

Increased stress reactivity: a mechanism specifically associated with the positive symptoms of psychotic disorder

T. Lataster^{1*}, L. Valmaggia², M. Lardinois¹, J. van Os^{1,2} and I. Myin-Germeys^{1,3}

¹ Department of Psychiatry and Psychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University Medical Centre, The Netherlands

² Institute of Psychiatry, King's College London, UK

³ School of Psychological Sciences, University of Manchester, UK

Background. An increased reactivity to stress in the context of daily life is suggested to be an independent risk factor underlying the positive symptoms of psychotic disorder. The aim of this study was to investigate whether positive symptoms moderate the association between everyday stressful events and negative affect (NA), known as stress reactivity. This hypothesis was put to the test in patients with a diagnosis of psychotic disorder.

Method. The Comprehensive Assessment of Symptoms and History (CASH) and the Positive and Negative Syndrome Scale (PANSS) were used to assess positive and negative symptoms. The experience sampling method (ESM), a structured diary technique, was used to measure stress reactivity and psychotic symptoms in daily life.

Results. Higher levels of positive symptoms (CASH: $B=0.14$, $p=0.005$; PANSS: $B=0.05$, $p=0.000$; ESM: $B=0.03$, $p=0.000$) and lower levels of negative symptoms (PANSS: $B=-0.05$, $p=0.001$) significantly moderate the association between unpleasant events and NA. No significant moderating effect was found for CASH negative symptoms. Moreover, the moderating effect of lifetime and current symptoms on the stress–NA association was significantly larger for those patients with predominantly positive symptoms (CASH: $B=0.09$, $p=0.000$; PANSS: $B=0.08$, $p=0.000$; ESM: $B=0.13$, $p=0.000$).

Conclusions. Patients with a ‘psychotic syndrome’ with high levels of positive symptoms and low levels of negative symptoms show increased reactivity to stress in daily life, indicating that stress reactivity is a possible risk factor underlying this syndrome.

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Introduction

The development of the fifth edition of the *Diagnostic Manual of Mental Disorders* has fueled the discussion about whether schizophrenia is a valid and useful entity (Kendell & Jablensky, 2003; Keller *et al.* 2011). Several authors have favored a combination of a dimensional and categorical approach in which patients have more or less psychopathology rated on several symptom dimensions (Cuesta & Peralta, 2008; van Os, 2009; van Os & Kapur, 2009; Tandon & Carpenter, 2012). Symptom dimensions may constitute more

homogeneous entities with similar symptom patterns, etiology, prognosis and possibly treatment. They may thus be interesting phenotypes both for molecular genetic studies and for revealing patterns of unique liability specifically associated with single symptom dimensions. Liddle (1987) describes a three-factor solution (positive, negative and disorganization). Dikeos *et al.* (2006) conclude that a five-factor structure is the best fit describing the distribution of symptoms across Kraepelinian divisions (mania, reality distortion, depression, disorganization and negative symptoms). McGrath *et al.* (2004, 2009) report nine- and five-factor solutions, both including negative and positive symptom factors. Thus, several symptom dimensions have been found with factor analyses (Liddle, 1987; Buchanan & Carpenter, 1994; Lindenmayer *et al.* 1994; McGrath *et al.* 2004, 2009; Dikeos *et al.* 2006; Jablensky, 2006; Villalta-Gil *et al.* 2006), with the positive and

* Address for correspondence: Dr T. Lataster, Department of Psychiatry and Psychology, Maastricht University Medical Centre, PO Box 616 (VIJV), 6200 MD Maastricht, The Netherlands.
(Email: t.lataster@maastrichtuniversity.nl)

negative symptom dimension being the most prominent.

The theoretical background for this positive-negative dichotomy dates back to the 1970s to 1980s, where positive and negative symptoms (Strauss *et al.* 1974), type I *versus* type II (Crow, 1980) and deficit-*versus* non-deficit schizophrenia (Carpenter *et al.* 1988) were first described, with coinciding construction of rating scales assessing this dichotomy (Andreasen & Olsen, 1982; Kay *et al.* 1987; Kirkpatrick *et al.* 1989). The positive (or 'reality distortion') symptom dimension typically constitutes delusions, hallucinations and positive formal thought disorder. The negative (or 'psychomotor poverty') dimension comprises problems with emotion experience (e.g. anhedonia, avolition, apathy) and emotion expression (e.g. blunted/restricted affect). Positive symptoms typically fluctuate over time periods of hours and even minutes whereas negative symptoms are thought to be fairly stable over time.

For the negative symptom dimension, a modest but consistent correlation has been found with cognitive impairments (Keefe *et al.* 2006; Dominguez *et al.* 2011; Lataster *et al.* 2012). Reports on possible risk factors for the positive symptoms of psychosis are less consistent. Aberrations in social cognition have been suggested. However, mixed results have been reported (Freeman, 2007; Versmissen *et al.* 2007; Lincoln *et al.* 2010). Alternatively, increased reactivity to the environment has been suggested.

