect data on stress, negative affect, aberrant salience, threat anticipation, and PE. Using a time-based design with stratified random sampling, this method allows for assessing moment-to-moment fluctuations in daily life. Feasibility, reliability, and validity of this method in individuals with a FEP and individuals with an ARMS has been demonstrated recently [16,17,31]. Further information on the ESM procedure and variables are presented in Table 1.

Table 1. ESM procedure[a] and measures[b] of stress, negative affect, aberrant salience, threat anticipation, and psychotic experiences

Domain	[b]ESM measures
Stress	
Event-related	Event-related stress was assessed with 1 item in which participants rated the most important event since the last beep on a 7-point Likert scale (-3 = "very unpleasant" to 3= "very pleasant). The item was reverse coded with higher ratings indicating higher levels of stress (a rating of -3 coded as 7 and a rating of 3 coded as 1).
Activity-related	The activity-related stress scale consisted of 3 items ("This activity is difficult for me", "I would prefer doing something else", "This is a pleasant activity" (reversed)) rated on a 7-point Likert (1= "not at all" to 7= "very much").
Social	Social stress was measured with a mean of 2 items. The first item asked participants to indicate "Who am I with?" (e.g., partner, family, friends, colleagues, acquaintances, strangers, others, nobody). The second item asked participants to rate their current social context on a 7-point Likert scale (1= "not at all" to 7= "very much") with 2 questions: 1) "I would prefer to be alone [if with someone]/I would prefer to have company [if alone]"; 2) "I find being with these people pleasant [if with someone]/it pleasant to be alone [if alone]" (reversed).
Negative affect	The negative affect scale consisted of 5 items asking participants to rate the extent to which they felt down, lonely, anxious, insecure, and annoyed on a 7-point Likert scale (1= "not at all" to 7= "very much").
Aberrant salience	Aberrant salience was assessed with 3 items ("Everything grabs my attention right now", "Everything seems to have meaning right now", and "I notice things that I haven't noticed before.") that were rated on a 7-point Likert scale (1= "not at all" to 7= "very much").
Threat anticipation	Threat anticipation was measured by asking participants to think about what might happen in the next few hours and rate the item "I think that something unpleasant will happen" on a 7-point Likert scale (1= "not at all" to 7= "very much").
Psychotic experiences	We used the ESM psychosis measure by Myin-Germeys et al., which consists of 8 items covering different aspects of mental states that are directly associated with psychotic experiences ("I feel paranoid", "I feel unreal" , "I hear things that aren't really there", "I see things that aren't really there", "I can't get these thoughts out of my head", "My thoughts are influenced by others", "It's hard to express my thoughts in words", and "I feel like I am losing control"). Participants were asked to rate the intensity of psychotic experiences on a 7-point Likert scale (1= "not at all" to 7= "very much"). These items have been reported to show high levels of internal consistency in previous studies (Cronbach's alpha=0.80) [38] as well as in the current study (Cronbach's α=0.90) [17]. They have been further shown to have good convergent validity with interviewer-rated measures of psychosis (r=0.45, P<0.001) the PANSS (r=0.45; P<0.001) [38] as well as good concurrent validity with negative affect (r=0.68, P<0.001) [17].

[a]*ESM procedure*: Over a period of 6 consecutive days, participants were prompted by the PsyMate "beep" signal to complete the ESM questionnaire 10 times a day at random moments within set blocks of time. Participants were provided with detailed instructions and a practice session as training in the use of the PsyMate during an initial briefing period. Participants were explained to stop their activity and respond to the above items when prompted by the beep signal as part of a comprehensive diary questionnaire assessing activities, feelings, thoughts, behaviors, social situations, and neighborhood surroundings in daily life. The assessment period started on any day of the week as selected by the participant, and the ESM questionnaire was available up to 10 minutes after the beep signal. In order to maximize the number of observations per participant, participants were contacted at least once during the assessment period to assess instruction adherence, identify any concerns associated with the method, and help participants with any problems in completing the ESM questionnaire. The participants' reactivity to and compliance with the method was assessed in a debriefing session at the end of the assessment period. In order to be included in the analysis, participants had to provide valid responses to at least one-third of the beep signals.

Statistical analysis

Multilevel moderated mediation models were fitted in MPlus, Version 7 [39], with multiple observations (level 1) being treated as nested within subjects (level 2). A detailed description of these models is included in the online supplementary methods. The total effect of each stress variable (event-related, activity-related, and social stress) in daily life (level 1) on intensity of PE (level 1) was apportioned into direct and indirect (or, synonymously, mediating) effects through negative affect, aberrant salience, and enhanced threat anticipation (level 1) using the product of coefficients strategy. Group (FEP, ARMS, controls) was used as the moderator variable (level 2) of direct and conditional indirect which allowed us to test whether conditional indirect effects were greater in (1) FEP than in controls, (2) ARMS than in controls, and (3) FEP than in ARMS [40-42]. We first fitted separate simple moderated multilevel mediation models: (1) with one independent variable for event-related stress, activity-related stress, or social stress, one mediator variable for negative affect, threat anticipation or aberrant salience, and one outcome variable for PE; (2) with one independent variable for negative affect, one mediator variable for threat anticipation or aberrant salience, and one outcome variable for PE; and (3) with enhanced threat anticipation as independent variable, aberrant salience as mediator variable, and PE as outcome variable. Based on evidence of mediation in these models, we next fitted a multiple multilevel moderated mediation model to examine the relative contribution of direct effects and specific indirect effects via these pathways simultaneously [43]. All analyses were adjusted for age, gender, ethnicity, level of education, employment status as potential confounders.

RESULTS

Basic sample characteristics

ESM data were collected for 165 participants (59 FEP, 51 ARMS, 55 controls). Fifteen participants were excluded from the analysis due to an insufficient number of valid responses (<19), resulting in a sample of 150 participants (51 FEP, 46 ARMS, 53 controls). The control group was slightly older and included more women than the FEP group (supplementary Table S1). ARMS and FEP individuals showed higher levels of stress, negative affect, aberrant salience, threat anticipation, and PE compared to controls (supplementary Table S2). The magnitude of correlations between stress, negative affect, aberrant salience, threat anticipation, and PE was moderate to small (supplementary Table S3).

Simple moderated mediation models

To examine pathways from stress to PE via negative affect, aberrant salience, and threat anticipation, we first fitted simple multilevel moderated mediation models (Table 2). Indirect effects of all markers of stress on intensity of PE via negative affect were significant at conventional levels (P< .05) in all groups. This indicated that an increase of stress was associated with higher levels of negative affect, which, in turn, was associated with more intense PE. The indirect effect of event- and activity-related stress was greater in ARMS than in controls (P< .05).

Models including pathways from stress to PE via threat anticipation showed that, in all 3 groups, the effects of event-related, activity-related, and social stress on PE were mediated via enhanced threat anticipation, with a similar magnitude of indirect effects across groups (Table 2).

When we examined models of stress, aberrant salience, and PE, there was a negative indirect effect of event-related stress on PE via aberrant salience in FEP individuals (B= −0.015, P= .011). When we inspected individual paths of this negative indirect effect, this indicated that higher levels of event-related stress were associated with less intense experiences of aberrant salience (B= −0.079,P= .010), which was, in turn, associated with less intense PE (B= 0.190, P< .001) in FEP individuals.

Turning to models of affective disturbance, threat anticipation, and PE (Table 2), some of the effects of affective disturbance on more intense PE were mediated via enhanced threat anticipation, independently of stress, in FEP individuals, controls and, at trend level, ARMS individuals. There was no evidence of an indirect effect of affective disturbance on PE via aberrant salience in any of the groups. Inspecting, finally, the model of threat anticipation, aberrant salience, and PE, the indirect effects of threat anticipation on PE via aberrant salience fell short of statistical significance in all 3 groups (Table 2).

Final multiple moderated mediation model

When we probed findings from simple moderated mediation models further, and examined indirect effects of stress, affective disturbance, threat anticipation, and aberrant salience in the multiple multilevel moderated mediation model, there was evidence that the indirect effects of all markers of stress on PE via more intense negative affect remained significant in all (all P < .049; Table 3, supplementary Figure S1). The relative contribution of this indirect effect, from

stress to PE through negative affect, was larger than the contribution of other indirect pathways. This was especially apparent in pathways from activity-related stress to PE, in which the total and total indirect effects were mostly accounted for by indirect effects through negative affect. The specific indirect effect from activity-related stress to PE via negative affect was significantly greater in ARMS than controls (B= 0.018, P= .039) and, at trend level, in FEP individuals than controls (B= 0.017, P= .072).

Turning to pathways from stress via threat anticipation to more intense PE, the indirect effects of activity-related stress via enhanced threat anticipation remained significant in FEP individuals (B= 0.011, P< .001) and controls (B= 0.005, P= .004), independently of pathways via negative affect, but was attenuated and ceased to be statistically significant in ARMS individuals. Further, there was evidence in FEP individuals and controls that some of the effects of activity-related and social stress were mediated via negative affect followed by threat anticipation and, then, PE. While the indirect effect of event-related stress on PE via aberrant salience remained significant in FEP individuals (B= −0.012, P= .009), there was strong evidence of a direct effect of aberrant salience on more intense PE in all three groups (independent of all other direct and indirect effects).

The indirect effect of negative affect on PE via threat anticipation remained significant, independently of the effects of stress, in FEP individuals and controls in the multiple mediation model. However, we found no significant indirect effects of affective disturbance and threat anticipation via aberrant salience.

Table 2. Total, direct, and conditional indirect effects of best fitting (simple) multilevel moderated mediation models of stress, negative affect, threat anticipation, aberrant salience, and psychotic experiences[a]

	FEP		ARMS		Controls	
	adj. B (95% CI)	P	adj. B (95% CI)	P	adj. B (95% CI)	P
Pathways via affective disturbance						
Event-related stress, negative affect, psychotic experiences						
Direct effect (Event-related stress → psychotic experiences)	0.007 (-0.018 – 0.033)	0.558	-0.002 (-0.037 – 0.032)	0.900	0.002 (-0.013 – 0.018)	0.789
Indirect effect[b] (Event-related stress → negative affect → psychotic experiences)	**0.035 (0.011 – 0.065)**	**0.011**	**0.053 (0.035 – 0.074)**	**<0.001**	**0.026 (0.015 – 0.039)**	**<0.001**
Total effect	0.042 (0.002 – 0.083)	0.040	0.050 (0.016 – 0.085)	0.005	0.028 (0.005 – 0.050)	0.016
Activity-related stress, negative affect, and psychotic experiences						
Direct effect (Activity-related stress → psychotic experiences)	0.053 (0.027 – 0.079)	<0.001	0.061 (0.028 – 0.093)	<0.001	0.015 (-0.008 – 0.037)	0.198
Indirect effect[b] (Activity-related stress → negative affect → psychotic experiences)	**0.085 (0.055 – 0.122)**	**<0.001**	**0.100 (0.066 – 0.138)**	**<0.001**	**0.055 (0.037 – 0.077)**	**<0.001**
Total effect	0.138 (0.097 – 0.180)	<0.001	0.161 (0.116 – 0.206)	<0.001	0.070 (0.034 – 0.106)	<0.001
Social stress, negative affect, and psychotic experiences						
Direct effect (Social stress → psychotic experiences)	-0.017 (-0.046 – 0.013)	0.262	0.024 (0.001 – 0.046)	0.039	0.012 (-0.005 – 0.029)	0.155
Indirect effect[b] (Social stress → negative affect → psychotic experiences)	**0.052 (0.029 – 0.079)**	**<0.001**	**0.070 (0.044 – 0.100)**	**<0.001**	**0.048 (0.031 – 0.068)**	**<0.001**
Total effect	0.035 (-0.009 – 0.078)	0.115	0.094 (0.060 – 0.127)	<0.001	0.060 (0.030 – 0.089)	<0.001
Pathways via aberrant salience						
Event-related stress, aberrant salience, psychotic experiences						
Direct effect (Event-related stress → psychotic experiences)	0.058 (0.020 – 0.095)	0.003	0.055 (0.023 – 0.087)	<0.001	0.030 (0.007 – 0.053)	0.010
Indirect effect[b] (Event-related stress → aberrant salience → psychotic experiences)	**-0.015 (-0.027 – -0.004)**	**0.011**	-0.005 (-0.017 – 0.004)	0.363	-0.002 (-0.006 – 0.002)	0.363
Total effect	0.043 (0.002 – 0.083)	0.038	0.050 (0.015 – 0.085)	0.005	0.028 (0.005 – 0.050)	0.015
Activity-related stress, aberrant salience, psychotic experiences‡	—		—		—	

Table 2. *(continued)*

	FEP		ARMS		Controls	
	adj. B (95% CI)	P	adj. B (95% CI)	P	adj. B (95% CI)	P
Direct effect (Social stress → psychotic experiences)	0.038 (-0.004 – 0.080)	0.075	0.094 (0.064 – 0.124)	<0.001	0.061 (0.033 – 0.088)	<0.001
Indirect effect[b] (Social stress → aberrant salience → psychotic experiences)	-0.003 (-0.015 – 0.008)	0.541	-0.001 (-0.011 – 0.013)	0.891	-0.001 (-0.005 – 0.006)	0.793
Total effect	0.035 (-0.009 – 0.078)	0.115	0.094 (0.060 – 0.127)	<0.001	0.060 (0.030 – 0.089)	<0.001
Negative affect, aberrant salience, psychotic experiences						
Direct effect (Negative affect → psychotic experiences)						
Indirect effect[b] (Negative affect→ aberrant salience → psychotic experiences)	0.026 (-0.001 – 0.046)	0.095	0.017 (-0.012 – 0.049)	0.443	0.017 (-0.004 – 0.030)	0.220
Total effect	0.187 (0.114 – 0.346)	<0.001	0.237 (0.128 – 0.346)	<0.001	0.173 (0.096 – 0.251)	<0.001
Threat anticipation, aberrant salience, psychotic experiences						
Direct effect (Threat anticipation → psychotic experiences)	0.144 (0.092 – 0.196)	<0.001	0.117 (0.073 – 0.161)	<0.001	0.091 (0.058 – 0.124)	<0.001
Indirect effect[b] (Threat anticipation → aberrant salience → psychotic experiences)	0.004 (-0.008 – 0.022)	0.563	0.002 (-0.009 – 0.017)	0.813	0.008 (0.000 – 0.021)	0.124
Total effect	0.148 (0.089 – 0.208)	<0.001	0.119 (0.070 – 0.167)	<0.001	0.099 (0.062 – 0.137)	<0.001
Pathways via threat anticipation						
Event-related stress, threat anticipation, psychotic experiences						
Direct effect (Event-related stress → psychotic experiences)	0.029 (-0.005 – 0.064)	0.093	0.034 (0.002 – 0.066)	0.036	0.020 (0.000 – 0.039)	0.047
Indirect effect[b] (Event-related stress → threat anticipation → psychotic experiences)	**0.013 (0.003 – 0.027)**	**0.034**	**0.016 (0.007 – 0.027)**	**0.003**	**0.008 (0.003 – 0.015)**	**0.008**
Total effect	0.042 (0.002 – 0.083)	0.038	0.050 (0.015 – 0.084)	0.005	0.028 (0.005 – 0.050)	0.015
Activity-related stress, threat anticipation, psychotic experiences						
Direct effect (Activity-related stress → psychotic experiences)	0.113 (0.078 – 0.148)	<0.001	0.136 (0.098 – 0.175)	<0.001	0.055 (0.025 – 0.085)	<0.001
Indirect effect[b] (Activity-related stress → threat anticipation → psychotic experiences)	**0.025 (0.011 – 0.043)**	**0.003**	**0.024 (0.011 – 0.039)**	**<0.001**	**0.015 (0.007 – 0.024)**	**<0.001**
Total effect	0.138 (0.078 – 0.148)	<0.001	0.160 (0.098 – 0.175)	<0.001	0.070 (0.025 – 0.085)	<0.001

Table 2. *(continued)*

	FEP		ARMS		Controls	
	adj. B (95% CI)	P	adj. B (95% CI)	P	adj. B (95% CI)	P
Social stress, threat anticipation, psychotic experiences						
Direct effect (Social stress → psychotic experiences)	0.020 (-0.019 – 0.059)	0.320	0.075 (0.045 – 0.104)	<0.001	0.050 (0.026 – 0.075)	<0.001
Indirect effect[b] (Social stress → threat anticipation → psychotic experiences)	**0.015 (0.003 – 0.031)**	**0.043**	**0.018 (0.008 – 0.031)**	**0.001**	**0.009 (0.003 – 0.017)**	**0.008**
Total effect	0.034 (-0.009 – 0.078)	0.118	0.093 (0.059 – 0.127)	<0.001	0.059 (0.030 – 0.089)	<0.001
Negative affect, threat anticipation, psychotic experiences						
Direct effect (Negative affect → psychotic experiences)	0.315 (0.239 – 0.391)	0.000	0.324 (0.235 – 0.412)	0.000	0.252 (0.188 – 0.316)	0.000
Indirect effect[b] (Negative affect → threat anticipation → psychotic experiences)	**0.030 (0.014 – 0.053)**	**0.002**	0.015 (-0.001 – 0.033)	0.072	**0.019 (0.009 – 0.031)**	**0.001**
Total effect	0.345 (0.257 – 0.433)	0.000	0.339 (0.250 – 0.428)	0.000	0.271 (0.199 – 0.343)	0.000

Note: FEP, First-Episode Psychosis; ARMS, At-Risk Mental State for psychosis; SD, standard deviation; df, degrees of freedom; vs., versus; CI, confidence interval; significant indirect paths (P<0.05) are presented in bold.

