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Identifying and treating predictors of psychotic symptoms

How findings from Experience Sampling research can help to improve the treatment of psychosis and the prediction of relapse

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Abstract

Using frequent self-report assessments throughout the day, Experience Sampling Method (ESM) studies have shown that psychotic symptoms fluctuate within short periods of time. These fluctuations are preceded by negative affect, worrying, sleep problems, or aberrant salience. The overarching goal of the present thesis was to use these insights from ESM studies to improve the treatment of psychosis and the prediction of relapses. For this purpose my colleagues and I developed a modular Internet intervention (EviBaS), which targets not only psychotic symptoms but several psychosis-related problems derived from ESM, such as worrying, depression and poor sleep. Studies 1 to 3 report the intervention's efficacy and its potential mechanisms of action. To address the high rates of psychotic relapse using knowledge from ESM studies, we conducted a one-year observational study, which examined ESM-derived variables as warning signs of symptom deterioration and psychotic relapses.

Due to different inclusion criteria, the EviBaS-related studies 1 (n = 101), 2 (n = 124) and 3 (n = 55) varied in sample size. EviBaS was efficacious in reducing psychotic symptoms, as indicated by a significant time x group interaction in the mixed model ANOVA comparing an eight-week treatment with EviBaS to a waitlist control condition (p = .047, d = -0.37). Linear mixed model analyses of study 2 indicated that the efficacy of EviBaS did not rely on improving worrying, negative affect, self-esteem, self-reported cognitive biases, and quality of sleep, as the course of these variables did not differ between groups. Likewise, the effect of said predictors on subsequent symptoms did not differ between groups. However, within the EviBaS intervention (i.e., without considering group differences), worrying ($p_{corrected}$ = .030) and quality of sleep ($p_{corrected}$ = .003) predicted subsequent psychotic symptoms. Thus, when participants worried more or slept worse, they reported more severe subsequent psychotic symptoms, suggesting that these variables would have been worthwhile treatment targets. Study 3 only considered voice hearers from the EviBaS Project and compared the intervention's mindfulness module to waitlist using an ANCOVA with mediation analysis. Completing the mindfulness module did not result in lower distress by auditory verbal hallucinations (p = .598, η_p^2 = 0.006) but it improved mindfulness (p = 0.015, η_p^2 = 0.115) and hallucinations overall (p = 0.001, η_p^2 = 0.214). The effect on hallucinations was mediated by improved mindfulness. Study 4 (n = 30) incorporated a one-week ESM phase followed by a one-year Follow Up period encompassing bi-weekly assessments. Negative affect ($p_{corrected}$ = .003) as well as aberrant salience ($p_{corrected}$ < .001) predicted subsequent short-term paranoia. Interestingly, aberrant salience was likewise a significant predictor of bi-weekly fluctuations of paranoia ($p_{corrected}$ < .001). No variables predicted relapse.

In sum, ESM findings offer promising starting points to improve the treatment and the prediction of psychotic symptoms. Our Internet intervention targeting ESM-derived variables was efficacious – but not via the expected pathways. Whereas mindfulness was associated with the intervention's efficacy, negative affect, worrying, or sleep were not. This pattern of results suggests that it would be worthwhile to improve EviBaS to target a wider range of outcomes. Regardless of its modes of action, however, the efficacy of EviBaS represents an important finding because it shows that Internet interventions for people with psychosis, which are currently very rare, represent a promising treatment approach. Study 4 suggests that people with psychosis should monitor feelings of aberrant salience continuously after remission because these can forecast deteriorations of paranoia two weeks in advance. Due to insufficient power, relapse analyses require replication and aberrant salience represents a worthwhile candidate predictor in future studies.

List of Papers

Paper 1:

Westermann, S., Rüegg, N., Lüdtke, T., Moritz, S., & Berger, T. (2020). Internet-based self-help for psychosis: Findings from a randomized controlled trial. *Journal of Consulting and Clinical Psychology, 88*(10), 937–950. https://doi.org/10.1037/ccp0000602

Paper 2:

Lüdtke, T., Pfuhl, G., Moritz, S., Rüegg, N. L., Berger, T., & Westermann, S. (2021). Sleep problems and worrying precede psychotic symptoms during an online intervention for psychosis. *British Journal of Clinical Psychology, 60*, 48–67. https://doi.org/10.1111/bjc.12270

Paper 3:

Lüdtke, T., Platow-Kohlschein, H., Rüegg, N., Berger, T., Moritz, S., & Westermann, S. (2020). Mindfulness Mediates the Effect of a Psychological Online Intervention for Psychosis on Self-Reported Hallucinations: A Secondary Analysis of Voice Hearers From the EviBaS Trial. *Frontiers in psychiatry*, 11, 228. https://doi.org/10.3389/fpsyt.2020.00228

Paper 4:

Lüdtke, T., Moritz, S., Westermann, S., Pfuhl, G. (in preparation). Aberrant Salience Predicts Fluctuations of Paranoia but not Relapse During a 1-Year Experience Sampling Study in People With Psychosis.

List of terms and abbreviations

Actigraphy	A method of monitoring activities or sleep patterns using a small sensor (mostly a wristwatch-like device)
ABC Schema	Short for “Activating event, Beliefs, Consequences”; represents the assumption that people’s interpretations of situations determine emotional reactions, not the situations themselves (part of CBT).
CAPE	Short for “Community Assessment of Psychic Experience”, a self-report questionnaire assessing inter alia psychotic experiences.
CBT	Short for “Cognitive Behavior Therapy” (or Cognitive Behavioral Therapy), a therapeutic approach, which focuses on challenging dysfunctional thoughts, beliefs, attitudes, as well as behaviors.
CI	Short for “Confidence Interval”.
Continuum hypothesis of psychosis	The hypothesis that psychotic experiences occur on a continuum, ranging from mild to severe symptoms. This view is opposed to the binary classification of “healthy” (no psychotic experiences) and “ill” (psychosis).
DSM-V	Short for “Diagnostic and Statistical Manual of Mental Disorders” (5^{th} edition), a book by the American Psychiatric Association listing diagnoses and diagnostic criteria.
DV-SA	Short for “Delusion and Voices Self-Assessment”, a self-report questionnaire assessing psychotic symptoms by Pinto et al. (2007).
Ecologically valid	A term related to Experience Sampling, meaning that assessments are valid because they take place in the everyday life of participants rather than the laboratory.
ESM	Short for “Experience Sampling Method”, an assessment method that incorporates frequent repeated assessments of short self-report questionnaires on a smartphone, handheld computer, or a booklet.
EviBaS	EviBaS is the name of the psychological Internet intervention that was at the core of papers 1 to 3 of this thesis (short for “Evidence-based Self Help”)
ICC	Short for “Intraclass Correlation Coefficient”, can be used as a measure of inter-rater reliability.
Intention to treat	An analysis in randomized controlled trials that considers data from every participant, irrespective of their treatment- or assessment adherence.
Intermediate assessments	Short assessments, which were conducted within study 2 to monitor the course of symptoms and candidate predictors.
Interventionist causal model approach	A methodological approach, which targets a putative causal factor in an intervention in order to assess whether the manipulation of the causal factor results in effects on an outcome of interest. For example, Freeman et al. assumed that worry is a causal factor for persecutory delusions, so they

	targeted worrying in an intervention and observed whether persecutory delusions improved as a consequence in a randomized controlled trial.
JTC	Short for “Jumping to Conclusions”, the tendency to gather less information than controls in a probabilistic reasoning task, such as the “Beads Task”.
Lagged regression	Regression analysis in which the predictor variable is measured at a preceding point in time
LSHS-R	Short for “Launay-Slade Hallucination Scale-Revised”, a self-report questionnaire assessing hallucinatory experiences.
MAAS	Short for “Mindful Attention and Awareness Scale”, a scale measuring mindfulness, which was a core outcome of study 3.
MCT	Short for “Metacognitive Training”, a therapeutic intervention developed by Moritz and colleagues addressing cognitive biases.
MINI	Short for “Mini International Neuropsychiatric Interview”, a structured clinician-administered diagnostic interview.
Negative affect	A composite measure of different negative mental states, such as feeling down, anxious, or lonely. Its components may differ from study to study.
NICE	Short for “National Institute for Health and Care Excellence”, national treatment guidelines from the United Kingdom.
Non-affective psychosis	Psychosis that does **not** occur as a secondary feature of an affective disorder (e.g., depression).
PANSS	Short for “Positive and Negative Syndrome Scale”, a clinician-administered rating tool to assess the symptom severity of schizophrenia and other psychotic disorders (“PANSS-PF” refers to the positive symptom factor of the PANSS).
Paranoia-CL	Short for “Paranoia Checklist”, a self-report questionnaire assessing paranoia.
Per protocol	An analysis in randomized controlled trials considering intervention group participants only if they completed the trial as planned.
Psychosis	In this thesis, psychosis is defined as occurrence of either hallucinations, or delusions, or both.
RCT	Short for “Randomized Controlled Trial”, an experimental research design comparing groups (often a treatment of interest compared to a control condition) to which participants are randomly allocated. This procedure eliminates sources of bias using chance.
Schizophrenia spectrum	A variety of disorders characterized by psychosis.

Schizotypy	Personality trait characterized by a predisposition to experience psychotic-like experiences. Related to the concept of the continuum hypothesis of psychosis.
SSL	Short for “Secure Sockets Layer”, an encryption method for web pages

1 Introduction

Is it possible to identify warning signs that forecast the worsening of psychotic symptoms or even relapses? And would treating these warning signs help to improve psychotic symptoms indirectly? My co-authors and I (in the following referred to as "we" also when I was the first author) conducted four studies to address these questions. In order to identify candidate warning signs of psychotic symptoms, we drew on knowledge from so-called ESM studies, which examine moment-to-moment symptom variability in the daily lives of participants, and applied this knowledge to new contexts. Given the large and diverse body of research on psychotic disorders, I will begin by defining important terms, first and foremost *psychosis*.

1.1 Psychosis

The terminology in research on psychosis can be confusing. The latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V; American Psychiatric Association, 2013) separates numerous disorders from the so-called *schizophrenia spectrum*, ranging from substance-induced psychotic disorder to delusional disorder, schizoaffective disorder or schizophrenia. Not only are diagnoses manifold, there can also be considerable heterogeneity in terms of symptoms between two patients with the same diagnosis (Sadock et al., 2017, pp. 1409 - 1410). To bring order to this heterogeneity, it is worthwhile to focus on specific symptoms rather than diagnoses. In fact, all of the aforementioned disorders share a common set of symptoms, namely *delusions* or *hallucinations*, also referred to as *psychosis* (Arciniegas, 2015). Hence, for the sake of clarity, I will refer to all study participants in the present thesis as people with psychosis, irrespective of their individual diagnosis. The only restriction that my co-authors and I applied across studies was that participants' psychotic disorders were not substance induced, not due to a neurological/organic disease and not due to a primary affective disorder. Consequently, this thesis refers to people with psychosis as people of different non-affective schizophrenia spectrum diagnoses who show at least one of the core psychotic symptoms delusions or hallucinations.

As mentioned before, *hallucinations* and *delusions* are at the core of this thesis, symptoms that are also referred to as *positive* symptoms in the context of schizophrenia. Hallucinations and delusions are probably the most fascinating features of psychotic disorders as they reflect the distorted perception of reality (i.e, impaired reality testing; Arciniegas, 2015). Hallucinations are defined as sensory perceptions in the absence of a corresponding external or somatic stimulus (Arciniegas, 2015). Depending on the sensory domain, hallucinations can be auditory, visual, olfactory, or tactile. On a side note, hallucinations are only classified as psychotic by the American Psychiatric Association (2013) if they occur without insight. As self-report scales were used across all studies, the present thesis defines hallucinations and delusions as psychotic even if participants show enough insight to report them in self-report scales (for the concordance with clinician-rated assessments, see Lincoln et al., 2010b). Auditory verbal hallucinations are one of the most common types of hallucinations with approximately three in four people with schizophrenia or schizoaffective disorder experiencing voice hearing at least once in their life (Thomas et al., 2007). Besides hallucinations, the present thesis focuses on delusions in all included studies. Delusions are fixed false beliefs, such as the false belief that one is being harmed, followed, or spied on. Delusions are maintained despite evidence that obviously and incontrovertibly contradicts the belief (Arciniegas, 2015). The aforementioned description is very rigorous in that delusional ideas are supposed to be imperturbable ideas that are held with full conviction, which is not always the case (Appelbaum et al., 2004); see section 1.2 for a

description of temporal dynamics of delusions. As for hallucinations, I therefore propose a more liberal definition of delusions in the present thesis, which considers false beliefs (e.g., paranoia) as psychotic, even if they are not held with full conviction continuously and even if participants can report them in self-report scales. The conceptualization of delusions and hallucinations in this thesis is influenced by the so called *continuum hypothesis* of psychosis. The continuum view emerged in response to the issue of discriminating between "healthy" and "ill" participants, and it suggests that rather than dichotomizing these categories, symptoms are best described on a continuum ranging from no symptoms to severe psychosis with a gradual course in between (van Os & Reininghaus, 2016). General population studies support this notion, indicating that psychotic experiences of varying intensity occur frequently outside of people with schizophrenia or other severe mental disorders (Rossler et al., 2015).

1.2 Fluctuating psychotic symptoms and their precursors

Interestingly, longitudinal studies (i.e., studies using repeated measures) indicate that there is not only a continuum of symptom severity between persons but also within a person, meaning that psychotic symptoms fluctuate over time. Appelbaum et al. (2004) conducted a longitudinal analysis on the stability of delusions, a symptom traditionally considered unalterable and stable over time (American Psychiatric Association, 2013). The authors recruited currently hospitalized patients with delusions and followed them up with psychiatric interviews in 10-week intervals over the period of one year. Only one third of the initially delusional participants reported delusions 10 weeks later, and only 15% showed delusions consistently across all assessments (Appelbaum et al., 2004). It is important to note that the sample consisted of people with different affective or substance induced diagnoses. Regardless of the heterogeneity of diagnoses, however; the temporal variability of delusions was striking. Smeets et al. (2013) conducted far less frequent assessments of delusions and hallucinations in a general population sample, but over a longer period of time. The authors conducted assessments in the years 1996, 97 and 99 to examine the long-term temporal stability of psychotic symptoms. Only 6.5% of people who displayed delusions at baseline, showed delusions at all three measurements. For people, who displayed hallucinations only, the proportion showing consistent hallucinations across measurements was 14.2%. People who suffered from both symptoms, showed the highest consistency of symptoms across time points (33.1%), indicating that the temporal stability of symptoms could depend on the severity of symptoms. So et al. (2012) compared the conviction of delusions 12 months apart and found a reduction for 38.4% of participants, an increase for 18.9%, and constant conviction for only 42.7%.

1.2.1 The Experience Sampling Method

The afore reviewed studies on the temporal variability of psychotic symptoms used assessments that were 10 weeks, one year, or even two years apart. One might argue that it is not surprising to find fluctuations of psychotic symptoms across such long time spans because many factors can affect the course of symptoms, such as psychiatric treatment with antipsychotics (e.g., Kahn et al., 2008) or psychotherapy (Bighelli et al., 2018; Jauhar et al., 2014). In order to get the full picture of symptom variability in psychosis, one must "zoom in" (Myin-Germeys et al., 2018) on the variability of symptoms in shorter periods of time. The so-called Experience Sampling Method (ESM; Myin-Germeys et al., 2009) provides the tools to do exactly that (see Figure 1). ESM studies (also referred to as EMA, Ecological Momentary Assessment) use highly frequent self-report assessments to capture momentary symptoms, emotions, thoughts, but also contextual factors, such as the current activity or

whereabouts (Myin-Germeys et al., 2009). Comparable to a structured diary, participants report variables of interest as they occur in their daily lives. ESM relies on the idea that behavior is driven by the momentary context (ecological psychology; Heft, 2013), which implies that it is important to measure behavior, emotions, and symptoms when they occur in everyday life. ESM assessments can be event-contingent (participants complete an ESM assessment when a certain event occurs), time-contingent (participants complete ESM assessments based on a time schedule), or a combination of both. Time schedules can be fixed or (pseudo-) random, the latter prevents that participants adapt their daily routines in response to the assessments, resulting in a more representative sample of assessments. ESM questionnaires need to be short so that they cause as little disruption of daily routines as possible, and items aim at capturing current states (e.g., "at the moment, I feel…"). Early ESM studies used booklets to capture momentary variables on short paper and pencil questionnaires, prompted by a beep, for example by a timer on a watch (e.g., Myin-Germeys et al., 2001). As part of technological advances, more recent studies used handheld computers or smartphones (e.g., Westermann et al., 2017), which are commonly used today (Myin-Germeys et al., 2018).

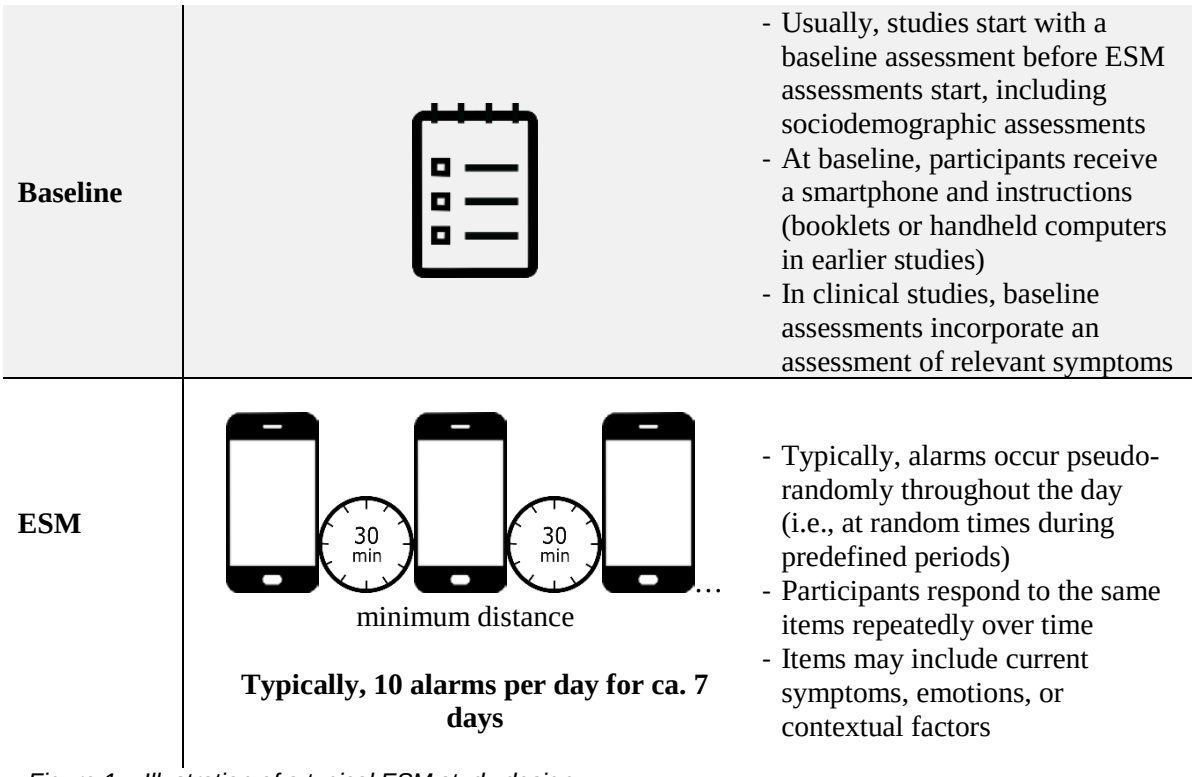


Figure 1 – Illustration of a typical ESM study design.

1.2.2 Using ESM to detect short-term symptom fluctuations

ESM studies offer the possibility to shed light on the short-term variability of symptoms (i.e., fluctuations across days or within the same day), and have thus enabled researchers to examine how people with psychosis experience their symptoms during the day rather than across years (Smeets et al., 2013) or weeks (Appelbaum et al., 2004). Oorschot et al. (2012) found that auditory and verbal hallucinations occur in episodes during the day rather than being present consistently. Out of 184 participants with schizophrenia spectrum diagnoses, 10 participants reported visual hallucinations only, 25 reported auditory hallucinations only, and 38 reported both visual and auditory hallucinations, highlighting the interconnection of these experiences. Hallucinations occurred at 22% of assessments, accumulating to M = 4.1 episodes on average over a six-day period. The results by Oorschot et al.

(2012) illustrate how ESM studies can grant insight into hallucinatory experiences and their variability that would remain undetected in other designs. As for hallucinations, the ESM method likewise helped to uncover the temporal variability of delusional experiences (Ben-Zeev et al., 2011). In a sample consisting of 144 participants with schizophrenia or schizoaffective disorders, 49% reported paranoia at least once over a one-week period (4 assessments per day). Rather than being present consistently for all patients (as one would expect given the DSM-V definition), paranoia occurred only at certain occasions during the one-week period. The frequency of paranoia differed between participants, ranging from 1 to 21 occasions with a mean of approximately 5. Interestingly, the likelihood experiencing paranoia was higher when a participant had experienced paranoia at the previous measurement, indicating that delusional experiences occur in episodes, similar to hallucinations. That means that once persecutory ideation occurs, it is very likely that it is still present three to six hours later. For other delusional subtypes (delusions of control, reference, and grandiosity), a very similar picture emerged (Ben-Zeev et al., 2012). Although there are occasional participants who report delusions consistently, the findings by Ben-Zeev et al. (2012) suggest that delusions occur in episodes during the week rather than being present consistently – similar to hallucinations.

1.2.3 Using ESM to uncover predictors of psychotic symptom variation

As reviewed above, ESM studies helped to uncover the short-term temporal dynamics of hallucinations and delusions. However, the method has many more advantages beyond the identification of temporal fluctuations. First, experience sampling enables researchers to conduct assessments that are *ecologically valid* (Myin-Germeys et al., 2018), meaning that participants respond to items in their real life rather than the laboratory. It allows to capture contextual factors, such as the place, the activity or the people that one interacts with, uncovering interactions of the individual with their environment. Unlike retrospective assessments, ESM is not dependent on the participant's ability recall certain events. This can be beneficial when participants suffer from cognitive impairments (Schaefer et al., 2013). To illustrate, the momentary assessment of affect in psychosis does not correlate with retrospective assessments when controlling for memory deficits (Blum et al., 2015), indicating that retrospective assessments can be flawed when memory deficits are prevalent. Finally and most importantly, ESM studies grant insight into underlying processes of symptom formation and variability over time. The following section reviews findings from ESM studies that helped us understand how psychotic symptoms emerge in the daily life of participants with psychosis.

One of the first studies in the field of ESM research in psychosis demonstrated that people with psychosis show increased negative emotional responses following daily life stressors when compared to first-degree relatives and control participants (Myin-Germeys et al., 2001). Different types of stress (i.e., event-related, activity-related, thought-related, and social stress) predicted momentary negative emotional responses; and for all effects, there was a significant interaction with group (Myin-Germeys et al., 2001). This finding, which was replicated in subsequent studies (e.g., Reininghaus et al., 2016) brought attention to an "affective pathway" of psychosis (Myin-Germeys & van Os, 2007). Myin-Germeys and colleagues established the term *negative affect* as a composite of different negative mental states, namely feeling down, guilty, insecure, lonely, and anxious, which was central to many following publications (as well as the present thesis). The pioneering work by Myin-Germeys et al. (2001) paved the way for many subsequent ESM studies, which further investigated associations of negative affective states and psychotic symptoms. To date, the effect of negative affect on paranoia has been replicated in several independent ESM studies, both in clinical and non-clinical samples (Ben-Zeev et al., 2011; Kramer et al., 2014; Luedtke et al., 2017; So et al., 2018). For example, in one

study anxiety and sadness significantly predicted the occurrence of persecutory ideation (i.e., impression that someone is spying on the person or plotting against them) at the following assessment, controlling for prior occurrences of persecutory ideation (Ben-Zeev et al., 2011). Adding alcohol or substance use as a covariate did not influence the effects. In addition, anxiety predicted subsequent levels of conviction and stress associated with the persecutory ideation, whereas sadness predicted distress only. The effect of negative affect on psychotic symptoms is well-established but its mediators and moderators are not clear, so far. ESM findings indicate that women with psychotic disorders show stronger increases in negative affect and stronger decreases in positive affect due to daily stressors than men with psychotic disorders (Myin-Germeys et al., 2004). Cognitive impairments, on the other hand, cannot explain the increased emotional reactivity to daily stressors, as indicated by studies that show no or negative associations of cognitive impairments and stress reactivity (Morrens et al., 2007; Myin-Germeys et al., 2003). Likewise, cognitive biases do not mediate the effect of negative affect on paranoia (Luedtke et al., 2017).

Not only did the work by Myin-Germeys and colleagues inspire several investigations of negative affect in ESM designs, it also gave rise to a plethora of subsequent ESM studies which examined other theory-driven candidate predictors of momentary psychotic symptoms that are – in part –related to negative affect. A seminal theoretical model, which has influenced the choice of candidate predictors in ESM studies, was the *cognitive model of persecutory delusions* (Freeman & Garety, 2014; Freeman et al., 2002; Garety et al., 2001). In short, the latest version of the model states that there are six proximal causal factors for the development of persecutory delusions, namely 1) a worry thinking style, 2) negative beliefs about the self, 3) interpersonal sensitivity, 4) sleep disturbance, 5) anomalous internal experience, and 6) reasoning biases (see Table 1). Of note, Freeman and Garety (2014) acknowledge daily stressors and major life events in their model as well, illustrating the overlap with the work by Myin-Germeys and van Os (2007). As reviewed in the following, ESM studies have provided evidence for many of the proposed causal factors that Freeman and Garety suggest in their model. The reviewed ESM studies conducted so-called *lagged* regression analyses, which allow the prediction of momentary psychotic symptoms through variables measured at a previous point in time (i.e., at a preceding ESM assessment).

Worrying: Momentary levels of worry and rumination predict not only subsequent persecutory delusional ideation, but also auditory hallucinations and the distress associated with these symptoms (Hartley et al., 2014).

Self-esteem: Udachina et al. (2014) showed that fluctuating momentary self-esteem (in contrast to stable self-esteem examined by Ben-Zeev et al., 2012) predicts subsequent paranoia throughout the day.

