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

Running title: Interplay between psychological processes and stress in psychosis

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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 three 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 three 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.

Key words: stress sensitivity/aberrant salience/threat anticipation/experience sampling method/first-episode psychosis/at-risk mental state

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 socio-environmental 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 towards 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.[4,5,21,23]

Stress-induced emotional and cognitive changes may result in anomalous experiences such as experiences of aberrant novelty and salience in vulnerable individuals.[4,28] 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),[3,4,29] 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.[3,29]

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),[30] a structured diary technique, in a sample of individuals with a first episode of 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.

[Insert Figure 1]

Method

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.[31] 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) [32]; 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,[33] 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;[31,34] command of the English language. Exclusion criteria were: prior experience of a psychotic episode for more than one week as determined by the CAARMS and Structured Clinical Interview for DSM Disorders;[35] previous treatment with an antipsychotic for a psychotic episode; IQ<60 measured with an adapted version of the WAIS.[31,36] 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 socio-demographic 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.[16,17,37] Further information on the ESM procedure and variables are presented in Table 1.

[Insert Table 1]

Statistical analysis

Multilevel moderated mediation models were fitted in MPlus, Version 7,[38] 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 a) FEP than in controls, b) ARMS than in controls, and c) FEP than in ARMS [39-41] 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.[42] 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 1). ARMS and FEP individuals showed higher levels of stress, negative affect, aberrant salience, threat anticipation, and PE compared to controls (Supplementary Table 2). The magnitude of correlations between stress, negative affect, aberrant salience, threat anticipation, and PE was moderate to small (Supplementary Table 3).

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<0.05) 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<0.05).

[Insert Table 2]

Models including pathways from stress to PE via threat anticipation showed that, in all three 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=0.011). 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=0.010), which was, in turn, associated with less intense PE (B=0.190, P<0.001) 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 three 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 $P<0.049$; Table 3, Supplementary Figure 1). 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 ($B=0.018$, $P=0.039$) and, at trend level, in FEP individuals than controls ($B=0.017$, $P=0.072$).

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<0.001) and controls (B=0.005, P=0.004), 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 threat anticipation followed by negative affect 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=0.009), 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.

[Insert Table 3]

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.

[Insert Figure 2]

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 modelling of ESM data,[43-46] 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.[16,17,37,47] 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.[48]

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 three 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 three distinct pathways (affective disturbance, aberrant salience, threat anticipation), which reflects the complexity of current models of the aetiology 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.[3-7,13,22,23] 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.[16,17,49,50] 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.[23,27] 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 towards 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.[51]

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.[28]

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[4,28] 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.[28] 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 anti-psychotic 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 aetiologies. 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.[11,52] 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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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)[53] as well as in the current study (Cronbach's α=0.90).[18] 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)[53] as well as good concurrent validity with negative affect ($r=0.68$, P<0.001).[18]

[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, behaviours, social situations, and neighbourhood 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.

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‡	—		—		—	
Social stress, aberrant salience, psychotic experiences						
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)	0.026 (-0.001 – 0.046)	0.095	0.017 (-0.012 – 0.049)	0.443	0.017 (-0.004 – 0.030)	0.220
Indirect effect[b] (Negative affect → aberrant salience → psychotic experiences)						
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

Table 2. *(continued)*

Pathways via threat anticipation

Pathway	FEP adj. B (95% CI)	FEP P	ARMS adj. B (95% CI)	ARMS P	Controls adj. B (95% CI)	Controls P
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
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

Δ Indirect effects

Pathway	ARMS vs. controls adj. B (95% CI)	P	FEP vs. controls adj. B (95% CI)	P	FEP vs. ARMS adj. B (95% CI)	P
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

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, employment status, area-related stress and outsider status

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

[‡] Model estimation did not terminate normally

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 (0.033 – 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
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

Table 3. *(continued)*

	FEP adj. B (95% CI)	FEP P	ARMS adj. B (95% CI)	ARMS P	Controls adj. B (95% CI)	Controls P
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 – 0.046)	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):

