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Autonomic arousal during psychosis spectrum experiences: Results from a high resolution ambulatory assessment study over the course of symptom on- and offset

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ABSTRACT

Introduction: Ecological momentary assessment (EMA) studies show that stressors trigger the onset or increase of psychotic symptoms. These studies, however, predominantly rely on large sampling intervals and self-report assessment. This study aims to identify the autonomic stress-response to psychosis-spectrum experiences by using a one-day high-resolution EMA with continuous skin conductance and heart rate monitoring in a sample with attenuated positive symptoms.
Methods: Sixty-two participants were equipped with a smartphone and wearable sensors to monitor skin conductance level (SCL) and heart rate variability (HRV) for 24 h. Every 20 min, participants answered questions on current stress, hallucination spectrum experiences (HSE), and paranoia. Sampling intervals were categorized into no event, pre-onset, event, pre-offset, and post-offset phases. We contrasted stress, SCL, and HRV between phases using multilevel regression models of sampling intervals nested in participants.
Results: For paranoia, we found alterations in the autonomic and self-reported stress response prior to the onset that persisted until the episodes had ended. For HSE, we found no effects. Exploratory separate analyses of the different items aggregated into HSE yielded diverging results for intrusive thoughts, perceptual sensitivity, and hallucinations.
Conclusion: Physiological parameters are sensitive indicators of the onset of paranoia, which holds implications for preventive mobile interventions. To further explore the autonomic stress-response associated with HSE, further studies of the different HSE are needed.

1. Introduction

Traditional (Nuechterlein and Dawson, 1984; Zubin and Spring, 1977) and more recent (Howes and Murray, 2014; Walker and Diforio, 1997) etiological models converge in the assumption that stressors trigger and maintain psychotic symptoms such as paranoia and hallucinations. Evidence from numerous ecological momentary assessment (EMA) studies supports this hypothesis. In these studies, the participants spend about a week reporting state-stress and symptom levels multiple times per day, usually in 90 min intervals. Based on this approximation to real-time assessment, EMA studies found self-reported stress and symptom intensity levels to co-vary (Peters et al., 2012; Reininghaus et al., 2016; Udachina et al., 2014; Varese et al., 2011) and self-reported stress to predict increases in positive symptom levels at the subsequent assessment (e.g., Ben-Zeev et al., 2011).

Only few studies have simultaneously investigated stress-levels prior to, during, and following momentary symptom episodes. A few notable exceptions (Delespaul et al., 2002; Oorschot et al., 2012; Thewissen et al., 2011) employed a symptom-phase approach: Based on the self-reported symptoms before and after each 90 min EMA sampling interval, they categorized intervals into different phases (i.e., the last phase before onset, symptom phases, and the phases before and after offset). However, 90 min sampling intervals only provide a rough picture of the total symptom-fluctuations in everyday life. In 50% of the people who experience hallucinations or delusions, symptoms occur only for seconds or minutes at a time (Steel et al., 2007). In other words, the majority of symptom episodes begin and end well within one standard 90 min sampling interval. There is thus considerable potential to improve the symptom-phase approach. Shorter sampling intervals will enable a more precise analysis of symptoms, precursors, and consequences.

Related to this, assessing stress-levels by self-report merely provides a state-indicator for one moment every 90 min or a retrospective report of the last 90 min. Thus, a considerable amount of momentary stress-fluctuations remains undetected in conventional EMA. Recent technical innovations, however, have enabled researchers to supplement EMA with continuous monitoring of

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autonomic arousal (e.g., Cella et al., 2017), which further increases the temporal resolution of stress parameter assessment. This is of particular interest as autonomic hyperarousal has been considered a core feature in the traditional vulnerability-stress-models of schizophrenia (Nuechterlein and Dawson, 1984), in which it is assumed to contribute to the deficient processing of stimuli. Furthermore, several cognitive models postulate an affective pathway to psychosis, in which negative emotions trigger symptom onset (Garety et al., 2001; Myin-Germeys and van Os, 2007). Finally, recent conceptualizations of psychosis posit that difficulties in down-regulating negative emotions may be related to altered autonomic regulation (Clamor et al., 2015).