It is well established that environmental stresses, such as life events (Bebbington *et al.* 1996), childhood trauma (Bebbington *et al.* 2004; Janssen *et al.* 2004; Varese *et al.* 2012) or bullying (Lataster *et al.* 2006), play a role in the development of psychotic disorder. Neuroticism questionnaires are often used to assess an individual's stress sensitivity, and it has been shown that people with schizophrenia report higher levels of neuroticism (Horan *et al.* 2005). Moreover, neuroticism scores have been associated with positive symptoms (Lysaker *et al.* 2003; Barrantes-Vidal *et al.* 2009) and with increased risk for psychosis at both the clinical and subclinical level (van Os & Jones, 2001; Krabbendam *et al.* 2002). In one experimental study using a speech stress task, higher levels of trait arousability (an individual's emotional and physiological reactivity to novel events) were found to be associated with positive and affective symptoms (Dinzeo *et al.* 2004). However, these findings were only partly replicated (i.e. a significant association for affective but not positive symptoms) in a later study (Dinzeo *et al.* 2008). Docherty *et al.* (2009) found that trait arousability moderated the association between life events and positive symptoms, with a significant association between life events and positive symptoms

for patients with high but not low levels of trait arousability. It has been suggested, however, that the subtler daily hassles also impact on psychosis outcome. In a series of studies by Myin-Germeys and colleagues (for a review see Myin-Germeys & van Os, 2007), an attempt was made to assess daily life stress reactivity in an ecologically valid manner using a structured diary technique, the experience sampling method (ESM). It was shown that patients with psychosis and their first-degree relatives are increasingly emotionally reactive to stress in the context of daily life (Myin-Germeys *et al.* 2001). Moreover, it was found that subtle everyday stresses are accompanied by an exacerbation of psychotic symptoms (Myin-Germeys *et al.* 2005). The results of two more recent studies further contribute to the notion that stress reactivity is, in part, a genetically determined risk factor for psychotic disorder, and more specifically for the positive symptom dimension (Lataster *et al.* 2009, 2010).

The aim of this study was to investigate whether the positive and negative symptom dimensions of psychotic disorder moderate the association between everyday stressful events and negative affect (NA), known as stress reactivity. Based on findings from previous studies, we hypothesized that high levels of positive symptoms would be specifically associated with this reactivity to stress in daily life.

Method

Subjects

The sample consisted of 77 patients with a diagnosis of a non-affective psychotic disorder. In selected representative geographical areas in The Netherlands and Belgium, patients were identified through representative clinicians working in regional psychotic disorder services whose case loads were screened for inclusion criteria. Subsequently, a group of patients presenting consecutively at these services as either out-patients or in-patients were recruited for the study.

Two trained research assistants and two psychologists conducted all of the interviews. The Positive and Negative Syndrome Scale (PANSS; Kay *et al.* 1987) was used to assess current psychiatric symptoms. The PANSS interviewers took part in an inter-rater reliability evaluation as part of a large Dutch national project on psychotic disorder (Korver *et al.* 2012), where intra-class correlations (ICCs) were calculated based on scores of 16 randomly selected raters who rated four videotaped interviews (ICC PANSS positive subscale score: 0.96; ICC PANSS negative subscale score: 0.91). The Comprehensive Assessment of Symptoms and History (CASH; Andreasen *et al.* 1992)

was completed to assess lifetime symptom history, yielding DSM-IV diagnoses (APA, 1994).

Inclusion criteria were: (1) lifetime occurrence of non-affective psychotic symptoms, according to DSM-IV criteria, (2) age 16–60 years and (3) sufficient command of the Dutch language. Exclusion criteria were: (1) brain disease, (2) history of head injury with loss of consciousness, (3) substance-related psychosis and (4) psychosis with a known organic cause. Written informed consent, conforming to local ethics committee guidelines, was obtained from all subjects.

ESM

The ESM was used to measure the emotional reaction to stress in the flow of daily life, called ‘stress reactivity’. ESM is a within-day, momentary self-assessment technique (Myin-Germeys *et al.* 2009; Oorschot *et al.* 2009). Subjects received a digital wristwatch and self-assessment forms collated in a booklet for each day. Ten times a day on 6 consecutive days, the watch emitted a signal (beep) at unpredictable moments between 07:30 and 22:30 hours. Subjects were asked to report immediately after each beep their thoughts, current context (activity, persons present, location), appraisals of the current situation, and mood. All self-assessments were rated on seven-point Likert scales. The ESM procedure was explained to the participants in an initial briefing session of about 45 min, where a practice form was completed to confirm that subjects were able to understand all questions and the seven-point Likert scale format. To minimize memory distortion, subjects were instructed to complete their reports immediately after the beep, and to record the time at which they completed the form. In the actual sampling week, participants were called by research staff to further ensure that they were complying with the instructions. The time the watch emitted a signal was compared to the time participants completed the report to ensure reliability of the completed reports. All reports completed more than 15 min after the beep were excluded from the analyses because previous research (Delespaul, 1995) has shown that reports completed after this interval are less reliable and consequently less valid. For the same reason, subjects with less than 20 valid reports (out of 60) were excluded from the analysis (Delespaul, 1995).