[a] Adjusted for age, gender, ethnicity, level of education and employment status

[b] Difference in indirect effects across groups (Δ indirect effects)

‡Model estimation did not terminate normally

	ARMS vs. controls		*FEP vs. controls*		*FEP vs. ARMS*	
	adj. B (95% CI)	P	adj. B (95% CI)	P	adj. B (95% CI)	P
Δ Indirect effects						
Event-related stress → negative affect → psychotic experiences	**0.027 (0.004 – 0.050)**	**0.023**	0.009 (-0.017 – 0.041)	0.536	-0.018 (-0.049 – 0.018)	0.295
Activity-related stress → negative affect → psychotic experiences	**0.045 (0.005 – 0.086)**	**0.030**	0.030 (-0.007 – 0.070)	0.125	-0.015 (-0.063 – 0.033)	0.544
Social stress → negative affect → psychotic experiences	0.022 (-0.011 – 0.057)	0.195	0.004 (-0.026 – 0.036)	0.801	-0.018 (-0.056 – 0.019)	0.335
Event-related stress → threat anticipation → psychotic experiences	0.007 (-0.011 – 0.018)	0.212	0.005 (-0.008 – 0.028)	0.468	-0.002 (-0.025 – 0.006)	0.757
Activity-related stress → threat anticipation → psychotic experiences	0.010 (-0.010 – 0.047)	0.250	0.010 (-0.007 – 0.030)	0.277	0.001 (-0.020 – 0.023)	0.961
Social stress → threat anticipation → psychotic experiences	0.009 (-0.003 – 0.023	0.160	0.006 (-0.009 – 0.023)	0.482	-0.004 (-0.020 – 0.014)	0.688
Negative affect → threat anticipation → psychotic experiences	-0.004 (-0.024 – 0.017)	0.721	0.011 (-0.009 – 0.036)	0.307	0.015 (-0.009 – 0.036)	0.240

Table 3. Total, direct, and conditional indirect effects of multiple multilevel moderated mediation models of stress on psychotic experiences via negative affect, threat anticipation and aberrant salience[a]

	FEP		ARMS		Controls	
	adj. B (95% CI)	P	adj. B (95% CI)	P	adj. B (95% CI)	P
Event-related stress						
Direct effect (Event-related stress → psychotic experiences)	0.015 (-0.008 – 0.038)	0.192	-0.005 (-0.030 – 0.021)	0.731	0.000 (-0.013 – 0.013)	0.965
Total indirect effect (Event-related stress)	0.005 (-0.010 – 0.021)	0.574	0.012 (-0.005 – 0.027)	0.124	0.008 (0.001 – 0.016)	0.030
Specific indirect effects[b]						
Event-related stress → negative affect → psychotic experiences	**0.012 (0.001 – 0.025)**	**0.049**	**0.017 (0.007 – 0.027)**	**0.001**	**0.008 (0.003 – 0.014)**	**0.002**
Event-related stress → aberrant salience → psychotic experiences	**-0.012 (-0.023 – -0.004)**	**0.009**	-0.006 (-0.017 – 0.002)	0.207	-0.002 (-0.006 – 0.001)	0.278
Event-related stress → threat anticipation → psychotic experiences	0.005 (-0.000 – 0.010)	0.072	0.001 (-0.001– 0.004)	0.236	0.002 (-0.000 – 0.003)	0.073
Event-related stress → negative affect → threat anticipation → psychotic experiences	0.000 (-0.000 – 0.001)	0.092	0.000 (-0.000 – 0.001)	0.222	**0.000 (0.000 – 0.000)**	**0.036**
Total effect (Event-related stress)	0.020 (-0.010 – 0.050)	0.194	0.008 (-0.021 – 0.037)	0.602	0.008 (-0.007 – 0.023)	0.312
Activity-related stress						
Direct effect (Activity-related stress → psychotic experiences)	0.051 (0.021 – 0.081)	0.001	0.034 (0.007 – 0.060)	0.014	0.004 (-0.015 – 0.022)	0.708
Total indirect effect (Activity-related stress)	0.058 (0.037 – 0.081)	0.000	0.061 (0.040 – 0.084)	0.000	0.034 (0.022 – 0.048)	0.000
Specific indirect effects[b]						
Activity-related stress → negative affect → psychotic experiences	**0.046 (0.030 – 0.064)**	**<0.001**	**0.047 (0.033 – 0.062)**	**<0.001**	**0.029 (0.020 – 0.039)**	**<0.001**
Activity-related stress → aberrant salience → psychotic experiences	-0.001 (-0.010 – 0.010)	0.896	0.009 (-0.004 – 0.025)	0.219	0.000 (-0.004 – 0.005)	0.949
Activity-related stress → threat anticipation → psychotic experiences	**0.011 (0.005 – 0.017)**	**<0.001**	0.004 (-0.002 – 0.010)	0.191	**0.005 (0.002 – 0.008)**	**0.004**
Activity-related stress → negative affect → threat anticipation → psychotic experiences	**0.002 (0.001 – 0.003)**	**0.003**	0.001 (-0.000 – 0.001)	0.201	**0.001 (0.000 – 0.001)**	**0.007**
Total effect (Activity-related stress)	0.109 (0.075 – 0.142)	0.000	0.094 (0.061 – 0.128)	0.000	0.038 (0.012 – 0.063)	0.003

Table 3. *(continued)*

	FEP		ARMS		Controls	
	adj. B (95% CI)	P	adj. B (95% CI)	P	adj. B (95% CI)	P
Social stress						
Direct effect (Social stress → psychotic experiences)	-0.029 (-0.058 – -0.001)	0.044	0.001 (-0.021 – 0.022)	0.962	-0.001 (-0.014 – 0.012)	0.844
Total indirect effect (Social stress)	0.018 (0.004 – 0.031)	0.010	0.013 (-0.004 – 0.031)	0.136	0.019 (0.009 – 0.030)	0.000
Specific indirect effects[b]						
Social stress → negative affect → psychotic experiences	**0.017 (0.008 – 0.028)**	**0.001**	**0.018 (0.006 – 0.032)**	**0.006**	**0.021 (0.013 – 0.031)**	**<0.001**
Social stress → aberrant salience → psychotic experiences	-0.003 (-0.014 – 0.005)	0.466	-0.006 (-0.016 – 0.004)	0.239	-0.004 (-0.009 – 0.001)	0.129
Social stress → threat anticipation → psychotic experiences	0.003 (-0.002 – 0.008)	0.220	0.001 (-0.000 – 0.004)	0.285	0.001 (-0.000 – 0.002)	0.326
Social stress → negative affect → threat anticipation → psychotic experiences	**0.001 (0.000 – 0.001)**	**0.009**	0.000 (-0.000 – 0.001)	0.201	**0.000 (0.000 – 0.001)**	**0.013**
Total effect (Social stress)	-0.012 (-0.044 – 0.021)	0.481	0.014 (-0.013 – 0.041)	0.318	0.018 (0.003 – 0.032)	0.017
Negative affect						
Direct effect	0.255 (0.197 – 0.314)	0.000	0.260 (0.192 – 0.327)	0.000	0.220 (0.173 – 0.267)	0.000
Total indirect effect						
Negative affect → threat anticipation → psychotic experiences	**0.009 (0.004 – 0.015)**	**0.002**	0.003 (−0.001 – 0.007)	0.188	**0.004 (0.002 – 0.007)**	**0.002**
Total effect (Negative affect)	0.264 (0.203 – 0.325)	0.000	0.263 (0.196 – 0.329)	0.000	0.224 (0.176 – 0.271)	0.000
Threat anticipation						
Direct effect (Threat anticipation → psychotic experiences)	0.075 (0.044 – 0.106)	0.000	0.019 (-0.009 – 0.04	0.184	0.033 (0.014 – 0.052)	0.001
Aberrant salience						
Direct effect (Aberrant salience → psychotic experiences)	0.156 (0.105 – 0.207)	0.000	0.210 (0.142 – 0.278)	0.000	0.134 (0.086 – 0.183)	0.000

Note: Overview of total, direct, and indirect effects of significant paths from simple moderated multilevel mediation models (see table 2). FEP, First-Episode Psychosis; ARMS, At-Risk Mental State for psychosis; SD, standard deviation; df, degrees of freedom; vs., versus; CI, confidence interval; correlated mediators, r (negative affect, aberrant salience) =-0.02, P=0.667, r (aberrant salience, threat anticipation)=0.34, P=0.001; significant specific indirect paths (P<0.05) are presented in bold.

[a] Adjusted for age, gender, ethnicity, level of education, employment status, area-related stress and outsider status

[b] Difference in specific indirect effects across groups (Δ indirect effects):

Table 3. *(continued)*

	ARMS vs. controls		*FEP vs. controls*		*FEP vs. ARMS*	
	adj. B (95% CI)	P	adj. B (95% CI)	P	adj. B (95% CI)	P
Δ Indirect effects						
Event-related stress → negative affect → psychotic experiences	0.009 (-0.003 – 0.020)	0.129	0.004 (-0.009 – 0.018)	0.582	-0.005 (-0.020 – 0.012)	0.520
Event-related stress → aberrant salience → psychotic experiences	-0.004 (-0.020 – 0.008)	0.404	**-0.011 (-0.021 – -0.001)**	**0.037**	-0.006 (-0.021 – -0.001)	0.370
Event-related stress → negative affect → threat anticipation → psychotic experiences	0.000 (-0.000 – 0.000)	0.824	0.000 (-0.000 – 0.001)	0.301	0.000 (-0.000 – 0.001)	0.431
Activity-related stress → negative affect → psychotic experiences	**0.018 (0.001 – 0.036)**	**0.039**	0.017 (-0.001 – 0.037)	0.072	-0.001 (-0.022 – 0.021)	0.928
Activity-related stress → threat anticipation → psychotic experiences	-0.001 (-0.008 – 0.006)	0.848	0.006 (-0.001 – 0.013)	0.084	0.007 (-0.002 – 0.015)	0.126
Activity-related stress → negative affect → threat anticipation → psychotic experiences	0.000 (-0.001 – 0.001)	0.994	0.001 (0.000 – 0.002)	0.062	0.001 (-0.000 – 0.003)	0.109
Social stress → negative affect → psychotic experiences	-0.004 (-0.018 – 0.012)	0.642	-0.004 (-0.017 – 0.009)	0.534	-0.001 (-0.017 – 0.015)	0.950
Social stress → negative affect → threat anticipation → psychotic experiences	0.000 (-0.001 – 0.000)	0.379	0.000 (-0.000 – 0.001)	0.446	0.000 (-0.000 – 0.001)	0.141
Negative affect → threat anticipation → psychotic experiences	-0.001 (-0.006 – 0.004)	0.659	0.005 (-0.001 – 0.011)	0.115	0.006 (-0.000 – 0.014)	0.090

DISCUSSION

Principal findings

This study sought to move beyond previous experience sampling investigations of single psychological processes in daily life to investigate specific pathways derived from contemporary models of psychosis and examine how momentary stress, affective disturbance, threat anticipation, and aberrant salience combine in the development of PE (figure 2). We found strong and consistent evidence that momentary stress increases the intensity of PE via pathways through affective disturbance in FEP individuals, ARMS individuals, and controls, with only weak evidence of greater indirect effects in FEP and ARMS individuals than controls. There was further evidence that the effects of activity-related stress via threat anticipation remained significant, independently of pathways via affective disturbance, in FEP individuals and controls but not ARMS individuals. We also found some evidence of pathways from activity-related and social stress via affective disturbance followed by threat anticipation and, then, PE in FEP individuals and controls. A negative indirect effect was evident for the pathway of event-related stress on PE via aberrant salience in FEP individuals. We found no evidence of indirect effects of affective disturbance and threat anticipation via aberrant salience. The latter retained, however, a significant direct effect on PE.

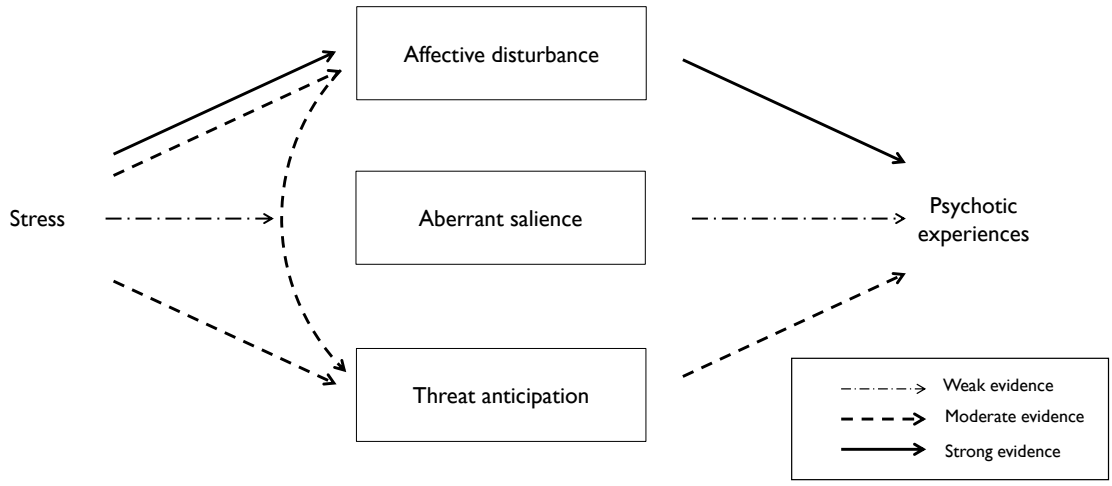

Figure 2. Schematic representation main findings across groups. This figure gives an overview of all consistent indirect effects of stress on psychotic experiences via pathways through affective disturbance, enhanced treat anticipation, and aberrant salience. Only findings with at least one significant indirect path in at least one group were considered in this representation. See Supplementary figure 1. for a detailed breakdown of significant (P<0.005) indirect effects per group and per marker of stress.

Methodological considerations

The current findings should be viewed in the light of potential limitations. First, we used cross-sectional and not time-lagged, multilevel moderated mediation models to investigate specific pathways due to sample size restrictions, providing insufficient power for fitting such computationally intensive models. This did not allow us to examine the *temporal* order of these variables as one important criterion for establishing causality. Hence, analyses using time-lagged models of larger samples are now needed to further elucidate the complex interplay of, and potential reciprocal associations between, psychological processes and momentary stress over time. However, the current study was the first to investigate and systematically test, in daily life, the indirect effects of stress on PE via pathways through affective disturbance, threat anticipation, aberrant salience and PE that have been repeatedly proposed in conceptual models of psychosis. Specifically, we tested a comprehensive, fully adjusted multiple multilevel moderated mediation model in a sample of controls, ARMS individuals, and FEP individuals, allowing us, at the same time, to minimize the potential impact of illness chronicity and other consequences of psychotic disorder. As such, this study advances previous research using network modeling of ESM data [44-47], which have not yet investigated indirect effects of stress, negative affect and other psychological mechanisms in the development of PE.

Second, ESM data collection is time-intensive and possibly associated with assessment burden for participants and, in turn, selection bias. However, previous research has shown that the ESM is a feasible, reliable, and valid assessment method in various populations [16,17,31,48]. Applying this method enabled us to study the interplay of psychological processes in everyday life where these processes and their association with PE naturally occur.