In support of these conceptualizations of the role of altered autonomic regulation in psychosis, an increased tonic skin conductance level (SCL), which is an indicator of sympathetic autonomic arousal, was found during acute psychotic states (Dawson et al., 2010; Maina et al., 1995; Schell et al., 2005). Moreover, laboratory studies showed that SCL increases prior to hallucination onset in patients with psychosis (Levine and Grinspoon, 1971) and during anomalous bodily experiences (i.e., the rubber hand illusion; Braithwaite et al., 2014) in healthy participants. Hence, momentary hyperarousal co-occurs with anomalous experiences across the continuum of psychotic experiences. Another prominent focus of autonomic deregulation research in schizophrenia is heart rate variability (HRV). HRV is an indicator of parasympathetic activity regulated by central-peripheral neural feedback mechanisms that allow individuals to adapt physiological, perceptional, and cognitive processes (Thayer and Siegle, 2002). A meta-analysis of 34 studies found HRV to be reduced in psychosis relative to controls (Clamor et al., 2016). Furthermore, a review outlined that reduced HRV correlates with the severity of suspiciousness, feelings of persecution, and psychotic symptoms in general (Montaquila et al., 2015). Finally, low levels of HRV have been shown to prospectively predict the onset of hallucinations in an EMA study with patients with psychosis (Kimhy et al., 2017). Thus, there is some evidence that autonomic stress indicators co-vary with and predict positive symptoms. So far, however, no study has investigated the autonomic stress-response over the full course of psychotic symptom episodes.

There is a particular dearth of research on the autonomic stress-response prior to and after symptom *off*set, for which several hypotheses appear theoretically plausible: The first of these is rooted in etiological models that conceptualize positive symptoms as a reaction to stress (Howes and Murray, 2014; Nuechterlein and Dawson, 1984; Walker and Diforio, 1997; Zubin and Spring, 1977): Based on these models, successful adaptation to stress or cessation of the stressor precedes symptom offset. Thus, one would hypothesize that stress-parameters return to resting levels *before* symptom offset. A second hypothesis can be deduced from the fact that symptoms themselves often, but not always, lead to distress (Birchwood, 2003; Peters et al., 1999). Extending on this, we can define psychotic symptoms as stressors in their own right. People with psychosis who are confronted with a stressor in a laboratory environment show a prolonged self-reported (Perry et al., 2011) and autonomic stress-reaction (Castro et al., 2008) after the stress induction had ended. Thus, we could hypothesize that the stress response persists even *after* symptom offset. Finally, it is also conceivable that different symptoms elicit differing stress-responses. For example, hallucinations are experienced as sensory events (i.e., as self-generated stressors), thus their onset may be more likely to induce a stress-response that persists after symptom offset. In contrast, paranoia was shown to have positive short-term effects, such as the relief that comes with having an explanation (Maher, 1988) or the short-term preservation of self-esteem by blaming others (Lincoln et al., 2014). In this regard, paranoia could be understood as a dysfunctional cognitive coping strategy to deal with external stressors. In this case, we would expect reduced stress-levels prior to symptom offset.

This study aimed to identify the stress-response over the course of psychosis-spectrum experiences (PSE) in a one-day high-resolution EMA with 20-minute sampling intervals and continuous SCL and heart rate monitoring in a community sample with attenuated levels of positive psychotic symptoms. We assessed fluctuations in PSE, including paranoia and hallucination spectrum experiences (HSE; ranging from subclinical experiences to auditory hallucinations). We examined self-reported and physiological stress-reactions during (1) phases without PSE events, (2) phases prior to PSE onset, (3) phases with continuously reported PSEs, (4) PSE phases prior to offset, and (5) post-offset phases. We expected to find (A) increases in self-reported stress and SCL and a decrease in HRV preceding the onset of PSEs and (B) coinciding with PSE symptom-phases. Moreover, for all PSEs, we explored whether (C1) self-reported stress and SCL will continue to be elevated and HRV will continue to be reduced or (C2) whether these parameters decrease in the pre-offset and the post-offset phases.

2. Methods

2.1. Procedure

Potential participants were screened for attenuated positive symptoms. Participants with an extent of self-reported symptoms above the median of a large German reference sample (i.e., *Med* = 8.00; Schlier et al., 2015) were invited to our lab for a baseline assessment. After providing informed consent, the participants were equipped with an electrocardiogram sensor and an electrodermal activity sensor. Next, the participants completed a battery of self-report questionnaires on emotion-regulation (Ebert et al., 2013; Loch et al., 2011), cognitive schemata (Fowler et al., 2006), and traumatic experiences (Hooper et al., 2011), which are reported elsewhere (e.g., Krkovic et al., 2018). Following this, they were equipped with a Motorola Moto G smartphone with a pre-installed movisensXS EMA application (movisens GmbH). The smartphones were programmed to allow only the use of the EMA application.

After a demonstration of the alarm followed by the EMA-questionnaires, the participants were able to ask questions about the EMA procedure. Subsequently, participants left the laboratory and the 24-hour EMA started. During this time, the sensors recorded continuously whereas the EMA questionnaires were presented every 20 min (±60 second random variation), starting at 9 am and ending/pausing at 10 pm. Each participant received prompts to provide self-report data at 38 time-points. The participants were instructed to follow their normal daily routine during the assessment period, but to abstain from taking a shower, bathing, or partaking in straining physical activity in order to guarantee continuous sensor-readings. After 24 h, the participants returned to the lab to finish the study and to return the sensors and smartphone.