Assessment of mood and stress

Measures of mood and stress were derived from the ESM reports as follows.

Assessment of mood

ESM NA was assessed at each beep with six mood-related adjectives (down, guilty, insecure, lonely, anxious, angry/irritated) rated on seven-point Likert scales (1 = not at all, 7 = very). Mean scores on these six mood questions were used as a measure of NA in the analyses (Cronbach’s $\alpha=0.85$).

Assessment of stress

In accordance with previous work, stress was conceptualized as the subjectively appraised stressfulness of distinctive events (event-related stress) (Lataster *et al.* 2010). To measure event-related stress, the subject was asked to report, after each beep, the most important event that had happened between the current and the previous report. This event was subsequently rated on a bipolar Likert scale (–3 = very unpleasant, 0 = neutral, 3 = very pleasant). The responses were recoded to allow high scores to reflect high levels of stress (–3 = very pleasant, 0 = neutral, 3 = very unpleasant).

Assessment of symptoms

Current positive and negative symptoms

All subjects were assessed with the PANSS (Kay *et al.* 1987) at the end of the ESM week (assessment period of 2 previous weeks, thereby also covering the ESM week). The PANSS comprises positive, negative and general symptom scales. For the present study we used the positive and negative symptom scales, each of which include seven items scored on a seven-point scale (1 = absent, 7 = extreme). The mean scores on both the positive and negative scales were used. In addition, the momentary ESM items ‘I feel suspicious’, ‘I see things’ and ‘I hear voices’ were combined into one mean ESM positive symptom score.

Lifetime positive and negative symptoms

The lifetime occurrence of positive and negative symptoms of schizophrenia was measured with the CASH (Andreasen *et al.* 1992). A mean score on CASH section 6 (delusions) and section 7 (hallucinations) formed the positive symptom score (Cronbach’s $\alpha=0.75$) used for the analyses. The negative symptom variable (Cronbach’s $\alpha=0.60$) comprised scores on items assessing lifetime emotion experience (section 11 ‘apathy’, section 12 ‘anhedonia’) and current problems with emotion expression as observed by the interviewer (section 15 ‘observation of flattened affect’). All scores on sections 11, 12 and 15 used for the negative symptom variable were recoded to

match the 0/1 coding of the items that comprised the positive symptom variable (0=absent and 1–5=present).

Analyses

ESM data have a multi-level structure: multiple observations (level 1) are nested within subjects (level 2), who were in some cases ($n=8$) part of sib pairs (level 3). To take the three-level grouping structure of the data (ESM beep level observations, subject, sib pair) into account, multi-level random regression analysis (Snijders & Bosker, 1999) was applied in Stata version 11.2 (StataCorp, 2009), using the `XTMIXED` command. Mixed models are characterized as containing both fixed and random effects. All analyses were conducted with standardized dependent variables using the `STD` command in Stata, yielding standardized values for each specified variable with mean (0) and standard deviation (1).

Association between stress reactivity and positive and negative symptoms

Multi-level linear regression analyses were conducted to examine the moderating effect of the positive and negative symptoms of schizophrenia, measured with the CASH, PANSS and ESM, on the association between daily life event-related stress and NA. For these analyses, NA was entered in the model as the dependent variable and mean scores on CASH and PANSS positive and negative symptoms and ESM positive symptoms, the ratings on event-related stress and their interactions (stress \times symptoms) were the independent variables (general model: $NA = B_0 + B_1\text{event-stress} + B_2\text{symptoms} + B_3\text{event-stress} \times \text{symptoms} + \text{residual}$). The interaction term was the focus of these analyses because the hypothesis required testing whether positive and negative symptoms moderated the association between stressful events and NA intensity. In the case of significant interaction effects, stratified analyses were performed using the `MARGINS` command in Stata to calculate the effect sizes of the interactions between symptoms (see the section on sensitivity analyses for details on how symptom scores were stratified) on the one hand and stress on NA on the other.