Third, the magnitude of the indirect effects was, overall, small, with the greatest indirect effects being evident for pathways from stress to negative affect to PE. This was particularly evident for the longer indirect pathways via negative affect and threat anticipation. In mediation analyses using the product of coefficients strategy, longer indirect pathways are, by definition, of smaller magnitude, given their computation is based on the product of a higher number of individual path coefficients. In the current study, individual path coefficients (supplementary Figure 1) were of similar magnitude to what has been observed in previous ESM studies. In ESM studies, effects of this magnitude may be considered important given they occur in the flow of daily life and, thereby, have a considerable cumulative impact on individuals over time [49]. However, while total and total indirect effects of the indirect pathway with the largest

magnitude from activity-related stress to PE were mostly accounted for by specific indirect effects through negative affect, even for this pathway a fair proportion of the total effect was still explained by the direct effect, suggesting evidence of partial mediation via this pathway. Hence, a number of other unmeasured factors and mechanisms may be operating on this and other pathways investigated that would need to be added before full mediation of the effects of stress on PE may be observed. Also, while indirect pathways of stress via affective disturbance were specifically related to intensity of PE as an outcome, differences in magnitude of indirect effects across the 3 groups were, overall, small, and most differences were not statistically significant at conventional levels, possibly due to limited statistical power to detect such small differences. However, it is noteworthy in this context that ARMS and FEP individuals reported, on average, higher levels of stress, negative affect, aberrant salience, threat anticipation, and PE than controls (supplementary Table 2). This tentatively suggests that, even if the magnitude of differences in indirect effects across groups was small, the greater prevalence of stress in ARMS and FEP individuals may contribute to the development of PE via pathways through negative affect (and, in FEP individuals, higher levels of negative affect via threat anticipation and so forth).

Fourth, we investigated a number of a priori hypothesized, specific indirect effects of event-related, area-related and social stress via 3 distinct pathways (affective disturbance, aberrant salience, threat anticipation), which reflects the complexity of current models of the etiology of psychosis. This may have, nonetheless, inflated type I error and resulted in over- or under-estimation of indirect effects. Therefore, careful replication in independent samples is required before firm conclusions can be drawn. However, pathways to psychosis have frequently been tested in isolation, thereby, ignoring the complexity involved and the potential impact of unmeasured impact or confounding by other pathways. All specific indirect effects reported in the final multiple moderated mediation model were included simultaneously to examine their relative contribution, which reflects a considerable advance over previous research, primarily testing pathways via affective disturbance, threat anticipation, and aberrant salience in isolation.

Comparison with previous research

Recently, a number of integrated models of psychosis have implicated stress, affective and cognitive processes in the onset of psychosis and specifically posited that, in individuals with heightened vulnerability of biopsychosocial origin, the effects of stress on PE are mediated via

pathways through affective disturbances, anomalous experiences, and cognitive biases [3,5-7,13,22,23,28]. While these models are now common ground and highly cited in psychosis research, attempts to systematically test comprehensive models of the complex interplay between psychological processes and stressful contexts and experiences in the origins of psychosis remain sparse [21,22].

Elevated emotional reactivity to minor stressors has received great attention as a putative underlying mechanism in psychotic disorders [13,16,17]. Individuals with increased familial and psychometric risk for psychosis have been found to experience an increased emotional reactivity to minor stressors in daily life [16,17,50,51]. More generally, various models of psychosis have posited that the effects of stress are mediated via affective disturbance [3-5] and may reflect what has previously been coined an affective pathway to psychosis [13]. Our findings provide new evidence in support of this proposition, as this is the first ESM study to report that affective disturbance *mediates* the link from momentary stress to PE in daily life across different stages of early psychosis. In contrast to findings from previous research suggesting some degree of specificity for certain types of stressors for the formation of PE [18], we found evidence that the effects of all stress variables (i.e., event-related, activity-related, and social stress) were mediated via pathways through affective disturbances. Further, while indirect effects of activity-related stress were greatest, there was no strong evidence of differences in magnitude of indirect effects via affective disturbance for different types of stressors.

Changes in the emotional response to stress have moreover been linked to cognitive biases such as enhanced anticipation of threat [22,27]. It has been suggested that enhanced threat anticipation combines with affective disturbance in the development of PE [4,27]. However, the precise nature of this pathway remained unclear. The current results point toward a link from stressful contexts and experiences to affective disturbance, followed by threat anticipation and, in turn, the formation of PE. This corroborates the prominent role ascribed to (stress-induced) affective disturbances such as symptoms of anxiety, which cognitive models of psychosis consider to be key in enhancing anticipation of threat and, in turn, intensity of PE [23,27]. However, this pathway via enhanced threat anticipation was attenuated and ceased to be statistically significant in ARMS individuals, while controlling for pathways via affective disturbance in our final adjusted model. This finding may tentatively suggest a greater relevance of affective pathways rather than pathways via threat anticipation

in the prodromal period of psychosis when a considerable proportion experience comorbid anxiety and depression [52].

We did not find evidence in support of our hypotheses that aberrant salience mediated the effects of threat anticipation and negative affect on PE. What is more, event-related stress was associated with a slight decrease in aberrant salience, which, in turn, was associated with less intense PE in FEP individuals, who all (but one) received prior or ongoing treatment with antipsychotic medication. While tentative, the effects of antipsychotic medication may in part explain the finding of event-related stress on decreased aberrant salience in FEP individuals [29]. More importantly, however, aberrant salience retained, independently of stress, a substantial direct effect on PE, which supports previous propositions by cognitive models and neurobiological approaches [4,29] that experiences of aberrant salience occur as a result of dopamine release independent of cue and context due to hyperactivity of the mesolimbic dopaminergic system [29]. In other words, augmented levels of aberrant salience may not be due to current contextual factors such as momentary stress, but primarily play a role in the formation of PE if genes, early neurological insults and adverse social environments impacted and sensitized the dopaminergic system at a developmentally earlier stage [3-5]. Clinically, our findings suggest that the antipsychotic effects on dopamine dysregulation in FEP individuals may target one potential pathway, but not the pathways of stress via affective disturbance and threat anticipation on psychosis to the same extent.

CONCLUSIONS

This study provides evidence on the interplay between psychological processes and stress in the origins of psychosis and, thereby, contributes to improving our understanding of psychoses as disorders with very complex etiologies. Our findings underscore the important role that affective disturbance, particularly emotional reactivity, and threat anticipation may play as putative mechanisms through which stress impacts on the formation of PE. Evidence on the psychological processes, and their interplay with stress, underlying the occurrence and persistence of PE in daily life is vital for gaining a better understanding of when and how to intervene to reduce intensity of PE. This, then, provides the basis for translational research using ecological interventionist causal models targeting these psychological processes in daily life through novel, personalized ecological momentary interventions that deliver treatment in the real-world and in real-time, tailored to what individuals need in a

given *moment* and *context* through interactive delivery schemes [11,53]. Developing and evaluating these interventions with the goal of promoting resilience to stress and achieving sustainable change in intended psychosis outcomes under real-world conditions is of considerable public health importance and an important next step toward preventing onset and improving long-term outcomes of psychosis.

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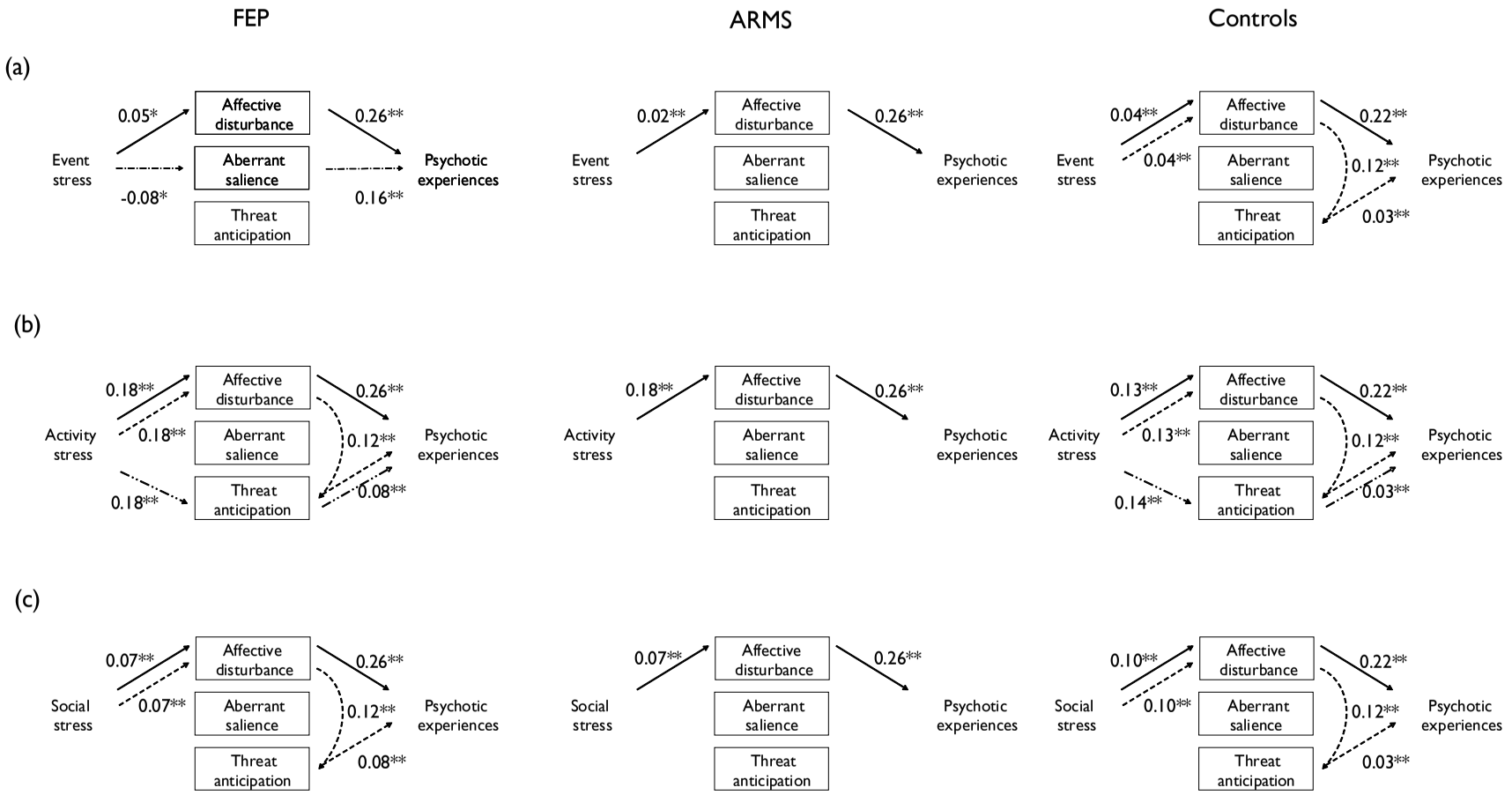
SUPPLEMENTARY MATERIALS

Statistical analysis

ESM data have a multilevel structure, such that multiple observations are nested within subjects. Multilevel moderated mediation models were fitted in MPlus, Version 7,[54] to control for within-subject clustering of multiple observations [43,55], using the MLR estimator, which allows for the use of all available data under the relatively unrestrictive assumption that data is missing at random if all variables associated with missing values are included in the model. In a two-level model, multiple observations (level 1) were treated as nested within subjects (level 2). The total effect of stressful contexts and experiences (event-related, activity-related, and social stress) in daily life (level 1) on intensity of psychotic experiences (level 1) was apportioned into direct and indirect (or, synonymously, mediating) effects through negative affect, aberrant salience, and enhanced threat anticipation (level 1) using the product of coefficients strategy. This strategy quantifies the point estimate of the indirect effect as the product of the coefficient of independent variable on mediator variable (path a) and the coefficient of mediator variable on dependent variable (path b). We used statistical software by Selig and Preacher [56] for computing Monte Carlo confidence intervals and assessing statistical significance of indirect effects, given their advantages over rival methods in the context of multiple multilevel mediation models [43,57]. Group (FEP, ARMS, controls) was used as the moderator variable (level 2) of direct and conditional indirect effects in all analyses based on a multilevel moderated mediation approach, in which the moderator variable is the predictor of the a and b paths (see above) and the strength of the indirect effect of the level 1 independent variable depends on the level 2 moderator variable [43,58]. This allowed us to test whether conditional indirect effects were greater in a) FEP than in controls, b) ARMS than in controls, and c) FEP than in ARMS by computing differences in conditional indirect effects using the model constraint command in MPlus [54] and calculating respective Monte Carlo confidence intervals [55,57]. We first fitted separate simple moderated multilevel mediation models (including variables associated with missing values (i.e., age, group) [12]): 1) with one independent variable for event-related stress, activity-related stress, or social stress, one mediator variable for negative affect, threat anticipation or aberrant salience, and one outcome variable for psychotic experiences; 2) with one independent variable for negative affect, one mediator variable for threat anticipation or aberrant salience, and one outcome variable for psychotic experiences; and 3) with enhanced threat anticipation as independent variable,

aberrant salience as mediator variable, and psychotic experiences as outcome variable. Based on evidence of mediation via negative affect, threat anticipation and aberrant salience in these models, we next fitted a multiple multilevel moderated mediation model to examine the relative contribution of direct effects and specific indirect effects via these pathways simultaneously [43]. All analyses were adjusted for age, gender, ethnicity, level of education, employment status and, based on findings from previous ESM research [12], area-related stress and outsider status as potential confounders by including these variables as predictors of each mediator and dependent variable.



Supplementary Figure S1. Display of individual path coefficients for significant indirect effects (i.e., the product of individual path coefficients; shown in Table 3) of a) event-related stress, (b) activity-related stress, and (c) social stress on psychotic experiences via affective disturbance (——►), aberrant salience (—·—►), threat anticipation (—··—►), and via affective disturbance *and* threat anticipation (-------►). Findings are displayed separately for FEP individuals, ARMS individuals, and controls. * P<0.05; ** P<0.001

CHAPTER FIVE

Modeling the moment-to-moment interplay between stress and affective disturbances in pathways to psychosis: an experience sampling study

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ABSTRACT

Background. Several models propose that the effects of momentary stress on psychotic experiences are partly mediated through affective disturbance. However, attempts to systematically test comprehensive models of this pathway in daily life remain sparse. Also, although longitudinal effects of momentary stress on psychotic experiences via indirect effects of affective disturbance have been suggested, to date, they have not been tested systematically. The aim of the current study was to investigate whether momentary stress increases the intensity of psychotic experiences via affective disturbance in daily life. Furthermore, the reverse pathway from psychotic experiences to stress, via affective disturbance was investigated.

Method. The Experience Sampling Method was used in a pooled data set of six studies with 245 individuals with a diagnosis of psychosis, 165 unaffected first-degree relatives, and 244 healthy control individuals. Multilevel moderated mediation models were fitted to investigate indirect effects across groups at one measurement occasion/cross-sectionally. In addition to that, we fitted multilevel cross-lagged panel models to investigate indirect effects in the proposed pathways across two measurement occasions.

Results. Evidence on indirect effects from cross-sectional models indicated that, in all three groups, effects of stress on psychotic experiences were mediated by negative affect. We furthermore found evidence that effects of psychotic experiences on stress were mediated by affective disturbance in all three groups. Only in controls, there was evidence of a longitudinal indirect effect of stress on psychotic experiences via negative affect.

Conclusions. Our findings suggest strong fluctuations for the proposed affective pathway to psychosis and, more tentatively, a rapid vicious cycle of stress impacting psychotic experiences, and vice versa, via affective disturbances. This, in turn, highlights the importance of investigating reciprocal effects between these aspects.

INTRODUCTION

Recently, the psychosis phenotype has widely been characterized as a continuum of severity and persistence of psychotic experiences. Supporting the notion of a continuum, subclinical expressions of psychotic symptoms are prevalent among the general population [1], associated with a family history of psychotic disorders [2], and an increased risk for developing a psychotic disorder [1,3]. In recent years, studies have implicated a variety of different putative, psychological mechanisms that may be involved in the development and persistence of psychotic experiences along the continuum of psychosis [4-9].