The project was approved by the local ethics committee and the participants were compensated with 15€. Psychology students received partial course credit for participation.

2.2. Materials

2.2.1. Screening

Attenuated positive symptoms at baseline were measured with the 20 item positive symptoms frequency scale of the Community Assessment of Psychic Experiences (CAPE; Stefanis et al., 2002). Participants rated the life-time frequency of experiences of paranoia, bizarre experiences, hallucinations, grandiose ideas, and magical thinking on four-point Likert scales (0 = “never”, 1 = “sometimes”, 2 = “often”, 3 = “nearly always”). The positive symptom scale of the CAPE and its German translation were shown to be sufficiently valid and reliable (Schlier et al., 2015).

2.2.2. EMA questionnaires

Paranoia was assessed with the three item state version (Schlier et al., 2016) of the Paranoia Checklist (Freeman et al., 2005). Participants indicated to what extent each item (e.g., "I need to be on my guard against others") applied to them "at the moment before the beep" on an 11-point scale (0="not at all"; 10="very much"). The multilevel reliability was acceptable for the within-subject-level ($\alpha = 0.62$), and excellent for the between-subject-level ($\alpha = 0.92$).

HSEs were assessed with an abbreviated version of the Continuum of Auditory Hallucinations − State Assessment (CAHSA; Schlier et al., 2017a) that was developed for this study. It included the following four items: (1) "Fantasies, daydreams or thoughts I have had were vivid and intense" for vivid daydreaming, (2) "My thoughts seemed almost real or overwhelming (e.g., thoughts came faster than I could express them or seemed as if I could really hear them)" for intrusive thoughts, (3) "My hearing has been sensitive (e.g., I felt distracted by everyday noise or distant sound)" for perceptual sensitivity, and (4) "I have heard something others could not hear (e.g., random noise sounding like someone mumbling or hearing a voice in my head)" for auditory hallucinations. Participants indicated to what extent each statement applied to them during the 20-min interval preceding the beep on an 11-point scale (0="not at all"; 10="very much"). The multilevel reliability for the scale was poor at the within-subject-level ($\alpha = 0.51$), whereas it was good at the between-subject-level ($\alpha = 0.83$).

Self-reported stress was assessed with four items referring to the previous 20 min rated on 11-point scales (0="not at all"; 10="very much"). The items (based on Gaab et al., 2005) included self-ratings of arousal and stress (two items: "the situation stressed me", "I was calm and relaxed") and of subjective control (two items: "I could influence the situation", "I felt helpless in face of the situation"). The multilevel reliability was acceptable for the within-subject-level ($\alpha = 0.73$) and the between-subject-level ($\alpha = 0.64$).

2.2.3. Physiological data

Heart rate and SCL were measured with the Movisens ecgMove and Movisens edaMove, respectively. Both devices are small $62.3 \times 38.6 \times 11.5$ mm ambulatory sensors. The reusable, non-polarizing sintered Ag/AgCl-EDAmove-electrodes were attached to the inner wrist of the non-dominant arm with a wristband and recorded SCL using a sample rate of 32 Hz. The ecgMove was attached to the left side of the chest with two disposable, self-adhesive Ag/AgCl-electrodes (Ambu® BlueSensor VL). For electrodermal activity, the range-corrected SCL was calculated for each participant. For HRV, the root mean square of successive normal-to-normal interval differences (RMSSD) was calculated, which reflects parasympathetic activity (Bauer et al., 2008) and was shown to be a more homogenous measure in psychosis than the alternative high frequency HRV (Clamor et al., 2016). Automated calculation of SCL and RMSSD and correction for potential artifacts (e.g., by disturbances in electrode connection) was performed in DataAnalyzer (Movisens GmbH) and yielded one-minute intervals, which were then averaged for 20(±2) minute intervals between two successive assessment alarms.

2.3. Participants

Prescreening of 292 participants from the community with the CAPE positive symptom scale yielded 67 participants with a sum score ≥8 who were recruited for this study. Five participants were excluded from the analyses because they failed to respond to at least half of the EMA self-assessments. This resulted in a final sample of 62 participants (71.6% female, age: $M = 23.01$, $SD = 4.63$). The majority of the participants were of German nationality (85.5%). Most participants were currently enrolled in university (79.0%) and 46.8% of the sample worked for six or more hours per week. Eight participants reported to have received a mental illness diagnosis at some point in their life. The average CAPE sum-scores were 15.89 ($SD = 4.31$) for positive symptoms, 15.87 ($SD = 6.35$) for negative symptoms, and 10.03 ($SD = 3.80$) for symptoms of depression.

