Aberrant salience predicts fluctuations of paranoia two weeks in advance during a 1-year Experience Sampling Method study in people with psychosis

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An extended version of the manuscript is available at osf.io/em6v9.
The Experience Sampling Method (ESM) has improved our understanding of psychosis considerably [1]. Not only has ESM shed light on the moment-to-moment variability of psychotic symptoms, it has equally helped to identify micro-level precursor variables that forecast symptom exacerbations a couple of hours in advance. Among others, established ESM-derived precursors are negative affect [2] and aberrant salience [3], the attribution of novelty and significance to irrelevant stimuli [4]. Learning that these variables precede within-day symptom fluctuations raises the question whether they likewise allow the prediction of larger-scaled symptom deteriorations to target the high rates of relapse in psychosis [5]. In fact, recent evidence lends support to the idea that ESM- and relapse-precursors overlap, with negative mood and anxiety being significant predictors in both settings [2, 6].

The overarching research question of the present study was whether micro-level ESM-findings hold in larger-scaled time frames. We addressed this question by comparing the effects of negative affect and aberrant salience on subsequent psychotic symptoms between a one-week ESM-phase (10 assessments per day) and a one-year Follow-Up-phase (fortnightly assessments including relapse assessments every two months).

**Methods**

Data collection took place between March 2018 and May 2019. Inclusion criteria were age (18-65), sufficient command of the German language, a verbal IQ of 85 or higher, a verified non-affective psychotic disorder (past or current), and filling in a document listing emergency contacts (for safety reasons). Exclusion criteria were dementia, a severe neurological disorder, severe substance-use, and suicidality. The ethics committee of the German Psychological Association approved the study (ID: SM082017) and participants provided written informed consent.
After a face-to-face baseline interview consisting of the Mini International Neuropsychiatric Interview [7], the Positive and Negative Syndrome Scale [8], and the Community Assessment of Psychic Experiences [CAPE; 9], participants completed one week of smartphone-based ESM-assessments with 10 pseudo-random alarms per day in intervals of at least 30 minutes (plus additional event-contingent assessments). ESM-items, rated on visual analogue scales, covered anxiety (“I feel anxious”), self-esteem (“I feel worthless”), worrying (“My worries overwhelm me”), and sadness (“I feel sad”), which we aggregated to negative affect. Further, we included five items from the “increased significance” subscale of the Aberrant Salience Inventory [10], for example: “Do certain trivial things suddenly seem especially important or significant to you?”. Outcomes were paranoia (“I feel suspicious”) and auditory verbal hallucinations (“I hear voices no one else can hear”).

Follow-Ups started directly after the ESM phase. For one year, participants completed fortnightly online assessments, which included the same aforementioned ESM-items complemented by items on sleep quality and medication adherence. Every two months, the Follow-Up-questionnaire included an extensive relapse assessment based on adapted criteria by Csernansky et al. [11]. One of the following self-reported criteria had to be met: Hospitalization, increased psychiatric care and 25% increase of CAPE total score, deliberate self-injury, suicidal ideation, violence towards others (including property damage), or clinical deterioration.

To examine the effect of ESM-derived precursors on subsequent psychotic symptoms, we conducted linear mixed model analyses, which account for the nested structure of the data [12]. First, we assessed the effect of negative affect (t-1) as well as aberrant salience (t-1) on subsequent psychotic symptoms (t0), controlling for preceding psychotic symptoms (t-1). Subsequently, we added the assessment type (ESM vs. Follow-Up) as well as the “precursor x
assessment type” interaction. The interaction term indicated whether the effect of the respective predictor on subsequent symptoms differed between ESM- and Follow-Up-assessments. To identify precursors of relapse, we ran a logistic mixed model with relapse as the outcome and adherence to medication, quality of sleep, negative affect, and aberrant salience as predictors (measured approximately 2 weeks before the relapse-assessment). Across analyses, predictors were person-mean-centered. We used two-sided tests with \( p \)-values of .05, corrected for multiple tests [13]. Visit osf.io/em6v9 for the pre-registered report.

**Results**

The final sample consisted of \( n = 30 \) participants who provided \( M = 57.07 \) ESM-assessments (for sample characteristics, see supplementary materials). Two participants did not participate in Follow-Ups, leaving \( n = 28 \) participants who provided \( M = 18.47 \) Follow-Up-assessments. We hypothesized that negative affect and aberrant salience would predict subsequent psychotic symptoms. As shown in Table, both variables predicted paranoia but not hallucinations in ESM-assessments. In fortnightly Follow-Ups, only the effect of aberrant salience on subsequent paranoia reached corrected significance, which means that aberrant salience functioned as a predictor of paranoia consistently within days and across weeks. This interpretation was supported by a non-significant interaction of aberrant salience and assessment type (\( b = 0.103, SE = 0.077, t(1167.07) = 1.340, p = .181 \)). In contrast, the effect of negative affect on paranoia was lower in Follow-Up-assessments, as indicated by a significant interaction (\( b = -0.186, SE = 0.087, t(1172.36) = 2.147, p = .032 \)).

In exploratory analyses, we examined whether the effect of aberrant salience on paranoia was contingent on antipsychotic medication, given that both variables are related to dopaminergic processes [14]. The effect was significantly lower in medicated participants.
(interaction coefficient: \( b = -0.763, SE = 0.158, t(386.08) = 4.827, p < .001 \)), suggesting that aberrant salience is a stronger predictor of paranoia in unmedicated participants.

**Please insert Table 1 about here.**

In the logistic mixed model, no variable predicted relapse, likely due to the small number of relapses (13 participants relapsed) and thus insufficient power (all \( p \)'s >= .195; see supplementary materials).

**Discussion**

Comparing within-day ESM-assessments to fortnightly Follow-Ups we found that aberrant salience predicted paranoia consistently in both settings. An evident clinical implication of this result is that people with psychosis (or their caretakers) could benefit from monitoring feelings of aberrant salience continuously to anticipate symptom deteriorations early. This implication should be treated with caution, though, as a constant focus on internal states could increase the fear of relapse, which might in turn lead to a higher risk of recurring symptoms [15].

This study was a first attempt to improve the early prediction of psychotic symptom exacerbation using predictors and methods from ESM-research. Albeit preliminary, our findings indicate that the ESM-based approach is promising and that aberrant salience could be an interesting candidate warning sign in sufficiently-powered future studies.
References


Tables

Table 1. Lagged effects of negative affect and aberrant salience on subsequent paranoia and auditory verbal hallucinations (AVHs), separately for ESM- and Follow-Up-assessment periods.

<table>
<thead>
<tr>
<th>Precursor</th>
<th>coefficient (b)</th>
<th>SE</th>
<th>t</th>
<th>p</th>
<th>FDR</th>
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<tr>
<td><strong>Smartphone ESM-assessments</strong></td>
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<tr>
<td>Negative affect, outcome paranoia</td>
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</tbody>
</table>

Note. Predictors are participant-mean-centered; all models contain participant-mean-centered outcome symptoms at t-1 as covariates. FDR = False Discovery Rate-corrected values based on 8 tests, according to Benjamini and Hochberg [13].