Elevated stress sensitivity is a psychological mechanism that has been widely studied in daily life using ecological momentary assessment strategies, such as the Experience Sampling Method (ESM) [10,11]. Stress sensitivity has been conceptualized as increased mood and psychotic reactivity to daily events and minor disturbances and has been found in both psychotic patients and individuals with an increased risk of developing a psychotic disorder (familial and psychometric) [10,12-15]. Also, several models propose that the effects of stress on psychotic experiences are partly mediated through experiences of affective disturbance [10,16]. Elevated emotional reactivity to minor stress was associated with more intense psychotic experiences in daily life in a group of patients with a first episode of psychosis when compared to healthy controls [12]. Also, independently of stress, affective disturbance has been associated with psychotic experiences across different stages of the psychosis development [17-21]. Elevated levels of negative affect, for instance, have been found to precede experiences of paranoia in individuals with psychotic disorder, in individuals at psychometric risk [17] as well as in a general population twin sample.

However, to date, little data has been published on the reverse of the above suggested pathway. Psychotic experiences themselves may be seen as the source of distress [22,23] that may link to disturbances in affect. Affective disturbance may then be driving the appraisal of experiences and contexts as stressful. Psychotic experiences may therefore, as well be seen as a predecessor rather than merely a *consequence* of momentary stress. In line with this thought, recent work by Rapado-Castro and colleagues [24] suggests a link between subclinical symptoms and distress in at-risk individuals, which, in turn, has been associated with an increased risk of transition to psychosis [21].

Although the body of literature on the link of minor daily stress, affective disturbances and psychotic experiences is growing, and several integrated models have been proposed, to date,

only little attention has been paid to how these processes combine in the formation of psychotic experiences in daily life. Using cross-sectional multilevel mediation models, a recent study by our group showed that minor daily stress increases psychotic experiences via pathways through affective disturbances [25]. This indirect effect was greater in individuals at-risk and first-episode psychosis individuals than in healthy control subjects. In another recent study, we applied the network approach to psychopathology to elucidate the dynamic interplay of momentary experiences, contextual factors and psychotic experiences longitudinally [26]. Findings implied that affective disturbance had an intermediary position between minor daily stress and psychotic experiences.

The aim of the current study was twofold. First, we attempted to study cross-sectionally how momentary stress and affective disturbance combine to increase the intensity of psychotic experiences in daily life, and vice versa. Second, we attempted to test these pathways longitudinally. We used the Experience Sampling Method in three populations varying on the psychosis continuum: individuals with a psychotic disorder, relatives of individuals with a psychotic disorder, and healthy control individuals. The current study thus tested the following main hypotheses: (i) the cross-sectional effect of momentary stress on psychotic experiences is mediated by experiences of affective disturbance; (ii) the cross-sectional effect of psychotic experiences on momentary stress is mediated by experiences of affective disturbance; (iii) the longitudinal effect of momentary stress on psychotic experiences is mediated by experiences of affective disturbance; and (iv) the longitudinal effect of psychotic experiences on momentary stress is mediated by experiences of affective disturbance.

METHODS

Samples

We used data from six different studies [15,23,27-29] (see supplementary table S1 for in- and exclusion criteria of these studies) that used a similar ESM protocol. Participants were classified either as (i) 'healthy' control individuals (i.e. neither a personal diagnosis nor a family history of psychotic disorder/symptoms), (ii) first-degree relatives of individuals with a psychotic disorder, or (iii) individuals with a psychotic disorder.

All studies included in this paper were approved by the local medical ethics committee. All further procedures and analyses were performed according to the ethical standards formulated by this committee.

Table 1. ESM procedure[a] and measures of stress, negative affect, and psychotic experiences

Domain	[b]ESM measures
Momentary stress	We used a composite measure of momentary stress combining aspects of event-related stress, activity related stress and social stress. This composite score was calculated by computing the row mean.
Event-related	Event-related stress was assessed with 1 item. In this item participants rated the most important event since the last beep on a 7-point Likert scale (-3 = "very unpleasant" to 3= "very pleasant). The item was reverse coded with higher ratings indicating higher levels of stress (a rating of -3 coded as 7 and a rating of 3 coded as 1).
Activity-related	The activity-related stress scale consisted of 3 items ("This activity is difficult for me", "I would prefer doing something else", "This activity is challenging") rated on a 7-point Likert (1= "not at all" to 7= "very much").
Social	Social stress was measured with a mean of 2 items. First, participants had to answer the question "Who am I with?" (e.g., partner, family, friends, colleagues, acquaintances, strangers, others, nobody). Then, participants were asked to rate their current social context on a 7-point Likert scale (1= "not at all" to 7= "very much") with 2 questions: 1) "I would prefer to be alone [if with someone]"; 2) "I find being with these people pleasant [if with someone]" (reversed).
Negative affect	We used the mean of five ESM items to measure negative affect. In line with earlier work we used the following items asking participants to rate the extent to which they felt down, lonely, anxious, insecure, and annoyed on a 7-point Likert scale (1 = "not at all" to 7 = "very much") [25].
Psychotic experiences	We used the an ESM psychosis measure which consists of 6 items covering different aspects of mental states that are directly associated with psychotic experiences ("I feel paranoid", "I feel unreal", "I hear things that aren't really there", "I see things that aren't really there", "I can't get these thoughts out of my head", and "I feel like I am losing control"). Participants were asked to rate the intensity of psychotic experiences on a 7-point Likert scale (1= "not at all" to 7= "very much").

[a]*ESM procedure:* Over a period of 6 consecutive days, participants were prompted by the PsyMate "beep" signal to complete the ESM questionnaire 10 times a day at random moments within set blocks of 90 minutes. Participants were provided with detailed instructions and a practice session as training in the use of the PsyMate. Participants were explained to stop their activity and respond to the above items when prompted by the beep signal as part of a comprehensive diary questionnaire assessing activities, feelings, thoughts, behaviours, social situations, and surroundings in daily life. The assessment period started on any day of the week as selected by the participant, and the ESM questionnaire was available up to 10 minutes after the beep signal. In order to maximize the number of observations for every participant, participants were contacted at least once during the assessment period to assess instruction adherence, identify any concerns associated with the method, and help participants with any problems in completing the ESM questionnaire. The participants' reactivity to and compliance with the method was assessed in a debriefing session at the end of the assessment period. In order to be included in the analysis, participants had to provide valid responses to at least one-third of the beep signals.

Experience Sampling Method (ESM)

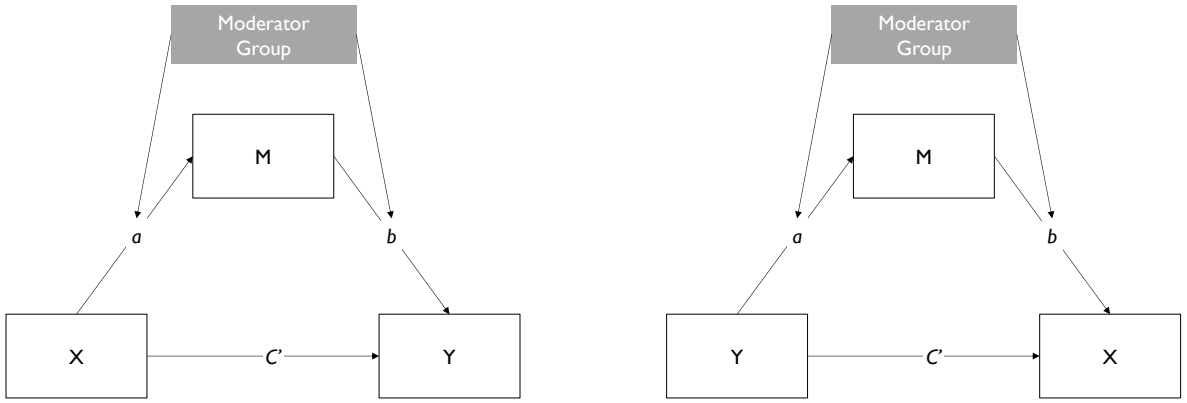
In all studies, ESM (a structured diary technique) was used to study minor stress in everyday life (see Table 1). Individuals received a diary and a wristwatch which was programmed to beep 10 times a day (between 7:30 AM and 10:30 PM) for five (Aripiprazol study [29]) or six days (remaining studies) at semi-random intervals (random within 90-minute time frames). Thus, the time lag between the measurements was, on average, approximately 90 minutes. Further information on the ESM procedure and the variables used in the current study are presented in Table 1.

Statistical analysis

Data from ESM studies have a hierarchical structure with multiple observations nested within subjects. We therefore fitted multilevel moderated mediation models in Mplus, Version 7 [30], to control for within-subject clustering of multiple observations. We did this using the MLR and MLF estimators, which allowed us to use all available data under the relatively unrestrictive assumption that data is missing at random if all variables associated with missing values are included in the model [31,32]. We used a two-level model, where multiple observations (level-1) were treated as nested within subjects (level-2).

Cross-sectional multilevel moderated mediation models. The total effect of momentary stress in daily life (level-1) on intensity of psychotic experiences (level-1) was apportioned into direct and indirect effects through negative affect using the product of coefficients strategy. With this strategy, we can quantify the point estimate of the indirect effect as the product of the coefficient of independent variable on the mediator variable (path a) and the coefficient of mediator variable on dependent variable (path b). Given its advantages over other methods in the context of multilevel mediation models, we used an R package by Selig and Preacher for computing Monte Carlo confidence intervals and assessing statistical significance of indirect effects [32,33]. Group (patients, relatives, controls) was used as the moderator variable (level-2) of direct and conditional indirect effects in all analyses. We did this based on a multilevel moderated mediation approach, where the moderator variable is the predictor of the a and b paths (see Figure 1) and the strength of the indirect effect of the level-1 independent variable depends on the level-2 moderator variable [32,34]. By doing this, we could test whether conditional indirect effects were greater in a) patients than in controls, b) relatives than in

controls, and c) patients than in relatives by computing differences in conditional indirect effects using the model constraint command in Mplus [30] and calculating respective Monte Carlo confidence intervals [32,34,35].

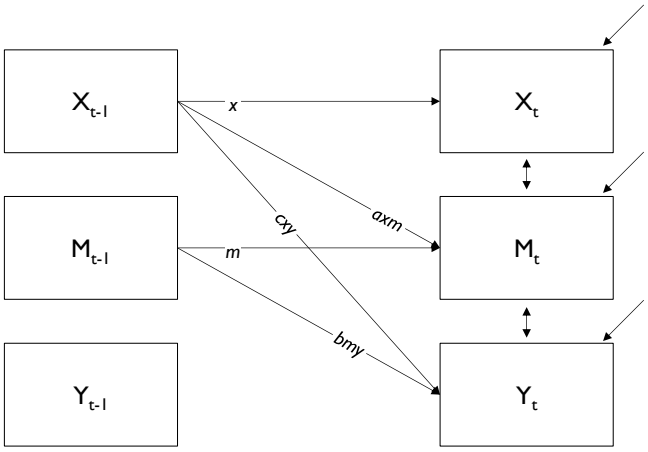


(a) (b)

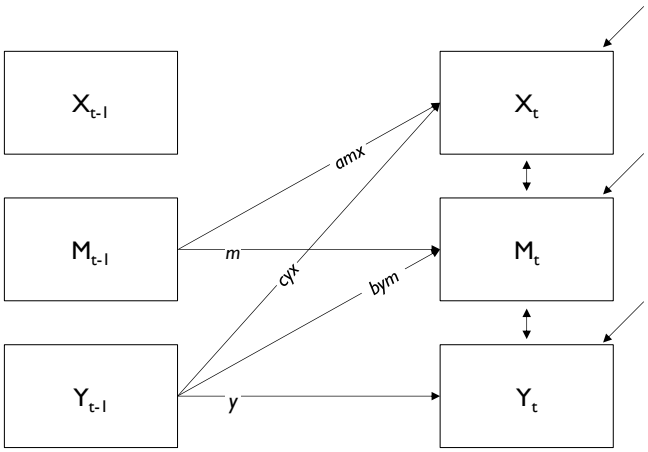
Figure 1. Schematic display of cross-sectional moderated mediation models. Display of pathways tested within each group: (a) Momentary stress (X) on psychotic experiences (Y) via negatives affect (M); (2) psychotic experiences (Y) on momentary stress (X) via negative affect (M). All models were controlled for age and gender.

Longitudinal multilevel moderated mediation models. In a first step, we fitted an autoregressive model to estimate autoregressive effects of momentary stress at t-1 on momentary stress at t, negative affect at t-1 on negative affect at t, and psychotic experiences at t-1 on psychotic experiences at t. In order to assess longitudinal mediation, we fitted a multilevel moderated cross-lagged panel model for a half-longitudinal design (CLPM) as proposed by Preacher [31]. In a half-longitudinal design, an indirect effect of an independent variable (X) on a dependent variable (Y) via a mediator variable (M) is estimated using data of two measurement occasions (see Figure 2). The total effect of momentary stress at t-1 on psychotic experiences at t was apportioned into direct and indirect effects of negative affect at t, again, using the product of coefficients strategy. Using this strategy, we can quantify the point estimate of the indirect effect as the product of the coefficient of independent variable on the mediator variable (path a) and the coefficient of mediator variable on dependent variable (path b). For example, the point estimate of the indirect effect of momentary stress (X_{t-1}) on psychotic experiences (Y_t) through negative affect (M_t) is quantified as the product of the coefficient of momentary stress (X_{t-1}) on negative affect (M_t) (path *axm*, in Figure 2c) and the coefficient of negative affect (M_{t-1}) on

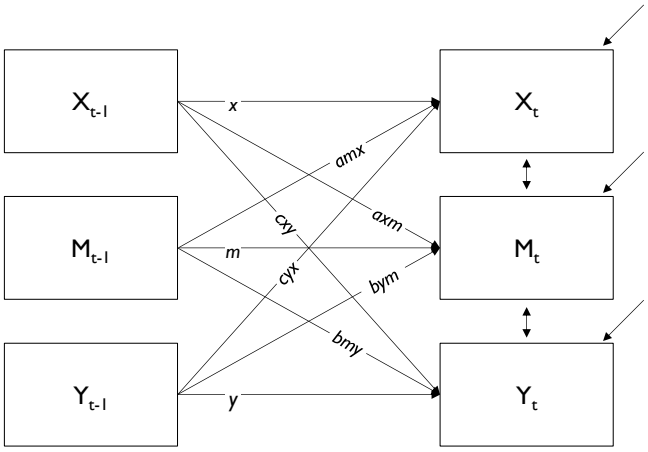
psychotic experiences (Y_t) (path *bmy*, in Figure 2c). In the same model, we proceeded likewise with the effect of psychotic experiences at t-1 on momentary stress at t via negative affect at t. Monte Carlo confidence intervals were computed for indirect effects according to the above mentioned procedure [32,33]. Again, group (patients, relatives, controls) was used as the moderator variable (level-2) of direct and conditional indirect effects in the analyses. Differences in conditional indirect effects between groups were subsequently computed using the model constraint command in Mplus [30]. Prior to running this comprehensive model, we fitted two separate models: One with pathways from momentary stress to psychotic experiences through negative affect (Figure 2a) and another one including pathways from psychotic experiences to momentary stress via negative affect (Figure 2b).



(a)



(b)



(c)

Figure 2. Schematic display of cross-lagged panel models. Display of pathways tested within each group: (a) Momentary stress at t-1 (X_{t-1}) on psychotic experiences at t (Y_t) via negatives affect at t (M_t); (b) psychotic experiences at t-1 (Y_{t-1}) on momentary stress at t (X_t) via negative affect at t (M_t); (c) all pathways tested in one comprehensive model. All models controlled for age and gender.

RESULTS

Basic sample characteristics

Basic sample characteristics and aggregate ESM scores for momentary stress, negative affect, and psychotic experiences are presented in Table 2. Both patients and relatives differed significantly from controls in aggregate ESM scores for momentary stress, negative affect and psychotic experiences. Interestingly, for momentary stress, aggregate ESM scores of patients and relatives resembled the most, while for negative affect and psychotic experiences, aggregate scores of relatives and controls were more similar.