Sleep: Several ESM studies have investigated the effect of the quality of sleep on psychotic symptoms at the following day. Kasanova et al. (2020) found that poor self-reported quality of sleep predicted both morning paranoia as well as negative affect in a sample consisting of paranoid patients, non-paranoid people with psychosis, and people scoring high on schizotypy traits. In a similar setting, Mulligan et al. (2016) could show that reduced subjective and objective sleep efficiency preceded next-day auditory hallucinations in a sample of people with schizophrenia, while objective sleep fragmentation assessed via actigraphy as well as reduced subjective sleep quality predicted greater paranoia and delusions of control. In a similar study, low actigraphy-derived sleep efficiency predicted

persecutory symptoms at the next day in a sample consisting of both healthy controls and individuals with persecutory delusions (Kammerer et al., 2021).

Anomalous internal experiences: Ben-Zeev et al. (2012) examined different types of delusions (delusions of control, reference, and grandiosity) and their predictors in lagged ESM analyses. Hallucinations, which can be conceptualized as anomalous experiences, predicted the occurrence of subsequent delusions, irrespective of their type.

Reasoning biases: In addition to time-varying variables, Ben-Zeev et al. (2012) examined the effect of stable variables on the occurrence of delusions, namely self-esteem and the Jumping to Conclusions bias (JTC). JTC refers to the amount of evidence that participants gather in a probabilistic reasoning task, in that people with psychosis base decisions on insufficient evidence (for detailed information, see Dudley et al., 2016). The term stable means that the authors assessed said variables only once and not repeatedly over time. Trait JTC predicted delusions of control. Whereas Ben-Zeev et al. (2012) considered JTC a stable variable, Luedtke et al. (2017) examined JTC as a time-variant predictor that fluctuates over time and found that variable JTC predicted subsequent paranoia.

Most of the aforementioned studies were conducted in samples consisting of people with psychosis or schizotypy, which might give the impression that negative affect, worrying, or sleep are associated with psychotic experiences predominantly in people with severe psychiatric disorders. However, this is not the case. Rather, many of these effects are not exclusive to people with psychiatric diagnoses. For example, effects of negative affect (Kramer et al., 2014) or quality of sleep (Hennig & Lincoln, 2018) are universal rather than specific to psychosis.

Table 1 – The causal factors contributing to persecutory delusions proposed by the cognitive model of persecutory delusions (Freeman & Garety, 2014).

CAUSAL FACTOR	DESCRIPTION
A WORRY THINKING STYLE	Worrying is the "expectation of the worst happening" and consists of repeated negative thoughts about potential adverse outcomes (Freeman et al., 2015a). Putatively, worry causes paranoia because it makes people think about implausible ideas repetitively.
NEGATIVE BELIEFS ABOUT THE SELF	Also referred to as low self-esteem. People who feel bad about themselves (e.g., "I am worthless") can develop feelings of being different or apart and hence vulnerable, which can lead to paranoia.
INTERPERSONAL SENSITIVITY	Interpersonal sensitivity is defined as 'feeling vulnerable in the presence of others due to the expectation of criticism or rejection' (Bell & Freeman, 2014). Fears of social evaluation putatively lead to paranoia because they cause self-focus, worry, or negative affect.
ANOMALOUS INTERNAL EXPERIENCE	Unexplained arousal, depersonalization (i.e., feeling detached from oneself), or perceptual disturbances (e.g., illusions; Horga & Abi-Dargham, 2019). Misinterpretations of these experiences can lead to paranoia when a person tries to make sense of them.
INSOMNIA/ SLEEP DISTURBANCE	Insomnia (i.e., difficulties initiating or maintaining sleep; Riemann et al., 2017) but also other sleep disturbances lead to paranoia by increasing negative affect and anomalous experiences.
REASONING BIASES	A "Jumping to Conclusions" (JTC; Dudley et al., 2016) reasoning bias in psychosis leads to the acceptance of delusional ideas on the basis of insufficient information. The model further considers belief confirmation (Nickerson, 1998) and less use of analytic reasoning as contributors of paranoia.

Note. The model also acknowledges stress, drug use, negative affect, and other factors in the development of paranoia but this table only depicts the six central factors.

In addition to the aforementioned cognitive model of persecutory delusions, another important model of psychosis formation influenced the variables that were addressed in ESM research, namely Kapur's model of *psychosis as a state of aberrant salience* (Kapur, 2003); for a description see Table 2. In a nutshell, the model assumes that stimulus-unrelated bursts of dopamine lead to the aberrant attribution of salience to stimuli that are not inherently salient. The resulting experiences can lead to hallucinations or delusions. Several ESM studies were based on this model by examining whether momentary fluctuations of aberrant salience predict subsequent psychotic symptoms. An emerging body of research suggests that increased aberrant salience predicts increases of subsequent psychotic symptoms (a composite of both hallucinatory and delusional experiences) across healthy participants, participants at risk for psychosis and first episode psychotic patients (Klippel et al., 2017; Reininghaus

et al., 2016; Reininghaus et al., 2019). Moderation analyses revealed stronger effects of aberrant salience on psychotic symptoms for people at risk for psychosis compared to non-clinical controls (Reininghaus et al., 2016). In order to confirm the proposed direction of effects (i.e., aberrant salience preceding rather than following psychotic symptoms), So et al. (2018) tested both directions of effects and could show that aberrant salience in fact predicts paranoia, but not vice versa. This finding further strengthens the validity of aberrant salience as a predictor of paranoia.

A final candidate predictor of psychotic symptoms that received limited recognition in ESM studies so far is *experiential avoidance*. Experiential avoidance is defined as a) the unwillingness to remain in contact with private experiences, such as bodily sensations, thoughts, and emotions, and b) attempts to eliminate such experiences (Hayes et al., 2004). To simplify this rather bulky definition, one can think of experiential avoidance as the counterpart of a mindful and accepting engagement with negative experiences. Theoretical considerations suggest that experiential avoidance is implicated in a wide range of clinical problems and disorders. The underlying rationale is that a person who tries to suppress or otherwise avoid negative emotions that occur in response to stressors is unable to deal with negative emotions in a healthy way. Engaging in unhealthy *coping strategies*, such as worrying or even substance use to avoid negative feelings, eventually leads to psychological disorders. A coping strategy is "an action, a series of actions, or a thought process used in meeting a stressful or unpleasant situation or in modifying one's reaction to such a situation" according to the dictionary for psychology by the American Psychological Association. Udachina et al. (2009) proposed a specific pathway of paranoia formation through experiential avoidance. The authors suggest that people with psychosis use experiential avoidance in response to highly unstable self-esteem, in an attempt to avoid feelings of low self-worth (Bentall et al., 2001; Murphy et al., 2018). In experience sampling studies, experiential avoidance predicts momentary paranoia both in healthy participants (Udachina et al., 2009) as well as paranoid patients with psychosis (Udachina et al., 2014). In addition, experiential avoidance partly mediates the effect of low self-esteem on paranoia, supporting the proposed hypothesis. However, the authors likewise found support for the opposite direction of effects, namely self-esteem mediating the effect of experiential avoidance on momentary paranoia. Interestingly and in accordance with theoretical considerations, the negative effect of experiential avoidance increased under high stress (Udachina et al., 2014).

To summarize, the pioneering work by Myin-Germeys et al. (2001) initiated a series of ESM studies, which examined theory driven predictors of momentary psychotic symptoms in mostly time-lagged analyses of symptom variability throughout the day. The majority of predictors can be described as negative states of affect (e.g., anxiety, sadness), cognition (e.g., worry), or behavior (e.g., sleep), all of which are *transdiagnostic* problems. Aberrant salience is an exemption hereof as it is not a negative mental state per se but rather a qualitatively different state, which appears to be specific to psychosis. The resulting ESM studies have helped psychological research on psychosis to advance because they uncovered temporal symptom dynamics and time-lagged predictors of these fluctuations. Not only were these findings important to better understand psychoses, they also gave rise to a crucial follow-up question: Is it possible to treat predictors of momentary psychotic symptoms in order to prevent psychotic symptoms from occurring?

Table 2 – The model of psychosis as a state of aberrant salience (Kapur, 2003)

MODEL ASSUMPTIONS	DESCRIPTION
DOPAMINE AS A MEDIATOR OF SALIENCE	According to the model, (mesolimbic) dopamine is a crucial component in the attribution of *salience*, meaning that stimuli (events but also thoughts) grab attention, drive action, and influence goal-directed behavior. Through this process, the neural representation of a neutral external stimulus turns into a salient representation (either attractive or aversive).
STIMULUS-INDEPENDENT DOPAMINE TRANSMISSION IN PSYCHOSIS	Dopamine only *mediates* the aforementioned process of salience attribution, meaning that a stimulus becomes salient through dopaminergic processes because it is actually contextually relevant. In psychosis however, a dysregulated dopamine transmission leads to a **stimulus-independent** release of dopamine. In turn, this release of dopamine causes aberrant assignment of salience to external objects and internal representations. Dopamine becomes the cause rather than the mediator of salience.
CONSEQUENCES OF ABERRANT SALIENCE – EARLY STAGES	The model proposes that an increased release of dopamine precedes psychotic episodes. In this phase, patients experience exaggerated importance of certain percepts and ideas.
ABERRANT SALIENCE AND DELUSIONS	Delusions are a *top-down* cognitive explanation for the experiences of aberrant salience in an effort to make sense of them. The content of the delusion depends on the "psychodynamic" themes relevant to the individual as well as the patient's context. Arriving at a delusional explanation provides "insight relief" or "psychotic insight", and the patient searches for further confirmatory evidence.
ABERRANT SALIENCE AND HALLUCINATIONS	The model explains hallucinations as abnormally salient internal representations of percepts and memories.
ANTIPSYCHOTICS DAMPEN SALIENCE	The effectiveness of antipsychotics, which uniformly block dopamine, relies on their ability to dampen salience. However, antipsychotics likewise dampen salience of objects and ideas that one loves and desires, which explains why recipients of antipsychotics find them unpleasant.

1.3 Treating predictors of psychotic symptoms

ESM studies are regression-based, meaning that they do not encompass experimental manipulations of variables but only "natural" variability between and within participants. Consequently, ESM studies do not allow drawing causal conclusions. Nonetheless, the temporal ordering of predictors and

outcomes in ESM studies as well as the strong theoretical foundation of many predictor variables (Freeman & Garety, 2014; Kapur, 2003) suggest that ESM-based predictors represent worthwhile treatment targets for psychological interventions. The rationale behind this *interventionist causal model approach* (Kendler & Campbell, 2009) is to treat a predictor of symptoms in order to indirectly reduce the psychotic symptoms which the predictor causes (tentatively). Not only allows this approach to examine associations between putative causal factors and symptoms experimentally, it also coincides well with wishes and needs of people with psychosis who perceive the treatment of neuropsychological and affective problems as important (Freeman et al., 2019; Moritz et al., 2017). Accordingly, in many respects it seems worthwhile to target ESM-derived correlates of psychosis in psychological treatments. So far, there are few but very promising trials. Freeman et al. (2015a) examined a brief intervention based on cognitive behavioral therapy (CBT; for a description, see Table 3) targeting worry. The intervention led to reduced worrying and persecutory delusions in people with non-affective psychosis displaying persistent persecutory delusions. Reduced worrying mediated the effect on persecutory delusions. For sleep problems, findings are less coherent. In a randomized controlled trial, a CBT-based 10-week sleep intervention reduced insomnia, paranoia, and hallucinations in healthy participants, and insomnia mediated the effect on both paranoia and hallucinations (Freeman et al., 2017). In people with psychotic disorders, CBT-based sleep interventions likewise improved sleep but not psychotic symptoms (Freeman et al., 2015b; Hwang et al., 2019). However, it must be noted that these interventions targeted psychotic symptoms only as secondary outcomes, so the effect of sleep interventions on delusions and hallucinations remains open to question. CBT-based treatments for depressive symptoms in psychosis are rare despite their capability to improve functional outcome in psychosis (Upthegrove et al., 2017). A first trial found effects of a depression-focused intervention on depressive symptoms only whereas psychotic symptoms remained unaffected (Moritz et al., 2016). Other interventions have targeted cognitive biases, such as JTC, which served as a predictor of momentary psychotic symptoms in one ESM trial (Luedtke et al., 2017). The metacognitive training (MCT; Moritz & Woodward, 2007) aims at ameliorating psychotic symptoms by reducing, inter alia, participants' proneness to cognitive biases. Whereas early meta-analyses yielded mixed findings (e.g., van Oosterhout et al., 2016), the latest meta-analyses suggests that the metacognitive training improves psychotic symptoms (Eichner & Berna, 2016; Liu et al., 2018; Philipp et al., 2019). Finally, several studies have examined mindfulness- and acceptance-based interventions in psychosis. Mindfulness-based interventions aim at improving psychosis-related distress by targeting several of the aforementioned predictors, such as worry and rumination (Nolen-Hoeksema et al., 2008) and experiential avoidance (Vilardaga et al., 2013). Experiential avoidance is defined as the counterpart of the mindfulness-based emotion regulation strategy "experiential acceptance", which is characterized by a non-reactive, accepting, and mindful awareness of one's own perceptions. One early meta-analysis found that mindfulness-based interventions are effective at reducing hospitalization rates but also negative and affective symptoms in psychosis (Khoury et al., 2013), whereas a second meta-analysis found effects on total psychotic symptoms and positive symptoms, but not on negative symptoms of schizophrenia (Cramer et al., 2016). A recent meta-analysis concluded that acceptance- and mindfulness-based approaches effectively improve overall symptomatology and hospitalization rates, with improvements on a wide variety of symptoms, such as negative symptoms, depression, social functioning, mindfulness, and acceptance, but no effects on positive symptoms (Jansen et al., 2020). From a theoretical point of view, mindfulness interventions help participants to embrace present experiences in a nonjudgmental way without avoiding or suppressing them (Khoury et al., 2013) thereby reducing distress, for example, caused by auditory verbal hallucinations (Vilardaga et al., 2013). Conceptually, mindfulness

should help people who experience auditory verbal hallucinations to be aware of the potentially unpleasant sensation. For example, mindfulness is negatively correlated with hallucinations and associated distress (Strauss et al., 2015). Taken together, there is emerging evidence that targeting ESM-derived predictors of psychotic symptoms in psychological interventions can be beneficial for patients.

Referring back to the question at the end of section 1.2.3 ("can we improve psychotic symptoms by treating ESM based predictors?"), the answer would be "partly". For some predictors, evidence is convincing (e.g., worrying), for others there is so far no evidence that the indirect approach leads to reductions of psychotic symptoms (e.g., depression). Nonetheless, it seems worthwhile to address all ESM based predictors of psychotic symptoms because all of the reviewed interventions resulted in some benefit for patients – even if it was not an immediate measurable improvement of psychotic symptoms.

1.3.1 Internet interventions

The previous section illustrated that it is worthwhile to target predictors of psychosis in psychological interventions. But how should such an intervention be delivered? In a conventional face-to-face setting or in an online setting? The vast majority of afore reviewed interventions are delivered in a face-to-face setting whereas only a fraction of the interventions are delivered via the Internet (e.g., Freeman et al., 2017), perfectly illustrating the general scarcity of Internet interventions in psychosis. This shortage represents an important treatment gap because an online format seems very worthwhile to use the Internet to improve the dissemination of psychological treatments – especially in psychosis. The following section provides an overview on this topic.

Today, a large body of research has accumulated indicating that established variants of CBT for psychosis effectively reduce positive symptoms, both in research settings (Morrison et al., 2014; Tarrier et al., 1998) and in clinical practice (Krakvik et al., 2013; Lincoln et al., 2012). Although effect sizes are lower than for other disorders, such as depression (for a review on CBT in adult depression, see Cuijpers et al., 2013), CBT for psychosis is recommended in national guidelines (e.g., the NICE guidelines; see Kuipers et al., 2014) just as it is for other disorders. Despite these similarities, the dissemination of CBT-based interventions via the Internet differs drastically between psychosis and other diagnoses. For depression (Karyotaki et al., 2017) as well as anxiety disorders (Domhardt et al., 2019), numerous Internet-based interventions have been developed and evaluated over the past years (in the following, the term *Internet intervention* is used). In contrast, Internet interventions for psychosis are very rare (e.g., Gottlieb et al., 2017; Gottlieb et al., 2013) and their efficacy remains unclear to date. The shortage of evidence-based Internet interventions delivering CBT for people with psychosis is problematic because Internet interventions have great potential to improve the dissemination of psychological interventions for psychosis, which is poor currently (Haddock et al., 2014). Internet interventions can reach people who do not have access (or chose not to use) face-to-face psychotherapy, which make up approximately 40% of patients with psychosis (Mojtabai et al., 2009).

1.3.1.1 Properties of Internet interventions according to Anderson (2016)

Several definitions of Internet interventions exist. Barak et al. (2009) proposed the definition "a primarily self-guided intervention program that is executed by means of a prescriptive online program operated through a website and used by consumers seeking health- and mental-health related

assistance. The intervention program itself attempts to create positive change and or improve/enhance knowledge, awareness, and understanding via the provision of sound health-related material and use of interactive web-based components" (Barak et al., 2009, p. 5). Andersson et al. (2008) define Internet interventions as "a therapy that is based on self-help books, guided by an identified therapist which gives feedback and answers to questions, with a scheduling that mirrors face to face treatment, and which also can include interactive online features such as queries to obtain passwords in order to get access to treatment modules" (Andersson et al., 2008, p. 164). The definition of Anderson and colleagues is stricter in that it includes *guidance* as a feature of Internet interventions. Guidance refers to personal support by a moderator during the intervention, in the form of feedback, answers to open questions, or reminder messages (Andersson, 2016).

Usually, Internet interventions require an online platform (i.e., a website) through which participants enter the intervention with personal login data. Using an online platform to access the intervention comes with several advantages when compared to classical face-to-face therapy. Participants can contact moderators via text messages (embedded within the intervention) whenever necessary rather than only during face-to-face meetings. Also, a history of personal communication is saved within the system, enabling the participant to access previous conversations. The participant can use the intervention whenever they want and there is no need for scheduled appointments. Then again, an important disadvantage of Internet interventions is that there is no direct contact between a therapist and the client. Therefore, contents of the intervention can be misunderstood and negative reactions by the client (e.g., elevated negative affect in response to a module of the intervention) might remain undetected. Most Internet interventions convey contents via text, either on screen or as a downloadable file. Further they can contain video files, audio files, or pictures. Regarding their content, Internet interventions mostly present self-help materials in an online format. Thus, most Internet interventions can be described as interactive self-help books, enriched with several advantages, such as the contact with a moderator, or the usage of other media formats. Similar to classical psychotherapy, Internet interventions usually encompass treatment durations of 5 to 15 weeks and they follow a modular structure, with each module addressing a certain topic. Some Internet interventions require participants to complete all modules, others allow tailoring, meaning that participants may choose which modules they wish to complete.

1.3.2 The EviBaS intervention

ESM studies have identified numerous predictors of symptom fluctuations (e.g., worry; Hartley et al., 2014), which can be targeted successfully in psychological interventions (e.g., Freeman et al., 2015a). At the same time, Internet interventions are a highly accessible and effective way of delivering self-help materials for various disorders (e.g., anxiety and depression; Andrews et al., 2018). Consequently, it seems reasonable to provide people with psychosis with an Internet intervention that targets one or more evidence-based predictors of psychotic symptoms to improve not only correlates of psychosis (e.g., improve self-esteem) but potentially also psychotic symptoms. The Internet-based format could be particularly suited for people with psychosis because many people with psychosis have neuropsychological deficits (Schaefer et al., 2013), so that they could benefit from the possibility to repeat modules and to re-read self-help materials. Further, people with psychosis are a stigmatized group (Dickerson et al., 2002), so the anonymity of Internet interventions could circumvent treatment barriers of face-to-face approaches.

Given the numerous potential benefits that come with an online-based intervention targeting predictors of psychotic symptoms, we have developed a comprehensive psychological Internet intervention titled *EviBaS* (short for: Evidence Based Self-Help). The principal investigators Prof. Westermann, Prof. Moritz, Prof. Berger, and the corresponding working groups at the University of Bern, Switzerland, and University Medical Center Hamburg, Germany, collaborated on the development of the EviBaS intervention. The CBT-based intervention is guided, meaning that trained and supervised study staff with at least a bachelor's degree in psychology assist participants through a secure messaging system. The EviBaS intervention encompasses 11 modules in total – one introductory module, one module on relapse prevention and nine modules targeting persecutory delusions, auditory verbal hallucinations, as well as worrying, low levels of mindfulness, poor social competence, low self-esteem, depression, sleep problems, and cognitive biases. Hence, the intervention (a) addresses psychotic symptoms directly and (b) targets potential predictors of psychosis to ameliorate symptoms indirectly (seven modules). Modules contain educational components and exercises conveyed via text, audio, and video files. Paper 1 of this thesis presents findings from a multi-center randomized controlled trial evaluating the efficacy of EviBaS in a sample of people with verified psychotic disorders.

The evaluation of EviBaS in a randomized controlled trial can reveal whether EviBaS is efficacious in reducing psychotic symptoms because it compares the course of symptoms over time between an intervention group and a waitlist control group. However, the trial does not reveal the underlying processes through which the intervention is efficacious. Therefore, the current thesis incorporates two further papers that are concerned with EviBaS. These papers report findings regarding potential mechanisms of symptom change during the intervention. Paper 2 presents analyses using an ESM-like methodology of repeated measures during the 8-week randomized controlled trial to reveal predictors of momentary psychotic symptoms over time. As EviBaS covers a wide range of ESM-based predictors, the analyses of paper 2 aimed at investigating which of the targeted variables predict the course of psychotic symptoms during the intervention. If, for example, within-participant fluctuations of negative affect predict subsequent symptom fluctuations, then one can assume that improving affect is an important treatment target in an online intervention such as EviBaS. Paper 3 reports findings from a different approach to investigate mechanisms of change during the EviBaS trial. As described in section 1.2.3, experiential avoidance (the counterpart of mindfulness-based experiential acceptance) is associated with psychotic symptoms in ESM assessments and mindfulness interventions are associated with numerous positive outcomes in psychosis. As the stress-reducing features of mindfulness should be particularly beneficial for people who experience hallucinations, which cause considerable distress (Birchwood & Chadwick, 1997), we examined whether EviBaS improved distressing auditory hallucinations through improvements of mindfulness in a mediation analysis.

Table 3 – The basic principles of cognitive behavior therapy (CBT) according to Wright (2006).

PRINCIPLES	DESCRIPTION
ORIGINS OF CBT	Aaron Beck introduced the theory behind CBT in the 1960s, focusing mainly on depression and anxiety. Today, there are variants of CBT for many other conditions, including psychotic disorders.
THE CBT MODEL	The CBT model assumes that a person's emotions and behavior are influenced by the cognitive appraisal of situations. Hence, not the situation itself, but the interpretation of a situation influences one's behavior and feelings (and is hence targeted).
GENERAL METHODS OF CBT	The therapeutic relationship in CBT can be described as collaborative empiricism, which means that the therapist and client collaborate as a team to identify maladaptive cognitions and behavior, test the validity of these cognitions and behaviors, and to revise them. The aim is to gain skills to manage one's problems. As other therapies, CBT relies on nonspecific elements of the therapeutic relationship, such as rapport, understanding, or empathy. Furthermore, CBT is very structured, including agenda setting, homework, and manualized intervention methods.
COGNITIVE METHODS OF CBT	The most important technique is to ask questions that encourage the client to break patterns of dysfunctional thinking (e.g., Socratic questioning). Other techniques include imagery, role-play, or rehearsal exercises.
BEHAVIORAL METHODS OF CBT	The most common techniques in depression treatment are the scheduling of activities. In anxiety, the key behavioral method is exposure to feared stimuli, accompanied by relaxation or breathing techniques – the latter being universal and applicable to other disorders as well.

1.4 Using ESM-findings to improve the prediction of relapse

Insights from ESM studies can not only inform the treatment of symptoms, they can potentially also help to prevent symptoms from re-emerging. Paper 4 reports analyses, in which we examined whether short-term symptom predictors from ESM studies represent worthwhile candidate predictors of relapse in psychosis.

The risk of relapse is high in people with psychosis. Depending on the time frame, relapse rates range from 49% within 3 years (Pelayo-Teran et al., 2017) to 82% within 5 years (Robinson et al., 1999). This very pessimistic view regarding the course of psychosis is not new. In fact, more than a century ago Emil Kraepelin stated that dementia praecox, as he termed schizophrenia, would inevitably deteriorate (for a review on the history of relapse research, see Taylor & Jauhar, 2019). Given the high rates of relapse, it is not surprising that there are numerous studies that examined predictors of relapse, summarized in reviews (e.g., Olivares et al., 2013) or even meta-reviews (e.g., Lecomte et al., 2019).

Olivares et al. (2013) concludes that medication non-adherence as well as stress, depression, and substance abuse are associated with a higher risk of relapse. The studies reviewed by Olivares and colleagues provide very important information about *general* risk factors. For example, a person who is non-adherent to medication is at higher risk to relapse over a certain period of time when compared to an adherent person. However, such between-person risk factors do not tell us anything about the momentary triggers of relapse (i.e., within-person time-variant predictors). In fact, only a small fraction of the existing literature on relapse predictors deals with within-person time-variant predictors of relapse, such as prodromal symptoms that forecast relapse, in prospective repeated-measures studies. Unlike stable predictors of relapse (e.g., age of psychosis onset; Pelayo-Teran et al., 2017), time-variant predictors can help to gauge the risk of an upcoming relapse at any given time. Referring back to the example of medication adherence, a time variant predictor would inform us about the risk of relapse when a person stops taking their medication at a certain point in time rather than the risk of relapse comparing adherent and non-adherent persons. Eisner et al. (2013) reviewed available studies on time-variant predictors of relapses. The authors focused on the sensitivity and specificity of prodromal symptoms, also referred to as early signs of relapse (e.g., anxiety, dysphoria, or insomnia). Sensitivity values ranged from 10% to 80% (median = 61%) and specificity values ranged from 38% to 100% (median = 81%). One of the studies that Eisner et al. reviewed included up to bi-weekly diagnostic meetings in 339 outpatients over two years (Gaebel & Riesbeck, 2007). The authors found that participants reported trouble sleeping prior to a relapse (sensitivity = 39%, specificity = 78%), as well as being tense and nervous (sensitivity = 37%, specificity = 79%). More recent approaches that tried to identify what happens before a relapse occurs used passive smartphone data to detect anomalous behavior (Barnett et al., 2018; Buck et al., 2019). The quantity and duration of outgoing calls as well as the amount of total text messages changed prior to a relapse in one study (Buck et al., 2019).