In the final sample, 84.95% of all EMA self-reports were completed. Heart rate was successfully recorded for 95.82% and SCL for 98.59% of the time-intervals, resulting in combined self-report and heart rate for 81.46% and combined self-report and SCL for 83.93% of all time-segments.

2.4. Data analysis

Data was analyzed using R 3.2.2 (R Core Team, 2015). All analyses were random intercept, fixed slope multilevel-regression analyses of assessment intervals (level 1) nested in participants (level 2). Dependent variables were self-reported stress, SCL, and RMSSD. As the independent variables, five-category factors of PSE interval type were calculated based on the Paranoia Checklist and CAHSA mean scores, respectively, in a two-step procedure. First, we calculated the 95%-reliable difference score for the CAHSA- and Paranoia-Checklist mean scores based on the within-subject reliability, and the full sample standard deviations. All intervals with CAHSA scores ≥2.33 (i.e., reliably different from 0) were marked as intervals with HSEs reliably present, whereas intervals with CAHSA scores below 2.33 were marked as intervals with no HSEs reported. Similarly, all intervals were marked as intervals with paranoia reliably present for Paranoia Checklist scores ≥1.51 (or not present when Paranoia Checklist scores were below 1.51). Thereafter, and separately for HSE and paranoia, each of the 20 min intervals was categorized as belonging to one of the following five different phases (see also Fig. 1):

- "*no event phase*" (reference category), when the respective PSE was not reported at the time interval itself, the preceding time-interval, and the following time interval,
- "*pre-onset phase*" if the respective PSE was not reported for the time interval itself, but was followed by a time interval with PSE reliably present,
- "*event phase*" if the PSE was reliably present at the time interval itself and the following interval,
- "*pre-offset phase*" if the PSE was reliably present during the time interval itself, but not at the following interval,
- "*post-offset phase*" if the PSE was reported at the preceding phase, but neither during the time interval itself nor at the following interval.

Self-reported stress, SCL, and RMSSD were analyzed in three random-intercept, fixed slope multilevel analyses of time intervals nested in participants for HSEs and paranoia, respectively; stress levels in pre-onset, event, pre-offset, and post-offset phases were contrasted with the stress levels in the no event phases. To provide an estimate of potential bias due to alpha-error-inflation, Bonferroni-Holm corrected p-values were calculated. We performed all analyses on the full sample first, but controlled for conflation of between- and within-subject effects by excluding participants who either experienced no PSE at all during the assessment period (i.e., participants with only no event phases) or constantly experienced PSE (i.e., participants without no event phases) and repeating the multilevel regressions.

Finally, due to the low internal consistency of the CAHSA, we added four exploratory analyses based on the four CAHSA-items. All procedures mirrored the main analysis for HSE and paranoia, with the exception that since no reliable difference scores were available for single item measures, all item scores above zero were defined as an indicator for the presence of the respective HSE.

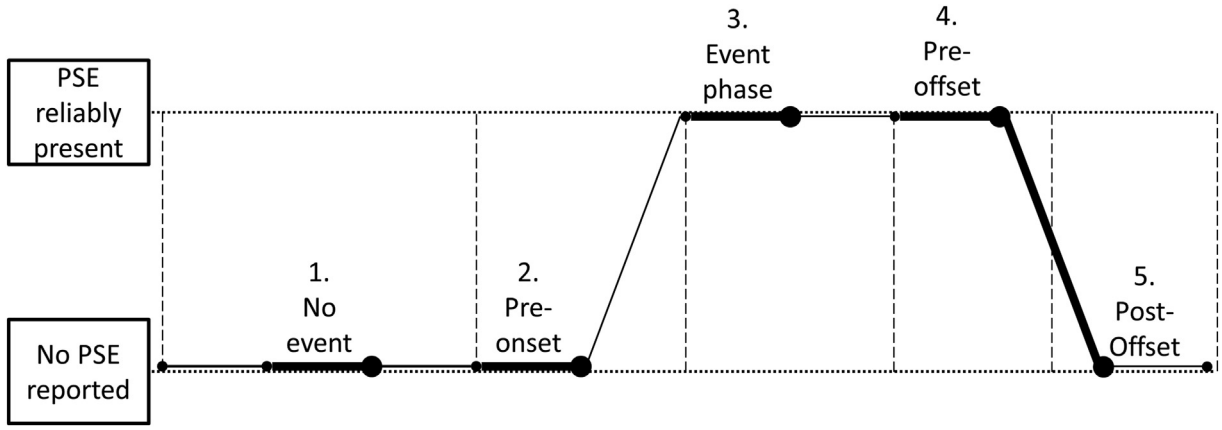

Fig. 1. Definition of event-phases based on the symptom status prior to, during, and following the interval from which stress-indicators were analyzed (bold lines and dots).