Table 2. Sample characteristics and aggregate ESM scores for momentary stress, negative affect and psychotic experiences in patients, relatives, and controls

	Patients	Relatives	Controls	Patients vs. controls	Relatives vs. controls
N	245	165	244	—	—
Mean age (S.D.)	35.3 (10.8)	36.8 (12.6)	36.5 (10.8)	—	—
Age range	16 — 64	16 — 63	16 — 64	—	—
Gender					
Male (%)	111 (46)	68 (41)	111 (44)	—	—
Female (%)	132 (54)	97 (59)	132 (56)	—	—
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Δ B (95% CI)	B (95% CI)
Stress	2.68 (1.03)	2.60 (0.95)	2.49 (0.96)	-0.193 (-0.282 – -0.104)	-0.120 (-0.219 – -0.021)
Negative affect	1.89 (1.09)	1.34 (0 .67)	1.29 (0.55)	-0.613 (-0.724 – -0.502)	-0.053 (-0.177 – 0.070)
Psychotic experiences	1.65 (0.93)	1.11 (0.31)	1.09 (0 .25)	-0.560 (-0.654 – -0.466)	-0.018 (-0.123 – 0.087)

Cross-sectional multilevel moderated mediation models

To examine pathways from momentary stress to psychotic experiences via negative affect and the reverse from psychotic experiences to momentary stress via negative affect, we fitted two separate multilevel moderated mediation models (Table 3). The indirect effect of momentary stress on intensity of psychotic experiences via negative affect was significant at conventional levels ($P<.05$) in all groups. This indicated that an increase in stress was associated with higher levels of negative affect, which, in turn, was associated with more intense psychotic experiences. The relative contribution of this indirect effect was larger than the contribution of the direct pathway from momentary stress to psychotic experiences. This indirect effect was significantly greater in patients than in controls ($\Delta=0.001$; 95% CI [0.000 - 0.002]), greater in controls than

in relatives (Δ=0.014; 95% CI [0.016 - 0.012]), and greater in patients than in relatives (Δ=-0.015; 95% CI [-0.017 - -0.013]).

Turning to findings of psychotic experiences on momentary stress, there was evidence that the effect of psychotic experiences on momentary stress was significantly mediated by levels of negative affect in all three groups. Overall, the magnitude of these indirect effects was larger than those of reverse pathways (effects of stress on psychotic experiences via negative affect). The indirect effect was largest in controls (B=0.355; 95% CI [0.351 - 0.358]), second largest in patients (B=0.323; 95% CI [0.203 - 0.214]), and smallest in relatives (B=0.208; 95% CI [0.313 - 0.333]). Again, the relative contribution of this indirect effect was larger than the contribution of the direct effect from psychotic experiences to momentary stress. The indirect effect of psychotic experiences on momentary stress via negative affect was significantly different in all three groups. It was significantly greater in controls than in relatives (Δ=-0.032; 95% CI [-0.043 - -0.021]), greater in controls than in patients (Δ=-0.147 95% CI [-0.151 - -0.143]), and greater in patients than in relatives (Δ=0.115 95% CI [0.104 - 0.126]).

Longitudinal multilevel moderated mediation models

Model fit statistics are presented in supplementary Table S2. The comprehensive cross-lagged panel model showed a significantly better fit to the data than the autoregressive model or separate cross-lagged panel models. Results of the autoregressive model can be found in Table 4. Levels of momentary stress, negative affect and psychotic experiences at t-1 were significantly associated with levels at t (all p=0.000).

When we probed findings from the cross-sectional multilevel moderated mediation models, and examined indirect effects of momentary stress on psychotic experiences, and vice versa, indirect effects of psychotic experiences on momentary stress simultaneously in one longitudinal cross-lagged panel model with two time points, there was no evidence that the effect of momentary stress on psychotic experiences was mediated by negative affect in any of the three groups (Table 5). Interestingly, effects of psychotic experiences on momentary stress were mediated by negative affect in controls (B=0.005; 95% CI [0.001 - 0.007]). However, this did not hold true for the group of relatives and patients.

Table 3. Total, direct, and conditional indirect effects of cross-sectional multilevel moderated mediation models of stress, negative affect, and psychotic experiences, vice versa[a]

	Patients	Relatives	Controls
	adj. B (95% CI)	adj. B (95% CI)	adj. B (95% CI)
Momentary stress, negative affect, psychotic experiences			
Direct effect (Momentary stress → psychotic experiences)	**0.026 (0.022 – 0.029)**	**-0.010 (-0.016 – -0.004)**	**0.009 (0.005 – 0.012)**
Indirect effect[b] (Momentary stress → negative affect → psychotic experiences)	**0.058 (0.056 – 0.060)**	**0.043 (0.042 – 0.045)**	**0.057 (0.055 – 0.058)**
Total effect	**0.084 (0.080 – 0.087)**	**0.033 (0.027 – 0.039)**	**0.066 (0.062 – 0.070)**
Momentary psychotic experiences, negative affect, momentary stress			
Direct effect (Psychotic experiences → momentary stress)	**0.128 (0.107 – 0.148)**	**0.141 (0.119 – 0.162)**	**0.207 (0.187 – 0.226)**
Indirect effect[b] (Psychotic experiences → negative affect → momentary stress)	**0.323 (0.203 – 0.214)**	**0.208 (0.313 – 0.333)**	**0.355 (0.351 – 0.358)**
Total effect	**0.464 (0.445 – 0.482)**	**0.336 (0.319 – 0.353)**	**0.561(0.545 – 0.578)**

Note: SD, standard deviation; vs., versus; CI, confidence interval; significant indirect paths (P<0.05) are presented in bold. [a] Adjusted for age and gender

	Relatives vs. controls	*Patients vs. controls*	*Patients vs. Relatives*
	adj. B (95% CI)	adj. B (95% CI)	adj. B (95% CI)
Δ Indirect effects			
Momentary stress → negative affect → psychotic experiences	**-0.014 (-0.016 – -0.012)**	**0.001 (0.000 – 0.002)**	**-0.015 (-0.017 – -0.013)**
Psychotic experiences → negative affect → momentary stress	**-0.032 (-0.043 – -0.021)**	**-0.147 (-0.151 – -0.143)**	**0.115 (0.104 – 0.126)**

Table 4. Autoregressive effects (t-1 → t) of momentary stress, negative affect and psychotic experiences in patients, relatives, and controls

	Patients	Relatives	Controls
	B (95% CI)	B (95% CI)	B (95% CI)
$Stress_{t-1}$ → $stress_t$	0.174 (0.143 – 0.204)	0.147 (0.112 – 0.183)	0.146 (0.121 – 0.171)
Negative $affect_{t-1}$ → negative $affect_t$	0.278 (0.241 – 0.315)	0.192 (0.145 – 0.239)	0.187 (0.151 – 0.222)
Psychotic $experiences_{t-1}$ → psychotic $experiences_t$	0.279 (0.236 – 0.322)	0.252 (0.190 – 0.315)	0.169 (0.115 – 0.223)

Table 5. Total, direct, and conditional indirect effects of longitudinal multilevel moderated mediation models of stress, negative affect, and psychotic experiences[a]

	Patients	Relatives	Controls
	adj. B (95% CI)	adj. B (95% CI)	adj. B (95% CI)
Momentary stress, negative affect, psychotic experiences			
Direct effect (Momentary stress (t-1) → psychotic experiences (t))	-0.006 (-0.020 – 0.006)	0.000 (-0.005 – 0.005)	0.001 (-0.004 – 0.006)
Indirect effect[b] (Momentary stress (t-1) → negative affect (t)→ psychotic experiences (t))	0.001 (-0.001 – 0.001)	0.001 (-0.001 – 0.001)	0.000 (-0.000 – 0.000)
Total effect	-0.005 (-0.020 – 0.009)	0.001 (-0.005 – 0.007)	0.002 (-0.004 – 0.007)
Psychotic experiences, negative affect, momentary stress			
Direct effect (Psychotic experiences (t-1) → momentary stress (t))	0.041 (-0.014 – 0.087)	0.055 (-0.076 – 0.164)	0.002 (-0.096 – 0.085)
Indirect effect[b] (Psychotic experiences (t-1) → negative affect (t)→ momentary stress (t))	0.008 (-0.000 – 0.020)	0.013 (-0.009 – 0.153)	**0.005 (0.001 – 0.007**)
Total effect	0.048 (-0.006 – 0.095)	0.068 (-0.063 – 0.177)	0.008 (-0.091 – 0.091)

Note: SD, standard deviation; vs., versus; CI, confidence interval; significant indirect paths (P<0.05) are presented in bold. [a] Adjusted for age and gender

	Relatives vs. controls	*Patients vs. controls*	*Patients vs. Relatives*
	adj. B (95% CI)	adj. B (95% CI)	adj. B (95% CI)
Δ Indirect effects			
Momentary stress (t-1) → negative affect (t)→ psychotic experiences (t)	**0.000 (0.000 – 0.001)**	0.000 (-0.001 – 0.001)	0.000 (-0.001 – 0.001)
Psychotic experiences (t-1) → negative affect (t)→ momentary stress (t)	0.008 (-0.008 – 0.021)	0.003 (-0.006 – 0.164)	-0.005 (-0.020 – 0.007)

DISCUSSION

Principal findings

It was the central aim of the current study to investigate how stress and affective disturbances combine to increase intensity of psychotic experiences and to establish a temporal order thereof. We found that, cross-sectionally, an increase in stress was associated with higher levels

of negative affect, which, in turn, was associated with more intense psychotic experiences consistently across the three groups. Patients showed greater indirect effects of momentary stress on psychotic experiences than both relatives and controls, with relatives presenting the lowest values. Cross-sectional modelling of data further indicated that effects of psychotic experiences on momentary stress were mediated by levels of negative affect in all three groups. The strength of this indirect effect differed significantly in all three groups, with controls showing the largest values. There was, however, no evidence of temporal priority of stress and affective disturbances over psychotic disturbances, and in patients and relatives, psychotic experiences and affective disturbances over stress. Only in controls, we found that effects of psychotic experiences on momentary stress were mediated by affective disturbance.

Methodological considerations

The current findings should be viewed in the light of potential limitations. First, longitudinal models in the current study did not yield evidence for longitudinal effects across two measurement occasions. As has been proposed by Shiffman and colleagues, in ESM research, it is important that assessment schemes fit the phenomenon of interest and the estimation of how rapidly it is expected to vary [36]. In our study, lags between measurements were on average 90-minutes. Possibly, effects of stress on psychotic experiences, and vice versa, may have been too transient to be lingering from one moment to the next. Another possibility is, that lag duration in the current study was too long to detect changes, that, in fact, may be there. It would therefore be of interest to investigate, whether reducing the duration of lags, and therefore the time elapsed between measurement occasions, would produce different findings.

Second, in the current study we employed cross-sectional models as well as cross-lagged panel models of two measurement occasions to investigate how momentary stress and negative affect combine to increase psychotic experiences, and vice versa. Although fitting full cross-lagged panel models of three measurement occasions as described by Preacher [31] would have been a natural next step, we deem it unlikely that these models would have yielded evidence on temporal order given there was no evidence on this in cross-lagged panel models of two measurement occasions and the magnitude of indirect effects was very small and, for some, even trivial. However, this may be an important extension in the modeling strategy for future research.

Third, despite a number of benefits, pooling data from six different ESM studies may possibly entail disadvantages and may have produced a certain heterogeneity within the three groups of our sample. However, study protocols, in- and exclusion criteria were reviewed carefully before combining the six datasets. All studies employed comparable ESM protocols, using watches and booklets, on six (in one study five) consecutive days. Also, the in- and exclusion criteria for patients, relatives, and controls (see also supplementary Table S1) were comparable across the combined studies. We therefore believe that the heterogeneity has been kept to a minimum in the current study and may not provide a problem.

Fourth, ESM measures are based on subjective reports of participants and may therefore be less reliable, since for example, not all subjects may interpret questions in the same way. In addition, ESM data collection can be very time-intensive and possible be associated with assessment burden. Previous research, however, has shown that the ESM is a feasible, reliable, and valid assessment method in a variety of different populations [15,37,38]. Also, in all of the combined six studies, participants were extensively briefed on the ESM by a trained researcher prior to start of data collection, to ensure correct interpretation of the employed items and proper use of the data booklet and preprogrammed watch [13,15,23,27-29].

Comparison with previous research

In recent years, elevated reactivity to momentary stress has been suggested an important putative underlying mechanism in psychotic disorders [10,15,38]. In line with that, individuals with an increased risk for psychosis have been found to experience elevated levels of reactivity to momentary, minor stressors in daily life [13,15,38,39]. This has previously been coined the affective pathway to psychosis [10]. When turning to stress in more general terms, different models of psychosis have posited that the effects of stress are mediated by affective disturbance [6,7,40]. A recent study by our group provided new evidence for this proposition and found that the cross-sectional effects of momentary stress on psychotic experiences were indeed mediated by affective disturbances in daily life across different stages along the psychosis continuum [25]. Although, our findings are cross-sectional and therefore are insufficient for establishing a temporal order, we succeeded in replicating earlier findings suggesting that effects of stress on psychotic experiences are mediated by affective disturbance.

It has been proposed that psychotic experiences themselves may be distressing [22,23,41,42] and in many cases it is the experiences of distress with symptoms that leads to

the individual contacting psychiatric services [43]. In the current study, we investigated whether psychotic experiences are associated with affective disturbance, which in turn may be linked to increases in experiences of momentary stress. To our knowledge, so far, there is no study that examined this pathway in its entity in daily life. We found that in all three groups the effects of psychotic experiences were mediated by negative affect, with patients and controls showing the largest effects. Also, the magnitude of indirect effects in this cross-sectional pathway was considerably larger than those of the reverse (from momentary stress to psychotic experiences via affective disturbance), tentatively suggesting a greater impact of psychotic experiences on stress via negative affect than of stress on psychotic experiences through negative affect. Based on our findings, we can hypothesize that the occurrence of psychotic experiences may alter the appraisal of stress in daily life via experiences of affective disturbance. We believe that this pathway should receive more attention in future ESM studies, in order to get a better understanding of the momentary impact that psychotic experiences may have on the individual.

Relatives of patients with a psychotic disorder carry an increased risk for developing a disorder themselves [44] and have been reported to show increases in the intensity of subtle psychotic experiences and affective disturbance in reaction to momentary stress [45,46]. The findings of the current study, however, point towards a certain resilience in relatives of patients. Both relatives and patients showed similar mean levels of momentary stress that were larger than those experienced by controls. However, when looking at mean values of negative affect and psychotic experiences, levels of relatives were closer to those of controls and significantly smaller than those of patients. Furthermore, relatives showed the smallest effect magnitudes when compared to the other two groups. Based on these findings we can hypothesize that although relatives experience similar levels of momentary stress as patients in everyday life, these are linked to a smaller increase in negative affect and psychotic experiences. Our findings do not support the hypothesis that familial risk modifies how stress impacts psychotic experiences via affective disturbance, which has been proposed previously [15,47,48].

Conclusion

Taken together, our findings suggest strong fluctuations for the proposed affective pathway to psychosis and, more tentatively, a rapid vicious cycle of stress impacting psychotic experiences, and vice versa, via affective disturbances. This, in turn, highlights the importance of investigating

reciprocal effects between these aspects in future studies. The question, then, remains, whether rapid cycling of stress, affective disturbances and psychotic experiences contributes to persistence of psychotic experiences over time.