The challenge in research on relapse is to identify variables that change within a person before a relapse occurs (i.e., warning signs of relapse). From a methodological point of view, ESM studies aim at something very similar; the only difference being that ESM focuses on warning signs of momentary symptoms rather than relapses. In ESM studies, repeated measures allow examining fluctuations of symptoms within participants over time, which can be predicted through preceding time-variant warning signs. If we could apply this methodology to the framework of relapse prediction, ESM could hence provide a very suitable assessment method. Interestingly, there is in fact considerable overlap of short-term ESM predictors and the early signs of relapse that Eisner et al. (2013) identified in their review. Sleep problems (Kasanova et al., 2020), but also negative affective states, such as anxiety or depressed mood (Ben-Zeev et al., 2011; Luedtke et al., 2017) predict upcoming subsequent momentary symptoms in ESM studies. All of these variables likewise serve as warning signs of relapse (e.g., Gaebel & Riesbeck, 2007). The overlap of ESM-predictors and previously identified relapse predictors suggests that the underlying processes of short-term symptom fluctuations and long-term relapse formation could be the same. Although relapse and paranoia represent different outcomes, we nonetheless set up the hypothesis for paper 4 that we can use ESM-derived predictor variables to predict long-term symptom fluctuations and hopefully even occurrences of relapse.

Study 4 incorporated a 7-day ESM phase followed by a one-year assessment phase with bi-weekly online-questionnaires designed to monitor the course of symptoms and candidate predictors. This design enabled us to directly compare short- and long-term associations of predictor variables and psychotic symptom fluctuations. At the same time, it allowed us to capture relapses over the one-year

period and to examine their predictors. Since the repertoire of ESM-based candidate predictors is extensive, my colleagues and I had to make a choice on the variables that were most promising as relapse predictors in the planning phase of study 4. Out of the established ESM-based predictors I chose negative affect (i.e., sadness, anxiety, low self-esteem, and worrying) and aberrant salience as candidates for the long-term prediction of symptoms and relapses. This choice was made because aberrant salience has a strong theoretical foundation (Kapur, 2003), is introspectively accessible (Cicero et al., 2010), and a well-established precursor in ESM studies (Reininghaus et al., 2016; So et al., 2018). Further, aberrant salience is theoretically (Kapur, 2003) and empirically (Miyata, 2019) associated with dopamine functioning (see also Table 2). Thus, aberrant salience may signal the emergence of subsequent symptoms or relapses through underlying dopaminergic processes. Finally, aberrant salience is specific to psychosis rather than a correlate of general psychopathology, such as sleep problems or depression. Negative affect, on the other hand, is by far the most well-established predictor of psychotic symptoms in ESM studies, researched for 20 years (Myin-Germeys et al., 2001). Consequently, study 4 incorporated it as the second candidate relapse predictor because it can be considered a promising warning sign.

1.5 Aims of the thesis

The overarching goal of the present thesis was to apply the knowledge from ESM studies to the treatment of psychosis as well as the prediction of psychotic relapse. Study 1 presents findings from a randomized controlled trial, which evaluated EviBaS, a psychological Internet intervention for people with psychosis. What is special about EviBaS is that it targets not only psychotic symptoms but also a variety of ESM-based variables that represent important predictors of psychotic symptoms in participants' everyday lives, such as depressed mood, poor sleep, poor self-esteem, low mindfulness, and others. Thus, the aim of paper 1 was to examine whether treating ESM-based predictors of psychotic symptoms (as well as psychotic symptoms themselves) results in a reduction of psychotic symptoms. Due to the heterogeneity of the targeted constructs in the EviBaS intervention, paper 1 cannot tell us about the mechanisms of change that occur during the intervention. Studies 2 and 3 address this research question by examining which processes occur during the EviBaS intervention. Paper 2 aims at answering this question by applying an ESM-like methodology to data obtained during the EviBaS Project. Using short intermediate online assessments, study 2 examines whether EviBaS improves ESM-derived predictor variables (e.g., sleep, worry, negative affect) and whether these variables predict subsequent fluctuations during the intervention. If changes of certain predictor variables precede subsequent psychotic symptom fluctuations, then one can assume that these predictor variables represent the most important treatment targets in a comprehensive intervention such as EviBaS. Study 3 tried to achieve the same goal as study 2 but using a different method. Using a mediation approach, study 3 examined whether improvements of mindfulness represent a mechanism of change in the treatment of distressing auditory verbal hallucinations. For this purpose, we drew a subsample of people from the EviBaS trial who reported auditory verbal hallucinations. Further, we only considered participants who used the mindfulness section of EviBaS. We hypothesized that EviBaS would lead to reduced distress by auditory verbal hallucinations and that this effect would be mediated by improved mindfulness.

Whereas studies 1 to 3 deal with the treatment of ESM-derived predictors of psychotic symptoms, study 4 examined a different application for findings from ESM studies. Given the high rates of relapse in psychosis, study 4 aimed at identifying predictors of long-term fluctuations of psychotic symptoms (measured bi-weekly over a period of one year) and potentially even relapse. ESM studies

are very similar to prospective studies on warning signs of relapse: Using repeated measures, both types of research designs try to identify within-participant changes of variables that precede a symptom exacerbation. The only (yet striking) difference is that ESM studies examine effects that occur over very short periods of time whereas relapse prediction studies examine effects across weeks. We hypothesized that we could use ESM-based predictors in bi-weekly online assessments to predict long-term symptom fluctuations and potentially relapses. In study 4, we made use of established ESM variables (e.g., worry or aberrant salience) but also of established methods from ESM research, such as short self-report scales and lagged regression based analyses.

2 Methods

The present thesis incorporates four papers. Three of these papers belong to the same overarching project, namely the *EviBaS Project*, a multi-center research project evaluating the efficacy of the EviBaS intervention. Although the samples for paper 1 to 3 are not identical due to differing inclusion and exclusion criteria for each trial, the samples do overlap considerably. Paper 4, on the other hand, reports findings from an independent study, unrelated to the EviBaS Project. Samples of all four studies consist of participants with lifetime non-affective psychotic symptoms, verified with the Mini International Neuropsychiatric Interview (MINI; Lecrubier et al., 1997). Thus, participants across studies represent a homogeneous group of people in terms of symptoms. Table 4 provides an overview of the four included studies.

To avoid confusion regarding the names/labels of each study, I will briefly introduce the wording that I am going to use throughout. The *EviBaS Project* refers to the overarching project that resulted in studies 1 to 3. The EviBaS Project is not the same as the EviBaS Efficacy Study (although this study is unequivocally the central study of the project). Rather, the EviBaS Project is comprised of all three EviBaS-related studies, aiming at not only assessing EviBaS' efficacy but also its mechanisms of change. In contrast to the EviBaS Project, I will refer to each of the individual studies conducted within the project as study 1 (*EviBaS Efficacy Study*), study 2 (*EviBaS Intermediate Assessment Study*), and study 3 (*EviBaS Mindfulness Study*). Although these studies originate from the same project, I believe that it is justified to call them stand-alone studies because of their unique features, as described in the following sections. I will refer to the last study simply as study 4 (*ESM Study*). There is no need to differentiate between the terms "project" and "study" because the ESM Study is a stand-alone study. To summarize, I will use the term EviBaS Project when I am referring to the entirety of studies 1 to 3, and I will use the respective term study 1, 2, 3, or 4 when I am referring to the individual studies that are reported in separate papers.

2.1 Participants and recruitment

The EviBaS Project's primary goal was to evaluate an Internet intervention, so it was sensible to recruit participants mainly through the Internet. For this purpose, we set up a webpage, which listed information on the trial, data security, and contact information. We advertised the project in online forums for people with mental health problems and we used e-mails to reach out to former study participants who wished and consented to be informed about studies. Further, we advertised the project online using "google ads". We reached out to candidate participants in Germany and Switzerland. In contrast to the EviBaS Project, the ESM Study incorporated a face-to-face assessment, which required participants to be present at the study site in Hamburg, Germany. Consequently, we focused our recruitment efforts on the area of Hamburg and surrounding areas. We reached out to

former participants, we contacted psychiatric wards of local hospitals, self-help groups, and assisted living facilities. We advertised the study using leaflets, posters, and within a local newspaper. Again, we used online advertisements (google ads) but restricted recruitment efforts to the relevant area in and around Hamburg rather than nation-wide.

Table 4 – Overview of included studies

	STUDY 1	**STUDY 2**	**STUDY 3**	**STUDY 4**
SHORT TITLE	EviBaS Efficacy Study (EviBaS Project)	EviBaS Intermediate Assessment Study (EviBaS Project)	EviBaS Mindfulness Study (EviBaS Project)	ESM Study
GOAL	To evaluate efficacy of EviBaS intervention	To identify predictors of symptom change during EviBaS	To examine efficacy of the mindfulness module of EviBaS	To predict long-term symptom fluctuations and relapses
DESIGN	RCT	ESM Design	RCT subgroup analysis	ESM Design
SAMPLE	*n* = 101 with psychosis, from EviBaS Project (above symptom threshold)	*n* = 124 with psychosis from EviBaS Project (no symptom threshold)	*n* = 55 with psychosis from EviBaS Project (with auditory hallucinations)	*n* = 30 with psychosis
MAIN OUTCOME	Post-treatment symptoms (PANSS-PF, LSHS-R, Paranoia CL)	Momentary auditory verbal hallucinations and paranoia (ESM)	Post-treatment distress by voices (subset of items from DV-SA) and LSHS-R.	Momentary auditory verbal hallucinations and paranoia (ESM); relapse

Notes. EviBaS is the name of the psychological Internet intervention (Ruegg et al., 2018), which targets hallucinations, persecutory delusions, and ESM-derived predictors of psychosis in 11 web-based modules. ESM = Experience Sampling Method, RCT = Randomized controlled trial. The symptom threshold of the EviBaS Efficacy Study refers to a score of 3 or higher on current delusions, hallucinations, or suspiciousness/persecution. PANSS-PF = positive factor (according to van der Gaag et al., 2006) of the Positive and Negative Syndrome Scale (Kay et al., 1987). LSHS-R = Launay–Slade Hallucination Scale (Launay & Slade, 1981; Lincoln et al., 2009). Paranoia CL = Paranoia Checklist (Freeman et al., 2005). DV-SA = Delusion and Voices Self-Assessment (Pinto et al., 2007).

We conducted all studies in accordance with the Declaration of Helsinki. All participants provided informed consent before the study and we obtained ethical approval of respective ethics committees before we conducted the studies. As the EviBaS Project incorporated study sites in Germany and Switzerland, we obtained ethical approval from ethics committees in both countries from the Ethics Committee of the Canton of Bern, Switzerland (KEK 03/14) and the German Psychological Society (SM052015_CH). The ESM Study was approved by the ethics committee of the German Psychological Association (ID: SM082017). In accordance with good clinical practice, the EviBaS Efficacy Study was prospectively registered with clinicaltrials.gov (ID: NCT02974400, November 28, 2016). Likewise, we registered the analyses for the EviBaS Intermediate Assessment Study (https://osf.io/gn8u5, registered February 27, 2019) as well as the ESM Study (https://osf.io/em6v9, registered September 12, 2018) with osf.io. Only study 3 (EviBaS Mindfulness Study) was not registered.

Figure 2 displays the recruitment process and the overlap of samples of all included studies. Papers 1, 2, and 3 all relied on data from the EviBaS Project (depicted on the left-hand side of Figure 2) but the focus on different research questions resulted in varying sample sizes. Detailed inclusion criteria for each study are as follows.

Study 1 (EviBaS Efficacy Study): We included participants if they were (a) 18 years old or older, (b) showed sufficient command of the German language, (c) had access to the Internet, (d) provided informed consent, (e) fulfilled criteria for the diagnosis of a schizophrenia spectrum disorder, (f) received simultaneous pharmacological and/or regular psychiatric or psychological care (for reasons of safety), and (g) fulfilled criteria for at least mild (≥ 3) delusions, hallucinations, or suspiciousness/persecutory delusions according to the PANSS (Kay et al., 1987; for a description, see section 2.4.1). We excluded participants in case of (a) acute suicidality, (b) an acute danger for others, (c) a neurological disease of the central nervous system that requires treatment, and (d) unwillingness to formulate an "emergency plan". The mandatory emergency plan listed persons that participants could contact in case of an emergency (e.g., a local psychiatrist).

Study 2 (EviBaS Intermediate Assessment Study): The inclusion criteria for study 2 were identical to study 1 (i.e., 18 or older, Internet access, command of German language, concurrent psychiatric treatment, no neurological disease, no suicidality, no danger towards others, and an emergency plan). However, there are two differences to study 1. First, participants had to fulfill the diagnosis of a psychotic disorder according to the MINI interview rather than a schizophrenia spectrum diagnosis. This difference is very subtle and affected only $n = 2$ people that were part of study 1 but not of study 2. The MINI requires two symptoms from the psychosis spectrum for a diagnosis of a psychotic disorder. Hence, participants with isolated psychotic symptoms (e.g., only auditory verbal hallucinations) in the absence of other psychotic symptoms do not receive the diagnosis although they are part of the schizophrenia spectrum. See section 2.4.1 for a description of the MINI interview. The second difference to study 1 was that we included participants who did not fulfill the symptom severity threshold of study 1 regarding delusions, hallucinations, or suspiciousness/ persecutory delusions.

Study 3 (EviBaS Mindfulness Study): Paper 3 presents analyses in a subgroup of participants from the EviBaS Efficacy Study (study 1). Hence, inclusion and exclusion criteria are identical to the EviBaS Efficacy Study (including the symptom severity threshold), with two additional criteria. First, we only considered participants who reported lifetime auditory verbal hallucinations because the main outcome

of the study was hallucination-related distress. Second, we only considered participants from the EviBaS group if they completed the mindfulness module because the paper focused on the intervention's effect on mindfulness.

Study 4 (ESM Study): Participants for study 4 were sampled independently from the EviBaS Project but inclusion criteria were almost identical. We included participants (a) if they were 18 to 65 years old, (b) if they showed sufficient command of the German language, (c) if they reached a verbal IQ score of ≥ 85 (according to the WST; Schmidt & Metzler, 1992), and (d) if they fulfilled criteria for a non-affective psychotic disorder according to the MINI (Lecrubier et al., 1997). We excluded participants with a diagnosis of dementia or a severe neurological disease, and if they fulfilled the diagnostic criteria of a severe substance use disorder or high suicidality according to the MINI. Finally, we excluded participants who refused to fill in the aforementioned emergency plan.

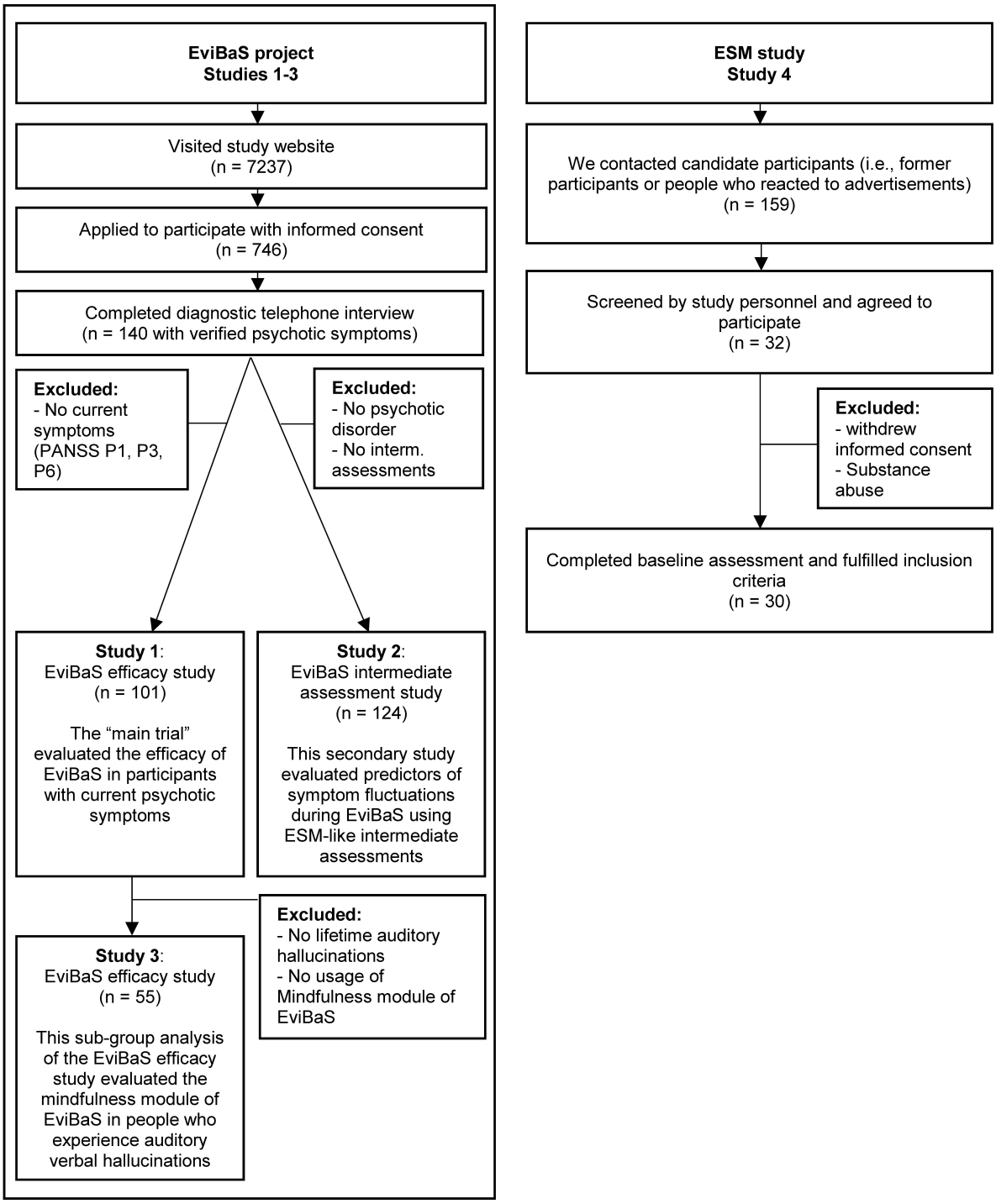


Figure 2 – Overview of the four samples, their recruitment, and their overlap

2.2 Study design

2.2.1 Design of studies 1, 2, and 3 (EviBaS Project)

For the sake of parsimony, the following section summarizes the study designs for papers 1 to 3 because they are all part of the EviBaS Project. Interested persons learned about the study and visited the study website. Directly after providing informed consent, candidate participants completed an online assessment consisting of several self-report questionnaires (implemented in QuestBack Unipark®, www.unipark.com). Within the online assessment, participants completed several sociodemographic questions as well as multiple questionnaires on psychotic symptoms (see section 2.4). If necessary, the survey platform automatically excluded participants who did not meet inclusion criteria (e.g., if they reported to be younger than 18). When a participant successfully completed the online assessment, the study coordinator inspected the participant's responses to the online assessment and assigned an independent assessor who contacted the participant for a diagnostic telephone interview (including inter alia the MINI and the PANSS). Assessors received extensive training (approximately 8 hrs.) and continuous supervision. They showed good interrater agreement as indicated by an intraclass correlation coefficient of .82. Setting up the emergency plan was also part of the telephone interview. After the telephone interview was completed, the study coordinator decided whether a participant could be included and randomized on the basis of the combined information from the online assessment and the telephone interview. If participants fulfilled all inclusion criteria except the current symptom severity threshold (see section 2.2.1), participants were randomized within a secondary track of the project (these participants were later considered in analyses for paper 2). We randomized participants using an electronic randomization service (www.random.org). From December 2016 to May 2018, n = 140 participants were randomized to the waitlist condition or the EviBaS condition, n = 101 of which were part of the EviBaS efficacy trial.

We allocated participants randomly to one of two conditions. One group received immediate access to the EviBaS intervention, whereas the second group received delayed access. The immediate access group received access to EviBaS and an accompanying smartphone application for eight weeks. The delayed access group received access to EviBaS after a waiting period which lasted 8 weeks for participants of the EviBaS efficacy trial (study 1) and 6 months for the asymptomatic participants who were part of the EviBaS immediate assessment study (study 2). After eight weeks, all participants completed a second online assessment (post assessment), which was accompanied by a second telephone interview for participants of the EviBaS efficacy trial but not for asymptomatic participants. Between the baseline and post assessment all participants completed so-called *intermediate assessments* that we used to monitor the course of psychotic symptoms and their predictors over time using frequent online assessments. Participants of the immediate access group completed the intermediate assessments when they logged into the EviBaS intervention (with a maximum frequency of twice in six days), whereas the delayed access participants completed the intermediate assessments once per week (we invited them via e-mail). The ESM-like intermediate assessments were programmed as short online assessments and they are at the core of paper 2.

The primary outcome for paper 1 was a composite score of positive symptoms of psychosis, which encompassed two self-report scales as well as the PANSS interview. Consequently it was crucial that assessors were blind to a participants' group allocation to avoid biased ratings. To ensure blinding, we asked participants to keep their group allocation confidential when talking to the assessors during the post assessment telephone interview. After each interview, assessors guessed which group a

participant belonged to and we compared their guesses to the actual allocation. Assessors were unable to correctly guess group allocation, indicating that blinding was successful.

2.2.2 Design of study 4

The design of study 4 differed considerably from studies 1 to 3 because it was purely observational. Study 4 aimed at identifying predictor variables of short- as well as long-term symptom fluctuations and potentially even relapses in psychosis. The study consisted of four distinct parts that are depicted in Figure 3. Candidate participants completed a structured face-to-face baseline interview including the MINI and the PANSS (for a description, see section 2.4.1) to assess inclusion and exclusion criteria as well as relevant diagnoses and psychotic symptom severity. After the baseline assessment (and if inclusion criteria were met), the participant received a study smartphone (Motorola G3, 5-inch screen), which they kept for approximately one week to complete an ESM assessment phase. The experimenter explained the functions of the smartphone as well as the ESM items. The ESM assessments were designed to capture the predictors *negative affect* and *aberrant salience* (for a detailed description, see section 2.4.2.4) as well as momentary psychotic symptoms repeatedly throughout the day. By doing so, we aimed at identifying predictors that forecast subsequent fluctuations of psychotic symptoms. The alarms that signaled a due ESM assessment occurred pseudo-randomly ten times per day between 9:00 a.m. and 9:00 p.m. with a minimum distance of 30 minutes in between. Participants could additionally activate ESM assessments manually. After approximately one week, participants returned the smartphone and completed a brief post-ESM assessment. After the post-ESM assessment, the Follow Up phase started, consisting of up to 24 online assessments over the course of one year (every two weeks). These bi-weekly Follow Up assessments included the same items as the ESM smartphone assessments (plus few additional items) and served the same purpose, namely identifying predictors of fluctuating psychotic symptoms – this time with a considerably larger distance between measurements. Every two months, the Follow Up assessment included an extensive assessment of psychotic relapse (for a detailed description, see section 2.4.2.4). Hence, the design of study 4 allowed us to not only to identify predictors of short- and long-term symptom fluctuations but also of relapses.

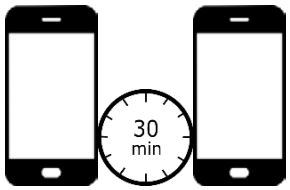
1. Baseline		- Face-to-face meeting, ca. 2 hrs. - Interview (MINI, PANSS) and self-report questionnaires
ESM Period started directly after the Baseline assessment		
2. ESM	 min. distance	- 70 scheduled assessments, 10 per day for 7 days, 98 sec. - ESM Items: paranoia, verbal hallucinations, aberrant salience, negative affect…
Post-ESM assessment took place when participants returned smartphone after ca. 7 days		
3. Post-ESM		- Face-to-face meeting, ca 20 min. - Questionnaire: Experiences ESM - Instructions Follow Ups
Follow Ups started ca. one week after the Post-ESM assessment		
4. Follow Up	 distance	- 24 scheduled assessments, bi-weekly for one year, 13 min. duration - ESM items (identical to ESM) - Follow Up items: Sleep, medication adherence, relapse-expectation, etc. - Bi-monthly relapse assessments, 43 min., questionnaires identical to baseline

Figure 3 – Overview of the trial design of study 4 (ESM Study)

2.3 The EviBaS intervention

The EviBaS intervention was at the core of the majority of papers that are part of the present thesis. For a general description of the intervention, please see section 1.3.2. The following section provides a more in-depth illustration with a specific focus on the mindfulness module, which was relevant for paper 3. The EviBaS intervention encompasses eleven modules (introduction, paranoid ideation, voice hearing, self-esteem, sleep hygiene, metacognition, depression, mindfulness, worrying, social competence, and relapse prevention). The working groups of the principal investigators Stefan Westermann, Steffen Moritz, and Thomas Berger collaborated its development. All contents of the intervention are based on established CBT-models and techniques (for an overview of CBT principles, please see Table 3). The authors of the modules used evidence-based treatment manuals as templates and selected suitable exercises, which they then adapted for an online self-help format. For example, the module on depression relied on materials on behavioral activation by Schaub et al. (2013) as well as cognitive restructuring techniques (i.e., the correction of depression-related thinking styles) from the metacognitive training for depression (D-MCT; Jelinek et al., 2013). The module authors wrote text passages, inserted suitable pictures, designed worksheets, and – if applicable – recorded audio files and video files to provide psychoeducation or instructions for exercises. An optional smartphone application accompanied the intervention, which enabled participants to complete exercises in their daily lives. Participants could for example use a scheduling plan within the app in order to plan activities, to record their mood before and after their activities, and to note obstacles that might keep them from completing planned activities. As mentioned in section 1.3.2, the rationale of the EviBaS intervention was to target individual symptoms and predictors of psychotic symptoms rather than a disorder as a whole (Freeman & Garety, 2014). Another important principle of the intervention was

autonomy. As psychoses are severe mental disorders often characterized by a lack of insight (see section 1.1), many patients report little involvement in decisions about their treatment (for a review, see Stovell et al., 2016) although they are motivated to avoid being patronized by others (Westermann et al., 2015). To address this issue, the EviBaS intervention enabled participants to choose which modules they would like to complete. Only the introductory module as well as the final module on relapse prevention were mandatory. Also the wording of the modules continuously emphasized autonomy. For example, modules introduced models or exercises as "suggestions" that participants could adopt if they related to them. The intervention encouraged users to critically examine whether they considered a proposed model plausible. Given this background, we did not expect participants to complete all 11 modules. Instead, we considered eight modules as full adherence (corresponding to one module per week during the eight week intervention period). For a description of each module, see Table 5.