3. Results

3.1. Descriptive results

The grand means and frequency of the stress indicators and PSE recording during EMA are summarized in Table 1. Regarding phase prevalence for paranoia, 21 participants reported no paranoia or had insufficient data to identify any event-related paranoia phase and 2 participants did not report any no event phase; regarding HSEs, 22 participants reported no HSEs or insufficient data to identify the event-related phases and 6 participants did not report any no event phase.

3.2. Autonomic arousal in relation to paranoia phases

For paranoia, we found roughly u-shaped curves for all stress parameters over the course from no event to post-offset phases (see Fig. 2, right). As can be seen in Table 2, pre-onset phases were associated with increased self-reported stress and decreased RMSSD. Furthermore, event phases yielded significant increases in self-reported stress and SCL and a significant decrease in RMSSD. Finally, we found continuing differences from no-event phases in self-reported stress, SCL, and RMSSD at pre-offset. In the post-offset phases, no stress parameter was significantly different from the corresponding no event phase level (see Table 2), indicating a decrease in stress with symptom offset. All results remained stable when the participants with no and constant PSEs were excluded (see online supplements, Table S1).

3.3. Autonomic arousal in relation to HSE phases

Regarding HSE-phases, no significant differences in self-reported stress, SCL levels or RMSSD were found (see Table 2, left and Fig. 1, left). When the four items were analyzed separately, we found decreased RMSSD in intrusive thought event ($b = -6.102$, $T = -3.61$, $p_{corr} = 0.015$) and pre-offset phases ($b = -7.239$, $T = -4.02$, $p_{corr} = 0.003$), increased SCL in perceptual sensitivity pre-onset ($b = 0.094$, $T = 4.02$, $p_{corr} = 0.003$), event ($b = 0.088$, $T = 3.96$, $p_{corr} = 0.004$) and pre-offset phases ($b = 0.089$, $T = 3.60$, $p_{corr} = 0.016$), and increased self-reported stress in perceptual sensitivity event ($b = 0.600$, $T = 4.20$, $p_{corr} = 0.001$) and pre-offset phases ($b = 0.576$, $T = 3.90$, $p_{corr} = 0.004$) as well as in hallucination event ($b = 0.920$, $T = 4.22$, $p_{corr} = 0.001$) and pre-offset phases ($b = 0.812$, $T = 4.18$, $p_{corr} = 0.001$, see online supplements, Table S2).

4. Discussion

In this study, we found a consistent pattern of alterations in self-report and autonomic parameters over the course of paranoia event phases, but no consistent results regarding HSEs.

4.1. Paranoia as a potentially dysfunctional stress-response

There was an autonomic response in the form of a combined increase in self-reported stress and a decrease in parasympathetic activity prior to the start of the paranoia episodes that persisted over the course of the episode but ended with the offset. Moreover, these alterations were accompanied by a delayed increase in sympathetic activity (i.e., SCL) during event-phases. This is in line with Montaquila et al.'s (2015) recent review on the interplay between the parasympathetic and sympathetic nervous systems in psychosis. Their findings converge on the assumption that diminished levels of parasympathetic activity constitute a vulnerability for psychosis: Low levels of parasympathetic activity reduce vulnerable people's capacity to recover from stress, which leads to a dominant state of sympathetic arousal over the course of the disorder. Arguably, our findings show a micro-level version of this autonomic response mechanism within singular state-paranoia episodes.

Table 1
Mean, standard deviation, skew, range, and frequency of psychosis-spectrum experiences during EMA assessment.

Variable	M	SD	Skew	Range[a]	Intervals with PSE reliably reported		Participants with at least one interval with PSE reported	
					n	%	n	%
Self-reported stress	3.33	1.80	−0.43	0–10	–	–	–	–
SCL (range corrected)	0.35	0.27	0.8	0–1	–	–	–	–
RMSSD (ms)	40.85	23.74	1.49	3.55–149.03	–	–	–	–
Hallucination spectrum experiences	1.55	1.70	1.09	0–9	539	27.07%	40	64.52%
Paranoia	0.75	1.25	1.92	0–7	400	20.09%	43	69.35%

Note. EMA = ecological momentary assessment, PSE = psychosis-spectrum experiences, SCL = skin conductance level, RMSSD = root mean square of successive normal-to-normal interval differences; a = range of reported results, possible range was 0–10 for all PSE types.

