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

Thies Lüdtke[1, 2], Steffen Moritz[3], Stefan Westermann[1], and Gerit Pfuhl[2]

[1] MSH Medical School Hamburg, Am Kaiserkai 1, 20457 Hamburg, Germany

[2] UiT – The Arctic University of Norway, Hansine Hansens veg 18, N-9019 Tromsø, Norway

[3] University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20251 Hamburg

Author Note

Thies Lüdtke https://orcid.org/0000-0003-2019-3842

Steffen Moritz https://orcid.org/0000-0001-8601-0143

Stefan Westermann https://orcid.org/0000-0002-4785-0024

Gerit Pfuhl https://orcid.org/0000-0002-3271-6447

Correspondence should be addressed to Thies Lüdtke, MSH Medical School Hamburg, Am Kaiserkai 1, 20457 Hamburg, Germany. Email: thies.luedtke@medicalschool-hamburg.de.

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

1. Myin-Germeys, I., et al., *Experience sampling methodology in mental health research: new insights and technical developments.* World Psychiatry, 2018. **17**(2): p. 123-132. DOI: 10.1002/wps.20513.

2. Lüdtke, T., et al., *Negative affect and a fluctuating jumping to conclusions bias predict subsequent paranoia in daily life: An online experience sampling study.* J Behav Ther Exp Psychiatry, 2017. **56**: p. 106-112. DOI: 10.1016/j.jbtep.2016.08.014.

3. Reininghaus, U., et al., *Stress Sensitivity, Aberrant Salience, and Threat Anticipation in Early Psychosis: An Experience Sampling Study.* Schizophr Bull, 2016. **42**(3): p. 712-22. DOI: 10.1093/schbul/sbv190.

4. Kapur, S., *Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia.* Am J Psychiatry, 2003. **160**(1): p. 13-23. DOI: 10.1176/appi.ajp.160.1.13.

5. Pelayo-Teran, J.M., et al., *Rates and predictors of relapse in first-episode non-affective psychosis: a 3-year longitudinal study in a specialized intervention program (PAFIP).* Eur Arch Psychiatry Clin Neurosci, 2017. **267**(4): p. 315-323. DOI: 10.1007/s00406-016-0740-3.

6. Buck, B., et al., *mHealth-Assisted Detection of Precursors to Relapse in Schizophrenia.* Front Psychiatry, 2021. **12**(822): p. 642200. DOI: 10.3389/fpsyt.2021.642200.

7. Lecrubier, Y., et al., *The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI.* European Psychiatry, 1997. **12**(5): p. 224-231. DOI: 10.1016/S0924-9338(97)83296-8.

8. Kay, S.R., A. Fiszbein, and L.A. Opler, *The positive and negative syndrome scale (PANSS) for schizophrenia.* Schizophr Bull, 1987. **13**(2): p. 261-276. DOI: 10.1093/schbul/13.2.261.

9. Stefanis, N.C., et al., *Evidence that three dimensions of psychosis have a distribution in the general population.* Psychol Med, 2002. **32**(2): p. 347-58. DOI: 10.1017/s0033291701005141.

10. Cicero, D.C., J.G. Kerns, and D.M. McCarthy, *The Aberrant Salience Inventory: a new measure of psychosis proneness.* Psychol Assess, 2010. **22**(3): p. 688-701. DOI: 10.1037/a0019913.

11. Csernansky, J.G., R. Mahmoud, and R. Brenner, *A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia.* N Engl J Med, 2002. **346**(1): p. 16-22. DOI: 10.1056/NEJMoa002028.

12. Twisk, J.W.R., *Applied Mixed Model Analysis*. 2 ed. Practical Guides to Biostatistics and Epidemiology. 2019, Cambridge, MA: Cambridge University Press DOI: 10.1017/9781108635660.

13. Benjamini, Y. and Y. Hochberg, *Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing.* Journal of the Royal Statistical Society: Series B (Methodological), 1995. **57**(1): p. 289-300. DOI: 10.1111/j.2517-6161.1995.tb02031.x.

14. Miyata, J., *Toward integrated understanding of salience in psychosis.* Neurobiol Dis, 2019. **131**: p. 104414. DOI: 10.1016/j.nbd.2019.03.002.

15. Gumley, A.I., et al., *Fear of recurrence: results of a randomized trial of relapse detection in schizophrenia.* Br J Clin Psychol, 2015. **54**(1): p. 49-62. DOI: 10.1111/bjc.12060.

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.*

Precursor	coefficient (b)	*SE*	*t*	*p*	*FDR*
Smartphone ESM-assessments					
Negative affect, outcome paranoia	0.184	0.057	3.255	.001	.003
Aberrant salience, outcome paranoia	0.187	0.043	4.395	< .001	< .001
One-year Follow-Up-assessments					
Negative affect, outcome paranoia	0.026	0.074	0.353	.724	.724
Aberrant salience, outcome paranoia	0.366	0.068	5.387	< .001	< .001
Smartphone ESM-assessments					
Negative affect, outcome AVHs	0.058	0.036	1.623	.105	.168
Aberrant salience, outcome AVHs	0.038	0.027	1.406	.160	.183
One-year Follow-Up-assessments					
Negative affect, outcome AVHs	0.093	0.043	2.198	.029	.057
Aberrant salience, outcome AVHs	0.069	0.043	1.621	.106	.141

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].