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SUPPLEMENTARY MATERIALS

Table S1. Overview of in- and exclusion criteria of merged studies

Study	N	
PREVENT [23]	N=26 Healthy controls	Inclusion criteria controls: (i) age between 18 and 45 Exclusion criteria controls: (i) current axis I disorder as assessed with the Structured Clinical Interview for DSM-IV [49] (ii) family history of psychotic disorder
MAPS [15]	N=139 Healthy controls (n=49); First-degree relative (n=47); Psychotic disorder (n=43)	Inclusion criteria for all participants: (i) age between 18 and 55 (ii) sufficient command of the Dutch language Exclusion criteria controls: (i) current use of psychotropic medication (ii) family or personal history of psychotic symptoms Inclusion criteria relatives: (iii) first-degree relatives with a lifetime occurrence of psychotic symptoms Exclusion criteria relatives: (i) lifetime occurrence of psychotic symptoms Inclusion criteria patients: (i) normal physical examination results (ii) lifetime occurrence of psychotic symptoms as assessed with the Life Chart , the Brief Psychiatric Rating Scale, the Positive and Negative Syndrome Scale (PANSS) [50], and the Operational Criteria Checklist for Psychotic illness (OPCRIT) [51] Exclusion criteria patients: (i) endocrine, cardiovascular, or brain disease (ii) excessive use of alcohol (≥5 standard units per day) (iii) weekly use of illicit drugs (iv) history of head injury with loss of consciousness (v) need for inpatient care
GROUP [52]	N=219 Healthy controls (n=83); First-degree relative (n=70); Psychotic disorder (n=66)	Inclusion criteria for all participants: (i) age between 16 and 55 (ii) sufficient command of the Dutch language Exclusion criteria controls: (i) first-degree relative with a psychotic disorder as assessed with the Family Interview for Genetic Studies [53] Inclusion criteria relatives: (ii) first-degree relatives with a lifetime occurrence of psychotic symptoms Exclusion criteria relatives: (i) use of steroid medication (ii) current axis I disorder (iii) lifetime history of psychotic disorder Inclusion criteria patients: (iii) DSM-IV diagnosis of nonaffective psychotic disorder as assessed with the Comprehensive Assessment of Symptoms and History [54] or Schedules for Clinical Assessment for Neuropsychiatry version 2.1 [55] Exclusion criteria patients: (i) brain disease (ii) history of head injury with loss of consciousness (iii) substance-related psychosis (iv) psychosis with a known organic cause
STRIP [52]	N=138 Healthy controls (n=48); First-degree relative (n=48); Psychotic disorder (n=42)	

(continued) **Table S1.** Overview of in- and exclusion criteria of merged studies

Study	N	
ZAPP [27,28]	N=113 Healthy controls (n=38); Psychotic disorder (n=75)	Inclusion criteria for all participants: (i) age between 18 and 65 (ii) sufficient command of the Dutch language Inclusion criteria controls: (i) average range score on symptom dimensions (between the 45th and 55th percentile) of the Community Assessment of Psychic Experiences (CAPE) [56] Exclusion criteria controls: (i) high scores on paranoid items (90th percentile) on the CAPE Inclusion criteria patients: (i) ICD-10 diagnosis of psychotic disorder as assessed with OPCRIT computer program [51], PANSS [50], and the Life Chart [57] (ii) current paranoid and/or positive psychotic symptoms or remitted psychotic symptoms as assessed with the PANSS [50] (items P1, P3, P5, P6, and G9)
Aripiprazole [29]	N=19 Psychotic disorder	Inclusion criteria patients: (i) age between 18 and 65 (ii) sufficient command of the Dutch language (iii) DSM-IV diagnosis of schizophrenia as generated with the OPCRIT computer program [51] (iv) insufficient therapeutic response to antipsychotic treatment (v) current use of a traditional dopamine antagonist antipsychotic Exclusion criteria patients: (i) hospitalization within 2 month prior to study (ii) endocrine, cardiovascular, or brain disease; history of neuroleptic malignant syndrome (iii) pregnancy or lactation (in women)

Table S2. Model fit statistics for cross-sectional, auto-regressive, cross-lagged panel mediation models

	Model fit statistics				
	LL	**FP**	**AIC**	**BIC**	**SABIC**
Auto-regressive model[a]	-46268.60	39	92615.21	92926.22	92802.28
Cross-lagged panel model (Momentary stress → negative affect → psychotic experiences)	-46149.10	51	92400.20	92806.91	92644.83
Cross-lagged panel model (Psychotic experiences → negative affect → momentary stress)	-46151.44	51	92404.87	92811.58	92649.50
Combined cross-lagged panel model[b]	-46046.42	63	92218.84	92721.24	92521.03

Note. LL=Log-Likelihood, FP=Free Parameters; AIC=Aikaike Information Criterion; BIC=Bayesian Information Criterion; SABIC= Sample-Size Adjusted Bayesian Information Criterion; [a] Model includes pathway from momentary stress to psychotic experiences, and vice versa; [b] Model includes longitudinal pathway from momentary stress to psychotic experiences via negative affect, and vice versa.

CHAPTER SIX

Ecological momentary interventions in psychiatry

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ABSTRACT

Purpose of review: In this review, we discuss feasibility, content, and where possible efficacy of ecological momentary interventions (EMIs) in psychiatry. EMIs adopt mobile devices, such as personal digital assistants or smartphones, for the delivery of treatments in the daily life of patients. We will discuss EMIs in the field of schizophrenia, bipolar disorder and major depression disorder, as well as one generic, transdiagnostic EMI.

Recent findings: The few studies that are available all underscore feasibility and acceptability of mobile health approaches in patients with severe mental illness. In terms of content, there is a huge variety in approaches ranging from a mixture of face-to-face contacts augmented with EMI components to a fully automated EMI. With regard to efficacy, only two randomized clinical trials have been conducted, supporting the efficacy of EMIs in mental health. Evidence seems to point toward greater efficacy when EMI is integrated with real-life assessment using experience sampling methodology, preferentially tailoring the intervention toward the specific needs of the individual as well as toward those moments when intervention is needed.

Summary: The review demonstrates that mobile health may be an important asset to the mental health field but underscores that it still is in its very early ages. In the discussion, we point toward ways of improving EMIs for severe mental illness, changing our perspective from testing feasibility to testing efficacy and ultimately implementing EMIs in routine mental health services.

INTRODUCTION

Rapid technological advances have opened new vistas for providing services to patients with psychiatric disorder. eHealth developments such as web-based interventions, serious gaming, or virtual reality treatments are all being investigated as treatment alternatives in mental health [1]. In this review, we will focus on a specific approach within the wide array of eHealth interventions, namely mobile health (mHealth). mHealth adopts mobile devices, such as personal digital assistants or smartphones, for the delivery of treatments in the daily life of patients, while they are engaging in their daily life activities. These interventions, also called ecological momentary interventions (EMIs), extend the therapy beyond the clinical setting into real life [2-4]. So far, mHealth and EMIs have proven useful in a wide range of health-related areas, its methods being deployed for the treatment of diabetes, asthma, weight loss, or smoking [5]. However, few studies have investigated the possibilities and the efficacy of EMIs for the treatment of severe mental illness.

This is surprising as there are many reasons to believe why EMIs could fundamentally contribute to a better outcome for this patient population. First, many people suffering from mental health problems never receive treatment. A European study showed that well over one-third of the population in any given 12-month period suffers from a mental disorder, most of which are not treated [6]. EMIs could lower the threshold to receive treatment, by making it cheaper and more easily accessible to a wider range of people. Second, adherence to both pharmacological and psychological treatment may improve using real-life monitoring and intervention, for example, by using behavioral prompts or reminders. Third, the integration of assessment and treatment in real life allows for individually tailored interventions; tailored not only to the symptoms and needs that are relevant to a specific individual, but also to providing treatment at moments when it is most needed, for example, at moments of high symptom intensity or at specific risk moments. Research has shown huge inter-individual variation in symptom patterns and associated risk profiles [7], underscoring the need for an individualized person-tailored approach. Fourth, most treatments are aimed at acquiring new skills and inducing changes in behavioral patterns. It is questionable whether conducting a therapy mainly in the therapist's office is the best approach to achieve changes that translate into individuals' real lives.

So, overall, an EMI approach, combining real-world assessment of symptoms and behavioral patterns based on experience sampling methodology (ESM) [8,9] or ecological

momentary assessment [10], with real-world delivery of treatment, seems to be a promising prospect for patients with severe mental illness. Yet, only a few studies report on EMIs in mental health. This questions whether EMIs are indeed feasible in patients with severe mental illness. Furthermore, what is the relevant content for these EMIs and do they indeed improve outcome in patients with severe mental illness? In the following review, we will discuss the feasibility, content and, where possible, efficacy of EMIs for schizophrenia, bipolar disorder, and major depressive disorder as well as one generic, transdiagnostic EMI. Based on the findings, we will then discuss ways of improving EMIs for severe mental illness.

Schizophrenia

Early mHealth approaches using text-messaging to support cognitive behavioral therapy already suggested feasibility in patients with psychotic disorder [11]. There is now one smartphone application, FOCUS, which is specifically developed to provide automated real-time and real-world illness management support to individuals with schizophrenia [12]. FOCUS consists of five modules targeting medication adherence, coping with symptoms, mood regulation, sleep problems, and improving social interaction [13]. For each module, evidence-based techniques such as cognitive restructuring, behavioral tailoring, social skills training, anger management, sleep hygiene, and behavioral activation are implemented. For each patient, three of these five modules are selected: medication adherence and two other 'high priority' areas.

The FOCUS app prompts study participants to provide a self-report three times daily, each time on a different treatment target. The patient's response determines the nature of the subsequent interventions they will receive. Furthermore, participants can access all intervention content 'on demand' whenever they need it. In a feasibility study, 33 individuals with schizophrenia used FOCUS for 1 month. Only one patient dropped out of the study and over 90% of the patients found FOCUS easy to use and useful, thus providing support for the feasibility, acceptability, and usability of FOCUS in this group of severely ill patients. Patients reported a decrease in Positive and Negative Syndrome Scale (PANSS) positive symptoms and PANSS general psychopathology, as well as a decrease in depression. No difference in PANSS negative symptoms was found. However, this pilot study did not use a control group, so the efficacy of FOCUS remains to be demonstrated [12].

FOCUS has some clear strengths. The app has been very carefully designed in close collaboration with patients, clinicians, and technicians [13]. It has been optimized in terms of

user friendliness, usability, and acceptability. It is tailored to the person's needs, it targets a wide array of problems, making it more applicable to a broader range of patients and the on-demand service is a clear asset, providing study participants with the tools to help themselves.

However, in contrast with the detailed and extensive information on the technological developments, much less information is available on the actual content of the intervention. The authors have selected evidence-based strategies and state that these have been translated to the mobile context, without providing much detail on how it was done and what the consequences were for the content of the treatment. Furthermore, each assessment inquires about one target area only, possibly limiting the scope for tailoring the treatment to the moment when it is most needed. Adding a more extensive self-report, possibly incorporating ESM, could be helpful in this respect.

Bipolar disorder

Monitoring of mood and sleep as well as the identification of early warning signals have always been crucial elements in the treatment of bipolar disorder. A real-life monitoring system, MONitoring, treAtment and pRediction of bipolAr Disorder Episodes (MONARCA), was tested as an extension of the traditional mood charts, providing patients with visual feedback on self-report assessments of mood, sleep, activity, and medication. A single-arm feasibility trial in 12 patients showed feasibility and usability over a 14-week period [14]. Another study piloted a handheld computer-delivered intervention designed to improve treatment adherence in bipolar disorder including two assessments per day over a period of 2 weeks. Again, feasibility and acceptability was demonstrated in 14 patients with bipolar disorder [15].

The first randomized clinical trial testing EMIs in patients with bipolar disorder used personalized real-time intervention for stabilizing mood (PRISM), an augmentative mobile EMI aimed at self-monitoring of mood states as well as planning action steps to address both symptoms and early warning signs [16]. Patients are prompted to fill out a survey identifying current context and mood state twice a day. Based on the reported symptoms or on the reported triggers or early warning signals, patients then receive predefined and personalized action steps. The patients also receive graphical representations of the self-reported mood items.

PRISM was tested in a 6-month randomized controlled trial in 104 patients with bipolar disorder. All patients started with four sessions of face-to-face intervention to identify an action

plan that specifies adaptive responses to depressive and manic symptoms on the one hand and early warning signs and triggers of illness exacerbation on the other. Then, patients were randomized into 10 weeks of either PRISM or paper-and-pencil mood monitoring once a day. Overall, the study showed that the PRISM intervention was highly feasible and acceptable. Furthermore, a significant decline in depressive symptoms was found in the PRISM condition compared to the paper-and-pencil mood chart. However, these effects were lost over the 24-week follow-up period. No effects were found on the secondary outcomes of mania or self-reported functional impairment [16].

The person-tailored approach, providing individualized action steps in response to self-reported mood and early-warning signs is clearly the strength of PRISM. The randomized clinical trial provides evidence on efficacy and is testing the active component of this mHealth approach as it compares PRISM with a paper-and-pencil mood chart. This study is thus one of the first to provide evidence for the added value of EMI in patients with severe mental illness. However, this study also points toward the limitation that patients did not manage to reach sustainable change. After the active phase of treatment, symptom levels in both groups converged.

Major depressive disorder

Two EMI studies have been published for patients with major depressive disorder. Mobilyze is a mobile phone and internet-based intervention, combining an EMI with an interactive website for behavioral skills training and e-mail support from a coach [17]. Participants were asked to provide their mood state five times a day and received tailored feedback in the form of a message being sent reinforcing improvement or suggesting a website tool in the case of deterioration. The website provided nine didactic lessons on principles of behavioral activation, each lesson being paired with an interactive tool to apply the treatment concepts discussed in the lesson in real life. The aim was to help patients get an insight into their daily activities and behaviors and based on that identify behaviors they would like to engage in more or less frequently. In a pilot study, eight participants were included, one of which dropped out because of technical problems. Both self-reported and evaluator-rated depressive symptoms decreased significantly over time [17].

The second study aimed to provide patients with insight into personal, contextualized patterns of positive affect, to ultimately induce behavioral change [18]. The therapy consisted

of 6 consecutive weeks of EMI using a palmtop (PsyMate) on 3 days per week. Patients received a signal at 10 random time points a day and were then asked to fill out a survey on their current positive and negative affect and the context (e.g., social context, current activities). Each week, participants received standardized feedback on these reports specifically focusing on the context related to positive affect. The standardized feedback did not include any instructions on what the person should change; it only provided information regarding the contextualized patterns of positive affect.

A randomized clinical trial was conducted in 102 depressed patients receiving antidepressant medication, who were randomized in three arms: EMI feedback, ESM but no feedback, and treatment as usual. Results showed that both the ESM without feedback and the EMI feedback condition resulted in a significant and clinically relevant decrease in depressive symptoms (both clinician-rated and self-report) compared to treatment as usual condition. However, 6 months after the end of therapy, depressive symptoms continued to improve in patients in the EMI feedback arm but not in the ESM only group [18]. Both the EMI feedback and the ESM condition resulted in behavioral change, with an increase in talking and a decrease in doing nothing/resting or being alone over time [19].

Both studies integrated real-life assessments of mood and context with real-time intervention; whereas Mobilyze integrated person-tailored feedback with access to a website tool, the EMI feedback study used the aggregated ESM information to increase awareness, and induce behavioral change. The EMI feedback study demonstrated that integrating real-life assessment and intervention may create a completely new therapy and, as such, moved beyond a mere extension of existing therapies into real-life context. However, the feedback was provided in a weekly face-to-face contact session with the researcher, making it a time-consuming and intensive treatment. It remains to be seen whether computerized and automated feedback would render the same results.

Acceptance and commitment therapy in daily life

Finally, generic EMI modules could be developed that extend beyond disorder-specific approaches and can be administered across diagnoses. One example is acceptance and commitment therapy (ACT) in daily life (ACT-DL) [20]. ACT-DL is an ACT-based EMI aimed at transferring skills and insights learned during weekly face-to-face ACT sessions into the practice of daily life. In addition to eight 45-min ACT sessions where the ACT methods are

introduced, patients engage in an 8-week mobile intervention that requires active exercise of ACT principles during the day. Patients are exercising the different ACT components within the scope of their current momentary experiences, making it a contextualized and person-focused approach. ACT-DL combines ESM self-monitoring, which supports raising awareness of one's inner experiences, with visual cues and brief ACT exercises. Moreover, patients are guided toward acting according to personal values, which they consider to be insufficiently present in their life [20]. An earlier version of the ACT-DL was piloted in 161 patients with varying Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, diagnoses, demonstrating feasibility and acceptability of ACT-DL [20]. Currently, a randomized clinical trial is testing its effectiveness in patients at ultra-high risk for psychosis (trial number NTR4252).

DISCUSSION

The few studies that are available all underscore feasibility and acceptability of mHealth approaches in patients with severe mental illness, which is in line with a recent qualitative report on the use of smartphone interventions in 394 patients [21]. Patients find it useful and show good compliance rates. In terms of content, there is a huge variety in approaches ranging from a mixture of face-to-face contacts augmented with EMI components to a fully automated EMI. With regard to efficacy, there is a very limited amount of research available to date. Overall, the limited evidence supports the efficacy of EMIs in mental health. Evidence seems to point toward greater efficacy when EMI is integrated with real-life assessment using ESM, preferentially tailoring the intervention toward the specific needs of the individual as well as toward those moments when intervention is needed, as was already pointed out by Heron and Smyth [3]. This review demonstrates that mHealth may be an important asset to the mental health field but underscores that it still is in its very early ages. What are the steps that need to be taken to push this field forward?

First, most progress so far has been made on the technological level. However, every research group is developing its own platform and app. Developing platforms that can be used across studies, across different EMIs and across diagnoses may boost clinical studies investigating efficacy, as such fostering clinical implementation. In addition, we need sophistication at the level of the feedback that is given to patients and clinicians. Intuitive and easy-to-use contextualized feedback should be further developed and refined in close collaboration with the different stakeholders. Furthermore, we need sophisticated algorithms

that define the individualized and person-tailored moments when feedback should be provided. Machine learning techniques could be applied to monitor and learn to recognize a patient's state and context [17] to eventually provide person-tailored contextualized feedback. However, this would require a large number of observations.