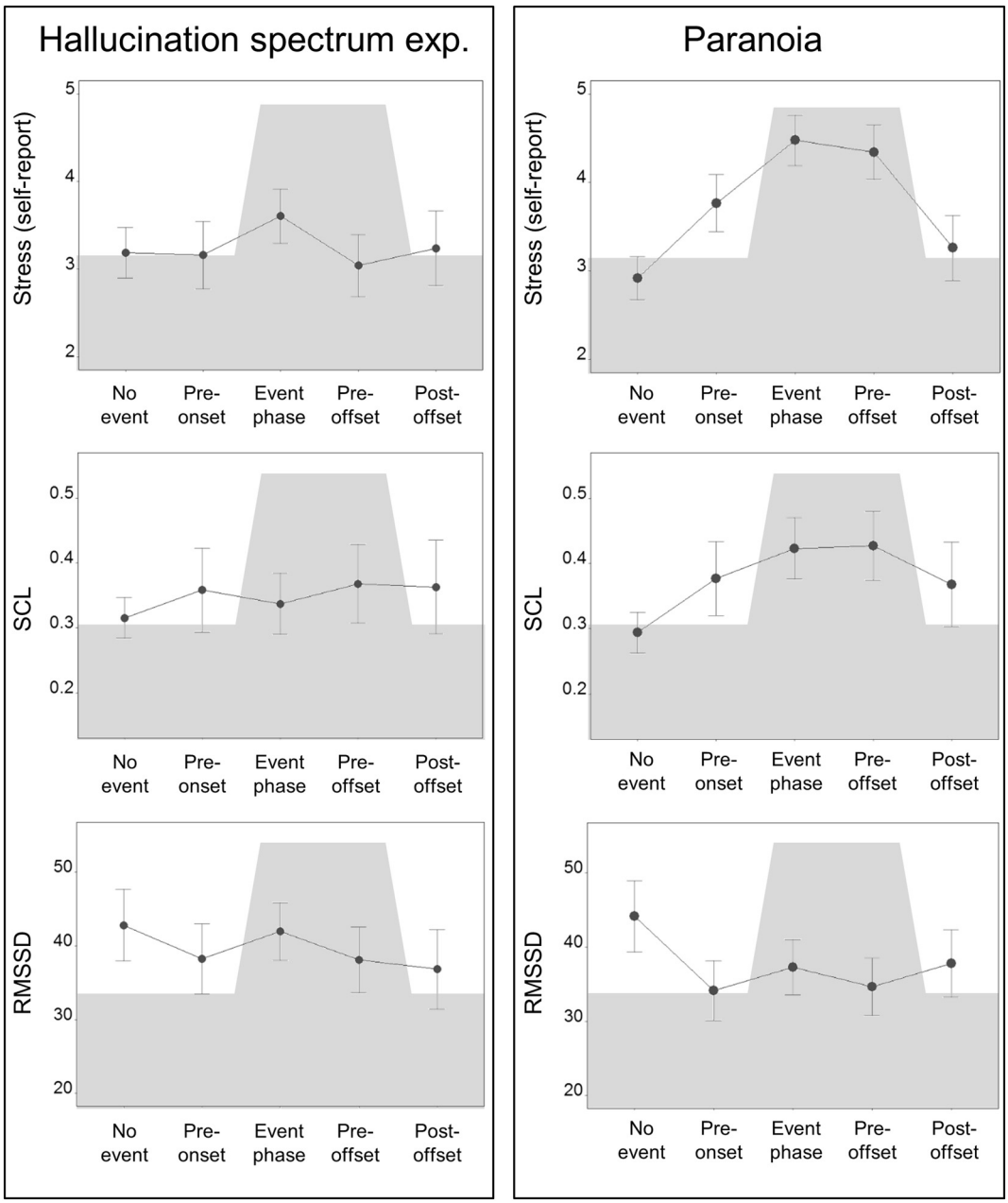

Fig. 2. Stress-response in event phases of hallucination spectrum experiences and paranoia (predicted values from multilevel regression and uncorrected 95% confidence intervals).

Of importance, all stress-parameters returned to baseline-levels at post-offset, which may point towards a short-term self-regulatory function of paranoid thinking. In line with this, short term benefits of paranoid beliefs have been demonstrated in terms of reduced self-reported negative affect (Lincoln et al., 2014) and a lower subsequent heart rate (Clamor and Krkovic, 2018). This pattern of findings is in line with the notion that paranoia may be a cognitive coping style that yields short-term relief (Bentall et al., 1994; Maher, 1988) that contributes to symptom persistence in the long-term. More research into the cognitive, emotional, and autonomic processes associated with the offset of paranoid thinking is needed to further corroborate this hypothesis and test it in clinical populations.