Δ Indirect effects

|	ARMS vs. controls adj. B (95% CI)	P	FEP vs. controls adj. B (95% CI)	P	FEP vs. ARMS adj. B (95% CI)	P
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	0.000 (-0.001 – 0.001)	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	-0.004 (-0.018 – 0.012)	0.642	0.000 (-0.000 – 0.001)	0.446	-0.001 (-0.017 – 0.015)	0.109
Social stress → threat anticipation → psychotic experiences	0.000 (-0.001 – 0.000)	0.379	0.000 (-0.000 – 0.001)	0.141	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
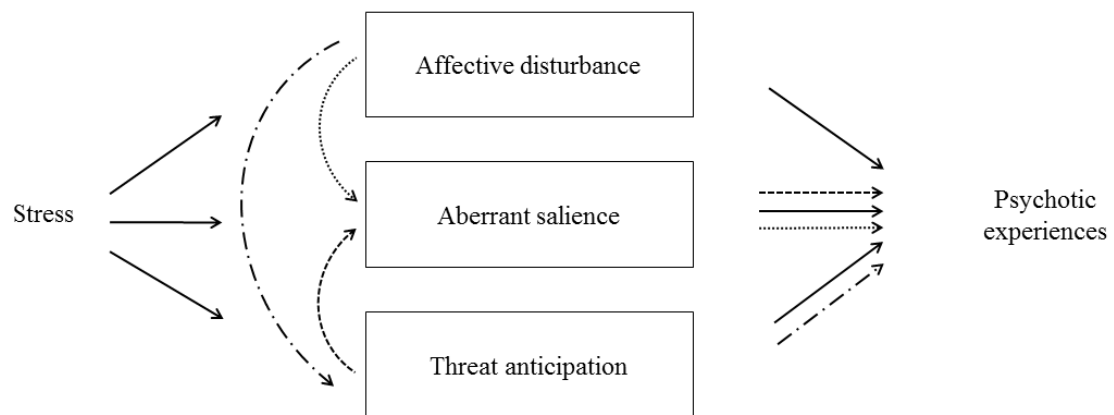
Figure 1. Schematic representation of pathways tested within each group: The following hypotheses were tested within each group: (1) stressful contexts and experiences in daily life increase the intensity of psychotic experiences through their impact on affective disturbance, enhanced threat anticipation, 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 age, gender, ethnicity, level of education, employment status, area-related stress and outsider status as potential confounders
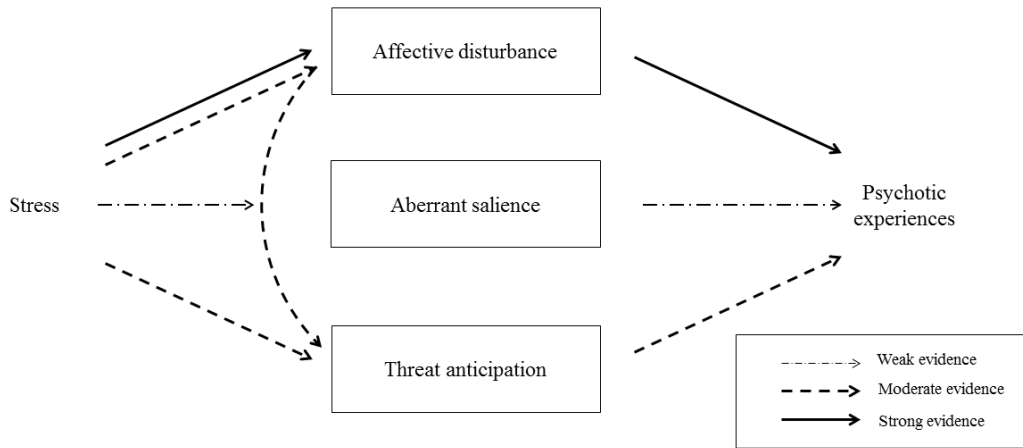
Figure 2. Schematic representation of main findings across groups. This figure gives an overview of indirect effects of stress on psychotic experiences via pathways through affective disturbance, enhanced threat anticipation, and aberrant salience. Only findings with at least one significant indirect path in at least one group were considered in this representation. See Supplementary Figure 1 for a detailed breakdown of significant (P<0.05) indirect effects for each group and marker of stress. For pathways through affective disturbance, strong and consistent evidence (———→) was observed across all three groups. For pathways through threat anticipation as well as through affective disturbance and threat anticipation (- - - - -→), the strength and consistency of evidence was, overall, moderate across the three groups. Overall, weak and inconsistent evidence was found for pathways through aberrant salience (–·–·–·→).