Table 5 – Modules of the EviBaS intervention

MODULE	DESCRIPTION
INTRODUCTION (MANDATORY)	Module introduces ABC schema (thoughts, emotions, and actions interact) and leverage points for treatment; encourages reflection on values/goals
PARANOID IDEATION	Module refers to ABC schema; normalizes feelings of persecution; introduces a psychological model of delusions as a result of search for meaning due to abnormal experiences (Freeman & Garety, 2014; Kapur, 2003)
VOICE HEARING	Module normalizes voice hearing; introduces a psychological model of voices and distress; offers coping strategies (e.g., detached mindfulness); encourages cognitive disputation of interpretations of voices
SLEEP	Module introduces a vicious cycle model of sleep problems; discusses sleep hindering thoughts or environmental factors and how to reduce them
SELF-ESTEEM	Module provides psychoeducation on self-worth; helps to visualize personal strengths; challenges automatic thoughts that reduce self-esteem
META-COGNITION	Module focuses on cognitive biases such as Jumping to Conclusions using playful exercises derived from the MCT (Moritz & Woodward, 2007)
DEPRESSION	Module introduces the spiral model of depressive thoughts, feelings and behaviors; offers leverage points: behavioral activation (planning of activities) and challenging depressive thoughts (e.g., negative filter)
MINDFULNESS	Module provides information on mindfulness; differentiates mindful from evaluative thoughts; provides mindfulness exercises
WORRYING	Module differentiates solvable and unsolvable problems; discusses meta-cognitions regarding worry (positive attitudes towards worrying, etc.); introduces problem-solving skills
SOCIAL COMPETENCE	Module differentiates assertive, unsecure and aggressive social behaviors; discusses implicit social behavior rules
RELAPSE PREVENTION	Module emphasizes importance of balancing stress and relaxation; helps to identify relapse warning signs and to develop prevention plan

The following example illustrates how it was for participants to work with the EviBaS intervention. A participant would visit the study website and log in using their individual login data (participants set their own username and password). Upon the first login, participants can watch a video, which provides an overview of the program's functions. On the home screen (for a screenshot, see Figure 5), the participant can choose from various modules (on the left-hand side of Figure 4) or worksheets (depicted on the right-hand side of Figure 4). The program saves participant's progress from previous

sessions, so that participants can continue from where they left. A typical module consists of 21 webpages and takes about 30 to 60 minutes to complete. When starting a module, a participant receives information on the respective topic (e.g., on mindfulness) without a particular focus on psychosis. Participants then learn more about how the topic is relevant for their mental health and how they can improve their well-being by practicing related skills (e.g., being more mindful in everyday life). The module contains exercises which help the participant to apply contents to their personal life and to implement skills regularly. The worksheets are comparable to homework in classical CBT. The smartphone application summarizes the worksheets from the intervention to facilitate implementation into everyday life. Whenever a participant wishes to download a webpage, they can export a pdf file. This can be particularly helpful if participants prefer reading printed versions of the web pages. Also, they can highlight pages (using a little star-symbol) as personal favorites within the program. At the end of each module, the main points are summarized, and users can write feedback and ask questions, which the moderator addresses within few days.

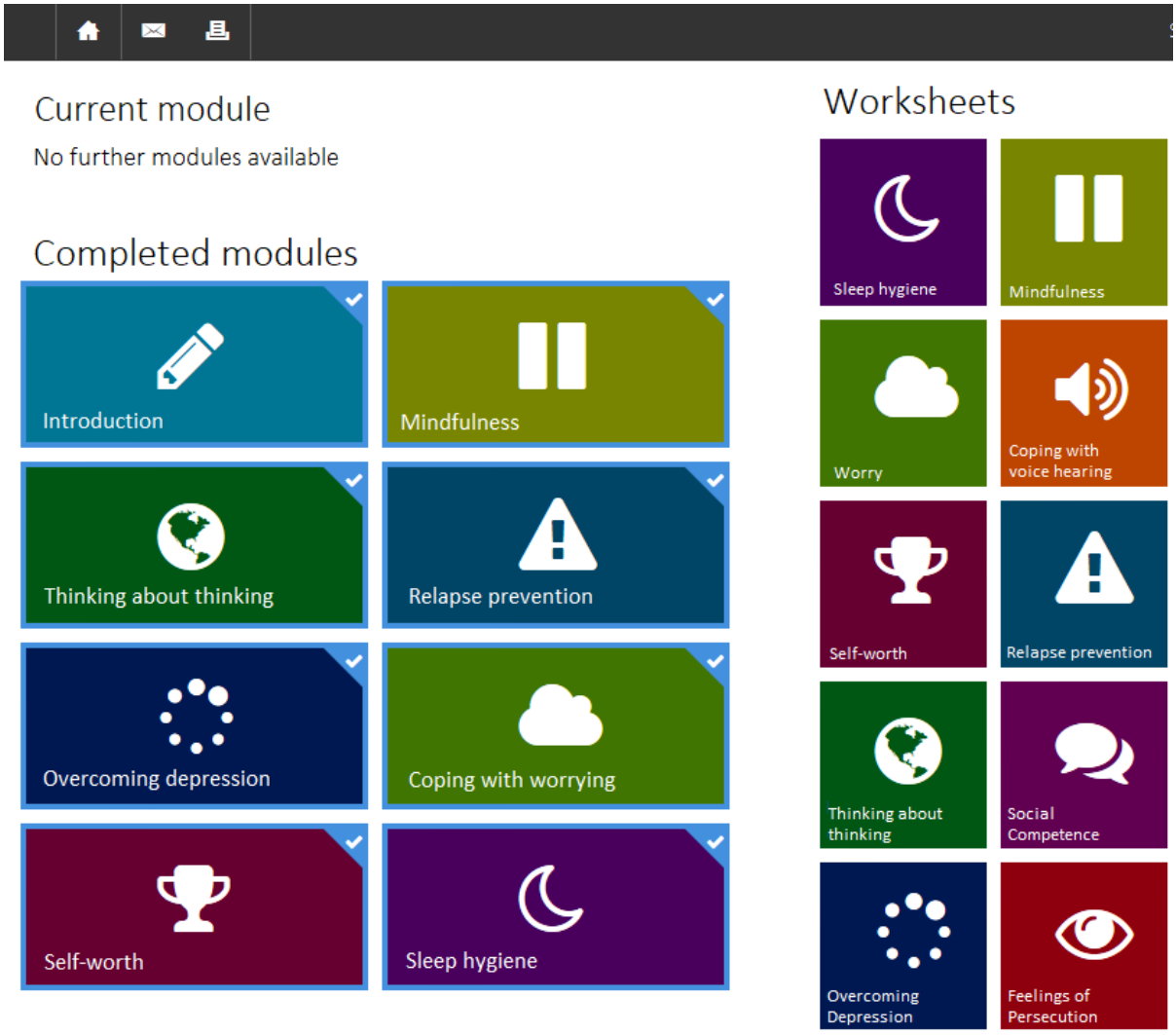


Figure 4 – Translated screenshot of EviBaS home screen showing 8 out of 11 modules

Whenever a participant had a question or when they encountered a problem, they could contact their personal moderator using a secure messaging system within the EviBaS program. At least once a week, moderators checked participants' progress, gave feedback, and sent reminder e-mails if

necessary – always ensuring participants' autonomy. Moderators had at least a bachelor's degree in psychology and received supervision by an experienced CBT therapist.

In order to ensure data security, the communication between client's devices and the server, which encompassed the EviBaS intervention, was SSL encrypted. Further, participants could only access the intervention using a personal username and password (which they set themselves upon first login). Finally, we instructed participants not to enter any identifying information in EviBaS worksheets or messages to the moderator (i.e., no names, e-mail addresses etc.).

2.3.1 The mindfulness module

For paper 3, we conducted a subgroup analyses in which we considered intervention participants only if they completed the mindfulness module of the EviBaS intervention. The module consists of 24 web pages, which contain text passages, pictures, and audio files (recorded by an experienced CBT therapist). Over the first 13 pages, the module provides psychoeducation on mindfulness, illustrates its historical origins and its effects on psychological health as well as presumed associations with psychosis. Subsequently, the module introduces mindfulness exercises, such as breathing exercises, the "S.T.O.P." exercise (stop, take a mindful breath, observe your feelings and thoughts and proceed with your activity), and the "body scan" exercise (a mindful observation of bodily sensations). Figure 5 depicts the "inner smile" exercise.

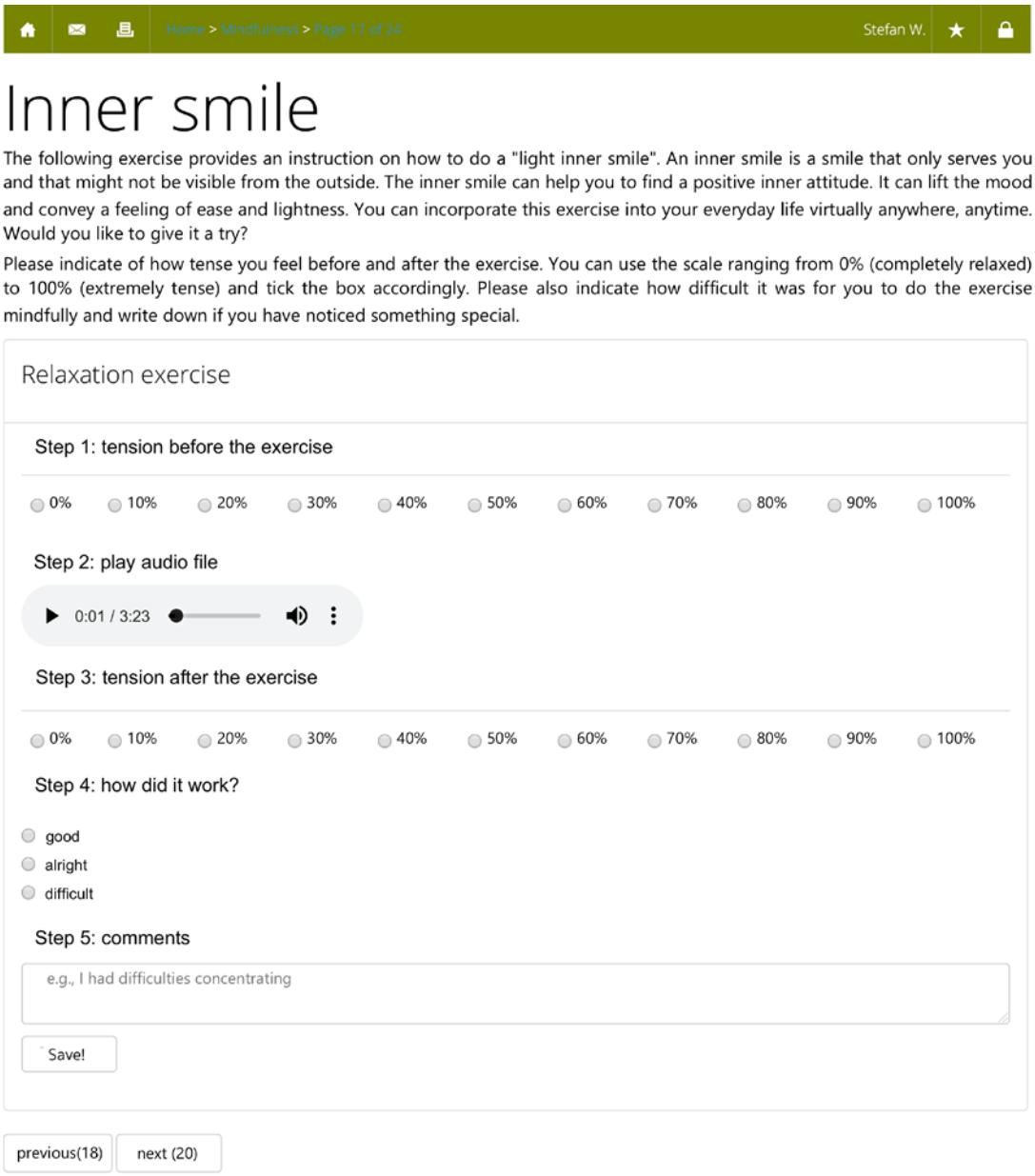


Figure 5 – Screenshot of the mindfulness module (part of EviBaS intervention)

2.4 Measures

Despite small differences regarding inclusion and exclusion criteria (see section 2.2), the target population was the same across all studies of this thesis, namely people with lifetime non-affective psychotic symptoms. The following section therefore summarizes baseline measures for all studies. In contrast, outcome measures differed between studies so that separate sections for each study are necessary. For the sake of parsimony, the following section will focus on measures that are relevant for the analyses presented here. We provide comprehensive lists of measures in the respective study protocols and registrations of the EviBaS Project (Ruegg et al., 2018) and the ESM Study (https://osf.io/em6v9).

2.4.1 Baseline measures of psychopathology

Across studies, we used the Mini International Neuropsychiatric Interview (MINI; Lecrubier et al., 1997) to assess relevant psychiatric disorders in a structured diagnostic interview. The MINI allows verifying diagnoses according to the DSM-V criteria (American Psychiatric Association, 2013). The MINI interview shows similar reliability and validity compared to extensive clinical interviews but can be administered in shorter time (mean 18.7 ± 11.6 minutes, median 15 minutes). It is organized in modules corresponding to different diagnostic categories (e.g., psychotic disorders) so that one can select a subset of modules if needed. For all included studies, we used the MINI to verify diagnoses of psychotic disorders. Further, the MINI allowed us to assess disorders, which resulted in exclusion, such as affective disorders with psychotic features (all studies) or severe alcohol- or substance use disorders (study 4). In order to measure psychotic and global symptom severity, we included the Positive and Negative Syndrome Scale in all studies (PANSS; Kay et al., 1987). The PANSS measures a wide range of positive, negative, and global symptoms of psychosis and showed good internal consistency in the present studies (e.g., Cronbach's $\alpha = .85$ in study 2). The interviewer rates PANSS symptoms using detailed rating criteria on a scale from 1 to 7. Seven items are designed to capture positive symptoms (delusions, disorganization, hallucinations, etc.), another seven items are designed to assess negative symptoms (blunted affect, emotional withdrawal, poor rapport, etc.), and 16 items capture global symptoms, such as anxiety or feelings of guilt. Interestingly however, empirical data do not confirm the originally intended three-factor solution for the PANSS, so we relied on a five-factor solution by van der Gaag et al. (2006) for studies 1 and 4. The positive symptom factor according to van der Gaag and colleagues, which was part of the composite outcome in study 1, consists of delusions (P1) + hallucinations (P3) + suspiciousness/persecution (P6) + grandiosity (P5) + somatic concern (G1) + unusual thought content (G9) + lack of judgment and insight (G12) + active social avoidance (G16) – difficulty in abstract thinking (N5), with a total score ranging from 1 to 55. For all other studies, the PANSS merely served as a descriptive measure of symptom severity rather than an outcome. As PANSS total scores can be difficult to interpret, we refer to Leucht et al. (2005) to categorize PANSS total scores into categories, such as mildly or moderately ill. We administered the MINI and PANSS interview in a face-to-face setting in the ESM Study (study 4) and via telephone in the EviBaS Project (studies 1-3). Administering the PANSS via telephone made it difficult to rate certain aspects of psychopathology. For example, assessors had to rate blunted affect using only the verbal cues that a participant provided, and they had to omit the item on mannerisms and posturing (G5) because it was impossible to judge habitual gestures.

2.4.2 Predictors and outcome measures

2.4.2.1 Outcome measures of the EviBaS efficacy trial (study 1)

The EviBaS intervention's main goal was to reduce positive symptoms of psychosis and associated burden, so the outcome of study 1 comprised a composite of positive symptom measures. The composite score consisted of the positive factor of the PANSS (PANSS-PF according to van der Gaag et al., 2006), the Launay–Slade Hallucination Scale (LSHS-R; Launay & Slade, 1981; Lincoln et al., 2009), and the Paranoia Checklist (Freeman et al., 2005; Lincoln et al., 2010a; Lincoln et al., 2010b). As mentioned before, the positive factor of the PANSS comprised the items P1 + P3 + P5 + P6 + G1 + G9 + G12 + G16 – N5, with an ICC of 0.84 (95% confidence interval: 0.70 to 0.95; two-way mixed, single measures, conservative absolute agreement). The LSHS-R has adequate psychometric properties and an internal consistency of $\alpha = .79$ (Lincoln et al., 2009). The internal consistency was $\alpha = .87$ in our sample. On 12 items, the LSHS-R measures subclinical as well as pathological

hallucinatory experiences on 5-point Likert scales ranging from 0 (*certainly does not apply to me*) to 4 (*certainly applies to me*). Scores range from 0 to 48 with higher scores reflecting more severe symptoms. The Paranoia Checklist measures the frequency, conviction and associated distress of paranoid thoughts. The three subscales show excellent internal consistency (Cronbach's $\alpha = .9$ or higher; Freeman et al., 2005), which was confirmed in the EviBaS Efficacy Study (Cronbach's $\alpha = .95$ or higher). In order to obtain the composite outcome measure, we first standardized each continuous outcome (PANSS-PF, LSHS-R, and Paranoia Checklist) by subtracting the mean at baseline and dividing by the baseline standard deviation (i.e., z-scores). Subsequently, we averaged the three standardized scores. The main reason for computing the composite score was to reduce the number of confirmatory tests. However, it also enabled us to consider participants in analyses who did not provide data for one of the individual outcomes at post assessment because we computed the composite when at least two of the three outcomes were present. After assessing the effect on the composite score, we examined each individual outcome in secondary analyses.

In addition to the primary outcome of positive symptoms, the EviBaS Efficacy Study examined a multitude of secondary outcomes, which aimed at measuring improvements of predictor variables of psychotic symptoms. The majority of these secondary outcomes is not relevant for the present thesis so that they are only mentioned briefly in Table 6. One exception is a questionnaire which measures mindfulness that was at the core of paper 3 of this thesis (for a description, see section 2.4.2.3).

Table 6 – Secondary outcomes of the EviBaS Project

TARGET	MEASURE	DESCRIPTION
PSYCHOTIC SYMPTOMS	Delusion and Voices Self-Assessment (DV-SA; Pinto et al., 2007)	Self-report measure for delusions and auditory verbal hallucinations
SLEEP	Insomnia Severity Index (ISI; Bastien, 2001)	7 items, satisfactory psychometric properties (Bastien, 2001)
SELF-ESTEEM	Rosenberg Self-Esteem Scale (RSES; Rosenberg, 1965)	Self-esteem measure, satisfactory internal consistency (Roth et al., 2008)
DEPRESSION	Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001)	9-item depression questionnaire, excellent internal consistency (Kroenke et al., 2001)
MINDFULNESS	Mindful Attention Awareness Scale (MAAS; Brown & Ryan, 2003)	6-point Likert scales, measures ability to mindfully experience current moment
WORRYING	Penn State Worry Questionnaire – Abbr. (PSWQ-A; Hopko et al., 2003)	8 items, good to excellent internal consistency (Crittendon & Hopko, 2006)
SOCIAL SKILLS	Interpersonal Competence Questionnaire (ICQ; Coroiu et al., 2015)	We used two ICQ subscales: *Initiation of relationships* ($\alpha = .73$) and *negative assertion* ($\alpha = .75$; Coroiu et al., 2015)
MOTIVES	Incongruence questionnaire (K-INK; Grosse Holtforth & Grawe, 2003)	Measures the realization of motivational goals (e.g., autonomy)

QUALITY OF LIFE	WHO Quality of Life (WHO-QoL-BREF; Harper et al., 1998)	Measures quality of life, Cronbach's α = .66 – .84 (Harper et al., 1998)
STIGMA	Internalized Stigma of Mental Illness (ISMI; Boyd et al., 2014)	We used the short version, excellent internal consistency (Sibitz et al., 2013)
TREATMENT EVALUATION	Client Satisfaction Questionnaire (CSQ; Attkisson & Zwick, 1982)	Satisfaction with treatment, Cronbach's α = .93 (Attkisson & Zwick, 1982)
SIDE EFFECTS	Questionnaire Side Effects Psychosis and Internet (QueSPI)	Negative effects of Internet interventions for psychosis (newly developed)
REASONING	Box Task (Andreou et al., 2015)	Probabilistic reasoning paradigm to assess cognitive biases

2.4.2.2 Predictors and outcome measures of the EviBaS Intermediate Assessment Study (study 2)

Within the EviBaS Project, participants completed a series of intermediate assessments, which we included in order to obtain a fine-grained view on fluctuations of psychotic symptoms and putative causal factors over time (analyzed in paper 2). Intermediate assessments consisted of 14 items with visual analogue scales. Two items (α = .42) captured psychotic symptoms, 'I feel suspicious', adapted from previous ESM trials (Kramer et al., 2014; So et al., 2018) and 'I hear voices that no one else can hear', which was self-generated. One item assessed worry 'My worries overwhelm me', adapted from the aforementioned Penn State Worry Questionnaire (Stober & Bittencourt, 1998). We measured negative affect using two items (α = .80). The first item 'I am feeling down, depressed, or hopeless' stems from the Patient Health Questionnaire-9 (Kroenke et al., 2001). The second item 'I feel anxious' was based on previous ESM trials (Kasanova et al., 2020; Kramer et al., 2014). The item on self-esteem 'I am satisfied with myself' was adapted from the Rosenberg Self-Esteem Scale (Rosenberg, 1965). We included two items to assess self-reported cognitive biases in an attempt to capture a tendency to make decisions based on insufficient evidence (as measured with experimental paradigms, such as the Box Task, see Table 6). The item 'When I am certain about something then I must be correct' was inspired by the Beck Cognitive Insight Scale (Beck et al., 2004). With the reverse-coded item 'I consider as much information as possible before I make a decision' we tried to assess Jumping to Conclusions. Unfortunately, the items correlated negatively so that we analyzed them separately. We assessed quality of sleep with the item 'The quality of my sleep is good'. The unspecific wording enabled us to capture different kinds of sleep problems (Kasanova et al., 2020). The remaining items of the intermediate assessments were not relevant for any of the papers of the present thesis. Participants rated all items according to how they felt at the current moment (except for sleep). For certain analyses of study 2, we calculated a composite score of predictor variables (the sum of worry, negative affect, self-esteem, self-reported cognitive biases, and quality of sleep; α = .60). As for study 1, the rationale of the composite score was to reduce the number of confirmatory tests.

2.4.2.3 Outcome measures of the EviBaS Mindfulness Study (study 3)

In the EviBaS Mindfulness Study (study 3) we analyzed a subsample from study 1 to examine effects of the mindfulness module of the EviBaS intervention on mindfulness and distressing auditory verbal hallucinations. For this purpose, we drew a subset of participants who reported auditory hallucinations

(lifetime) and we only considered participants from the immediate access group in the analyses if they completed the mindfulness module. We hypothesized that completing the mindfulness module would reduce distress associated with auditory hallucinations and that this effect would be mediated by increased mindfulness, so our primary outcome was *distress by voices*. We drew a subset of items from the Delusion and Voices Self-Assessment questionnaire (DV-SA; Pinto et al., 2007), in order to capture negative feelings associated with auditory verbal hallucinations. The DV-SA is a 15-item self-report questionnaire that consists of a delusions subscale as well as a voices subscale. For study 3, we drew a subset of items from the voices subscale, which measure voice-related *distress*, *obedience*, *control*, *interference with relationships*, and *interference with activities* (e.g., 'Last time you heard the voices, did the voices make you feel upset or distressed?'). We disregarded other items, for example on the frequency of voices, because we hypothesized that a mindful and accepting approach would not necessarily reduce the amount of voices but rather the distress that they cause. The original voices scale of the DV-SA shows good internal consistency of $\alpha = 0.83$, with test-retest reliability ranging from 0.86 to 0.96 (Pinto et al., 2007) and our newly created subscale on distress and disturbance was internally consistent as well (Cronbach's $\alpha = .83$). One important issue with our primary outcome was that we translated the DV-SA specifically for the EviBaS Project. As we considered it problematic to rely on a so far non-validated questionnaire as the primary outcome, we chose to include a second outcome capturing hallucinatory experiences, namely the LSHS-R, which was also part of the composite outcome in study 1 (Launay & Slade, 1981; Lincoln et al., 2009). The LSHS-R measures a broader construct than the *distress by voices* subscale but it is conceptually similar (one example item is 'I have been troubled by hearing voices in my head') and its German version is validated and established (Lincoln et al., 2009). We examined both outcomes in separated analyses for study 3. The underlying question of paper 3 was whether improvements of mindfulness would result in less distress by voices, so we included mindfulness as a second outcome. We measured mindfulness using the Mindful Attention and Awareness Scale (MAAS; Brown & Ryan, 2003). On 6-point Likert scales, the MAAS measures participants' ability to mindfully experience the current moment. We used the German version of the MAAS, which shows good internal consistency (Cronbach's $\alpha = 0.83$), good test-retest reliability ($r = 0.82$), and correlations with subjective well-being indicating validity (Michalak et al., 2008).

2.4.2.4 Predictors and outcome measures of the ESM Study (study 4)

Study 4 had three major goals, namely a) to identify ESM-based predictors of short-term symptom fluctuations within the same day, b) to examine whether these short-term predictors also function as predictors of long-term (i.e., bi-weekly) symptom fluctuations, and c) to examine whether said predictors might even serve as warning signs for full-blown relapses. To answer these research questions, we conducted smartphone-based ESM assessments for one week, followed by bi-weekly online assessments over the course of one year, including bi-monthly relapse assessments. Conceptually, study 4 is very similar to study 2, as both rely on frequent self-report measures. In fact, there is considerable overlap between aforementioned *intermediate assessments* and the ESM assessments described below. The major difference between studies 2 and 4 is that one study examined predictors of naturally occurring symptom fluctuations (study 4), whereas the other examined predictors of symptom fluctuations that are potentially caused by the EviBaS treatment (study 2).