Sensitivity analyses

To test whether the moderating effect of positive symptoms on the association between event-stress and NA was stronger in those subjects with predominantly positive symptoms, the multi-level linear regression analyses were repeated comparing those subjects who scored high on positive symptoms and low on

negative symptoms assessed with the CASH (CASH high positive: 1 if positive symptom score ≥ 0.5 and negative symptom score < 0.5 , $n=14$; 0 in all other cases, $n=50$) and the PANSS (PANSS high positive: 1 if positive symptom score ≥ 2 and negative symptom score < 2 , $n=13$; 0 in all other cases, $n=51$). For the PANSS, we tested whether moderating effects of negative symptoms on the stress–NA association was different for those subjects with high negative and low positive symptoms (PANSS high negative: 1 if negative symptom score ≥ 2 and positive symptom score < 2 , $n=7$; 0 in all other cases, $n=57$). For the ESM-psychosis variable, stratification was chosen at the beep level, comparing the association between event-stress and NA on those beeps where scores on ESM psychosis were high (score ≥ 2.5 , $n=224$ beeps) versus all beeps where ESM psychosis was low (score < 2.5 , $n=2342$ beeps).

To test the relative independence of the moderating effect of positive symptoms on the stress–NA association, two multi-level linear regression models were fitted (for CASH lifetime and PANSS current symptoms) with the stress \times positive symptoms and stress \times negative symptoms interaction terms entered simultaneously in the model.

Results

Subjects and descriptives

The final sample consisted of 77 patients; of these, five dropped out of the study before finishing the ESM reports and 72 completed the ESM reports. A further eight subjects were excluded because they had less than 20 valid ESM self-reports or a large number of missing values on event-related stress (also leading to less than 20 valid ESM reports for the analyses; i.e. 64 subjects remained), yielding a total of 2568 beeps with a mean of 40 beeps per subject. Demographic and clinical statistics of the sample are shown in Table 1, and the mean scores for the independent and dependent variables are shown in Table 2.

Association between stress reactivity and positive and negative psychotic symptoms

The multi-level random regression analyses conducted to examine the associations between CASH, PANSS and ESM positive and negative symptom scores on the one hand and the association between stress and NA (i.e. ‘stress reactivity’) on the other, showed significant positive interaction effects for current (PANSS and ESM) and lifetime (CASH) positive symptoms, and a significant negative or inverse

Table 1. Demographic and clinical characteristics

Age (years)*, mean (s.d.), range	29.4 (9.3), 17–56
Gender ^a , <i>n</i> (%)	
Male	42 (66)
Female	22 (34)
Civil status ^a , <i>n</i> (%)	
Married or living together	13 (20)
Divorced	3 (5)
Never married	48 (75)
Work situation ^a , <i>n</i> (%)	
Working	12 (19)
Unemployed	44 (69)
School/education	8 (12)
Education ^a , <i>n</i> (%)	
Secondary school	6 (9)
Higher education	58 (91)
PANSS sum score (min–max), mean (s.d.), range	47.9 (12.6), 30–97
Positive syndrome scale (7–49), mean (s.d.), range	12.3 (4.7), 7–26
Negative syndrome scale (7–49), mean (s.d.), range	10.4 (4.0), 5–23
General syndrome scale (16–112), mean (s.d.), range	25.2 (6.4), 16–50
Age at first psychotic episode (years) ^a , mean (s.d.), range	23.1 (7.2), 13–44
Illness duration (years), mean (s.d.), range	6.2 (6.9), 1–40
Number of episodes ^a , mean (s.d.), range	2.3 (1.8), 1–12
CASH DSM-IV Axis I diagnosis lifetime (<i>n</i>)	
Schizophrenia	40
Schizo-affective disorder	9
Psychotic disorder NOS	7
Brief psychotic disorder	5
Delusional disorder	2
Schizophreniform disorder	1

PANSS, Positive and Negative Syndrome Scale; CASH, Comprehensive Assessment of Symptoms and History; NOS, not otherwise specified; s.d., standard deviation.

^a None of these variables were significantly associated with the main outcome (negative affect), and were therefore not included as confounders in the regression models.

interaction effect for current negative symptoms as measured with the PANSS. No significant interaction effect was found for lifetime negative symptoms as measured with the CASH (Table 3).

Sensitivity analyses

Stratified analyses showed that the association between event-stress and NA was stronger for those subjects who scored high on CASH, PANSS or ESM positive symptoms and low on negative symptoms (Table 3). By contrast, subjects who scored high on PANSS negative symptoms but low on PANSS positive symptoms showed a weaker association between event-stress and NA (Table 3).

The multi-level linear regression models with the two interactions (stress \times positive symptoms and stress \times negative symptoms) entered simultaneously in the model showed that the moderating effect of positive symptoms on the stress–NA association remains significant after controlling for the moderating effect of negative symptoms on this association [CASH lifetime: $B=0.14$, 95% confidence interval (CI) 0.045–0.238, $p=0.004$; and PANSS current: $B=0.06$, 95% CI 0.028–0.082, $p=0.000$], supporting the relative independence of the stress \times positive symptom interaction in the NA model.