Supplementary Table 1. Basic sample characteristics

	FEP (n=51)	ARMS (n=46)	Controls (n=53)	Test statistic	p
Age (years), mean (S.D.)	28.3 (8.6)	23.6 (4.7)	35.0 (12.6)	$F=18.6$, df=2	<0.001
Gender, n (%)				$\chi^2=1.0$, df=2	0.612
Men	28 (54.9)	21 (45.7)	25 (47.2)		
Women	23 (45.1)	25 (54.4)	28 (52.8)		
Ethnicity, n (%)				$\chi^2=14.0$, df=10	0.174
White British	14 (27.5)	17 (37.0)	25 (47.2)		
Black African	17 (33.3)	7 (15.2)	8 (15.1)		
Black Caribbean	11 (21.6)	7 (15.2)	6 (11.3)		
Asian	1 (2.0)	1 (2.2)	3 (5.7)		
White Other	4 (7.8)	5 (10.9)	5 (9.4)		
Other	4 (7.8)	9 (19.6)	6 (11.3)		
Place of birth, n (%)				$\chi^2=1.9$, df=2	0.396
UK-born	32 (62.7)	34 (73.9)	33 (62.3)		
Non-UK-born	19 (37.3)	12 (26.1)	20 (37.7)		
Level of education, n (%)				$\chi^2=24.3$, df=4	<0.001
School	17 (33.3)	13 (28.9)	8 (15.1)		
Further	25 (49.0)	24 (53.3)	15 (28.3)		
Higher	9 (17.7)	8 (17.8)	30 (56.6)		
Employment status, n (%)				$\chi^2=28.5$, df=2	<0.001
Unemployed	30 (58.8)	15 (32.6)	5 (9.4)		
Other	21 (41.2)	31 (67.4)	48 (90.6)		
OPCRIT Psychotic disorder diagnosis[a], n (%)				–	–
Schizophrenia	15 (31.3)	–	–		
Delusional disorder	3 (6.3)	–	–		
Schizoaffective disorder	3 (6.3)	–	–		
Manic psychosis	7 (14.6)	–	–		
Depressive psychosis	7 (14.6)	–	–		
Psychotic disorder NOS	13 (27.1)	–	–		
SCID Comorbid affective disorder diagnosis, n (%)				–	–
Mood disorder	–	5 (10.9)	–		
Anxiety disorder	–	15 (32.6)	–		
Mood and anxiety disorder	–	3 (6.5)	–		
Psychotropic medication[b], n (%)				–	–
Antipsychotic[c]	40 (81.6)	5 (11.9)	0 (0.0)		
Atypical	36 (76.6)	5 (11.9)	0 (0.0)		
Typical	1 (2.1)	0 (0.0)	0 (0.0)		
Atypical and typical	1 (2.1)	0 (0.0)	0 (0.0)		
Antidepressant	11 (22.9)	17 (40.5)	0 (0.0)		
Other	12 (25.0)	4 (9.5)	9 (17.0)		
None	4 (8.2)	22 (52.4)	44 (83.0)		

Note: FEP, First-Episode Psychosis; ARMS, At-Risk Mental State for psychosis; S.D., standard deviation; df, degrees of freedom; OPCRIT, Operational Criteria system; SCID, Structured Clinical Interview for DSM Disorders; Missing values: [a]3, [b]6
[c] Antipsychotic medication in ARMS individuals was *not* for a psychotic episode (see exclusion criteria)

Supplementary Table 2. Aggregate ESM scores for stress, negative affect, aberrant salience, threat anticipation and psychotic experiences in FEP, ARMS, and controls

	FEP	ARMS	Controls	FEP vs. controls		ARMS vs. controls	
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	B (95% CI)	p	B (95% CI)	p
Stress							
Event	3.70 (0.77)	3.53 (0.74)	3.24 (0.69)	0.46 (0.37 – 0.55)	<0.001	0.29 (0.19 – 0.38)	<0.001
Activity	3.42 (0.90)	3.15 (0.78)	3.0 (0.50)	0.43 (0.34 – 0.52)	<0.001	0.15 (0.07 – 0.24)	0.001
Social	3.48 (0.89)	2.91 (0.84)	2.66 (0.72)	0.83 (0.72 – 0.92)	<0.001	0.25 (0.15 – 0.34)	<0.001
Negative affect	3.04 (1.23)	3.0 (1.08)	1.91 (0.70)	1.13 (1.05 – 1.21)	<0.001	1.10 (1.02 – 1.18)	<0.001
Aberrant salience	2.87 (1.27)	2.40 (1.13)	2.19 (1.22)	0.68 (0.59 – 0.77)	<0.001	0.21 (0.12 – 0.31)	<0.001
Threat anticipation	2.62 (1.25)	2.97 (1.33)	1.87 (0.84)	0.75 (0.65 – 0.85)	<0.001	1.11 (1.01 – 1.21)	<0.001
Psychotic experiences	2.55 (1.27)	2.40 (1.13)	1.47 (0.59)	1.08 (1.01 – 1.15)	<0.001	0.93 (0.86 – 1.01)	<0.001