ESM assessments (7 days, 10 times per day): The ESM smartphone assessments consisted of 17 items, rated on visual analogue scales. The following section only presents items that are relevant for paper

4. Please find the complete list of measured constructs in the Appendix. We assessed emotional valence (visual analogue scale ranging from *I feel very pleasant* to *very unpleasant*) and arousal (ranging from *very excited* to *very unexcited*). In addition, single items assessed anxiety ("I feel anxious"), self-esteem ("I feel worthless"), worrying ("At the moment, my worries overwhelm me"), and sadness ("I feel sad"). We aggregated anxiety, self-esteem, worrying, and sadness to a negative affect scale. As can be seen, the scale consists not only of affective states but also cognitions (e.g., a worry thinking style; Freeman & Garety, 2014), so it differs slightly from conventional negative affect scales. We used the same items as study 2 (EviBaS Intermediate Assessment Study) to capture psychotic symptoms, "I feel suspicious" and "I hear voices that no one else can hear". Unlike study 2, we analyzed paranoia and auditory verbal hallucinations as separate outcomes instead of using a composite score. We included five out of seven items of the *increased significance* scale of the aberrant salience inventory (Cicero et al., 2010) to measure aberrant salience. We chose a subset of items because we wanted to keep the ESM assessments as brief as possible. The items 27, 21, 1, 16, and 5 were selected based on their factor loadings (Cicero et al., 2010) and we adapted them slightly to capture current aberrant salience rather than general feelings. In addition, we changed the response format to the same visual analogue scale that we used throughout. One example item from the aberrant salience scale was: Do certain trivial things suddenly seem especially important or significant to you?

Follow Ups (one year, bi-weekly): The second phase of study 4 began directly after the ESM assessment phase and it was designed to capture long-term fluctuations of the same variables that were part of the one-week smartphone assessments. In addition, we amended the assessments slightly to capture a few extra constructs because Follow Ups occurred less frequently and were thus less demanding for participants. We assessed quality of sleep ("I would describe the quality of my sleep as *good*") and medication adherence, ("How much of the prescribed medication did you take in the past two weeks?"), the latter rated on a visual analogue scale ranging from 0% to 100%. We used the self-generated item "Do you think that you might experience a relapse in the near future?" to examine participants' relapse expectations at each Follow Up assessment. We included this item because we were interested in whether participants could anticipate a possible relapse, and if so, what criteria they used to make this prediction. The remaining items on drug abuse and alcohol abuse were not relevant for the present analyses.

Relapse assessments (one year, bi-monthly): We treated relapse as a binary variable meaning that it could either be absent (none of the criteria fulfilled) or present (at least one criterion fulfilled). Relapse criteria (based on Csernansky et al., 2002) are described in the following. The first criterion was hospitalization: Participants reported hospital admissions over a period of the previous two months preceding the current assessment. We also asked for the exact dates and the reasons for hospitalization, which we inspected manually afterwards. The second criterion was increased psychiatric care and a 25% symptom increase: We asked participants "Compared to the start of the study, did the psychiatric or psychological care that you received increase within the last 2 months?" and we explained what increased psychiatric or psychological care means. Additionally, we computed the difference of the Community Assessment of Psychic Experiences (CAPE; Stefanis et al., 2002) score compared to baseline to detect symptom increases of at least 25%. The CAPE was developed based on the Peters Delusion Inventory (Peters et al., 1999) to capture positive, negative, and depressive symptoms in general population samples. The third criterion was deliberate self-injury, which we assessed using the item "Please state if you deliberately injured yourself in the past week; if yes how often" from the Borderline Symptom List (BSL-23; Bohus et al., 2009). The fourth criterion

was suicidal ideation, which we assessed with the suicide item from the Beck Depression Inventory-II (BDI-II; Beck et al., 1996). We assessed the fifth criterion, violence towards others or property damage, using the item "Has there been a situation in the past 2 weeks where you physically attacked another person or where you destroyed the property of others?" which was self-generated. The sixth criterion was clinical deterioration, which we defined as a 50% symptom increase compared to baseline on the Brief Symptom Rating Scale (BSI-18; Derogatis & Fitzpatrick, 2004b). The reliable and valid German version of the BSI-18 measures symptoms of somatization, depression, and anxiety (Spitzer et al., 2011).

2.5 Data analysis

The studies of the present thesis can be separated into two groups in terms of statistical analyses. Studies 1 and 3 focused on the effect of an intervention (EviBaS) on a specific outcome, namely positive symptoms in study 1 and distress by voices as well as mindfulness in study 2. Therefore, these studies examined differences of a certain variable between a treatment group and a control group. For study 1, we used a mixed ANOVA, while study 3 relied on an ANCOVA. Time x group ANOVAs and ANCOVAs with baseline values as covariates are comparable methods when it comes to the examination of treatment effects. Studies 2 and 4, on the other hand, focused on frequent repeated measures, analyzed using lagged regression analyses of predictor-outcome associations within participants, a method typical for ESM studies. Hence, two papers focused on identifying group differences due to an experimental manipulation (allocation to EviBaS vs. waitlist), while the remaining two papers focused on observational regression-based analyses. In all studies, we conducted two-sided tests with conventional *p*-values of .05. All computations were conducted with SPSS (SPSS Inc., Chicago, Illinois), version 25 (study 3) and version 26 (all remaining studies).

2.5.1 Power calculations

ESM Study (study 4): Rather than conducting a power calculation for the ESM Study, we used previous ESM studies as a guide to gauge the necessary sample size. In a previous ESM study of our group (Luedtke et al., 2017), we successfully analyzed $n = 35$ participants who provided up to 8 ESM measures each. Other ESM studies found significant effects in similar sample sizes (e.g., $n = 41$ in Udachina et al., 2014), so we aimed for $n = 40$ participants for study 4.

EviBaS Project (studies 1-3): We conducted the power calculation for the EviBaS Project using G*Power 3 (Faul et al., 2007). The power calculation only applied to study 1 (the EviBaS Efficacy Study) and not to the secondary analyses of paper 2 and 3. We based our calculation on the clinical significance of expected effects (i.e., the practical or applied value or importance of the effect of an intervention; Kazdin, 1999) rather than estimating arbitrary effect sizes. We deemed a medium-sized or larger effect ($f \geq 0.25$) as clinically significant, so we aimed for a sample size sufficiently large to reveal such an effect. The power calculation resulted in a target sample size of 128 to detect a medium-sized effect using an ANCOVA with one covariate assuming a power of 80% and a conventional α-level of 5%. To compensate for an expected dropout rate of 10%, we increased the target sample size to 140.

2.5.2 Analyses in the EviBaS Efficacy Study (study 1)

To examine the effect of EviBaS on the composite score of positive symptoms, we conducted a mixed model ANOVA with the between-person factor condition (immediate access to the EviBaS

intervention vs. waitlist group) and the within-person factor time (baseline vs. post assessment). The model included the effect of time, group and the time x group interaction. A significant interaction indicates that the change of symptoms over time differs between groups. As mentioned before, the composite score of positive symptoms served as the primary outcome, so the interaction term indicates whether composite positive symptoms improve more in one group compared to the other. Subsequently, we conducted several secondary analyses on the components of the composite outcome (PANSS-PF, Paranoia-CL, and LSHS-R), as well as secondary outcomes (see Table 6).

First, we conducted intention to treat analyses, meaning that we considered all participants in the analyses irrespective of whether they provided data at the post assessment or not and irrespective of whether immediate access participants used EviBaS or not. Intention to treat analyses are recommended for clinical trials because they – inter alia – maintain the randomization of group allocation and provide a more realistic estimation of the treatment effect under real world conditions (Ranganathan et al., 2016). In addition to the intention to treat analyses, we conducted per protocol analyses, which only considered participants who completed at least four of the optimal number of eight modules of the EviBaS intervention. We computed effect sizes based on the estimated means and standard errors of the mixed effect model analyses.

2.5.3 Analyses in the EviBaS Mindfulness Study (study 3)

Study 3 was a secondary analysis based on study 1, in which we only analyzed people who reported lifetime auditory verbal hallucinations. Our hypothesis was that the mindfulness module of the EviBaS intervention would improve distress caused by auditory hallucinations and that this improvement would be mediated by improved mindfulness. Because we were only interested in people who used the mindfulness module, we excluded immediate access participants from the analyses if they did not complete the mindfulness module. Selecting subsamples from the EviBaS efficacy trial introduced several biases, which are discussed in section 0, but it enabled us to examine a possible mechanism of change (i.e., mindfulness) of the intervention on a specific outcome (i.e., distressing auditory verbal hallucinations) in an exploratory manner. Unlike study 1, study 3 relied on Analyses of Covariance (ANCOVAs) rather than mixed effects ANOVAs. The ANCOVA approach differs slightly from the ANOVA approach in that it compares the outcome between two groups (comparable to a *t*-test), while controlling for baseline values of the respective outcome. The resulting conclusions are the same in both cases (i.e., whether there are group differences in the outcome). We conducted ANCOVAs to examine baseline-corrected group differences of mindfulness (MAAS), distress by voices (self-generated scale based on the DV-SA), and hallucinations (LSHS-R) at post assessment. Apart from baseline scores, the ANCOVA models did not include additional covariates. We then conducted a mediation analysis to examine whether improved mindfulness accounted for group differences of distress by voices or hallucinations. We conducted the mediation analysis with group allocation as the independent variable, distress by voices as the outcome, pre-post change scores of mindfulness as the mediator, and baseline distress by voices as a covariate, using the PROCESS® macro for SPSS provided by Andrew Hayes (Hayes, 2017). The PROCESS® macro enables the reporting of robust bootstrap confidence intervals based on a resampling procedure with 5,000 samples in our study (LLCI = lower level confidence interval, ULCI = upper level confidence interval). We repeated the analysis with LSHS-R scores instead of distress by voices (see section 3.1).

In sum, papers 1 and 3 both report group differences of a specific outcome after treatment. Whereas study 1 modeled time as a within-person factor (repeated measures ANOVA), study 3 controlled for baseline scores using a covariate-approach (ANCOVA).

2.5.4 Analyses in the EviBaS Intermediate Assessment Study (study 2)

All papers incorporated in this thesis are longitudinal studies, meaning that participants were assessed repeatedly over time. Studies 2 and 4, however, differed from studies 1 and 3 in that they included much more frequent measurements, similar to the procedure known from ESM-designs (i.e., short repeated assessments on momentary symptoms, enabling a fine-grained view on temporal variability). In study 2, these ESM-like assessments were called *intermediate assessments* and we included them in the EviBaS trial in order to monitor psychotic symptoms and predictor variables (e.g., negative affective states) over time. Given this "nested" data structure (measurements clustered within participants), we used linear mixed models to account for the dependency of measurements within the same participant. Mixed models are flexible in handling missing data (Twisk, 2019, p. 150) so that we did not need to impute missing values. For hypothesis 1 of study 2, we tested whether a composite score of repeatedly measured predictor variables (worry, negative affect, self-esteem, self-reported cognitive biases, and quality of sleep) improved more in the immediate access group compared to the waitlist group. This analysis resembles the analysis in study 1 (EviBaS Efficacy Study) because it was designed to detect group differences regarding a specific outcome. The analysis relied on intermediate assessment data obtained between baseline and post-assessment. The statistical model included time, group (immediate vs. delayed access), and the time x group interaction. The composite score of predictor variables served as the outcome. Unlike the baseline and post assessments in study 1 that occurred at fixed time points, intermediate assessments took place at different points in time during the intervention compared to the waiting period (upon EviBaS login vs. once per week, see section 2.2.1). To obtain a comparable number of assessments in both groups for hypothesis 1, we aggregated the assessments, resulting in one value per week per participant. For hypothesis 2, we conducted lagged regression analyses (i.e., the predictor variable is measured at a previous point in time; t-1) to examined if the composite score of predictors (t-1) predicted subsequent psychotic symptoms (t0) differently in the two groups (immediate vs. delayed access). The model included momentary psychotic symptoms (t0) as the outcome, the composite score of precursors (t-1), group (immediate vs. delayed access), and the group x composite score (t-1) interaction as predictors, controlling for psychotic symptoms at t-1. Hypothesis 3 was at the core of study 2. We examined whether each individual predictor variable predicted subsequent psychotic symptoms during the EviBaS intervention. This procedure is virtually identical to the procedure used in ordinary ESM-studies (e.g., Luedtke et al., 2017), the main difference being that we analyzed data from people who participated in an intervention. We conducted separate analyses with each predictor at t-1 (e.g., worry) and momentary psychotic symptoms as the outcome (t0), while controlling for previous psychotic symptoms (t-1). We analyzed data from all participants taking part in the intervention, both immediate access participants and delayed access participants.

2.5.5 Analyses in the ESM Study (study 4)

Conceptually, the analyses of study 4 resembled the analyses in study 2. We conducted linear (for continuous outcomes) and logistic (for binary relapse analyses) lagged mixed model analyses. For hypothesis 1, we examined whether short-term ESM effects (within the same day) and long-term effects (across bi-weekly Follow Ups) were comparable. To do so, we assessed the effect of negative

affect (t-1) as well as aberrant salience (t-1) on subsequent momentary psychotic symptoms (t0), controlling for preceding psychotic symptoms (t-1) and subsequently added the assessment type (ESM vs. Follow Up) as well as the interaction of precursor and assessment type to the model. The interaction term indicated whether the effect of the respective precursor on subsequent symptoms differed between ESM and Follow Up assessments. Hypothesis 2 stated that we could use negative affect and aberrant salience to predict relapses in lagged mixed model analyses. As relapse was a binary variable, the statistical models were variants of logistic mixed models with relapse (yes/no) as the outcome and different predictor variables (adherence to medication, quality of sleep, negative affect, and aberrant salience) measured prior to the outcome.

The lagged mixed model analyses in studies 2 and 4 were similar. For example, all models included a random intercept but no random slopes and all participant-level predictor variables (e.g., negative affect or aberrant salience) were person-mean centered. In order to obtain centered variables, we calculated the within-participant mean and subtracted it from each value. Person-mean centering was crucial because we aimed at identifying processes occurring within participants, not between participants (for a discussion of this topic, see section 4.3). When predictors are not centered, the overall effect of a predictor is comprised of the difference between the mean values of two persons and between two time points within the same person. Person-mean centering eliminates between person variability and leaves only the variance within persons, which we were interested in. Another similarity between studies 2 and 4 was that we applied the Benjamini and Hochberg correction to control for the false discovery rate due to multiple tests (Benjamini & Hochberg, 1995).

3 Summary of results

ESM-based studies have shed light on the processes that occur prior to the emergence of psychotic symptoms in the daily life of people with psychosis. The overarching goal of the present thesis was to apply this knowledge to new contexts, namely the treatment of psychosis and the prediction of relapse. In addition, the thesis aimed at applying the assessment strategies (multiple repeated measures within participants) and statistical methods (lagged regression analyses) from ESM studies to much larger periods of time in order to find meaningful long-term warning signs of symptoms and possibly relapses. The following section will briefly summarize the main results of the four included studies. More detailed information, for example on baseline characteristics, secondary outcomes, or additional per-protocol analyses, can be found in the attached papers (papers are included at the end of the thesis).

3.1 Results of the EviBaS Project (studies 1 to 3)

The EviBaS Internet intervention (for a description, see section 2.3) targets feelings of persecution, hallucinations, as well as a variety of predictors of psychotic symptoms that have been identified in ESM studies, for example worrying and sleep problems. The first paper of this thesis, the EviBaS Efficacy Study, examined whether the intervention's approach of treating ESM-based predictors of psychosis was successful (6 out of 11 modules targeted ESM-based predictors of psychotic symptoms). In line with our hypothesis, the EviBaS intervention improved the primary outcome, which consisted of a composite score of 3 positive symptom measures (see section 2.4.2.1), as indicated by a significant interaction of time (baseline vs. post assessment) and condition (immediate access to EviBaS vs. delayed access); $F(1, 87.28) = 4.04$, $p = .047$. The size of the effect was small to medium $d = -0.37$, 95% CI [-0.67, -0.07]. Following up the significant effect on the composite score,

we examined effects on each of the outcome's components separately. We repeated the analysis with LSHS-R scores as the outcome to assess the intervention's effect on hallucinations specifically. The interaction of time x group reached significance, indicating that the overall effect was driven by an effect on hallucinations; $F(1, 88.22) = 7.15$, $p = .009$. The corresponding p-value withstood a Bonferroni Holm correction (the p-value of $p = .009$ was below the corrected value of .017). In contrast, there were no effects on the remaining individual outcomes (Paranoia Checklist: $F(1, 87.85) = 3.07$, $p = .083$; PANSS-PF: $F(1, 88.38) = 0.16$, $p = .686$).

Traditionally, effects on observer-rated outcomes such as the PANSS are considered to be more reliable than self-report measures in psychosis research (as reviewed in Lincoln et al., 2010b), but the results of study 1 were nonetheless very encouraging because they demonstrated that an Internet intervention which mainly targets predictors of psychotic symptoms efficaciously reduces symptoms of psychosis. Furthermore, the EviBaS intervention was safe as the number of adverse events was low (0.02 events per participant) compared to CBTp in outpatient settings (e.g., 0.18 in Lincoln et al., 2012) and the satisfaction with EviBaS was high (89% were satisfied with the program's quality). In per protocol analyses of participants who used the program regularly, the intervention had a significant effect on mindfulness, self-esteem, social skills, and psychological quality of life, although these effects did not withstand a conservative alpha correction.

The EviBaS intervention aimed at helping people with psychosis through various pathways. It combined methods of CBT and mindfulness-based techniques, it addressed several putative causal factors of psychosis ranging from sleep problems to depression, and it granted a lot of autonomy to the participants (e.g., participants could choose which modules they wished to complete). This comprehensive approach came with the limitation that it was difficult to identify the processes through which EviBaS was efficacious. Study 2, the EviBaS Intermediate Assessment Study, attempted to answer this question using an approach that resembles a typical ESM study design. Throughout the EviBaS study, we asked participants to complete short intermediate assessments on their personal computers. These short assessments captured momentary psychotic symptoms as well as a variety of potential predictors that are targeted in the EviBaS intervention (i.e., worrying, negative affect, self-esteem, self-reported cognitive biases, and quality of sleep, all of which represent predictors in ESM studies). Both immediate access participants as well as delayed access participants from the EviBaS Project completed these short assessments while using EviBas and while waiting, respectively. In addition to the participants from study 1, we incorporated participants in the analyses who failed to reach the symptom severity threshold of study 1, so that we were able to analyze data from $n = 124$ participants who provided $M = 10.32$ intermediate assessments each. Within study 2, we first examined whether a composite score of predictor variables (worrying, negative affect, self-esteem, self-reported cognitive biases, and quality of sleep) improved more in participants using EviBaS compared to waiting participants. Contrary to our hypothesis, the group x time interaction was non-significant, indicating that the course of composite predictor variables did not differ between groups ($b = -0.043$, $SE = .096$, $t = 0.449$, $p = .653$). Although this finding is subject to the important limitation that providing intermediate assessments was tied to the adherence to the intervention, it indicates that EviBaS intervention was not efficacious by improving worrying, negative affect, self-esteem, and so forth, but rather by improving psychotic symptoms directly. Subsequently, we examined if the composite score of predictor variables predicted momentary psychotic symptoms differently in the immediate access group compared to the delayed access group. We expected that an intervention that targets worrying, depression, and so forth would have an effect on how these variables interact with

psychotic symptoms. Contrary to our hypothesis, we again found no significant effect, indicating that the composite score of precursors did not predict subsequent momentary psychotic symptoms differently in the two groups (b = 0.031, SE = .032, t = 0.945, p = .345). This finding further substantiated the assumption that the efficacy of EviBaS was independent from its capacity to improve predictors of psychotic symptoms. Neither did the intervention improve composite predictors, nor did it affect the association of predictors and psychotic symptoms. Interestingly, however, we found that within the EviBaS intervention (i.e., without considering group differences), momentary worrying (b = 0.156, SE = 0.064, t = 2.438, $p_{corrected}$ = .030) and quality of sleep (b = -0.198, SE = 0.059, t = 3.359, $p_{corrected}$ = .003) predicted subsequent psychotic symptoms several days later. This effect means is that when participants experienced more worry or worse sleep than usual while using the EviBaS intervention, they reported more severe psychotic symptoms upon the next assessment. So, although EviBaS did not consistently improve worrying and quality of sleep over time, our analyses indicate that when these variables improved, they preceded (on average) an improvement of subsequent psychotic symptoms. Worrying and quality of sleep are therefore very worthwhile treatment targets and mechanisms of change during an intervention such as EviBaS. In sum, study 2 provided interesting insights into the variability of symptoms during an online intervention for people with psychosis. The results indicate that worrying and sleep are, in fact, important treatment targets but the efficacy of EviBaS was apparently not dependent on its ability to alter these variables.

In study 3, the EviBaS Mindfulness Study, we investigated another potential pathway that could explain the intervention's efficacy, namely *mindfulness*. We did not include mindfulness (or its counterpart experiential avoidance) in study 2 because we expected it to be associated with the *distress* elicited by psychotic symptoms – not the frequency or intensity of symptoms. We hypothesized that mindfulness would enable participants to experience psychotic symptoms (particularly hallucinations) in a nonjudgmental and thus less distressing way as suggested by the definition of mindfulness by Kabat-Zinn (2015) who describes mindfulness as "paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally" (p. 4). Unlike study 2, study 3 used a mediation approach rather than EMS-based analyses: We drew a subset of participants from the EviBaS Efficacy Study (study 1) of people who reported lifetime auditory verbal hallucinations and within this subgroup of participants, we compared the immediate access group (using EviBaS) to the delayed access group (waitlist). As our focus lied on the mindfulness components of EviBaS, we only considered participants from the immediate intervention group who used the mindfulness module. The resulting sample (n = 55) was considerably smaller than the one from the EviBaS Efficacy Study, with only n = 16 users of the mindfulness module and n = 39 delayed access participants (i.e., waitlist). Contrary to our hypothesis, the group who used the mindfulness module did not show lower distress by auditory verbal hallucinations at post assessment when compared to the delayed access group (F(1, 49) = 0.281, p = .598, η_p^2 = 0.006), although there was an effect on mindfulness (F(1, 49) = 6.346, p = 0.015, η_p^2 = 0.115). When we examined general hallucinations (LSHS-R) as the outcome, however, the intervention led to a significant improvement (F(1, 49) = 13.360, p = 0.001, η_p^2 = 0.214). Interestingly, the effect on hallucinations (LSHS-R) was mediated by improved mindfulness: Adding mindfulness change scores as a mediator reduced the group difference of hallucinations and the bootstrap confidence interval of the indirect effect confirmed a significant mediation (indirect effect: b = -1.618, CI [-3.747, -0.054]). There are several important limitations to study 3, which will be discussed in detail in section 0. In short, the subgroup analyses introduced biases and extinguished the positive features of randomized group allocation. Nonetheless, our findings provide a very promising starting point in understanding the efficacy of the EviBaS intervention. It is possible that the

intervention's effect on LSHS-R scores, which primarily brought about the intervention's overall efficacy, was partly due to effects on mindfulness. Although the analyses presented in paper 3 must be interpreted with caution due to their exploratory nature, they do suggest that improving mindfulness could be a mechanism of change, which coincides with findings from ESM trials (Udachina et al., 2014).

3.2 Results of the ESM Study (study 4)

Usually, ESM studies examine processes on a *micro level* (Myin-Germeys et al., 2018). They reveal small symptom fluctuations and their predictors that occur within very short periods of time, such as two to three hours in advance. Research on micro level processes helped us to better understand underlying pathways of symptom formation, but one might argue that we could improve the lives of people with psychosis more effectively if we were able to predict symptom fluctuations that lie further ahead – days or even weeks. Knowledge about more far reaching associations would enable patients, but also caregivers, family or friends to intervene before symptoms become so severe that they require intensive treatment. The crucial question is therefore whether within-day ESM associations generalize to less frequent assessments with longer time intervals between them. Study 2 provided first evidence that certain ESM-based predictor variables (i.e., worrying and poor sleep) could in fact be suited as predictors of symptom fluctuations that occur several days later during treatment. In study 4 we took this idea one step further. The underlying rationale was as follows. If micro fluctuations of negative affect, aberrant salience and other ESM-based predictors forecast micro fluctuations of psychotic symptoms shortly after, larger-scaled fluctuations of the same variables can potentially predict larger-scaled psychotic symptoms and potentially even full-blown relapses in assessments lying further apart. As reviewed in section 1.4, the risk of relapse is high in psychotic disorders and findings from ESM-studies could help to provide new candidate warning signs that would help people with psychosis and caregivers to mitigate or prevent upcoming symptom exacerbations.

To examine whether micro level effects of ESM studies generalize to long-term fluctuations of symptoms, we conducted a one-week ESM assessment period (10 assessments per day) followed by a one-year Follow Up period (bi-weekly online assessments) to measure short- and long-term fluctuations of negative affect (i.e., anxiety, sadness, worry, and self-esteem), aberrant salience, paranoia, and auditory verbal hallucinations. Apart from the devices used for sampling (smartphone vs. personal computer), ESM- and Follow Up assessments were virtually identical. We assessed occurrences of relapse in bi-monthly online assessments (using criteria, such as hospitalization, symptom deterioration or suicidal tendencies; Csernansky et al., 2002). Using linear and logistic mixed models, we examined predictors of psychotic symptoms and relapse. Thirty participants with verified psychotic disorders provided a total of 1194 ESM- and 416 Follow Up assessments. Negative affect ($b = 0.184$, $p_{corrected} = .003$) and aberrant salience ($b = 0.187$, $p_{corrected} < .001$) predicted subsequent paranoia in ESM assessments, substantiating established ESM findings. However, only aberrant salience remained a significant predictor of bi-weekly symptom fluctuations during the one-year Follow Up assessments ($b = 0.366$, $p_{corrected} < .001$). When we compared effects between the ESM- and the Follow Up phase using an interaction term of assessment type (ESM vs. Follow Up) and the respective predictor variable (aberrant salience, negative affect), a non-significant interaction confirmed that the association of aberrant salience and paranoia was not significantly different ($b = 0.103$, $SE = 0.077$, $t = 1.340$, $p = .181$). Unfortunately, none of the examined variables predicted relapse, likely due to the low number of people who relapsed overall ($n = 13$, 43%). Nonetheless, people with psychosis could benefit from our findings by monitoring feelings of aberrant salience

regularly to be able to anticipate an upcoming paranoid symptom deterioration. It is possible that the predictive value of aberrant salience relies on its associations with underlying dopaminergic processes as exploratory analyses indicated that antipsychotic medication served as both a moderator (the effect was significantly weaker in medicated participants; $b = -0.763$, $p < .001$) and confounder of aberrant salience's effect on paranoia (adding adherence to medication increased the effect by 42%).