The results of these stratified analyses showing effect sizes of stress on NA for the different subject categories (e.g. ‘high positive’) are shown in Figs 1 and 2.

Table 2. Mean scores on the (non-standardized) dependent and independent variables

Measure	<i>n</i>	Mean	S.D.	Range	
Stress					
Event-related stress	64	-1.35	1.7	-3 to +3	
Mood					
Negative affect (NA)	64	1.87	1.1	1-7	
CASH lifetime symptoms					
Positive symptoms	64	0.38	0.2	0.1-0.9	Association with ESM positive symptoms [<i>B</i> (95% CI), <i>p</i>] 0.45 (-0.007 to 0.912), 0.053
Negative symptoms	64	0.44	0.3	0-0.9	
PANSS current symptoms					
Positive symptoms	62	1.76	0.7	1-3.7	Association with ESM positive symptoms [<i>B</i> (95% CI), <i>p</i>] 0.32 (0.169-0.478), 0.000
Negative symptoms	62	1.49	0.5	1-3.3	
ESM positive symptoms	64	1.35	0.73	1-7	

CASH, Comprehensive Assessment of Symptoms and History; PANSS, Positive and Negative Syndrome Scale; ESM, experience sampling method; *B*, standardized regression coefficient; CI, confidence interval; *n*, number of subjects included in the analyses; S.D., standard deviation.

Discussion

In this study, a direct moderating effect of current and lifetime positive symptoms on the association between stressful events and NA (i.e. stress reactivity) was found in the context of daily life. No such association was found for lifetime negative symptoms, and current negative symptoms as measured with the PANSS were even found to be negatively associated with stress reactivity (i.e. higher levels of current negative symptoms showing a weaker moderating effect on the stress-NA association). More important, the results show that the association is particularly strong for those subjects who have predominantly positive symptoms.

Findings

The finding that high levels of positive symptoms moderate the stress-NA association is in accordance with previous studies showing an association between trait arousability and positive symptom scores (Dinzeo *et al.* 2004; Docherty *et al.* 2009). It also extends the finding of a momentary stress-induced increase in the intensity of positive psychotic experiences (Myin-Germeys *et al.* 2005) to a global pattern of increased stress reactivity in participants showing higher levels of positive symptoms. Moreover, the findings of this study suggest that negative symptoms have a significant beneficial effect on stress reactivity (i.e. higher levels of negative symptoms associated with a weaker effect of stress on NA). This is in accordance with the study by Scholten *et al.* (2006) showing that high activity of the Behavioral Inhibition System (BIS), a neural system that is sensitive to cues

of threat, is associated with low levels of negative symptoms, and a more recent finding that patients with high levels of negative symptoms have a lower risk for post-traumatic stress disorder (Strauss *et al.* 2011). The findings of the current study fit within an affective pathway to psychosis, suggesting that altered stress reactivity may be an independent and specific vulnerability marker for the positive symptom dimension of psychosis (Myin-Germeys & van Os, 2007).

An alternative explanation for the current results is that positive symptoms (delusions and hallucinations) increase the emotional reactivity to stress in daily life, rather than the other way around. However, *post-hoc* analysis showed no significant main effect of CASH and PANSS positive symptoms on event-stress. Similarly, the use of antipsychotic medication or presence of depression in these patients may have influenced the results, especially those regarding negative symptoms. However, controlling for these possible confounders did not substantially change the results.

How might stress reactivity contribute to psychosis?

Biological mechanisms

There are several biological models that can account for the relationship between positive psychotic symptoms and increased emotional reactivity to stress. A possible interpretation of the association is that minor stressors cause an increase in psychosis intensity. As this effect would suggest an enduring increase in the behavioral response to environmental stress, it could be described as behavioral sensitization (Myin-Germeys *et al.* 2005). Accordingly, *post-hoc* analyses showed that those patients with a longer

Table 3. Multi-level linear regression analyses assessing the moderating effect of CASH lifetime positive and negative symptoms, PANSS current positive and negative symptoms, and ESM momentary positive symptoms on the association between event-stress and NA (i.e. stress reactivity)