Note: ESM, Experience Sampling Method; FEP, First-Episode Psychosis; ARMS, At-Risk Mental State for psychosis; S.D., standard deviation; CI, confidence interval

Supplementary Table 3. Multivariate multilevel model correlations at beep level between the stress variables, negative affect, psychotic experiences, threat anticipation, aberrant salience, controlled for age and gender.

Association	FEP			UHR			Controls		
	CC	SE	95% CI	CC	SE	95% CI	CC	SE	95% CI
Event-related stress & negative affect	0.142	0.023	0.096 - 0.187	0.220	0.023	0.175 - 0.264	0.186	0.020	0.146 - 0.224
Social stress & negative affect	0.217	0.022	0.173 - 0.261	0.294	0.022	0.251 - 0.336	0.322	0.018	0.285 - 0.357
Activity stress& negative affect	0.321	0.021	0.279 - 0.362	0.403	0.020	0.363 - 0.442	0.376	0.018	0.341 - 0.410
Event-related stress & threat anticipation	0.096	0.023	0.050 - 0.142	0.146	0.023	0.010 - 0.191	0.121	0.020	0.082 - 0.161
Social stress & threat anticipation	0.113	0.023	0.067 - 0.159	0.186	0.023	0.140 - 0.230	0.127	0.020	0.087 - 0.166
Activity & threat anticipation	0.173	0.023	0.128 - 0.218	0.278	0.022	0.235 - 0.321	0.223	0.019	0.191 - 0.267
Event-related stress & aberrant salience	-0.091	0.023	-0.137- -0.045	-0.021	0.024	-0.069 - 0.026	-0.019	0.021	-0.059 - 0.021
Social stress & aberrant salience	-0.022	0.024	-0.068 - 0.025	-0.004	0.024	-0.051 - 0.043	-0.007	0.021	-0.047 - 0.033
Activity & aberrant salience	-0.010	0.024	-0.056 - 0.037	0.053	0.024	0.006 - 0.099	0.013	0.021	-0.027 - 0.053
Event-related stress & psychotic experiences	0.079	0.024	0.033 - 0.125	0.096	0.024	0.050 - 0.143	0.092	0.020	0.052 - 0.132
Social stress & psychotic experiences	0.068	0.024	0.022 - 0.114	0.188	0.023	0.142 - 0.233	0.182	0.020	0.143 - 0.221
Activity stress & psychotic experiences	0.227	0.022	0.183 - 0.271	0.284	0.022	0.241 - 0.327	0.212	0.020	0.173 - 0.250
Aberrant salience & negative affect	0.099	0.023	0.052 - 0.144	0.059	0.024	0.012 - 0.105	0.061	0.020	0.021 - 0.101
Threat anticipation & negative affect	0.249	0.022	0.205 - 0.292	0.830	0.051	0.699 - 0.907	0.265	0.019	0.228 - 0.302
Psychotic experiences & negative affect	0.464	0.019	0.427 - 0.500	0.482	0.018	0.446 - 0.518	0.464	0.016	0.432 - 0.495
Threat anticipation & psychotic experiences	0.262	0.022	0.218 - 0.304	0.214	0.023	0.169 - 0.259	0.237	0.019	0.198 - 0.274
Threat anticipation & aberrant salience	0.018	0.024	-0.028 - 0.065	0.011	0.024	-0.036 - 0.057	0.076	0.020	0.036 - 0.116
Psychotic experiences & aberrant salience	0.311	0.021	0.269 - 0.353	0.335	0.021	0.293 - 0.376	0.286	0.019	0.249 - 0.323