4 Discussion

Psychotic symptoms are associated with anxiety, depressed mood, compromised sleep, or excessive worrying (Freeman & Garety, 2014). Interestingly, these comorbid symptoms are not only consequences of psychosis (e.g., not being able to sleep because voices keep you awake) but also warning signs of upcoming symptoms (e.g., experiencing paranoia due to compromised sleep; Kasanova et al., 2020). Studies using the Experience Sampling Method (ESM) studies have greatly enhanced our understanding of how symptoms unfold in the daily lives of people with psychosis by shedding light on mechanisms of moment-to-moment symptom variation. In combination with experimental (e.g., Reeve et al., 2018) and theoretical considerations (Freeman & Garety, 2014), ESM studies have contributed to the development of a branch of interventions for people with psychosis, which focus on putative causal factors of psychotic symptoms to reduce psychotic symptoms indirectly (e.g., Freeman et al., 2015a). Following this approach, we have developed EviBaS, an Internet intervention for people with psychosis targeting not only psychotic symptoms but a plethora of ESM-based putative causal factors, such as worrying, sleep, self-esteem and so forth. In studies 1 to 3, we evaluated EviBaS and examined its potential modes of action to learn about whether targeting ESM-derived predictors can lead to an improvement of psychotic symptoms. Study 4 likewise aimed at applying knowledge from ESM studies to real world problems of people with psychosis but it used a different approach. Rather than treating predictor variables, study 4 used these variables as predictors of large-scaled symptom fluctuations and relapses in bi-weekly assessments.

4.1 Discussion of main findings

Across all papers, the present thesis aimed at improving the lives of people with psychosis using insights from ESM studies. Hence, one might argue that study 1 provided the most important finding of this thesis, namely that the EviBaS intervention is safe and efficacious. Interestingly, the size of the intervention's effect ($d = 0.37$) is comparable to face-to-face therapies in psychosis ($d = 0.36$), see Bighelli et al. (2018) for a review, although this effect must be interpreted in the light of important limitations (see section 0). So far, Internet interventions for people with psychosis are very rare so that it is difficult to compare our finding to similar trials. Nonetheless, there are a few trials that examined Internet- or computer-delivered interventions for people with psychosis: In a randomized controlled trial conducted by Gottlieb et al. (2017), the computer-delivered program "coping with voices" resulted in significantly greater increases of social functioning compared to usual care but there was no effect on the severity of auditory hallucinations. As the name suggests, the intervention targeted voices specifically rather than overall psychosis. Another difference to the EviBaS program was that participants completed "coping with voices" at a clinic rather than at home. Apart from these differences, the approaches were comparable (modular intervention, web-based, CBT-focused). At first sight, it might therefore be surprising that EviBaS improved hallucinations while "coping with voices" did not. However, this result might be due to the fact that Gottlieb et al. (2017) used a clinician rated interview to assess hallucination severity. In the EviBaS trial, the clinician-rated measure likewise showed no improvements, only self-report measures did. Moritz et al. (2016)

conducted a trial that used similar methods as the EviBaS Project, namely a randomized controlled design evaluating an intervention, which participants completed independently on their own personal computers. However, the treatment approach was very different in that the intervention called "HelpID" targeted depressive symptoms exclusively rather than symptoms of psychosis. The intervention resulted in medium to large effects on reduced depressive symptoms, but psychotic symptoms remained unchanged (Moritz et al., 2016). To our knowledge, there is only one Internet intervention study besides the EviBaS Efficacy Study that could demonstrate reductions of positive symptoms: Rotondi et al. developed and evaluated a telehealth website, which provided psychoeducational information and different therapy forums, accompanied by a four-hour workshop focused on psychoeducation (SOAR; Rotondi et al., 2005). The SOAR website followed a very interesting approach in that it incorporated family psychoeducation to help family members better cope with their relative's disorder. The trial resulted in a significant effect on positive symptoms in clinician rated interviews (Rotondi et al., 2010). The concept of the SOAR intervention was very different from the EviBaS Project in that it was not a conventional self-help application but rather a comprehensive intervention for families of people with psychosis – even including an extensive face-to-face component. Given the different scopes, it is difficult to compare the results directly. Nonetheless, one must acknowledge that an approach that incorporates the families of patients is very likely to be more efficacious in heavily impaired patients (see section 4.5 for future directions).

4.1.1 The complexity of EviBaS, curse and blessing

Comparing EviBaS to the few previous Internet interventions for psychosis (or related disorders) highlights several unique characteristics of our intervention, particularly in comparison to the efficacious web-based family intervention approach by Rotondi et al. (2010).

The complexity of the self-help format: Although EviBaS is a guided intervention, it delivers *self-help* materials in an online format, meaning that participants have to work through materials independently (apart from reminders and feedback by the guides) and with a high degree of autonomy. This format places high demands on participants in terms of motivation but also executive functions, such as attention, planning, or memory capacity. Overall, 32% of participants did not complete a single module and 14% of participants from the immediate access group dropped out of the study. Importantly, participants who dropped out had higher positive symptom severity at baseline, indicating that EviBaS might be too demanding for severely affected individuals (Rotondi et al., 2015). At the same time, it is one of EviBaS' biggest strengths to provide autonomy and control to patients. EviBaS perceives patients as competent and motivated, and it is oriented towards the treatment wishes of patients (Freeman et al., 2019; Moritz et al., 2017; Westermann et al., 2015). Possibly, neither SOAR nor EviBaS are suited for all people with psychosis. Rather, selecting a suitable approach based on participants' needs and wishes would be most appropriate. If a person is severely psychotic, they might benefit more from SOAR; if they are mildly psychotic and cognitively capable of completing self-help exercises, they might prefer EviBaS; and if they are currently in remission, they might strongly prefer EviBaS as it does not give the feeling of being "in need" of help by others.

The complexity of the intervention's contents: Not only was EviBaS complex in terms of requiring autonomy and motivation, it was also complex in terms of contents. EviBaS encompasses eleven modules, numerous work sheets, and it addresses a plethora of putative causal factors, ranging from sleep problems to depression. This excess of supply can cause confusion, especially when

conventional treatments (e.g., in inpatient care) provide few degrees of freedom. Instead of reducing the complexity for all participants, a promising approach might be to tailor interventions to the requirements and expectations of individuals or subgroups, meaning that those with high cognitive capacities can benefit from a demanding intervention but those with impairments can receive fewer or simpler modules.

4.1.2 Potential modes of action of EviBaS

As reviewed in section 4.1.1, EviBaS was extensive in terms of modules and contents, so a question which inevitably comes to mind is *how* EviBaS was efficacious. Were all of these modules necessary or would a trimmed down version work just as well? In view of theoretical considerations (Freeman & Garety, 2014) and ESM studies (Hartley et al., 2014; Kasanova et al., 2020), we hypothesized that the intervention's efficacy would be dependent on its capacity to improve causal factors (e.g., worrying, depression or sleep), which in turn lead to reduced psychotic symptoms. However, as reviewed in the following section, the potential modes of action appear to be different than expected.

Mindfulness might have played a very important part in the intervention's efficacy. Although the effect would not withstand a conservative Bonferroni correction, mindfulness improved consistently in intention to treat and per protocol analyses (the effect on mindfulness was confirmed in voice hearers in paper 3), indicating that increased mindfulness could be one mechanism of change through which EviBaS was efficacious. No other secondary outcome reached significance in intention to treat analyses (self-esteem, social skills, and psychological quality of life reached uncorrected significance in exploratory per protocol analyses, though). Based on the pioneering trials by Philippa Garety, Daniel Freeman and colleagues (Freeman et al., 2015a; Freeman et al., 2017; Freeman et al., 2015b) which made use of the so-called interventionist causal model approach, we would have expected that worrying and improvements of sleep problems would be particularly promising mechanisms of change but neither the ISI (measuring insomnia; Bastien, 2001) nor the PSWQ (measuring worrying; Hopko et al., 2003) reached significance.

In study 2, we approached the research question of potential mechanisms of change differently (using more frequent intermediate assessment data) but the conclusion remained the same. A composite score of worry, negative affect, self-esteem, self-reported cognitive biases, and quality of sleep did not improve more in the EviBaS immediate access group compared to the delayed access group. At first sight, this finding might seem surprising because worrying and sleep problems play such an important role in the formation of psychotic symptoms. On closer inspection, however, the results fit the literature. Although EviBaS originally aimed at improving both paranoia and hallucinations (as well as a variety of other symptoms), the data suggest that the efficacy of EviBaS (i.e., in intention to treat analyses) eventually relied mainly on reducing hallucinations rather than paranoia. As worry and quality of sleep are associated with the paranoia specifically (Freeman et al., 2015a; Freeman & Garety, 2014; Hartley et al., 2014; Kasanova et al., 2020), it is not surprising that the intervention's effect on hallucinations was not accompanied by an effect on worrying and insomnia. Albeit speculative, it is possible that the intervention's effect on paranoia could be enhanced by improving its capacity to reduce worrying and sleep problems. In line with this view, paper 2 showed that momentary worrying and quality of sleep predicted subsequent paranoia in users of EviBaS, although the intervention did not successfully improve these variables.

Whereas our data suggest that worrying and sleep problems were not responsible for the efficacy of EviBaS, improved mindfulness could be an important mechanism of change. Before discussing mindfulness as a potential mediator, it is crucial to acknowledge that mindfulness as a secondary outcome did not meet the conservative Bonferroni correction for multiple tests. Nonetheless, the effect occurred consistently in intention to treat, per protocol, and also in the subgroup analyses in paper 3, so that it will be discussed despite this caveat.

Mindfulness can be defined as "moment-to-moment, nonjudgmental awareness" (Kabat-Zinn, 2015) . The term *moment-to-moment* implies that mindfulness allows us to experience the present moment attentively rather than ruminating about the past or worrying about future events. Most importantly in the context of the EviBaS trial, however, is the term *nonjudgmental*, which means that a mindful perception of current experiences is detached from negative emotions or dissatisfaction with the current state. To illustrate, being mindful means to notice one's own bodily but also mental states attentively and to accept them as they are, without wishing they were different. In the context of ESM research, studies have focused on experiential avoidance (i.e., attempts to avoid unpleasant thoughts, feelings, or sensations; Udachina et al., 2014), which can be described as the opposite of a mindful and accepting way of dealing with negative emotions. From a theoretical point of view, we expected that learning mindfulness skills would help a person to experience uncontrollable negative states as less distressing and disrupting because of the ability to accept current experiences non-judgmentally. Therefore, we hypothesized that mindfulness would be particularly helpful when experiencing hallucinations, which are characterized as uncontrollable (Baumeister et al., 2017). We examined this hypothesis in paper 3. In a subgroup analysis of voice hearers, we found that EviBaS participants who completed the mindfulness module reported more mindfulness and reduced hallucinations (measured with the LSHS-R) at the post assessment. An additional mediation analysis revealed that mindfulness improvements (measured with the MAAS) accounted for 1.6 points of the 7.2 point-difference in LSHS-R scores between groups. This analysis indicated that the intervention's effect on hallucinations could be explained partly through its positive effect on mindfulness. Contrary to our hypothesis, we did not find an effect on distress and disruption caused by voices though. Initially, this pattern of results was surprising but a closer look at the content of the LSHS-R, our measure of hallucinations, provided possible explanations. The LSHS-R is a measure of hallucinatory experiences that is widely used in non-clinical populations. According to Waters et al. (2003), only a subset of the scale's items assesses distinct hallucinatory experiences, whereas half of the items tap on "vivid mental events". Vivid mental events are related to hallucinations but they are recognized by individuals as their own mental experiences rather than coming from the outside. One can describe these experiences as daydreams or uncontrollable thoughts (Waters et al., 2003). Several items from the "vivid mental events" factor of the LSHS-R measure experiences, which show overlap with mindfulness-related processes. For example, the first item captures difficulties in concentrating, which can be interpreted as the opposite of attentive mindfulness: "No matter how hard I try to concentrate, unrelated thoughts always creep into my mind". Other items refer to daydreams, which are conceptually and empirically opposed to mindful perceptions of the present moment (Mrazek et al., 2012). It is possible that the partial overlap of mindfulness and subclinical hallucinatory experiences (mind wandering or daydreams) was responsible for the partial mediation observed in study 3. Thus, mindfulness *was* an important mechanism of change but apparently in a different way than initially expected: Mindfulness was not related to the distress or disruptiveness component by hallucinations but it was probably rather related to the non-attentive component of subclinical hallucinations.

To sum up, the rationale of EviBaS was (a) to directly target psychotic symptoms and (b) to target putative causal factors contributing to these symptoms, many of which were derived from ESM studies. Results indicate that the intervention reduced psychotic symptoms – mainly driven by improvements of self-reported hallucinations rather than paranoia (in intention to treat analyses). Studies 1 to 3 paint a clear picture in terms of how this efficacy came about. The intervention's efficacy was unrelated to improvements of most putative causal factors, such as poor sleep, worrying, or negative affect. As these factors are associated with paranoia specifically (Freeman & Garety, 2014), this finding makes a lot of sense in the light of the intervention's inability to improve paranoia consistently. In contrast, improvements of mindfulness could explain the efficacy of EviBaS at least partly. Given the overlap of mindfulness and parts of the hallucination questionnaire, it is possible that EviBaS reduced daydreaming as well as intrusive thoughts, which are likewise components of (subclinical) hallucinatory experiences. Our findings substantiate that worrying and sleep problems represent important treatment targets in psychosis (study 2), although EviBaS did not successfully address them.

4.1.3 ESM can improve the prediction of long-term symptom fluctuations

The knowledge base about ESM predictors of psychotic symptoms significantly influenced the development of the EviBaS intervention although the intervention's efficacy was only marginally attributable to improvements of these predictors. Nevertheless, studies 1 to 3 showed that basic research findings from ESM studies can be of practical use for people with psychosis. In study 4, we found that ESM findings can be of practical use in an additional way by providing candidate predictors of long-term symptom fluctuations in bi-weekly online assessments. As reviewed in section 1.2.3, ESM studies have identified numerous short-term predictors of psychotic symptom fluctuations in assessment periods of few days. As these short-term predictors resemble long-term warning signs of psychotic relapse (e.g., depressed mood or compromised sleep), we hypothesized that one can draw on ESM-based predictors to predict long-term symptom fluctuations and potentially relapse. We compared predictor-symptom associations between an ordinary one-week ESM assessment phase and a subsequent Follow Up period lasting one year. Aberrant salience was a significant predictor of subsequent paranoia consistently in ESM and in bi-weekly Follow Up assessments but there was no effect on relapse. The results of study 4 imply that it is promising for people with psychosis to monitor aberrant salience in bi-weekly intervals because it can signal subsequent increases of paranoia several weeks in advance. Medication influenced aberrant salience's effect on paranoia as a moderator and confounder. Possibly, aberrant salience is most predictive in unmedicated participants because it is not dampened by antipsychotic medication (Kapur, 2003). One of the most important findings from study 4 was that ESM findings can provide information about predictor-symptom associations in much larger time frames. The following section provides a discussion of this finding.

4.2 ESM designs in new time frames

An overarching theme of study 2, the EviBaS Intermediate Assessment Study, and study 4, the ESM Study, was the application of assessment strategies from ESM research (i.e., repeated self-report assessments of momentary psychotic symptoms and putative predictor variables) as well as data analytical methods (i.e., time-lagged mixed model analyses) to a new setting and time frame. Usually ESM studies are conducted in a naturalistic setting of participants' everyday lives, encompassing smartphone-based assessments over a period of approximately one week (Myin-Germeys et al., 2018). In the present thesis, we applied many of the aforementioned ESM principles to the context of a psychological online intervention (study 2) as well as bi-weekly online assessments over a one-year Follow Up period. In both studies, we increased the distance between two consecutive assessments considerably when compared to conventional ESM studies, while using the same or very similar predictor variables of psychotic symptoms, such as negative affect or aberrant salience. This approach might seem counterintuitive at first glance because ESM studies deliberately try to uncover processes that are short-lived. For example, Kramer et al. (2014) examined associations of negative affect and paranoia in a general population sample and found that moments of negative affect resulted in an increase of paranoia over 180 subsequent minutes. Poor quality of sleep was likewise examined only as a short-term predictor of paranoia (i.e., immediately at the next morning; Kasanova et al., 2020). Given this background, one might argue that it is both a pointless and hopeless endeavor to change the distance between ESM assessments because momentary expressions of predictor variables, such as negative affect, should not have any effect on paranoia several days later (study 2), let alone two weeks later (study 4). We nonetheless held on to the idea that ESM based predictor-outcome associations could also apply to longer-distanced assessments because we assumed that short-term fluctuations of mood, worrying, aberrant salience, or paranoia occur around slower fluctuations (i.e., *trends*) of the same variables. This would imply that, for example, paranoia fluctuates rapidly from moment to moment during the day, but the average value of paranoia for each day changes at a slower

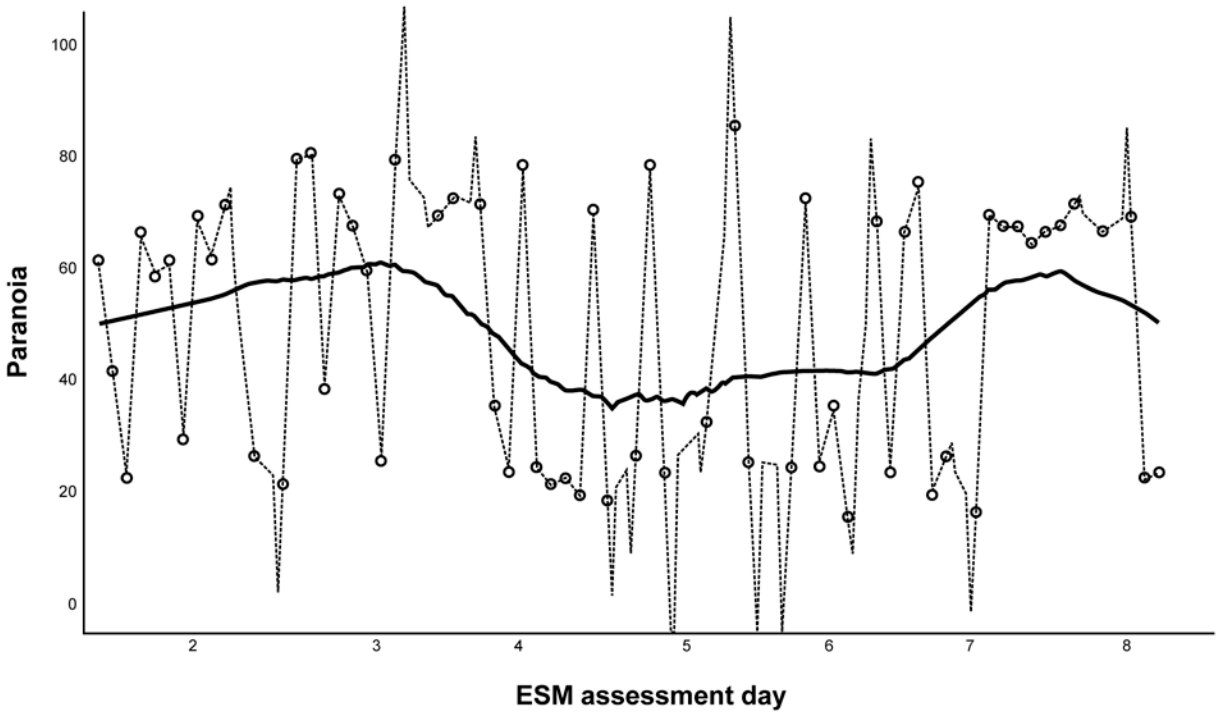


Figure 6 – Exemplary course of paranoia across one week of ESM. Y-axis displays raw scores from a visual analogue scale for paranoia (0 – 100), X-axis displays days.

rate across days or even weeks. Figure 6, which is based on 8 days of ESM data from one of our participants in study 4, illustrates this idea.

As the exemplary data in Figure 6 show, the paranoia scores for participant 6 fluctuate heavily within the same day. At the same time, a trend of slowly changing mean levels of paranoia becomes visible only when observing data points across several days. Please note that Figure 6 was created for purely descriptive purposes using 2 Loess-curves with different degrees of smoothing in an exploratory way. It is only meant to illustrate a theoretical point and should not be misunderstood as "proof". If we assume that ESM variables behave as depicted in Figure 6, it seems plausible that ESM assessments capture associations between rapid fluctuations of variables, whereas infrequent Follow Ups capture associations between slower trends of the same variables. Overall it was not free of risk to expect that ESM findings generalize to longer-distanced assessments but the potential benefit outweighed the risk because knowledge about symptom fluctuations that occur several days in advance would come with possibilities such as the prediction of treatment response or even relapses.

Eventually, the data suggested that not all but some findings from ESM studies hold in longer assessment periods. In intermediate assessments during the EviBaS intervention, we found that momentary quality of sleep predicted subsequent paranoia and auditory verbal hallucinations several days later, whereas momentary levels of worrying predicted subsequent paranoia. We only considered data points in the analyses if they were at least one day and up to 1.5 weeks apart. Hence, the distance between predictors and outcomes was much greater than in conventional ESM studies and effects were nonetheless observable. Momentary negative affect and self-esteem, on the other hand, did not predict subsequent psychotic symptoms several days later. This distinction is very interesting because all four variables are well-established in ESM trials, particularly negative affect (as reviewed in section 1.2.3). In study 4, we directly compared a 1-week ESM phase to a one-year Follow Up phase to examine the congruence of predictor-outcome associations across short- and long-term assessment periods. In accordance with study 2, we found that the effects of negative affect on paranoia were only short-term and not observable in bi-weekly online assessments. In contrast, aberrant salience, which was not assessed in study 2, predicted subsequent paranoia consistently in ESM and Follow Up assessments. Worrying, which we assessed as a stand-alone predictor in study 2, was part of the negative affect scale in study 4. We examined it separately in exploratory analyses of study 4, though, and found that worrying served both as a short-term (within the same day) and a long-term (across weeks) predictor of paranoia, further substantiating the results from study 2.

Post hoc, the pattern of results from studies 2 and 4 can be explained in the light of conceptual differences between negative affect as well as self-esteem on the one hand and sleep, worrying, or aberrant salience on the other hand. Affect is highly unstable in people with psychosis (Myin-Germeys et al., 2000) and stressful events are followed by higher levels of negative affect compared to controls (Myin-Germeys & van Os, 2007). These findings indicate that momentary negative affect does not follow long-term trends in people with psychosis but rather occurs randomly in response stressful events. This would explain why negative affect is a powerful predictor of short-term paranoia but not of long-term symptom fluctuations. Self-esteem likewise failed to predict psychotic symptoms several days later although it is predictive in short-term ESM studies (Udachina et al., 2014). Post hoc, the absence of long-term effects actually fits the literature well because momentary self-esteem appears to be highly unstable in people with psychosis, comparable to negative affect. The influential *paranoia as defense* model of persecutory delusions (Bentall et al., 1994) initially proposed that persecutory

delusions emerge in an attempt to restore low self-esteem. The rationale being that one regains high self-esteem if others are to blame for negative events rather than one-self (i.e., externalizing attributions). Based on empirical findings, the model had to be revised, however. Instead of restored self-esteem, participants with paranoia show highly unstable self-esteem, which fluctuates rapidly over time (for a review, see Murphy et al., 2018). Consistent with the model's predictions, the moment-to-moment variability of self-esteem predicts trait paranoia better than the overall level of self-esteem (Thewissen et al., 2008). Just as for negative affect, the randomness and strong variability of self-esteem could explain why it is not suited as long-term predictors of psychotic symptoms.

In contrast to negative affect and self-esteem, theoretical models describe worrying as both a momentary action as well as a more stable thinking style (i.e., a 'worry thinking style'; Freeman & Garety, 2014). Hence, conceptually it makes sense to assume that the action of worrying about future events occurs momentarily throughout the day, while the tendency to worry (the worry thinking style) changes at a slower rate, making it a suitable predictor of both short- and long-term symptom fluctuations. Quality of sleep naturally changes at a slow rate than negative affect or self-esteem so that it comes as no surprise that it served as a predictor of long-term symptom fluctuations in study 2 as well. It was nonetheless interesting to see that effects do not appear to be restricted to next-day paranoia. Lastly, aberrant salience predicted paranoia consistently in short- and long-term assessments, indicating that it is a predictor of both short- and long-term fluctuations of paranoia. Conceptually, aberrant salience has been described as part of the prodromal phase of psychosis, meaning that experiences of aberrant salience accumulate over periods ranging from days to years before illness onset (Kapur, 2003), so it is not surprising that aberrant salience served as an indicator of paranoia two weeks later in our study.

In hindsight, it was naïve to expect that all ESM findings generalize to longer assessment periods. Our findings suggest that momentary affective processes in particular are too transient to predict symptoms that occur days or even weeks later. Other predictors, such as aberrant salience, have the potential to serve as very early warning signs of symptom deterioration. A unique feature of aberrant salience is its specific association with psychosis. Worrying, depressed mood, or sleep problems occur across a variety of disorders (e.g., for worrying in generalized anxiety disorder see Goodwin et al., 2017) and are therefore not specific warning signs for psychotic symptom deterioration. Aberrant salience, on the other hand, is an experience that is linked to psychosis particularly – first and foremost through its implications with the dopamine hypothesis of psychosis (Kapur, 2003; Miyata, 2019). Therefore, our findings show that it is indeed worthwhile to draw on ESM research to identify candidate predictors of larger scaled symptom fluctuations. Certain predictors (highly variable negative affective states in particular) appear to be predictive only in conventional ESM settings.

4.3 ESM in psychotherapy research

Studies 2 and 4 demonstrated that it can be worthwhile to apply the Experience Sampling methodology to a new time frame. At the same time, study 2 also showed that it can be promising to apply ESM methods to the context of psychosis treatment. Whereas ESM studies usually observe the natural ebb and flow of symptoms in participants' daily lives, study 2 used ESM-like repeated assessments in participants undergoing treatment. As EviBaS aims at ameliorating the variables, which serve as predictors of psychotic symptoms in ESM studies, it was interesting to see how predictors and outcomes would be associated during treatment, when compared to naturalistic ESM settings.