4.2. Hallucination spectrum experiences as potential stressors

In contrast to the clear picture for paranoia phases, the results appear to become more complicated in phases of HSEs. For the HSE mean score, no significant results were found. This is in contrast to a previous study with patients with psychosis, in which significant decreases in parasympathetic activity predicted (i.e., preceded) auditory hallucination onset (Kimhy et al., 2017). One interpretation for these results based on the low within-subject reliability could be that we may have assessed the spectrum of hallucinatory experiences too broadly. The measure used was particularly constructed to assess the continuum beyond symptom-level experiences. In line with this, our exploratory analysis shows that "mild" subclinical HSE (i.e., vivid daydreams) yield no stress-response, whereas more severe HSE (i.e., intrusive thoughts, perceptual sensitivity) were accompanied by autonomic alterations. Contrary to this line of interpretation, auditory hallucinations were only accompanied by self-reported stress but not by autonomic alterations. Possibly, non-clinical-populations experience less distress due to hallucinations, which results in the well-recorded lack of need for treatment for these experiences (Larøi et al., 2012).

Table 2
Self-reported and physiological reaction to psychosis-spectrum experience phases. Results of multilevel regression models symptom phase (level 1 predictor) on the respective stress parameter (dependent variable).

Stress indicator	Phase	Paranoia				Hallucination spectrum experiences			
		b	SE	T	p_{corr}	b	SE	T	p_{corr}
Self-report	No event[a]	2.916	0.124	23.48	–	3.186	0.147	21.72	–
	Pre-onset	***+0.850***	***0.165***	***5.15***	***<0.001***	−0.025	0.197	−0.13	0.900
	Event	***+1.561***	***0.146***	***10.71***	***<0.001***	*+0.419*	*0.159*	*2.63*	*0.200*
	Pre-offset	***+1.425***	***0.156***	***9.16***	***<0.001***	−0.144	0.181	−0.80	≈1
	Post-offset	+0.344	0.188	1.83	0.871	+0.053	0.217	0.24	≈1
SCL	No event[a]	0.294	0.016	18.95	–	0.315	0.016	19.74	–
	Pre-onset	*+0.083*	*0.029*	*2.88*	*0.101*	+0.043	0.033	1.28	≈1
	Event	***+0.129***	***0.024***	***5.26***	***<0.001***	+0.022	0.024	0.90	≈1
	Pre-offset	***+0.133***	***0.027***	***4.87***	***<0.001***	+0.053	0.031	1.75	0.976
	Post-offset	*+0.074*	*0.033*	*2.25*	*0.517*	+0.048	0.037	1.28	≈1
RMSSD	No event[a]	44.151	2.446	18.05	–	42.777	2.484	17.22	–
	Pre-onset	***−10.008***	***2.065***	***−4.85***	***<0.001***	−4.562	2.431	−1.88	0.851
	Event	***−6.879***	***1.912***	***−3.60***	***0.009***	−0.823	2.001	−0.41	≈1
	Pre-offset	***−9.526***	***1.980***	***−4.81***	***<0.001***	*−4.684*	*2.285*	*−2.05*	*0.608*
	Post-offset	*−6.351*	*2.318*	*−2.74*	*0.149*	*−5.954*	*2.744*	*−2.17*	*0.574*

Note. Multilevel regression with the independent variable symptom phase. SCL = range-corrected skin conductance level, RMSSD = root mean square of successive differences, p_{corr} = Bonferroni-Holm corrected p-values. Significant results are printed in bold, significant results before Bonferroni-Holm correction are printed in italics.
[a] All other phase are contrasted to the respective "no event"-phase (intercept).

In sum, HSE in general neither classified as stressors nor as stress-responses. However, the in-depth analysis of separate types of HSE yielded significant differences from baseline stress levels - mainly in event and pre-offset phases. Thus, we speculate that some HSE (e.g., intrusive thoughts, perceptual sensitivity, hallucinations) classify as stressors in themselves that elicit a subjective and/or autonomic stress-response when experienced (Castro et al., 2008). If this is the case, these types of HSEs could contribute to the emergence of further symptoms via stress-sensitization: For example, previous research has linked differences in baseline or average HRV to problems in functional coping (e.g., greater self-reported difficulties in emotion regulation; Clamor et al., 2015; Williams et al., 2015). Consequently, the momentary decreases in HRV following some HSEs could increase the likelihood that the next stressor will trigger other symptom episodes, thus contributing to the stress-sensitization mechanism central to recent etiological models of psychosis (Howes and Murray, 2014; Walker and Diforio, 1997). Thus, further research on different types of HSEs with a more detailed (i.e., multiple item) assessment and in a clinical sample with potentially more symptom distress is warranted in order to fully understand the association between HSEs and autonomic stress parameters.