Second, we need to carefully think about the goals and the content of EMI. A survey among practitioners showed that in their view, mHealth approaches would be valuable in mental health if the system allowed for self-monitoring of symptoms and functioning, provided functions that support and expand services, and gave individuals tools they could access wherever and whenever needed [13]. Increasing accessibility and providing round-the-clock support definitely is important [22]. However, the question is whether this is ambitious enough. In addition to making treatment available to as many people as possible, we should also aim to improve existing interventions and even develop completely new ones. In addition to aiding patients in dealing with their disabilities, we should aim to create long-term and sustainable change [2]. To achieve this, we should shift our focus from the technological developments to the development of new content of these EMIs. Moving therapy out of the office into real life is more than just changing the delivery modus; it provides the opportunity for intervening in the day-to-day dynamics between the person and his/her environment that may be at the core of psychiatric symptoms. To make progress we need to improve our understanding of these daily life mechanisms. We need to understand in what context symptoms occur and how we could best intervene at the moments when they are occurring [4]. The limited evidence to date suggests that a true integration of ESM into the EMI is a necessity to achieve long-term behavioral changes. One step further is to include data from context-aware systems using sensor data that automatically provide input on relevant context variables [17].

Finally, we need to change our perspective from testing feasibility to testing efficacy and ultimately implementing EMIs in routine mental health services. Many therapists and researchers alike are skeptical about the technological 'gadgets' that are quickly entering the mental health arena. Rightfully so, as several have no evidence-based content nor have they been properly tested. This, however, should motivate us even more to further develop theoretically sound content and to conduct large-scale studies and randomized clinical trials providing real evidence for the added value of EMIs in the treatment of patients with severe mental illness.

CONCLUSION

The review demonstrates that mHealth may be an important asset to the mental health field but underscores that it still is in its very early ages. Only a few studies have been conducted to date, underscoring feasibility and hinting toward efficacy of EMIs in mental health. Both technological improvements and the development of new content of the EMIs will aid in changing the perspective from testing feasibility to testing efficacy and ultimately implementing EMIs in routine mental health services.

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CHAPTER SEVEN

General discussion

Humans are very complex. So are their emotions, thoughts and behaviors. The same holds true for the world we live in, every day we encounter a variety of different contexts and social situations. In science, reductionist approaches have long been the adopted strategies of choice to simplify the complexities of nature in order to understand them [1,2]. They have been quite successful, especially in physics, in reducing the complexity of nature to simple explanations [1]. An example is Isaac Newton, who succeeded to reduce all complex motions into three simple and straightforward laws. Also in psychiatry, reductionism and unimodal perspectives of psychiatric illnesses and phenomena have long been strived for [2]. For all major mental disorders alike, scientists have attempted to find that *one simple* explanation, no matter whether it were explanations of neurochemical, genetic or neuropathological nature. However, contemporary findings suggest that the etiological pathways of psychiatric symptoms are complex and interacting; and may therefore mismatch reductionist approaches [2]. Yet, when turning to statistical modeling, parsimony is still an important principle in psychiatry research, and models with few parameters are preferred over complex ones, if they prove to have a comparable explanatory power.

While reduced models may in general be very convenient for clinical practice and research, they may discount essential aspects of reality, as a possible pitfall of oversimplification. If we really want to find out why certain people struggle with stressors in daily life and develop complaints while others do not, we need to strive for methods that approximate and do this complexity justice. The central aim of this thesis was to investigate potential mechanisms and processes underlying the development of psychosis and elucidate them further by applying novel statistical methods to improve our understanding of the complex underpinnings of psychopathology.

MECHANISMS UNDERLYING THE DEVELOPMENT OF PSYCHOSIS

In search for processes and mechanisms underlying the development of psychosis, stress received great attention in research, when the vulnerability stress model was proposed by Zubin and Spring [3]. According to this model, different genetic, biological, psychological, and social factors, constitute an individual vulnerability level [3-5]. When stressors exceed this vulnerability level, psychiatric complaints emerge. Possibly, processes of stress-sensitization [6] may be underlying this vulnerability level and thereby link (early) environmental risk factors to increases in emotional reactivity to stress later in life. In **chapter two,** we found evidence

in a general population twin sample supporting this notion. More severe experiences of bullying and a lower subjective social status were associated with increased reactivity to an experimentally induced social stressor. The vulnerability stress model has been widely used in research and treatment of psychosis. The question, however, remains how stress exactly impacts on a person and increases the risk of developing psychiatric complaints [7,8]. Also, while this model proposes that stressors and vulnerability interact with each other, most studies have been focusing on studying either of them in isolation [8].

In the last two decades, technologies and innovative approaches have emerged and transformed the way we address research and investigate research questions in the field of psychopathology. Although intensive sampling strategies, such as the Experience Sampling Method (ESM), have long been part of psychology research [9], they in particular have benefited from recent technological developments. Here, the introduction of programmable watches, palm-top devices and mobile phone applications offered new possibilities to measure phenomena more regularly, and more importantly, in the daily life of individuals. In addition to overcoming limitations of recall bias, concerns of assessment error, and ecological validity of conventional research instruments, ESM research is capable of investigating time-varying subjective experiences close to when they occur in daily life [10-12]. ESM is able to capture small fluctuations in experiences and dynamic interactions thereof by measuring several times per day in different situations and contexts. Using ESM studies with time-based designs and stratified (semi-)random time sampling has proven valuable for elucidating the role that stress plays in psychosis further. As was already described in detail in **chapters three, four** and **five** of this thesis, reactivity to daily stress has repeatedly been suggested an important putative mechanism underlying the exacerbation of psychotic experiences [13]. This reactivity is characterized by an increased emotional response to minor stressors and routine daily hassles. Several studies have reported an elevated emotional reactivity to minor stressful events, activities, and social situations in individuals with a psychosis, and in individuals at increased familial and psychometric risk for developing a psychosis [8,14,15].

To further elucidate the stress-reactivity mechanism and involved underlying psychological processes, we applied a network approach as well as mediation models to ESM data in this thesis. We used the network approach to psychopathology to capture moment-to-moment associations, attempting to investigate not only whether there is evidence for micro-level associations but also whether we can establish a temporal order (**chapter three**). A time aspect was added by using time-lagged variables as predictors to the models.

This enabled us to investigate associations of experiences from one moment to the next. Especially with increased risk of developing psychosis, elevated levels of stress were directly associated with increases in affective and psychotic experiences the following moment. Also, with increases in risk for psychosis, the number of significant micro-level associations increased. We concluded that our findings are pointing towards stress-reactivity being a putative mechanism underlying the development of psychotic experiences. On a critical note, the analyses did not allow for statistical tests of indirect effects of stress on psychotic symptoms via affect. In **chapter four**, we tested these indirect effects of stress on psychotic experiences via affective disturbance and cognitive processes in one comprehensive cross-sectional model. This was achieved by fitting multilevel moderated mediation models to ESM data of three groups varying in risk for psychosis (individuals with a first episode of psychosis (FEP), individuals at an increased risk for psychosis (ARMS) and healthy control individuals). We found consistent evidence that stress increases the intensity of psychotic experiences via pathways through affective disturbance – in FEP individuals, ARMS individuals, and controls – with some evidence of greater indirect effects in FEP and ARMS individuals than controls. These findings were then replicated in the subsequent study (**chapter five**), in a different sample, which included three groups with a varying risk for psychosis. Additionally, we found evidence for an indirect effect from psychotic experiences on momentary stress via affective disturbance. Interestingly, the magnitude of this indirect effect was considerably larger than that of the reverse pathway (from stress to psychotic experiences via affective disturbance). To our knowledge, so far, no earlier study has investigated the effects of psychotic experiences on momentary stress through affective disturbance in daily life. Hypothetically, our findings point towards a comparably greater relevance of this pathway to the individual and at the same time suggest that increased levels of momentary stress in psychosis may be *caused* by psychotic experiences. This, in turn, may raise the question whether stress-reactivity really constitutes a link underlying the development of psychosis, or whether it is merely stress following psychotic symptoms. However, our findings from **chapter three, four** and **five** underline the relevance of momentary stress in the formation of psychotic experiences. More tentatively, bringing findings of **chapter five** together, at the moment that psychotic experiences may be present, rapid vicious cycles of stress impacting psychotic experiences, and vice versa, via emotional reactivity may ensue. Possible reciprocal effects between stress, emotional reactivity, and psychotic experiences, should be studied in future research, and should investigate how these associations may contribute to the persistence of psychotic

experiences over time. In addition to cross-sectional models, we further fitted cross-lagged panel models of two measurement occasions in **chapter five** to investigate associations longitudinally. In these models, we did not find evidence for longitudinal effects of stress on psychotic experiences via affective disturbance in any of the groups. Full cross-lagged panel models of three measurement occasions – as have previously been suggested by Preacher [16] – should be applied for further evidence of temporality.

In sum, the findings of **chapter three, four** and **five** underline the importance of stress-reactivity in the development of psychosis and the role that emotional reactivity may play as a putative mechanism through which stress impacts on the formation of psychotic experiences. Furthermore, our findings suggest complex interactions of psychological processes, stress and psychotic experiences in daily life and underline the need for methods that manage to embrace this complexity and are capable of, for instance, testing reciprocal relationships. We made first steps in testing the temporal order of associations by applying the network approach to multilevel models with time-lagged predictors in **chapter three** and cross-lagged panel models of two measurement occasions in **chapter five**. Following these steps further can provide very useful information on the causality of stress-reactivity in psychosis.

ECOLOGICAL MOMENTARY INTERVENTIONS

The central goal of psychiatry research is to develop prevention, treatment and rehabilitation strategies patients can benefit from. A recurring question then remains: How can new research, including work done in this thesis, be implemented best into (mental health) services? Several studies, including those presented in **chapter three**, **four** and **five**, suggest that stress-reactivity plays an important role in the development of psychotic experiences. This is the case along the continuum of psychosis, even before psychotic experiences reach the threshold being clinically significant complaints. Besides providing treatment strategies for severe symptoms of psychosis, it is worthwhile to implement preventive intervention strategies for individuals with subclinical complaints, targeting stress-reactivity in an early phase. As became apparent throughout this thesis, stress-reactivity is a dynamic process that is affected by, and interacts with, constant changes in the micro-level environment. Targeting stress-reactivity with intervention strategies delivered in real life, outside mental health services may therefore prove effective. These interventions are now commonly referred to

as Ecological Momentary Interventions (EMIs) and adopt mobile devices, such as palm-top devices or smartphones for the delivery of treatment in the daily life of individuals, while they are engaging in their everyday activities [17-19]. In **chapter seven,** we reviewed a variety of different interventions currently available for individuals with severe mental disorders, such as bipolar disorder, major depressive disorder, and psychotic disorder. Recent studies have suggested good feasibility and efficacy of EMIs in mental health. Although EMIs are still in their very early stages, they may be a promising addition to what is currently offered in mental health services. Technological improvements and development of new content, based on recent research findings, may aid EMIs even further to eventually become an integral part of mental health care.

These interventions can then be used to deliver treatment to individuals with (sub-) clinical complaints targeting stress-reactivity in the real world and in real life. One example of an intervention useful in this context, is Acceptance and Commitment Therapy (ACT) in Daily Life (ACT-DL) for individuals at-risk for developing a psychosis and individuals with a first episode of psychosis [20]. Just as in a conventional ACT intervention [21], the central aim is on the one hand to find other ways to approach unpleasant feelings and situations, and on the other hand, to determine personal values and take steps to invest in them again. In this group of individuals, it thereby targets stress-reactivity, altered reward-experience, and psychological flexibility. In addition to conventional weekly sessions with a therapist, patients receive a mobile phone application to practice learned skills and apply them directly in daily life.

FUTURE RESEARCH OF STRESS-REACTIVITY

So far, ESM has greatly improved our understanding of complex interactions of psychological processes, stress and psychotic experiences in daily life and several studies have found associations between stress-reactivity and psychotic experiences. However, these findings still provide insufficient evidence for the question whether these links are causal in nature. Building upon work done in this thesis, future research should be set up to investigate the causal nature of this putative mechanism.

Although differences in opinion still exist, there is some agreement of essential properties of causality [18,22]: First, there needs to be an association between the mechanism

and outcome, in our case between stress-reactivity and psychotic experiences, which we examined in **chapters three, four,** and **five.** Second, a temporal order needs to be established and it needs to be elucidated whether stress-reactivity precedes psychotic experiences. In **chapter three** and **five,** we made first steps in investigating this temporal order. Third, the direction of this association is of importance. Put differently, does a change in stress-reactivity lead to a change in psychotic experiences? Recently, these ideas have been further extended to what has been coined an interventionist causal model approach [18,23,24]. According to this idea, intervening and thereby altering putative causal factors is followed by changes in outcome. Once such a putative causal factor is identified, interventions should target this factor and subsequently lead to changes in outcome. An intervention targeting stress-reactivity should therefore have an impact on the psychotic outcome. However, as mentioned on several occasions throughout this thesis, this putative mechanism is by no means static, on the contrary, it is a very dynamic process that is in constant interaction with the (micro-level) environment. Therefore, it has been suggested that interventionist causal models should be applied to intensive longitudinal data as obtained in ESM studies [18]. Testing these models could provide information on several causal criteria at once (e.g., association, time order and direction). As proposed further above, EMIs, such as ACT-DL, could be used to target stress-reactivity in the daily life of the patient. The effectiveness of this ecological momentary intervention is currently investigated in an ongoing randomized controlled trial. Findings on the effect of this intervention on stress-reactivity may provide valuable information concerning the putative mechanism of stress-reactivity.

NETWORK MODELS IN TREATMENT

Triggered by movements such as the Quantified Self [25,26], monitoring lifestyle data, as well as fitness and health indicators is becoming increasingly popular to improve well-being and personal efficiency. An increasing number of people are using mobile apps and wearables to get a better insight into various aspects of their personal health, like their nutrition, blood pressure, sleep patterns and activity patterns [27]. Also, mental health monitoring has become a field of interest [28]. Tracking ourselves is becoming part of our lives.

Integrating self-tracking into mental healthcare, therefore, seems an obvious step. Providing patients with insights into their very own personal experiences may have various advantages [29]. Monitoring their own momentary data may help to create an awareness of

their own strengths and pitfalls (e.g., functional or dysfunctional behavioral patterns), thereby facilitating and reinforcing a sense of participation in their own care. In a recently conducted randomized controlled trial, depressive patients received a weekly summary of their ESM derived data [30]. The results of this study showed that this insight into personal data was effective in reducing depressive symptoms significantly.

In **chapter three** of the current thesis, we used the network approach to investigate longitudinal micro-level associations on group level. One possibility may be to create personalized networks, instead of group networks, for patients based on their own ESM data as an add-on diagnostic tool [31-33]. Such networks could then give an insight into how experiences cluster together and may help to create hypotheses on predictive relationships. For example, when looking at his/her own networks, a patient may see that when feeling stressed one moment, he/she often experiences feelings of anxiety the subsequent moment. Furthermore, such a network may visualize situations or activities where the patient is mostly satisfied and is less affected by symptoms.

Using personalized networks to provide feedback to patients may be a valuable addition to treatment in itself. In addition, decisions concerning beneficial intervention strategies can be made based on these networks [31,33]. In practice this may go as follows: Together with the therapist, patients can identify a number of central topics. Based on these topics, questions can then be generated that can subsequently be asked on several occasions on a number of consecutive days, using a dedicated device. Networks can then be created based on answers to these questions. These networks can provide new insights into specific micro-level associations meaningful for that particular patient, and can be used to establish an idea of potential causal pathways and to generate working hypotheses for treatment [31]. From a library of available exercises, the therapist can then select those that may be beneficial for the specific needs of the patient at a specific moment. These exercises could then be provided in the daily life of the patient.

Although the body of literature is accumulating and enthusiasm of possibilities the network approach holds for psychopathology is growing, research is still in its early days and caution will need to be exercised when using personalized networks in treatments [31,33,34]. A number of challenges concerning personalized networks remain, such as, the minimum required number of observations to create a reliable personalized network or the lag interval appropriate for the research question [31]. Also, until now, there have been no studies that

tested systematically whether personalized networks add something to clinical work and treatment. On a more general note, there is a recently emerged and ongoing debate concerning pitfalls of the network approach to psychopathology that still needs to be resolved. Central issues in this debate are the replicability and utility of networks with opinions on either side [35-38]. However, a lot of work is currently done to tackle those challenges to make sure that the network approach is applied appropriately to empirical problems [39]. Once these difficulties are overcome, the network approach to psychopathology may be very promising in dealing with complex micro-level dynamics for specific psychological problems and intra-individual time-series data.