	<i>n</i>	<i>B</i>	95% CI	<i>p</i>	χ^2
CASH positive symptoms					
Main effect of event-stress on NA	64	0.05	0.007–0.092	0.022	
Main effect of positive symptoms on NA	64	1.5	0.561–2.45	0.002	
Event-stress \times positive symptoms in the model of NA	64	0.14	0.042–0.232	0.005	8.0
Stratification: CASH predominantly positive symptoms (<i>n</i> = 13, score: 1, <i>n</i> = 51, score: 0)					
Main effect of event-stress on NA	64	0.08	0.065–0.103	0.000	
Main effect of positive symptoms on NA	64	0.55	0.111–0.992	0.014	
Event-stress \times positive symptoms in the model of NA	64	0.09	0.050–0.129	0.000	19.98
CASH negative symptoms					
Main effect of event-stress on NA	64	0.10	0.066–0.142	0.000	
Main effect of negative symptoms on NA	64	0.12	–0.614 to 0.844	0.757	
Event-stress \times negative symptoms in the model of NA	64	0.004	–0.070 to 0.078	0.914	0.01
PANSS positive symptoms					
Main effect of event-stress on NA	62	0.02	–0.029 to 0.074	0.399	
Main effect of positive symptoms on NA	62	0.36	0.089–0.629	0.009	
Event-stress \times positive symptoms in the model of NA	62	0.05	0.021–0.075	0.000	12.34
Stratification: PANSS predominantly positive symptoms (<i>n</i> = 7, score: 1, <i>n</i> = 57, score: 0)					
Main effect of event-stress on NA	62	0.09	0.068–0.109	0.000	
Main effect of positive symptoms on NA	62	0.55	0.111–0.997	0.014	
Event-stress \times positive symptoms in the model of NA	62	0.08	0.031–0.105	0.000	12.95
PANSS negative symptoms					
Main effect of event-stress on NA	62	0.19	0.138–0.238	0.000	
Main effect of negative symptoms on NA	62	–0.06	–0.399 to 0.275	0.720	
Event-stress \times negative symptoms in the model of NA	62	–0.05	–0.088 to –0.022	0.001	10.91
Stratification: PANSS predominantly negative symptoms (<i>n</i> = 7, score: 1, <i>n</i> = 55, score: 0)					
Main effect of event-stress on NA	62	0.12	0.099–0.134	0.000	
Main effect of negative symptoms on NA	62	0.16	–0.436 to 0.757	0.599	
Event-stress \times negative symptoms in the model of NA	62	–0.08	–0.146 to –0.023	0.007	7.25
ESM momentary positive symptoms					
Main effect of event-stress on NA	64	0.04	0.010–0.070	0.009	
Main effect of positive symptoms on NA	64	0.49	0.436–0.536	0.000	
Event-stress \times positive symptoms in the model of NA	64	0.03	0.015–0.053	0.000	12.70
Stratification: ESM momentary 'high' versus 'low' positive symptoms (<i>n</i> = 224 beeps, score: 1, <i>n</i> = 2342 beeps, score: 0)					
Main effect of event-stress on NA	64	0.09	0.074–0.108	0.000	
Main effect of positive symptoms on NA	64	0.84	0.704–0.981	0.000	
Event-stress \times positive symptoms in the model of NA	64	0.13	0.069–0.190	0.000	17.62

CASH, Comprehensive Assessment of Symptoms and History; PANSS, Positive and Negative Syndrome Scale; ESM, experience sampling method; NA, negative effect; CI, confidence interval; *n*, number of subjects included in the analyses; *B*, standardized regression coefficient. For the stratified analyses the *B* values represent the magnitude of the difference in effect between the high (1) versus low category (0).

illness duration (as a proxy for longer exposure to stress, coded as 0 = illness duration < 5 years and 1 = illness duration \geq 5 years) show larger increases in NA with everyday stressful events (i.e. a difference in effect size of 0.06, $\chi^2 = 10.3$, $p = 0.001$). It has been suggested that exposure to environmental stressors resulting in a chronic heightened glucocorticoid release may cause permanent changes in the

hypothalamic–pituitary–adrenal (HPA) axis. In line with this, it was shown that siblings of patients with a psychotic disorder have higher diurnal cortisol levels and increased cortisol reactivity to negative daily events relative to controls (Collip *et al.* 2011). Moreover, there is evidence suggesting that cortisol secretion is increased in patients prior to the onset of a first psychotic episode (Walker *et al.* 2010). Such a