4.3. Strengths and limitations

The brief sampling interval and the continuous assessment of physiological parameters constitute strengths of our approach. Furthermore, using reliable differences for threshold-calculation is a less arbitrary form of determining the presence of PSEs than previous procedures (e.g., scores above mid-scale: Delespaul et al., 2002; or scores above 0; Schlier et al., 2017b).

Nevertheless, some limitations need to be considered. First, there were no comparison groups (e.g., clinical vs. non-clinical psychotic like experiences) or control measures (e.g., phases of depression or social anxiety). Thus, little can be said about the generalizability of the results to clinical levels or whether the stress-response pattern is specific to psychotic or psychosis-like symptoms. Further studies are required to answer these questions. Second, the battery life of the autonomic monitoring limited the assessment period to one day of continuous, uninterrupted monitoring, which comes at the cost of reducing representativeness of the EMA for real life. Furthermore, 20-min sampling intervals possibly constitute stressful interferences with everyday life which increases the risk of measurement-reactivity. Future research, especially with more distressed patient samples that could not adhere to this taxing sampling scheme for longer periods of time, will need to find assessment strategies to avoid this problem. Some ideas would be to either extend the assessment interval (but subsequently lose some acuity of symptom phase assessment) or switch to a direct event-based reporting of symptom-onset and -offset at the very moment they begin and end (an EMA-method for which, to our knowledge, there is no psychosis-related research to date). Nevertheless, even if measurement reactivity reduced the external validity of the results in this study (e.g., mean stress-levels over the assessment period exceeding the usual stress-levels in everyday life), we can still assume internal validity of the comparison between the different event phases in the multilevel models. Third, some limitations of the HSE assessment need to be considered: The abbreviated assessment with single items per experience did not allow for event-phase classification based on reliable difference scores. Furthermore, the retrospective assessment for these experiences may have introduced some memory bias into the assessment, although this seems unlikely given the high frequency sampling procedure. Finally, whereas the prediction of averaged physiological data (20 min periods) aligns with the independent variable of this analysis (i.e., 20 min event intervals defined by the self-reported symptom levels prior to and after the respective phase), the prediction of momentary self-reported stress immediately prior to the end of the interval does not capture the overall stress level of the interval in an unbiased manner. Future studies could optimize this approach by assessing the subjective stress-level over the entire period since the last self-report. However, even in this case, biased reporting based on recency effects cannot be fully excluded.

4.4. Implications and conclusion

This is the first EMA study of experiences along the psychosis continuum that includes a high-resolution assessment of psychotic experiences and an assessment of both self-reported and physiological stress responses over the course of PSE episodes. Our results show that autonomic arousal parameters can be readily assessed using ambulatory devices and constitute informative additions to self-report to explore the predictors and immediate effects of

positive symptoms as well as potential symptom-specific stress signatures underlying paranoia and HSEs. Furthermore, for paranoia there is considerable overlap in the results based on autonomic indicators and self-reported stress measures. Future studies could extend these findings, for example by identifying crucial environmental factors that elicit stress responses (e.g., social stressors, Schlier et al., 2017b). Thus, the signal-to-noise ratio in future EMA-studies that investigate stress-responses could possibly be reduced and the sensitivity of predicting symptoms and symptom distress could be increased.

In terms of practical implications, there is a potential to replace or supplement self-report EMA with autonomic assessment in the future. One possibility would be to use autonomic assessment as an indirect measure of success for self-help strategies to reduce paranoia, which can be prompted in ecological momentary interventions. After symptom onset and the subsequent start of a momentary intervention, the decrease in autonomic parameters could be an indicator of symptom offset that could be programmed to dynamically stop the prompted momentary intervention and provide feedback to the user. Another possibility is to develop an early warning system for symptom onset based on autonomic assessment, which does not require user-input. However, these approaches need further research to determine and compare the sensitivity and specificity of self-reported and physiological stress parameters and to identify the physiological parameters that have sufficient predictive power to justify the extra technical effort. Thus, future studies need to build on our findings and replicate these results in patient samples, establish a threshold for a sufficiently specific prediction of symptoms based on autonomic parameters alone, and explore the potential of physiological stress parameters to optimize ecological momentary interventions.

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Declaration of competing interest

None.

Contributors

BS, KK and TML conceptualized the study. KK and BS conducted the study. BS analyzed the data and wrote the first draft of the manuscript. AC contributed to the analysis of the physiological data. TML contributed to interpreting and discussing the results. All authors edited and contributed to the manuscript and have approved of the final version.

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