4.3.1 Worrying and quality of sleep as predictors of psychotic symptoms during treatment

In study 2, we were able to identify worrying and quality of sleep as predictors of subsequent psychotic symptoms in participants who used the EviBaS intervention. These effects tell us that when a participant slept better or worried less than usual, they reported less symptoms at the next login. On a group level, however, worrying and sleep did not improve during treatment as indicated by null effects on respective secondary outcomes in the main trial. This pattern of results illustrates that the ESM-derived variables worrying and sleep problems represent important treatment targets, even though the EviBaS intervention was unsuccessful in treating them. We can conclude that whenever worrying or quality of sleep changed within participants, this was associated with subsequent symptoms, but the interventions efficacy did not rely on its ability to improve worrying and sleep. Albeit speculative, one would expect that the efficacy of EviBaS could be improved considerably if the intervention would consistently improve these variables.

The findings of study 2 coincide well with the literature. Worry and rumination are associated with paranoia in experimental (Martinelli et al., 2013) and ESM trials (Hartley et al., 2014), but most importantly, treating worry leads to improved persecutory delusions in people with psychosis (Freeman et al., 2015a), mediated by change in worrying. The influential model by Freeman and Garety (2014) assumes a causal relationship of worry with paranoia in particular. Our results from study 2 support this notion inasmuch as we found associations of worry with subsequent paranoia but not auditory verbal hallucinations. Conceptually, worrying is very similar to paranoia, although its connotation is much less pathological. As Freeman and Garety phrased it ‘worry brings implausible ideas to mind, keeps them there, and increases the distress that they cause’ (Freeman & Garety, 2014, p. 1180). As for worry, the effects of quality of sleep on subsequent symptoms during the EviBaS intervention were not surprising in the light of a large body of literature. Our findings coincide with cross-sectional (Koyanagi & Stickley, 2015), experimental (Petrovsky et al., 2014; Reeve et al., 2018), ESM- (Kasanova et al., 2020; Mulligan et al., 2016), and interventional trials in healthy participants (Freeman et al., 2017). So far, preliminary clinical trials in people with persecutory delusions did not show effects of sleep interventions on psychotic symptoms as a secondary outcome (Freeman et al., 2015b; Hwang et al., 2019) but as these trials did not examine psychotic symptoms as primary outcomes, future studies are necessary to make valid conclusions. To date, it is not entirely clear how sleep contributes to psychotic symptoms. Possibly, there is a mediating effect of negative affect of sleep quality (Kasanova et al., 2020; Rehman et al., 2018) or induced sleep loss (Reeve et al., 2018) on paranoia, meaning that poor sleep leads to increased negative affect, which in turn leads to paranoia. Further, sleep influences quality of life, emotion regulation, and cognitive functioning (Faiola et al., 2018; Grezellschak et al., 2017; Harvey, 2009), especially the regularity of sleep patterns (Sano et al., 2017).

4.3.2 Methodological considerations on using ESM in psychotherapy research

The idea of conducting ESM-like consecutive repeated measurements to identify underlying mechanisms of change during psychological treatment is not new. For example, Rubel et al. (2017) analyzed data from participants with various disorders who underwent psychotherapeutic outpatient treatment. At the end of each session, participants reported their experiences of the therapy session they had just completed (unlike at the beginning of each session in study 2 of this thesis). Participants

rated interpersonal experiences (i.e., the therapeutic relationship), problem coping experiences, and affective experiences (e.g., a deeper understanding of one's own emotions). All of these variables were associated with subsequent symptom improvements on a within-person level. In their paper, Rubel et al. (2017) highlight the importance of separating within- from between-participant variance in such analyses. In mixed models, effects contain both a within- and a between-subject component. To illustrate, if negative affect predicts subsequent psychotic symptoms, then this effect is comprised of two components. First, if a person has higher mean levels of negative affect than another person, they show higher momentary psychotic symptoms. Second, if a person reports higher negative affect than the same person usually does, they report more momentary psychotic symptoms (i.e., the simultaneous examination of person-level and within-person time-varying relationships, Ben-Zeev et al., 2012). The theoretical considerations by Rubel et al. (2017) therefore illustrate an important point. Intermediate assessments can be a useful tool to uncover processes that occur during treatment only if analyses focus on within- rather than between-person processes. However, even if one takes within-person centering into account, the conclusions that can be drawn from purely observational intermediate assessments are limited. For example, from paper 2, we cannot draw the conclusions that the EviBaS intervention was efficacious because of improved worry or sleep. Further, we cannot conclude that worry or sleep caused subsequent symptoms due to the regression-based design. We can only conclude that when these variables improved, this was associated with an improvement of psychotic symptoms shortly after.

The aforementioned constraints of ESM-like assessments in therapy research illustrate that it is difficult to interpret them independently from additional analyses. As studies 1 and 2 show, randomized controlled designs and ESM-like intermediate assessments can complement each other very well. Study 1 (and also group-based analyses of study 2) showed that EviBaS did not improve worrying or insomnia. This information is crucial to correctly interpret the intermediate assessment analyses (i.e., changes of worry and sleep are probably not due to the intervention). At the same time, the intermediate assessment analyses help to correctly interpret the findings from the EviBaS Efficacy Study in that worrying and sleep problems should have been addressed more efficiently to improve the interventions effect on psychotic symptoms. Consequently, a combination of a randomized controlled trial with additional intermediate assessments – as demonstrated in the EviBaS Project – is a very powerful design.

4.4 Limitations

Out of the four included studies, study 1 (the EviBaS Efficacy Study) was the most elaborate for various reasons. Only study 1 allowed drawing causal conclusions due to its randomized controlled research design. Further, it relied on clinician-rated interviews (in addition to self-report), which are considered the gold standard in psychosis research (e.g., PANSS interview), and it was the most innovative study of the thesis because it examined a newly developed Internet intervention in a so far underexplored population. Despite these positive features, there are constraints to the trial that limit its interpretability. First, we compared EviBaS to a waitlist control condition rather than an active control condition. Strictly speaking, the control condition was not a purely "waiting" condition because all participants were required to receive simultaneous pharmacological and/or regular psychiatric or psychological treatment, which one might consider sufficient to name the control condition "treatment as usual". However, as most participants were outpatients and we had little information about their treatment outside of the study, the wording seemed more appropriate. Waitlist control conditions are at risk of overestimating effect sizes but they can be useful for evaluating novel interventions (Mohr et

al., 2009). In a possible follow up study, a stronger control condition might be the better choice as it would control not only the natural course of symptoms but also non-specific effects of the intervention (e.g., interpersonal contact with a moderator). A second limitation was that the effect of the EviBaS intervention on composite psychotic symptoms was driven by improvements of only one of the three outcomes (a self-report hallucination measure), whereas the putatively more reliable PANSS interview showed no group differences. Due to the study's online design, we had to conduct the PANSS via the telephone, which might have resulted in ratings that are less sensitive to change. Finally, the immediate access group (i.e., the group that received EviBaS immediately) reported fewer years of the duration of their disorder compared to the control condition. This group difference at baseline occurred despite randomization, a process designed to eliminate differences through chance. It is possible that the difference in illness duration explained the effect of the EviBaS intervention. This explanation is unlikely, though, because groups did not differ regarding any other baseline variables (e.g., the number of hospitalizations) and adding illness duration as a covariate did not change the effect.

Whereas the issue of baseline differences was purely due to chance in study 1, the problem was much more pronounced in study 3. In study 3, we drew a subset of participants from the EviBaS Efficacy Study in order to compare people who used the mindfulness module to delayed access participants (in addition to selecting people who reported lifetime auditory hallucinations, see section 2.2.1). This resulted in groups that were no longer determined by randomization and hence likely affected by confounders. Only about 50% of participants from the voice-hearing sample of study 3 used the mindfulness module (usage of most modules was not mandatory, see section 1.3.2). It is very likely that this selection process resulted in a biased sample of people who were highly motivated and possibly even at risk to give socially desirable answers. In fact, there was a significantly higher proportion of female participants in the group of people who completed the mindfulness module. As female gender is associated with higher adherence in Internet interventions (Beatty & Binnion, 2016), the selection of mindfulness-module users is likely confounded by general adherence to the EviBaS intervention. Further, the analyses of paper 3 do not allow drawing the conclusion that the mindfulness module resulted in the observed effects on mindfulness. We did not evaluate a purely mindfulness-based intervention but a comprehensive Internet intervention, which targets mindfulness among other factors. As participants in study 3 did not use the mindfulness module exclusively but in combination with other EviBaS modules, it cannot be ruled out that other contents of the intervention were responsible for improved mindfulness. Administering the mindfulness module as a stand-alone intervention would probably not have yielded the same improvements of mindfulness or hallucinations. Unlike study 1, study 3 relied purely on self-report measures. In mindfulness research particularly, self-report measures have faced severe criticism (Grossman, 2008). Finally, the mediation approach does not allow drawing causal conclusions. Although a mediation analysis usually relies on the assumption that the mediator is causally related, the procedure itself is regression-based. It is important to acknowledge that this limitation (i.e., the lack of causal inferences) refers to all studies but study 1. Studies 2 and 4 relied on regression-based analyses as well. We cannot conclude that fluctuations of, for example, worrying caused subsequent paranoia despite their temporal ordering.

The EviBaS Project (studies 1 and 3) as well as the ESM Study (study 4) suffered from insufficient sample sizes. The sample size of $n = 101$ in the EviBaS Efficacy Study was below the target sample size of $n = 140$. Although a post hoc power analysis revealed that the final sample size was large enough to detect small to medium-sized effects, subtler effects were not detectable due to insufficient

power. The sample size problem became even more apparent when we drew a subset of participants for the EviBaS Mindfulness Study (study 3), in which the treatment group only consisted of $n = 16$ participants. In study 4, we aimed for $n = 40$ participants but only reached $n = 30$. This shortcoming affected relapse analyses specifically, as only $n = 13$ participants with relapses did not allow drawing sound conclusions. Another limitation that affected all studies was an unusually high proportion of female participants. Usually, samples of people with psychosis are predominantly male (e.g., 62% male in Lincoln et al., 2012). In the EviBaS Project, the high proportion of female participants (e.g., 58% in study 1) could be explained by the fact that the project evaluated an Internet intervention rather than a face-to-face treatment. High proportions of female participants are common in studies on Internet interventions for other disorders (e.g., 67% in trials on depression; Karyotaki et al., 2018). In study 4, the proportion of female participants was likewise high (53%).

Although each individual papers' methods must be interpreted with caution due to the aforementioned methodological constraints, one might argue that the conclusions drawn from the thesis as a whole are relatively robust. To illustrate, the results of study 2 indicate that worrying and sleep problems are important mechanisms of change during the EviBaS intervention. In itself, this finding is hard to interpret due to the regression-based design. However, in combination with the EviBaS efficacy trial, one can conclude that EviBaS was not efficacious through these processes (because it did not affect respective secondary outcomes) but that worrying and sleep are important treatment targets that EviBaS should have treated better. Study 3 was the least rigorous out of all studies given the post hoc subsample selection. Nonetheless, it plays a part in understanding the efficacy of the EviBaS intervention by providing a fine-grained examination of mindfulness. Paper 3 highlighted the overlap of the mindfulness outcome (MAAS; Brown & Ryan, 2003) and the hallucinations outcome (LSHS-R; Launay & Slade, 1981; Lincoln et al., 2009), which is important to understand how mindfulness might have served as a mediator of the intervention's efficacy. Finally, studies 2 and 4 demonstrated in independent samples that certain ESM-based predictor variables (i.e., worrying) can be promising predictors of larger scaled symptom fluctuations, while others are not (i.e., negative affect). This accordance of results strengthens each individual finding despite aforementioned limitations.

4.5 Future directions

The EviBaS Efficacy Study was a success. The trial was the first to develop and evaluate a psychological Internet intervention delivering self-help materials for people with psychosis in a relatively large randomized-controlled trial. EviBaS proved to be safe, mostly accepted by participants, and efficacious. At the same time, the EviBaS Project was only a first step in the young field of Internet delivered self-help for psychosis, offering starting points for several future directions. It goes without saying that one important goal will be the independent replication of EviBaS' efficacy in future studies. Irrespective of the methodological rigor of the EviBaS Project (e.g., the analysis plan was published; Ruegg et al., 2018), a replication will be necessary to validate findings – particularly in times of the replication crisis in psychology (Aarts et al., 2015). Preferably, a replication study should encompass a larger sample size to obtain more reliable estimates of effect sizes. However, future studies should not only replicate the efficacy of the intervention as it exists today. Rather, the intervention offers room for improvement. Despite the intervention's complexity (i.e., 11 modules targeting multiple psychosis-related problems), its efficacy appears to be limited to hallucinations whereas many secondary outcomes, such as worrying, sleep, or depression showed no significant improvements. Hence, it might be worthwhile to rework these modules. The intervention's inability to improve worrying is particularly critical because interventionist causal evidence (Freeman et al.,

2015a) suggests that a successful reduction of worrying leads to reduced persecutory delusions. If EviBaS would shift its focus more towards a reduction of worrying (e.g., add a second module or rework exercises), it is likely that the intervention would become more successful in reducing paranoia. In addition, future evaluations of EviBaS (or an improved version of it) should incorporate intermediate assessments, comparable to the ones from study 2. The EviBaS Intermediate Assessment Study has shown that incorporating brief intermediate assessments can be beneficial in a randomized controlled trial by enabling researchers to obtain a fine-grained comparison of symptom change as well as predictors of such improvements. However, in future studies, the focus of intermediate assessments should be defined clearer than it was in study 2. The problem with intermediate assessments in study 2 was that the sampling plan was different for the immediate access group and the delayed access group. Whereas we assessed symptoms and predictors upon login in the immediate access group, we assessed them in equidistant weekly assessments in the delayed access group (see section 2.2.1). This was problematic because the unmatched time points of measurements resulted in difficulties comparing the course of symptoms over time. If the focus is on treatment progression, the assessments should take place at the same time points, for example every seven days. If the focus is on mechanisms of change, however, assessments should take place at the *end* of a module, as proposed by Rubel et al. (2017), to examine what processes took place during the preceding session that might explain subsequent symptom improvements. The latter version would not require intermediate assessments in the control group.

Following up on the results of paper 3, it would be a very promising endeavor to assess the contribution of mindfulness on voice hearing in a methodologically more rigorous way. So far, the literature on mindfulness in psychosis is diverse, reporting various positive effects but no clear picture regarding specific effects on certain symptoms (Cramer et al., 2016; Jansen et al., 2020; Khoury et al., 2013). Based on this thesis, one would expect that mindfulness would improve hallucinations specifically rather than psychotic symptoms in general. It is still open to question which component of mindfulness affects hallucinations. Initially, we hypothesized that the acceptance component of mindfulness would be crucial to reduce the distress caused by hallucinations. Study 3, however, rather indicates that a reduction of daydreaming or mind wandering could represent a potential mechanism of change. A randomized controlled dismantling trial, as proposed by the interventionist causal model approach by Freeman and colleagues (Freeman et al., 2015a; Freeman et al., 2017), would be necessary to examine this question.

Study 4 offers several starting points for future studies as well. Study 4 brought attention to aberrant salience as a predictor of both short- and long-term paranoia. Although the study was insufficiently powered to detect predictors of relapse, it nonetheless seems very promising to follow up on the idea that self-reported aberrant salience represents a candidate relapse predictor. Aberrant salience stands out from the available candidate relapse predictors in many ways. First, it is a processes specifically linked to psychosis. Compromised sleep, worrying, or depressed mood are all related to a plethora of disorders (e.g., Goodwin et al., 2017; Harvey, 2009), whereas aberrant salience is theoretically grounded in a model on psychosis (Kapur, 2003). Further, predictors, such as compromised sleep, depression, anxiety, and others can be considered both precursors and outcomes of psychotic symptoms. From a theoretical perspective, it is equally plausible that paranoid thoughts keep a person awake as it is that compromised sleep causes later paranoia. Aberrant salience, in contrast, belongs to the prodromal phase of psychosis specifically (Kapur, 2003) and it appears unlikely that psychotic symptoms occur before feelings of aberrant salience. To arrive at more durable conclusions regarding

the prediction of relapse in a future trial, it would be worthwhile to include short diagnostic interviews to verify psychotic relapses in a more valid and reliable way. In study 4, we assessed relapses mostly on the basis of self-report, which is not ideal given that acute psychotic symptoms lack insight (Arciniegas, 2015). At the same time, frequent interviews can be off-putting for participants. A possible trade-off could be a combination of self-report and additional interviews when symptom thresholds are surpassed in self-reports. Most importantly, a future relapse prediction trial would require a much larger sample size, which will be difficult to acquire given the effort that is required from participants.

As reviewed above, there are many worthwhile future directions which arise from the EviBaS Project and the ESM Study. However, all of these ideas face the same problem: Even if we manage to improve assessment methods, intervention contents, or technical components, follow up projects based on the EviBaS Project or the ESM Study will always require participants who show a lot of insight, a high degree of motivation, and relatively good cognitive abilities. In clinical practice – particularly in inpatient treatment or assisted living facilities – such patients are the exception rather than the rule. One must acknowledge that complex self-help interventions or the autonomous monitoring of internal mental states to prevent relapses will only benefit a certain proportion of patients and that others will require alternative approaches. Family interventions appear to be effective in reducing the number of relapses and hospitalizations (Pharoah et al., 2010), so a final worthwhile future direction would be to use what we have learned from studies 1 to 4 and to combine it with family psychoeducation. To illustrate, EviBaS can be effective for functional patients with psychosis but if patients have too severe symptoms, EviBaS could be adapted to provide valuable information for family members (e.g., family members could take care of certain environmental factors that impair sleep of their relative with psychosis). The SOAR intervention has shown that such an approach can be efficacious (Rotondi et al., 2010). The same is true for the ESM Study: While highly functional patients will be able to monitor bursts of aberrant salience independently, others cannot. In cases of limited cognitive capacities, we should rather educate family members to pay attention to potential warning signs instead of relying on the patient's ability to monitor them.

From a methodological perspective, the present thesis has highlighted the advantages of symptom- rather than diagnosis-focused research. The EviBaS intervention reduced psychotic symptoms (composite outcome) but a closer look revealed that this effect only applied to hallucinatory experiences. Worrying and sleep problems predicted subsequent psychotic symptoms during the intervention, but eventually, the effect of worry was limited to paranoia (which coincides with theoretical considerations), and in the ESM Study, predictive effects of aberrant salience likewise only occurred for paranoia, not auditory hallucinations. The symptom focused approach of the present thesis was influenced by ESM research findings, which mainly focus on single symptoms rather than composite scores (e.g., Ben-Zeev et al., 2012; Luedtke et al., 2017; So et al., 2018). Future studies, both treatment as well as relapse prediction trials, could benefit from adapting this approach. For example, study 4 demonstrated that it can be a fruitful endeavor to predict bi-weekly fluctuations of paranoia rather than relapses. Relapses are complex events with different underlying symptom exacerbations (Csernansky et al., 2002). Possibly, the predictive value of previously examined predictors was limited because of the diversity of the outcome. Future studies should consider adopting the ESM-based approach of predicting exacerbations of certain symptoms rather than complex events in order to end up with more potent models.

Lastly, an important methodological future direction will be to move forward to "real" idiographic research. Idiographic research refers to the study of the individual – an individual's behavior, their cognitive processes, and personality (as reviewed in Piccirillo & Rodebaugh, 2019). In the context of ESM, idiographic research refers to examinations of individual symptom trajectories of participants rather than relying on group-level statistics. The ESM-based procedures used in this thesis give the impression of idiographic research because we examined repeated measures clustered within participants using person-mean centered predictors (studies 2 and 4 of the present thesis). In the end, however, all analyses were nomothetic (i.e., group-level based) because they relied on fixed effects that were estimated across the whole sample. It would be a very interesting approach to use ESM data in order to identify relevant symptom predictors for individuals rather than groups of people. Whereas sleep problems might be a symptom trigger for person "A", they might be irrelevant for person "B" who mainly experiences symptom exacerbations after excessive worrying. Particularly in the context of relapse prevention, individualized ESM assessments could provide a tool to identify idiographic risk factors. Such individualized approaches could not only improve the prediction of relapse, they would also give a person the impression that a treatment- or prevention program is truly tailored to their needs, which would eventually increase compliance and motivation.

4.6 Conclusions

The present thesis granted several insights into the variability of psychotic symptoms and their treatment. First and foremost, the Internet-based EviBaS intervention proved to be safe, accepted, and efficacious. Secondly, the intermediate assessment study indicated that worrying and sleep problems represent important treatment targets, which were not sufficiently addressed by EviBaS. Rather, the efficacy of EviBaS potentially relied on effects on mindfulness (study 3). Finally, study 4 showed that it is possible to predict bi-weekly symptom fluctuations of paranoia using self-reported aberrant salience, potentially paving the way for future studies of aberrant salience as a promising relapse warning sign. A closer look at these results, which at first appear convincing, reveals that much work still needs to be done. EviBaS appears to be efficacious through a very specific pathway of reducing hallucinatory experiences and increasing mindfulness. Other outcomes – particularly observer-rated interviews but also worrying, sleep problems, or depression – remained unaffected. Further, the intervention appears to be too demanding for heavily impaired participants. In short, there is much room for improvement. In addition, the ESM Study only represents a very first step in the endeavor of improving the prediction of relapse in psychosis. The underlying goal – predicting relapses – was not achieved and will require much larger samples in future studies.

The Experience Sampling Method was at the core of this thesis. Findings from ESM studies influenced the development of EviBaS, the selection of relapse predictors, and the intermediate assessment analyses. Grounding the thesis on ESM research shifted its focus towards individual symptoms and warning signs and away from overarching syndromes or diagnoses. Being at the intersection of nomothetic and idiographic research, this approach greatly benefited the present studies and I believe that it has the potential to exert positive influence on clinical research in general. So far, we have certainly not exhausted the potential of the Experience Sampling Method, and we should continue using it curiously but conscientiously to improve the lives of people with psychosis.

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Included papers

Paper 1

Paper 2

Paper 2

the british psychological society
promoting excellence in psychology

British Journal of Clinical Psychology (2020)

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Orginal article

Sleep problems and worrying precede psychotic symptoms during an online intervention for psychosis

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Objective. Experience sampling assessments (multiple assessments per day for approximately one week) indicate that positive symptoms fluctuate over time in psychosis. Precursors, such as sleep problems or worrying, predict these fluctuations. To date, it remains unclear whether the same precursors predict symptom variability also during treatment in an online intervention for psychosis, using assessments lying temporally further apart.

Methods. Participants completed brief intermediate online self-report assessments on their computers (up to every 7 days during a 2-month waiting period and up to twice every 6 days during a 2-month intervention period) within a randomized controlled trial. We monitored the course of paranoia, auditory verbal hallucinations, and their theory-driven precursors worrying, negative affect, self-esteem, self-reported cognitive biases, and quality of sleep in $n = 124$ participants ($M = 10.32$ assessments per participant; $SD = 6.07$). We tested group differences regarding the course of the composite of precursors, group differences regarding the effect of the composite on subsequent momentary psychotic symptoms, and the effect of each individual precursor on subsequent psychotic symptoms, using (lagged) linear mixed models.

Results. The course composite precursors over time and their lagged effect on subsequent momentary psychotic symptoms did not differ between groups. During the intervention, increased worrying and decreased quality of sleep preceded heightened momentary psychotic symptoms.

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Conclusion. The regression-based design does not allow drawing causal conclusions. However, worrying and sleep problems likely represent underlying mechanisms of psychotic symptom variability during online psychosis treatment, indicating that experience sampling findings from everyday life generalize to interventions with assessments lying several days apart.

Practitioner points

- Worrying and sleep problems represent important mechanisms of symptom fluctuations during an online intervention for people with psychosis.
- Our findings further support the notion that worrying and sleep problems are important treatment targets in psychological interventions for people with psychosis.
- Momentary levels of worrying and quality of sleep can signal subsequent fluctuations of psychotic symptom severity so practitioners should monitor these variables during treatment.
- Worrying seems to predict subsequent paranoia specifically during treatment whereas quality of sleep predicts both paranoia and auditory verbal hallucinations

The experience sampling method (ESM; Myin-Germeys et al., 2009) has shed light on the temporal dynamics of positive symptoms in people with psychosis. In ESM studies on psychosis, participants report momentary psychotic symptoms and hypothesized correlates in diary-like self-report assessments repeatedly throughout the day. The longitudinal data enable researchers to predict momentary psychotic symptoms through precursors measured at a previous point in time. Precursors encompass worry and rumination (Hartley, Haddock, Vasconcelos, Emsley, & Barrowclough, 2014), sleep problems (e.g., Kasanova, Hajduk, Thewissen, & Myin-Germeys, 2019; Mulligan, Haddock, Emsley, Neil, & Kyle, 2016), and low self-esteem, defined as negative views about the self, such as being ashamed of oneself (Udachina, Varese, Myin-Germeys, & Bentall, 2014). The 'jumping to conclusions' bias (Dudley, Taylor, Wickham, & Hutton, 2016) precedes subsequent momentary paranoia as well (Lüdtke, Kriston, Schröder, Lincoln, & Moritz, 2017). One of the most consistently found precursors of paranoia is negative affect, a term comprising states such as feeling low, anxious, or lonely (Ben-Zeev, Ellington, Swendsen, & Granholm, 2011; Lüdtke et al., 2017; So et al., 2018). Of note, the association of depression and paranoia seems to rely on the assessment frequency. When measured weeks apart, paranoia predicts depression rather than vice versa (Moritz, Goritz, McLean, Westermann, & Brodbeck, 2017; Moritz et al., 2019). In sum, ESM studies have identified several time-variant precursors of psychotic symptoms in everyday life of people with psychosis.