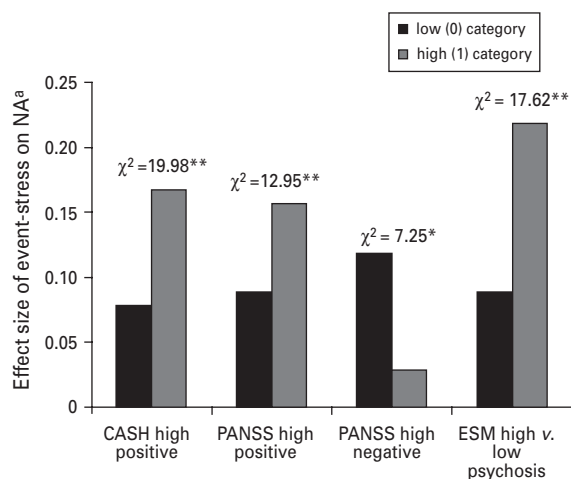


Fig. 1. Stratified analyses assessing the association between stress and negative effect (NA) for subjects with predominantly positive symptoms on the Comprehensive Assessment of Symptoms and History (CASH), the Positive and Negative Syndrome Scale (PANSS) or the experience sampling method (ESM) and predominantly negative symptoms on the PANSS compared to subjects with low scores respectively. Note that no stratified analyses were performed for CASH negative symptoms because the main interaction was not significant. ‘CASH high positive’ high (1) category: 95% confidence interval (CI) 0.140–0.208, $p=0.000$; ‘CASH high positive’ low (0) category: 95% CI 0.065–0.103, $p=0.000$; ‘PANSS high positive’ high (1) category: 95% CI 0.126–0.188, $p=0.000$; ‘PANSS high positive’ low (0) category: 95% CI 0.068–0.109, $p=0.000$; ‘PANSS high negative’ high (1) category: 95% CI –0.027 to 0.091, $p=0.293$; ‘PANSS high negative’ low (0) category: 95% CI 0.099–0.134, $p=0.000$; ‘ESM psychosis high’: 95% CI 0.162–0.279, $p=0.000$ versus ‘ESM psychosis low’: 95% CI 0.074–0.108, $p=0.000$.^a These are the ‘absolute’ B values (regression coefficients) per category as opposed to the B values representing the magnitude of the difference in effect between the high versus low category as presented in Table 3. * $p < 0.01$, ** $p < 0.001$.

stress-induced dysregulation of the HPA axis may give rise to increased subcortical dopamine (DA) receptor densities and DA release and may underlie the dopaminergic abnormalities that are generally thought to be involved in psychosis (van Winkel *et al.* 2008; Walker *et al.* 2008). Additionally, a dysregulated, subcortical hyperdopaminergic state may lead to stimulus-independent release of DA, which may take over the normal process of contextually driven salience attribution and lead to aberrant assignment of salience to external objects and internal representations (Kapur, 2003; Howes & Kapur, 2009). In accordance with this, there is evidence for increased dopamine synthesis in patients prior to onset of the first psychotic episode (Howes *et al.* 2011).

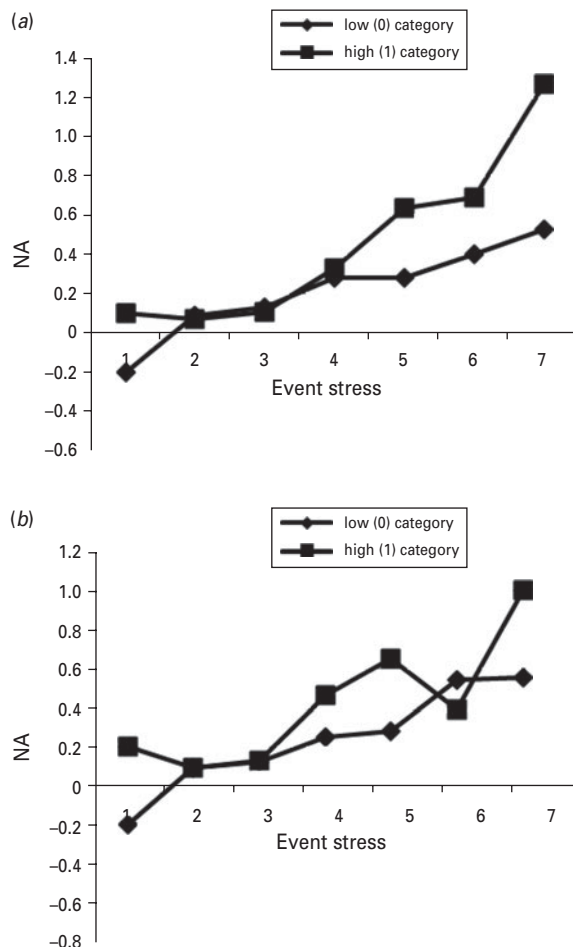


Fig. 2. The association between event-stress and negative effect (NA) for the ‘high’ and ‘low’ symptom categories of (a) Comprehensive Assessment of Symptoms and History (CASH) lifetime positive symptoms and (b) Positive and Negative Syndrome Scale (PANSS) current positive symptoms.