CONCLUDING REMARKS

This thesis set out with the central aim to investigate potential mechanisms and processes underlying the development of psychosis. Approaching symptoms and experiences as something dynamic that changes in interaction with the (micro-) environment always made sense intuitively, yet acknowledging it in study designs and methods has been a great milestone in psychopathology research of recent decades. Although, acknowledging these dynamics has been an essential step, studies examining dynamic processes over time remain outnumbered. Research conducted in this thesis brought us, one step further, by investigating underlying processes using novel methods.

This thesis provides new evidence on the dynamic interplay between psychological processes and stress in the origin of psychosis and, thereby, contributes to improving our understanding of psychosis with its very complex etiologies. The findings of this thesis underscore the important role that emotional reactivity may play as putative mechanism through which stress impacts on the formation of psychotic experiences. Understanding processes underlying the occurrence and persistence of psychotic experiences, is valuable to gain a better understanding of when and how to intervene best to reduce the intensity of psychotic experiences. In turn, these findings provide valuable ground for translational research that uses ecological interventionist causal models, that uses treatment delivered in the real world, targeting these psychological processes in daily life. Informed development of evidence based interventions promoting the resilience to stress and sustainable change in psychosis outcome in everyday life is of importance for public health. It can also be considered

an important next step toward preventing onset and improving long-term outcomes of psychosis.

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CHAPTER EIGHT

Valorization

Valorization has been defined as "the process of value creation from knowledge, by making it applicable and available for economic or societal utilization, and by translating it in the form of new business, products, services, or processes" (p.8) [1]. In this chapter we will elaborate on how work done in this thesis may be valuable for, and eventually affect, society and economy.

The total costs for healthcare in the Netherlands have been rising in recent years. Together with cardiovascular diseases, mental disorders are among the most costly complaints for healthcare services [2]. When turning to Europe as a whole, the costs for mood disorders have recently been estimated at 113.4 billion euro, 74.4 billion euro for anxiety disorders, and 93.9 billion euro for psychotic disorders [3]. These costs are the combination of direct healthcare costs, non-medical costs (e.g., costs for extra resources for social service and education), and indirect costs (e.g., costs due to work absence or early retirement). In patients with psychotic disorders, these indirect costs form with 64.9 billion euro the largest proportion [3]. These indirect costs may emerge from impairments, disability, premature death, and legal problems which are frequently linked to loss of productivity [4]. While these numbers provide a concise overview of societal costs linked to psychotic disorders, they fail to express the personal burden and suffering, which patients and their relatives may be experiencing. Patients suffering from psychosis are frequently confronted with some degree of stigmatization and discrimination [5-7]. This makes that a majority of patients and their families chose not to speak about their condition to others, which may increase their feeling of isolation from society even further. Although prevalence rates for developing a full-blown psychotic disorder are relatively low with 3-4% [8], it can be concluded that these disorders may be of substantial burden to the affected individual, his/her social circle, as well as for society as a whole.

Research of recent years points towards a heterogeneity in the course and outcome of psychosis, and contrasting to what has long been believed, remission and recovery likewise are considered realistic endeavors. As introduced in chapter one of this thesis, there is accumulating evidence of the continuum notion of psychosis, of severity and persistence of experiences. It has been suggested that treatment early on in the course of psychosis, during a first episode, improves chances of transition greatly, with remission rates of around 80% [9]. Knowledge of mechanisms and psychological processes involved in the complex etiology of experiences along this continuum may prove valuable for setting up interventions and prevention strategies early in order to minimize the personal and societal burden of psychosis.

The current thesis investigated processes and mechanisms underlying the development of psychosis. In particular, we focused on the role of stress and its dynamic interplay with psychological processes and psychotic experiences in daily life. We found new evidence that emotional reactivity may play an important role as a putative mechanism through which stress impacts on the formation of psychotic experiences. Although some work done in this thesis may seem rather fundamental in nature, on the long run, insights into the underlying dynamics may improve prevention and treatment options for patients and thereby reduce societal, economic, and personal burden linked to psychosis.

Better insights into processes underlying the occurrence and persistence of psychotic experiences are valuable to gain understanding of when and how to intervene best to reduce the intensity of psychosis. Our findings stress the importance of complex micro-level dynamics in daily life underlying the development of psychosis and underline the importance of studying it in daily life. This knowledge is especially relevant for interventions provided in daily life of patients – Ecological Momentary Interventions. With these real-life interventions, leveraged by mobile devices, such as smartphones, treatment can be delivered at any time, and in almost any location – there where patients experience complaints. In chapter six of this thesis we provided an overview of currently available interventions provided in daily life of patients. Available interventions do seem promising, however, it is crucial that processes these interventions are targeting are properly investigated before treatments are provided to patients. Furthermore, randomized controlled trials are needed to reliably investigate the effectiveness of these treatments.

Ecological Momentary Interventions may not only be valuable as add-on and stand-alone delivery of treatment, they open up new endeavors for personalized medicine, as interventions taking inter-individual differences into account can be provided more easily. As a further step, these interventions may not be only tailored to the individual needs of patients, but can even provide exercises in real-time and real-life, depending on specific experiences or symptoms at that very moment. Personalized treatment that targets symptoms or symptom clusters central to a person at a particular moment may increase the efficacy and efficiency. This, in turn, may possibly be linked to reductions in healthcare costs and may maximize the quality of life of patients.

In sum, through the chapters of this thesis, it became apparent that micro-level dynamics in general, and emotional reactivity to minor daily stress in particular, may play an

important role in the formation of psychotic experiences. Interventions targeting these processes in daily life may therefore prove valuable for the prevention and treatment of psychotic experiences. In order to eventually create value from research findings of this thesis, it is essential to bridge the gap between science and clinical practice and to reach out to people that have the capacity to directly impact healthcare – policymakers and healthcare professionals. All findings of this thesis are therefore published in peer-reviewed journals and presented at national and international conferences. Conference contributions and publications in peer-reviewed papers, furthermore, aid the communication with fellow researchers. This communication is essential to constantly keep on challenging currently established ideas of processes underlying mental illness. Especially research lines studying micro-level processes in daily life are benefitting greatly from recent and ongoing technological advances. These, in turn, make it increasingly feasible to track and monitor data of various modalities throughout everyday life of individuals, resulting in datasets of increasing complexity.

In order to create something meaningful to patients, their friends and relatives and society as a whole, it is essential that researchers, clinicians, and policymakers work together closely. Involvement of patients in scientific research is essential not only to receive input on, and gain insights into challenges they are facing, but also to obtain feedback on interventions, and possibly, on the usability of proposed technological tools. Involving clinicians as sounding boards in research projects can further provide valuable information on flaws of current treatment options and the feasibility of proposed solutions. In turn, together, scientists and clinicians may then create great impact on patients' prognoses, by improving current treatment strategies and their implementation in the clinic.

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EPILOGUE

Summary

In this thesis we set out to investigate potential mechanisms and processes underlying the development of psychosis. In **chapter two,** we investigated whether the determinants of reactivity to stress in a general population twin sample are genetic or environmental factors, or a combination of both. Using a novel task, we exposed adolescent and young adult twins to peer evaluation – one possible source of social stress – comparable to what they may experience daily in online social interactions. The proportion of variance in reactivity to peer evaluation due to genetic and environmental factors, as well as the association with specific *a priori* environmental risk factors (e.g., childhood trauma, bullying experiences), was then estimated. We found evidence that more severe experiences of bullying and a lower subjective social status were associated with increased reactivity to an experimentally induced social stressor.

In **chapter three,** we examined stress-reactivity by studying micro-level dynamics in daily life in three samples varying on the continuum of psychosis – healthy control subjects, relatives of individuals with a psychotic disorder with a certain genetic liability for developing the disorder as well, and patients with a psychotic disorder. We applied a network approach to psychopathology to the experience sampling method (ESM) data to gain insights into the mechanisms at the level of micro-dynamic moment-to-moment effects between stress, other daily experiences and psychotic experiences. In particular, with an increased risk for developing a psychosis, elevated levels of stress were directly associated with increases in affective and psychotic experiences at the next moment. Furthermore, we found evidence that the number of significant micro-level associations increased with a higher risk for developing a psychosis. The findings of this study point towards stress-reactivity being a putative mechanism underlying the development of psychotic experiences.

In recent years, various models of psychosis have suggested that experiences of stress contribute to the development of psychotic experiences via pathways of negative affect, cognitive biases, and anomalous experiences. In **chapter four,** we systematically tested comprehensive models of these pathways in three samples that varied on the continuum of psychosis – healthy control subjects, individuals with an at-risk mental state for psychosis, and individuals with a first-episode psychosis. We fitted multilevel moderated mediation models to ESM data to investigate how stress, enhanced threat anticipation, and experiences of aberrant salience combine to increase psychotic experiences in daily life. There was consistent evidence that stress increases the intensity of psychotic experiences via pathways through

affective disturbance – in FEP individuals, ARMS individuals, and controls – with some evidence of greater indirect effects in FEP and ARMS individuals than controls.

In **chapter five,** we investigated whether findings of the previous chapter replicate in a different sample. Additionally, we investigated longitudinal associations of momentary stress, negative affect and psychotic experiences across two measurement occasions. This sample again consisted of three groups varying in risk for psychosis – healthy control subjects, relatives of individuals with a psychotic disorder, and patients with a psychotic disorder. Again, we found consistent evidence that stress increases the intensity of psychotic experiences via pathways through affective disturbance. Additionally, we found evidence for an indirect effect from psychotic experiences on momentary stress via affective disturbance. Interestingly, the magnitude of this indirect effect was considerably larger than that of the reverse pathway (from stress to psychotic experiences via affective disturbance). Tentatively, taken together, these findings suggest that there may be rapid vicious cycles of stress impacting psychotic experiences, and vice versa, via emotional reactivity. Only in controls, there was evidence of a longitudinal indirect effect of stress on psychotic experiences via negative affect.

There is accumulating evidence for micro-level dynamics of momentary experiences, affect and symptomatology. Real-world delivery of treatment, therefore, seems a promising prospect for patients and individuals with an increased risk for developing a disorder. In **chapter six,** we conducted a concise review on the feasibility, content and efficacy of currently available ecological momentary interventions in psychiatry. Findings of this review suggest that mobile health may be an important asset to mental health care, while at the same time it underscores that it is still in its early stages. Based on our findings, we discuss ways to improve ecological momentary interventions (EMIs) for severe mental illness to ultimately implement them in routine mental health services.

In sum, this thesis provides new evidence on the dynamic interplay between psychological processes and stress in the origin of psychosis and, thereby, contributes to improving our understanding of the complex etiology of psychosis. Our findings underscore the important role of emotional reactivity as putative mechanism through which stress impacts on the formation of psychotic experiences. Understanding these processes involved in the development and persistence of psychotic experiences provides us with further insights concerning prevention and treatment.

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Publications

LIST OF PUBLICATIONS

Scientific publications in international peer-reviewed journals

Klippel A, Reininghaus U, Viechtbauer W, Decoster J, Delespaul P, Derom C, De Hert M, Jacobs N, Menne-Lothmann C, Rutten B, Thiery E, Van Os J, Van Winkel R, Myin-Germeys I, Wichers M (2018) Sensitivity to peer evaluation and its genetic and environmental determinants: findings from a population-based twin study. Child Psychiatry & Human Development.

Klippel A, Viechtbauer W, Reininghaus U, Wigman J, van Borkulo C, Myin-Germeys I, Wichers M (2017) The cascade of stress: a network approach to explore differential dynamics in populations varying in risk for psychosis. Schizophrenia Bulletin.

Klippel A, Myin-Germeys I, Chavez-Baldini U, Preacher KJ, Kempton M, Valmaggia L, Calem M, So S, Beards S, Hubbard K, Gayer-Anderson C, Onyejiaka A, Wichers M, McGuire P, Murray R, Garety P, van Os J, Wykes T, Morgan C, Reininghaus U (2017) Modeling the interplay between psychological processes and adverse, stressful contexts and experiences in pathways to psychosis: an experience sampling study. Schizophrenia Bulletin.

Snippe E, Viechtbauer W, Geschwind N, **Klippel A**, de Jonge P, Wichers M (2017) The impact of treatments for depression on the dynamic network structure of mental states: two randomized controlled trials. Scientific Reports.

Myin-Germeys I, **Klippel A***, Steinhart H*, Reininghaus U (2016) Ecological momentary interventions in psychiatry. Current Opinion in Psychiatry. *contributed equally

Wigman J, van Os J, Borsboom D, Wardenaar K, Epskamp S, **Klippel A**, MERGE, Viechtbauer W Myin-Germeys I, Wichers M (2015) Exploring the underlying structure of mental disorders: cross-diagnostic differences and similarities from a network perspective using both a top-down and a bottom-up approach. Psychological Medicine.

Submitted and in progress articles

Klippel A, Myin-Germeys I, MERGE, Reininghaus U Modeling the moment-to-moment interplay between stress and affective disturbances in pathways to psychosis: an experience sampling study. In preparation.

Steinhart H*, Vaessen T*, Batink T, **Klippel A**, Van Nierop M, Reininghaus U, Myin-Germeys I ACT in daily Life: a momentary intervention approach. In preparation. *contributed equally

Reininghaus U, **Klippel A***, Steinhart H*, Vaessen T*, Van Nierop M, Viechtbauer W, Batink T, Kasanova Z, Van Aubel E, Quee P, Demunter H, Van Winkel R, Marcelis M, Van Amelsvoort T, Van der Gaag M, De Haan L, Myin-Germeys I Efficacy of Acceptance and Commitment Therapy in Daily Life (ACT-DL): study protocol for a multi-centre randomized controlled trial. *contributed equally

Scientific communications related to this thesis

2017 Oral presentation at the Fall Conference of the Dutch Association for Cognitive Behavioral Therapy (Veldhoven, The Netherlands)

2017 Oral presentation at the 9th Scientific Meeting of the International Society for Research on Internet Interventions (Berlin, Germany)

2017 Poster presentation at Annual Meeting of the Society for Research in Psychopathology (Denver, USA)

2017 Oral presentation at the Annual Conference of the Society for Ambulatory Assessment (Luxembourg, Luxembourg)

2016 Poster presentation at the 5th Biennial Schizophrenia International Research Society Conference of the Schizophrenia International Research Society (Florence, Italy)

2015 Poster presentation at the Annual Meeting of the Society for Research in Psychopathology (New Orleans, USA)

2015 Oral presentation at the Conference of the Dutch Association of Psychiatry (Maastricht, The Netherlands)

2015 Poster presentation at the International Convention of Psychological Science (Amsterdam, The Netherlands)

Biography

Annelie Klippel was born June 25th, 1987 in Berlin, Germany. There, she attended Gerhart-Hauptmann-Oberschule (Gymnasium) and in 2004/2005, she spent one year in Québec, Canada, where she went to both an English- and a French-speaking high school. Back in Berlin, she graduated in 2007, majoring in Biology and English. After her graduation, she enrolled into a Business Psychology Program at the Business School Potsdam, Germany. As part of this study she performed internships at eBay International Inc. and Kienbaum Management Consultants. In summer 2010, she graduated with a Bachelor's degree in Business Psychology and moved to Enschede, the Netherlands, to continue her studies at the University of Twente. There, she completed a pre-Master's program in Psychology, before enrolling into the Master's program of clinical Psychology, with the specialization 'Mental Health Promotion' in February 2012. During this program she completed a clinical internship at the Benjamin Franklin academic psychiatric hospital at Charité Berlin, Germany. She obtained her Master's degree in Psychology in February 2013 after finishing her thesis on the effectiveness of a self-help intervention for patients with mood disorder. In July 2013, she moved to Maastricht, where she started her doctoral training at the Department of Psychiatry and Neuropsychology in the team of Prof. Myin-Germeys, Prof. Wichers and Dr. Reininghaus. In 2015 she also enrolled into a doctoral program at the Center for Contextual Psychiatry at the KU Leuven, Belgium, as part of a joint PhD degree. During her PhD, she was involved in several projects studying processes and mechanisms underlying the development of, and possible treatment options for, psychosis.