Note. CC, correlation coefficient; SE, standard error; 95% CI, 95% confidence interval
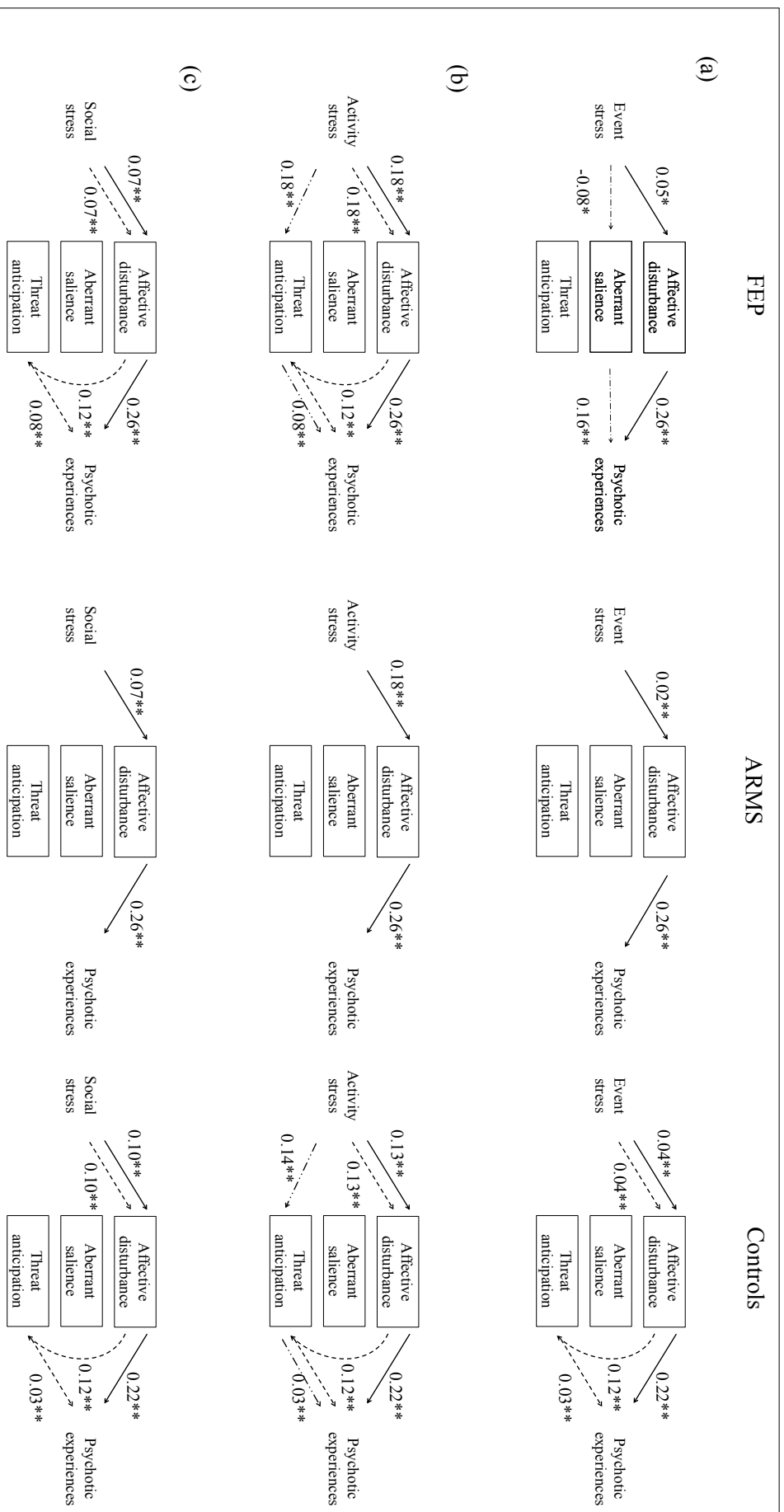
Supplementary Figure 1. Display of individual path coefficients for significant indirect effects (i.e., the product of individual path coefficients; shown in Table 3) of (a) event-related stress, (b) activity-related stress, and (c) social stress on psychotic experiences via affective disturbance (──────), 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

Online Supplementary Methods

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,[38] to control for within-subject clustering of multiple observations,[39, 42] 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[41] 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.[40, 42] 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.[40, 54] 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[38] and calculating

respective Monte Carlo confidence intervals.[40, 39] 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.[42] 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.