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

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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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Key words: Daily life stress, momentary assessment, negative affect, schizophrenia, symptom dimensions.

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
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 subter 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 wrist-watch 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 each 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 α = 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 α = 0.75) used for the analyses. The negative symptom variable (Cronbach’s α = 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 x symptoms) were the independent variables (general model: \( NA = B_0 + B_1\text{event-stress} + B_2\text{symptoms} + B_3\text{event-stress x symptoms} + \text{residual} \)). 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 $\geq 0.5$ 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 $\geq 2$ 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 $\geq 2$ 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 $\geq 2.5$, \( n = 224 \) 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 x positive symptoms and stress x 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
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 × positive symptoms and stress × 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: \(B = 0.14, 95\% \text{ CI} 0.045–0.238, p = 0.004\); and PANSS current: \(B = 0.06, 95\% \text{ CI} 0.028–0.082, p = 0.000\)], supporting the relative independence of the stress × 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.

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**Table 1. Demographic and clinical characteristics**

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

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

* None of these variables were significantly associated with the main outcome (negative affect), and were therefore not included as confounders in the regression models.
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 2. Mean scores on the (non-standardized) dependent and independent variables

<table>
<thead>
<tr>
<th>Measure</th>
<th>n</th>
<th>Mean</th>
<th>S.D.</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event-related stress</td>
<td>64</td>
<td>–1.35</td>
<td>1.7</td>
<td>–3 to +3</td>
</tr>
<tr>
<td>Mood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative affect (NA)</td>
<td>64</td>
<td>1.87</td>
<td>1.1</td>
<td>1–7</td>
</tr>
<tr>
<td>CASH lifetime symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>64</td>
<td>0.38</td>
<td>0.2</td>
<td>0.1–0.9</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>64</td>
<td>0.44</td>
<td>0.3</td>
<td>0–0.9</td>
</tr>
<tr>
<td>PANSS current symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>62</td>
<td>1.76</td>
<td>0.7</td>
<td>1–3.7</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>62</td>
<td>1.49</td>
<td>0.5</td>
<td>1–3.3</td>
</tr>
<tr>
<td>ESM positive symptoms</td>
<td>64</td>
<td>1.35</td>
<td>0.73</td>
<td>1–7</td>
</tr>
</tbody>
</table>

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.
illness duration (as a proxy for longer exposure to stress, coded as 0 = illness duration < 5 years and 1 = illness duration ≥ 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).

### 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)

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

CASH, Comprehensive Assessment of Symptoms and History; PANSS, Positive and Negative Syndrome Scale; ESM, experience sampling method; NA, negative affect; 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).
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).

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 im-
prove 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 psy-
chotic 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 em-
phasis on the context (hence the name ‘contextual
CBT’), and uses stress-reduction techniques (e.g. ele-
ments from mindfulness or acceptance and com-
mmitment 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 symp-
toms 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 re-
flexive 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 ob-
serving 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 in-
fluence the subjective appraisal of the environment.
However, the individual would still experience psy-
chosis or distress with an environmental event.

Conclusions
The results of the present study show a direct moder-
ating 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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Declaration of Interest

Professor van Os is/has been an unrestricted research grant holder with, or has received financial compensation as an independent symposium speaker from, Eli Lilly, BMS, Lundbeck, Organon, Janssen-Cilag, GSK, AstraZeneca, Pfizer and Servier. Professor Myin-Germeys has received financial compensation as an independent symposium speaker from BMS and Janssen-Cilag.

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