Psychological mechanisms

Psychological models suggest that triggering events may lead to the development of positive psychotic symptoms. These models posit that victimization experiences may lead to the formation of negative schemas about the self and the world (e.g. beliefs about the self as vulnerable to threat, or about others as dangerous) that facilitate external attributions, which may lead to the development of paranoid delusions (Bentall *et al.* 2001; Garety *et al.* 2001, 2007). Additionally, several affective processes, in particular neuroticism, depression and anxiety, have been hypothesized to play a role in the formation of psychotic symptoms (Bentall *et al.* 2001; Birchwood *et al.* 2005). Although findings on the association between neuroticism and specific symptoms are inconclusive (Horan

et al. 2008), some studies suggest a specific association with the positive symptom dimension (van Os & Jones, 2001; Krabbendam *et al.* 2002; Lysaker *et al.* 2003; Horan *et al.* 2005; Laroi *et al.* 2006). Moreover, one study reported a moderating effect of neuroticism on the association between positive schizotypy and measures of psychopathology and functioning in a non-clinical sample (Barrantes-Vidal *et al.* 2009). The results of the current study would suggest that small daily events trigger the type of affective disturbances that may facilitate the process whereby anomalous experiences become psychotic symptoms.

Clinical implications

The current results suggest that stress reactivity may be a vulnerability marker underlying the positive symptoms of psychosis. Clearly, these results are still a long way from offering direct therapeutic insight. However, if stress reactivity can truly be considered a specific area of vulnerability, it may be useful to tailor treatment aimed at reducing reactivity to stress in daily life. One possible way to do so is by reducing stress in the social environment of the patient (Pilling *et al.* 2002). Training patients to apply self-relaxation or self-distraction techniques seems to improve emotional well-being in chronic schizophrenia patients but not in early psychosis (Hodel *et al.* 1998). Previous studies have shown that cognitive behavioral therapy (CBT) reduces psychotic symptoms (Pilling *et al.* 2002) and also reduces distress caused by psychotic symptoms (Valmaggia *et al.* 2005), and there are some studies suggesting that it might reduce relapse rates (Gumley *et al.* 2006). The results of a more recent study suggest, however, that CBT helps in depression and emotional distress but not in psychosis relapse (Garety *et al.* 2008). Extending this therapy in such a way that treatment is additionally focused on emotional reactivity to stress in daily life may thus have positive effects on depression and distress that are experienced with psychotic symptoms. Of interest, the newest generation of CBT puts high emphasis on the context (hence the name 'contextual CBT'), and uses stress-reduction techniques (e.g. elements from mindfulness or acceptance and commitment therapy) to create a more 'open, active, and aware approach to living' (for a review see Hayes *et al.* 2011).

Methodological issues

The results should be viewed in the light of several methodological issues. First, the ESM measurements are based on subjective reports. Therefore, it can be argued that the results are not psychometrically

precise. However, although subjective reports are considered less reliable (e.g. do all subjects interpret or answer the questions identically?), previous research indicates that subjective reports can be valid, and that the validity of objective reports should not be taken for granted (Strauss, 1994).

Second, ESM is a daily life assessment technique in which subjects have to comply with a paper-and-pencil diary protocol without the researcher being present. However, some authors have cast doubt on the reliability and subject compliance in paper-and-pencil ESM studies, favoring the use of electronic devices (Stone *et al.* 2002; Broderick *et al.* 2003). In a comparative study, Green *et al.* (2006) concluded that both methods yielded similar results. In addition, a study using a signal-contingent random time sampling procedure with multiple observations per day, similar to the protocol used in the current study, found evidence that underscores the validity of the paper-and-pencil random time self-report data in the current study (Jacobs *et al.* 2005). Third, it is possible that our negative finding for lifetime negative symptoms is a consequence of the way these symptoms were assessed with the CASH, with a limited set of items. It has been suggested that the assessment of negative symptoms with the instruments available to date is complex and often unreliable (Horan *et al.* 2006; Blanchard *et al.* 2011) because they rely heavily on interviewer observations and on the patient's reflective capacity. Following this, our positive results showing a significant, but inverse, effect of current negative symptoms in the stress-NA association should be interpreted with caution. Fortunately, more reliable negative symptom measures are currently being developed, taking into account the patient's subjective needs and, for example, assessing in-the-moment flattening of affect by telling a joke and observing the patient's response to it (i.e. the Clinical Assessment Interview for Negative Symptoms; Blanchard *et al.* 2011).

Finally, stress reactivity has been defined as the emotional reaction to subjective stress. The current results are based on cross-sectional analyses and therefore the possibility of reverse causality cannot be excluded. There is a possibility that increased NA or increased levels of positive or negative symptoms influence the subjective appraisal of the environment. However, the individual would still experience psychosis or distress with an environmental event.

Conclusions

The results of the present study show a direct moderating effect of the positive symptoms of psychosis on the association between stressful events and NA in the

everyday life of patients with a psychotic disorder (i.e. stress reactivity). This association seems to be particularly strong for those subjects who have predominantly positive symptoms rather than negative symptoms. This study shows that stress reactivity is a core risk factor within the affective pathway leading to a psychotic syndrome with high levels of positive symptoms.

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