Although ESM studies do not allow drawing causal conclusions, theoretical models (Freeman & Garety, 2014) and experimental findings (e.g., Reeve, Emsley, Sheaves, & Freeman, 2018) indicate causal relationships between aforementioned precursors and psychotic symptoms. Hence, it appears promising to target precursors of psychotic symptoms in therapeutic interventions, especially because the treatment of symptom precursors seems to coincide well with wishes and needs of participants (Freeman, Taylor, Molodynski, & Waite, 2019; Moritz, Berna, Jaeger, Westermann, & Nagel, 2017). There is initial support for the efficacy of interventions that focus on precursors to alter psychotic symptoms indirectly. For example, Freeman, Dunn, et al. (2015) examined a brief intervention based on cognitive behavioural therapy (CBT) targeting worry. The intervention led to decreased persecutory delusions in people with non-affective psychosis with changes in worry mediating the effect. Findings are less consistent for sleep problems. One trial found that a sleep intervention reduced insomnia, paranoia, and

hallucinations in healthy participants, with insomnia mediating the effect on psychotic symptoms (Freeman et al., 2017). In clinical samples, CBT-based sleep interventions likewise improved sleep but not psychotic symptoms (Freeman, Waite, et al., 2015; Hwang, Nam, & Lee, 2019). It is important to note that psychotic symptoms only served as secondary outcomes in these trials. Hence, the effect of sleep interventions on psychotic symptoms has not yet been adequately tested. CBT-based interventions targeting depression, a key component of the precursor negative affect, are rare (Upthegrove, Marwaha, & Birchwood, 2017). In one trial, a CBT-based online intervention targeting depression improved depressive but not positive symptoms (Moritz et al., 2016). Metacognitive training (Moritz & Woodward, 2007) aims at reducing, inter alia, participants' proneness to cognitive biases, which served as a symptom precursor in one ESM study as well (Lüdtke et al., 2017). One meta-analysis yielded mixed findings (van Oosterhout et al., 2016), but the majority of meta-analyses suggest that the metacognitive training improves psychotic symptoms (Eichner & Berna, 2016; Liu, Tang, Hung, Tsai, & Lin, 2018; Philipp et al., 2019). Taken together, treating precursors of psychotic symptoms can be beneficial for people with psychosis.

Targeting precursors of psychotic symptoms online

Based on aforementioned studies, Westermann et al. (2020) have developed a psychological online intervention (EviBaS) targeting not only psychotic symptoms but also potential precursors of psychosis in guided self-help modules. The authors successfully evaluated EviBaS in a randomized controlled trial. The intervention led to a significant reduction in a composite score of positive symptoms (Westermann et al., 2020). As EviBaS covers the treatment of a wide range of precursors, the aim of the present study was to investigate which of the addressed precursors would predict the course of positive symptoms during the intervention. To do so, we monitored psychotic symptom fluctuations and their presumed precursors similar to the procedure used in ESM trials. Assessments took place every seven days in the waiting period and up to twice per six days during the intervention period. We expected that within-participant changes of the following precursors would represent underlying mechanisms of psychotic symptom variability during the intervention: worrying, negative affect, self-esteem, self-reported cognitive biases, and quality of sleep. Unlike the interventionist-causal model approach (Freeman, Dunn, et al., 2015), our examination of precursors and symptom fluctuations is observational. It enables us to test multiple underlying mechanisms of psychotic symptom variability in parallel while relying on longitudinal data with a relatively high temporal resolution. For the present analyses, we focused on the course of positive symptoms (auditory verbal hallucinations and paranoia) for two reasons. First, the EviBaS intervention targets positive symptoms specifically. Hence, we aimed at identifying precursors of these symptoms throughout the intervention. Second, we selected symptom precursors based on previous ESM studies, which uniformly examined positive symptoms of psychosis (e.g., Hartley et al., 2014; So et al., 2018; Udachina et al., 2014).

Aims of the study

The design enabled us to examine several research questions. First, the longitudinal assessments allowed us to monitor the course of precursors over time thus offering insight into moment-to-moment effects of the EviBaS intervention beyond its already established effect on composite positive symptoms (Westermann et al., 2020). Second, we were able

to examine which mechanisms of psychotic symptom fluctuations occurred during the online intervention. The intervention aimed to ameliorate numerous candidate precursors so it was interesting to examine which of these candidates served as actual precursors (i.e., mechanisms of change) of subsequent symptoms, representing variables that are worth monitoring during treatment. Our approach focused on within-participant effects to obtain a more idiographic view, which researchers have called for in psychological and psychotherapy research (Piccirillo & Rodebaugh, 2019). The within-participant approach goes beyond traditional assessments of treatment mechanisms (e.g., group-based mediation analyses) as it uncovers processes within participants over time. To our knowledge, this is the first study to examine within-participant moment-to-moment effects of potential mechanisms of change during an online intervention for psychosis. Third, our analyses provide insights regarding the generalizability of ESM findings to other contexts. Usually, ESM studies examine precursors and outcomes several times per day for a short period, such as one week (e.g., So et al., 2018). The rationale of ESM studies is that within-day associations between symptoms and preceding variables can improve our general understanding of the phenomenology and aetiology of psychopathology (Myin-Germeys et al., 2018). We hypothesized that within-day ESM processes could represent micro-level equivalents of larger-scale mechanisms of symptom fluctuations. To illustrate, momentary levels of worrying vary throughout the day and precede subsequent psychotic symptoms (Hartley et al., 2014). At the same time, worry as a response to a physical assault predicts paranoia four weeks later (Freeman, Thompson, et al., 2013). The underlying process is the same in both cases in that increased worry precedes psychotic symptoms. It is appealing to assume that within-day associations generalize to other contexts as this implies that ESM studies can generate knowledge about larger-scale processes, such as the prediction of relapse or the prediction of symptomatic improvements during treatment, as examined here. In the present study, we tested this assumption by applying the ESM methodology of precursor-symptom associations to an eight-week assessment period (the assessments were several days apart). In addition, the randomized controlled design of the EviBaS trial enabled us to compare associations between precursors and psychotic symptoms in different contexts, namely a waiting condition (i.e., comparable to usual ESM studies) and a treatment condition. We expected that precursors would improve due to the intervention in the treatment condition whereas we expected precursors to fluctuate naturally over time in the waitlist condition. By comparing these conditions, we could investigate whether precursors influence subsequent symptoms only if they vary naturally (as in typical ESM studies) or also when they vary due to a psychological treatment.

We hypothesized that precursors would improve more in the treatment (i.e., immediate access) group compared to the waitlist (i.e., delayed access) group (hypothesis 1), that precursors would predict subsequent psychotic symptoms differently in the two groups (hypothesis 2), and that each individual precursor would predict subsequent psychotic symptoms during participation in the EviBaS intervention across groups (hypothesis 3).

Methods

The study is a registered (https://osf.io/gn8u5) secondary analysis of intermediate assessment data obtained from the EviBaS trial. For results of the main trial, see Westermann et al. (2020). The EviBaS main trial is a pre-registered (NCT02974400, clinicaltrials.gov) multi-centre parallel-group assessor-blind randomized controlled trial

with an allocation ratio of 1:1 evaluating the feasibility and efficacy of a CBT-based psychological online intervention (EviBaS) for people with psychosis. The intervention was guided, meaning that trained and supervised study staff with at least a bachelor's degree in psychology assisted participants using a secure messaging system. The EviBaS intervention encompassed 11 modules in total – one introductory module, one module on relapse prevention and nine modules targeting persecutory delusions, auditory verbal hallucinations, as well as a list of correlates of psychosis, namely worrying, low levels of mindfulness, poor social competence, low self-esteem, depression, sleep problems, and cognitive biases. The intervention's approach was twofold. It addressed psychotic symptoms directly by providing psychological models that explain hallucinations and feelings of persecution while offering exercises to decrease the participant's burden (two modules). On the other hand, the intervention targeted potential precursors of psychosis in order to ameliorate symptoms indirectly (seven modules).

Out of the 11 modules only the introductory module that introduced general CBT concepts, such as the ABC protocol (i.e., activating event, belief, consequences), and the final module on relapse prevention were mandatory. The nine remaining modules were not mandatory and participants could choose the order in which they completed them. Modules contained educational components and exercises conveyed via text, audio, and video files. At the beginning of a module, the texts, illustrations, or video files introduced the module's respective topic usually accompanied by a fictitious case example. Then a CBT-based model explained associations with psychotic symptoms and offered 'leverage points' for interventions. In the following, the module introduced specific interventions (e.g., CBT-based advice on how to improve sleep, such as avoiding meals before going to bed, addressing thoughts that compromise sleep using ABC protocols, or practicing relaxation exercises). Most modules contained worksheets so that participants filled in their own experiences to customize exercises. The module's final page summarized the main points and offered the possibility to give feedback to the guide. Completing a typical module took approximately 30 to 60 minutes. To promote participants' sense of autonomy we did not require participants to complete all modules. Instead, we considered the completion of eight modules over eight weeks as full adherence.

Trial design

At baseline, participants completed a self-report online assessment as well as a diagnostic interview via telephone. After confirming the inclusion criteria, we used a web-based randomization tool (based on random.org, RRID: SCR_008544) to allocate participants to the 'delayed access group' or the 'immediate access group'. We use these terms because waitlist participants received delayed access to the intervention after the waiting period whereas intervention group participants received immediate access. After eight weeks we invited all participants to complete a second self-report online assessment (post-assessment).

Here, we report data from intermediate assessments that we conducted throughout the EviBaS trial, both during the waiting and the intervention period to monitor the course of symptoms and presumed precursors. While using EviBaS, participants completed the assessments whenever they logged in, up to two times in 6 days. When a participant accessed the online intervention using an internet browser the short online questionnaire appeared on the screen. We chose this assessment format because we hoped to minimize the burden for participants by combining the assessments with the intervention. Delayed access participants completed the intermediate assessments once per week (invited via e-

mail) throughout the eight-week period between baseline and post-assessment, and additionally for another eight weeks after receiving access to EviBaS (identical to the immediate access group). For analyses on precursors of momentary symptoms during the intervention (i.e., hypothesis 3), we used data from all participants irrespective of their initial group allocation as we were interested in the processes during the intervention and not in a comparison between groups (see the boxes in Figure 1 with thick outlines).

Recruitment

We recruited participants in Germany and Switzerland. Local ethics committees approved the study (Cantonal Ethics Committee Bern, ID 03/14; German Society for Psychology, ID SM052015_CH). We contacted potential participants from a database listing former participants with schizophrenia spectrum diagnoses who had previously given their consent and we advertised the study online. Furthermore, we reached out to psychiatrists and psychiatric institutions.

All participants provided informed consent prior to participation. Participants were eligible if they were 18 years of age or older, had access to the Internet, showed sufficient command of the German language, had a lifetime diagnosis of a non-affective psychotic disorder (verified in telephone interview), and reported receiving antipsychotic treatment or psychotherapeutic/psychiatric consultations at least monthly. A mandatory emergency plan listed persons that participants could contact in case of an emergency. We excluded participants if they refused to complete the emergency plan, if they reported a diagnosis of a neurological disease, if they displayed acute suicidality, or an acute danger towards others.

For the present secondary analysis, we analysed data from EviBaS participants and additional data from participants who were not part of the EviBaS main trial because they did not meet the positive symptom severity threshold (a PANSS score of 3 or higher on at least one of the following items: delusions, hallucinations, or suspiciousness / persecutory delusions). These 'secondary track' participants completed the trial the same as the main trial participants but with two differences, as depicted on the right-hand side of Figure 1. First, secondary track participants did not complete a telephone interview at post-assessment (which was irrelevant for the present analyses). Second, delayed access participants in the secondary track had to wait 4 months to receive access to the intervention whereas the delayed access participants of the main trial received access directly after completing the post-assessment. The proportion of secondary track participants was equal in the immediate access group and delayed access group (see Table 1).

Measures

We only describe relevant measures. For a description of all measures included in the EviBaS trial, see Rüegg et al. (2018).

Baseline measures

We report participants' cumulated antipsychotic dosages, indicating the percentage of the maximum dosage of a certain drug because chlorpromazine equivalents have faced criticism (Danivas & Venkatasubramanian, 2013). We administered an adapted version of the Mini International Neuropsychiatric Interview (MINI; Lecrubier et al., 1997) to verify

Table 1. Sample characteristics at baseline (N = 124)

Characteristics	Delayed access (n = 66)	Immediate access (n = 58)	Statistics
Demographics			
Age in years, mean (*SD*)	40.88 (9.84)	42.34 (10.85)	t (122) = 0.789, p = .432
Gender (female/male)	37/29	38/20	χ^2 (1) = 1.155, p = .282
Years of education, mean (*SD*)	11.64 (1.76)	11.93 (1.41)	t (122) = 1.019, p = .310
Clinical variables			
'Secondary track' participants (%)	18 (27%)	15 (26%)	χ^2 (1) = 0.031, p = .859
Diagnosis of current psychotic episode (%)	23 (35%)	28 (48%)	χ^2 (1) = 2.299, p = .129
Diagnosis of current depressive episode (%)	17 (26%)	20 (34%)	χ^2 (1) = 1.123, p = .289
Reported taking antipsychotic medication (%)	59 (89%)	47 (81%)	χ^2 (1) = 1.738, p = .187
Cumulated antipsychotic dosage, mean (*SD*)	42.19 (37.87)	34.58 (36.22)	t (117) = 1.116, p = .267
PANSS total score, mean (*SD*)	50.47 (13.53)	51.67 (14.95)	t (122) = 0.469, p = .640

Note. SD = Standard Deviation; Secondary track participants = number of participants who were not part of the EviBaS main trial because they did not meet the positive symptom severity threshold (a PANSS score of 3 or higher on at least one of the following items: delusions, hallucinations, or suspiciousness/persecutory delusions); diagnoses were assessed using the MINI; all participants had a diagnosis of a previous psychotic episode; cumulated antipsychotic dosage refers to the percentage of the maximum dosage of the antipsychotic drugs that a participant received (not all participants provided information, hence the smaller df).

relevant psychiatric diagnoses and the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) to measure psychotic symptom severity. The PANSS showed good internal consistency in our sample (α = .85). We administered PANSS and MINI via telephone.

Intermediate assessments

Participants completed a 14-item intermediate assessment questionnaire up to once per week during the waiting period and up to two times in six days during the intervention period. Two items (α = .42) captured psychotic symptoms, 'I feel suspicious', adapted from previous ESM trials (Kramer et al., 2014; So et al., 2018) and 'I hear voices that no one else can hear', which was self-generated. We assessed worry with the item 'My worries overwhelm me', adapted from the Penn State Worry Questionnaire-Past Week (Stober & Bittencourt, 1998). We measured negative affect using two items (α = .80). The first item 'I am feeling down, depressed, or hopeless' stems from the Patient Health Questionnaire-9 (Kroenke, Spitzer, & Williams, 2001). We adopted the second item 'I feel anxious' from previous ESM trials (Kasanova et al., 2019; Kramer et al., 2014). We assessed self-esteem using the reverse-coded item 'I am satisfied with myself' adapted from the Rosenberg Self-Esteem scale (Rosenberg, 1965). We included two items to assess self-reported cognitive biases. The item 'When I am certain about something then I must be correct' was inspired

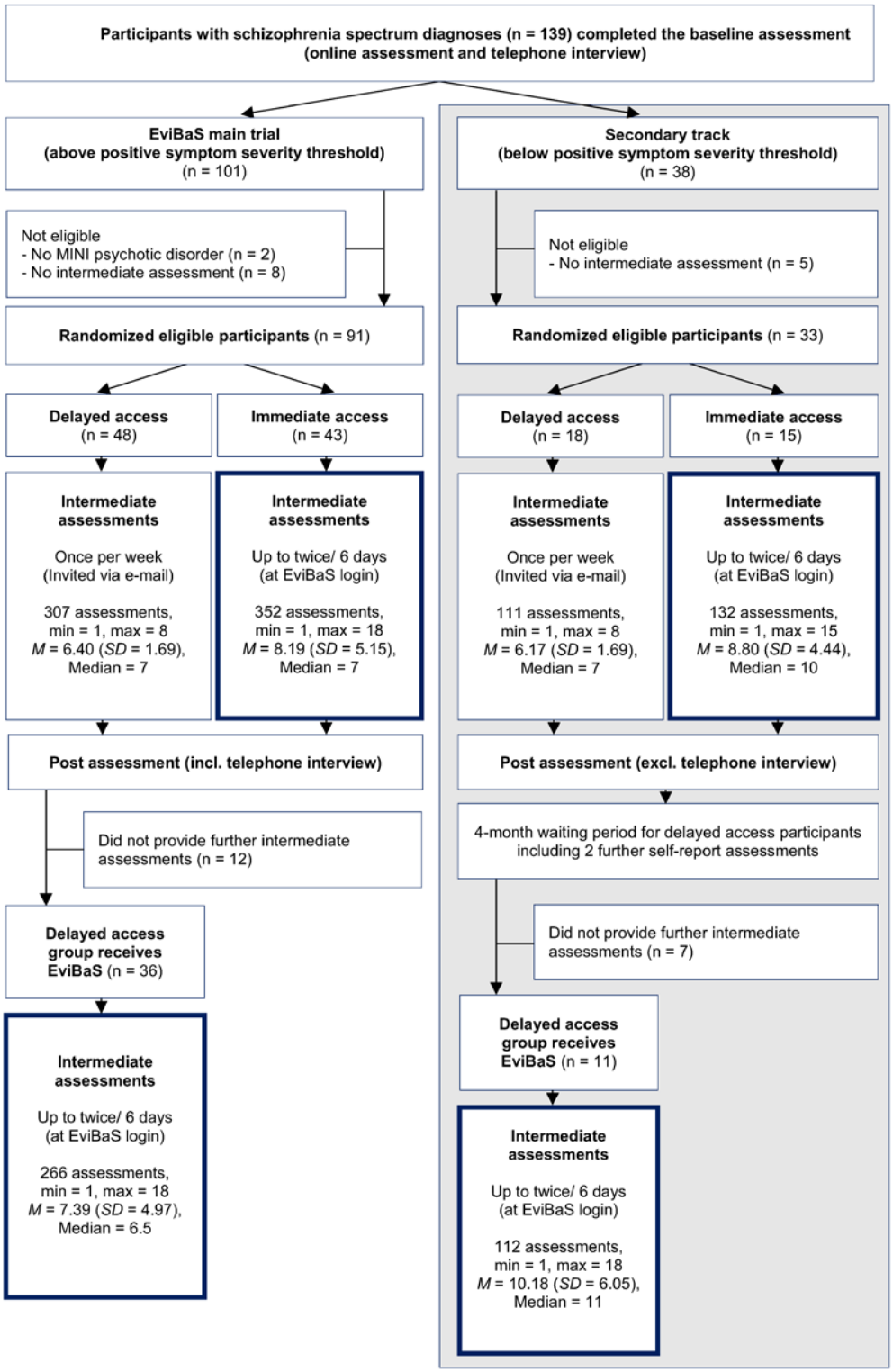

Figure 1. Flow chart (thick outlines highlight intermediate assessments used for hypothesis 3).

by the Beck Cognitive Insight Scale (Beck, Baruch, Balter, Steer, & Warman, 2004). The reverse-coded item 'I consider as much information as possible before I make a decision' aimed at assessing hasty data gathering. The items correlated negatively (after transforming the reverse-coded item), so that we analysed the items separately instead of using the scale ($r = -.277$). We assessed quality of sleep with the item 'The quality of my sleep is good'. We chose this unspecific wording to capture different types of sleep problems (Kasanova et al., 2019). The remaining items of the intermediate assessments were not relevant for the present analyses. Except for sleep, participants rated all items according to how they felt at the current moment. For analyses of hypotheses 1 and 2, we calculated a composite score of precursors defined as the sum of worry, negative affect, self-esteem, self-reported cognitive biases, and quality of sleep ($\alpha = .60$). The rationale of the composite score was to reduce the overall number of confirmatory analyses to maintain sufficient power.

Statistical analyses

We registered analyses prior to accessing the relevant data (https://osf.io/gn8u5). All analyses represent variants of linear mixed models. Mixed models allow accounting for the 'nested' structure of measurements clustered within participants, which is characteristic for longitudinal data. We did not impute missing values because mixed models are flexible in handling missing data (Twisk, 2019, p. 150).

For hypothesis 1 we tested whether the composite score of precursors (worry, negative affect, self-esteem, self-reported cognitive biases, and quality of sleep) improved more in the immediate access group compared to the delayed access group. The analysis relied on intermediate assessment data obtained between baseline and post-assessment. The statistical model included time, group (immediate vs. delayed access), and the time x group interaction. The composite score of precursors served as the outcome. Intermediate assessments took place at different points in time during the intervention compared to the waiting period (upon EviBaS login vs. once per week). To obtain a comparable number of assessments in both groups, we aggregated the assessments by averaging the respective outcome scores from the same week, resulting in one outcome value per week per participant. We aggregated scores only for hypothesis 1.

For hypothesis 2, we examined if the composite score of precursors (t-1) predicted subsequent psychotic symptoms (t0) differently in the two groups (immediate vs. delayed access). As for hypothesis 1, we only considered data from the first eight weeks. We conducted a lagged linear mixed model analysis with momentary psychotic symptoms (t0) as the outcome, the composite score of precursors (t-1), group (immediate vs. delayed access), and the group x composite score (t-1) interaction as predictors, controlling for psychotic symptoms at t-1.

For hypothesis 3, we examined if each individual precursor predicted subsequent psychotic symptoms during the EviBaS intervention. We conducted separate lagged linear mixed model analyses with each precursor (t-1) as the predictor variable (e.g., worry) and momentary psychotic symptoms as the outcome, while controlling for previous psychotic symptoms (t-1). We considered data from all participants taking part in the intervention, both immediate access participants and delayed access participants. As the reliability analysis revealed a negative correlation between the two self-reported cognitive bias items, we excluded the scale from the analyses for hypothesis 3 and examined the items separately in exploratory analyses. This was a deviation from the analysis plan.

All models included a random intercept but no random slope. For hypotheses 2 and 3, we person-mean-centred all time-variant predictors and covariates to obtain within-participant effects rather than between-participant effects. We calculated the within-participant mean and subtracted it from each value. One unforeseen issue was the distance between two consecutive measurements in lagged analyses (hypotheses 2 and 3). During the intervention, it was possible that two assessments from the same participant took place only minutes but also several weeks apart. Post hoc we set the minimum distance between two consecutive measurements to 24 hours because we expected the underlying mechanisms of symptom variability to require at least 24 hours to take place. We defined the upper limit as 252 hours (approximately 1.5 weeks) so that it would overlap with the one-week interval in the waiting period. If a value lied outside the range of 24 to 252 hours, we defined it as missing in lagged analyses (8.3%).

We used two-sided tests and conventional p-values of .05. We applied the Benjamini and Hochberg correction to control for the false discovery rate due to multiple tests (Benjamini & Hochberg, 1995). We conducted separate corrections for analyses 1 and 2 (two tests) and for analyses 3a to 3d (four tests). We used SPSS 25® (RRID: SCR_002865).

Results

Sample characteristics and adherence

Table 1 displays sample characteristics at baseline. Participants provided 1,280 data points in total. Each participant completed $M = 10.32$ ($SD = 6.07$) intermediate assessments on average (range = 1 to 25; median = 9.5). The aggregated data set that we used to compare the course of precursors between groups throughout the first eight weeks of the trial consisted of 600 assessments (hypothesis 1). With PANSS total scores of roughly 50, participants were mildly ill (Leucht et al., 2005). Ordered completion rates of EviBaS modules for the whole sample ($n = 124$) were as follows: Introduction (72%), self-esteem (43%), social competence (39%), mindfulness (36%), cognitive biases (35%), depression (34%), auditory hallucinations (32%), worrying (32%), persecutory delusions (30%), relapse (30%), and sleep (30%).

Hypothesis tests

Group comparisons

For hypothesis 1, we examined if using the EviBaS intervention led to an improvement of composite precursors (i.e., a sum score of negative affect, worrying, etc.) over time. We used aggregated intermediate assessment data from the first eight weeks of the trial to compare the temporal course between groups. Contrary to our hypothesis the group x time interaction was non-significant, indicating that the course of precursors over time did not differ between groups ($b = -0.043$, $SE = .096$, $t = 0.449$, $p = .653$). Hence the intervention did not improve the composite score of precursors compared to the waitlist condition. In fact, the main effect of time was non-significant both in the immediate access group ($b = -0.001$, $SE = .069$, $t = 0.013$, $p = .989$) and the delayed access group ($b = 0.041$, $SE = .067$, $t = 0.613$, $p = .540$), indicating that – across groups – precursors did not improve. For hypothesis 2 we examined if the composite score of precursors predicted subsequent momentary psychotic symptoms differently in the immediate access group compared to the delayed access group. The group x composite precursors

Table 2. Coefficients of lagged linear mixed model analyses within participants using EviBaS intervention (n = 105)

Precursor (t-1)	Unstandardized coefficient (b)	*SE*	*t*	*p*	*FDR*
Worry	0.156	0.064	2.438	.015	.030
Negative affect	0.046	0.034	1.350	.177	.237
Self-esteem	−0.007	0.069	0.106	.916	.916
Quality of sleep	−0.198	0.059	3.359	.001	.003

Note. Outcome = momentary psychotic symptoms (t0) defined as the sum of self-reported suspiciousness and auditory verbal hallucinations; all precursors are participant-mean-centred; all models contain participant-mean-centred psychotic symptoms at t-1 as covariates; we do not present coefficients for self-reported cognitive biases because of the scale's inconsistency; SE = Standard Error; FDR = False Discovery Rate-corrected values based on 4 tests, according to Benjamini and Hochberg (1995).

interaction was non-significant, indicating that the composite score of precursors did not predict subsequent momentary psychotic symptoms differently in the two groups (b = 0.031, SE = .032, t = 0.945, p = .345).

Analyses within the intervention (across groups)

For hypotheses 3 we conducted separate analyses to evaluate if each individual precursor (worry, negative affect, self-esteem, and quality of sleep) predicted subsequent momentary psychotic symptoms within the intervention only. We used data from all participants who completed intermediate assessments while using EviBaS irrespective of their initial group allocation. Please note that we conducted the analyses despite the insufficient internal consistency of the psychotic symptom scale because we wanted to adhere to the registered analysis plan. We addressed the problem in exploratory analyses, in which we analysed paranoia and auditory hallucinations as separate outcomes. Table 2 displays the model coefficients for each precursor. The effects of worry and quality of sleep on subsequent momentary psychotic symptoms remained significant after applying the Benjamini and Hochberg correction. The results indicate that more momentary worry, compared to a participant's average level of worrying, preceded more momentary psychotic symptoms at the following intermediate assessment throughout the intervention (b = 0.156, p_{FDR} = .030). Higher momentary quality of sleep, compared to a participant's average quality of sleep, preceded less momentary psychotic symptoms (b = −0.198, p_{FDR} = .003).

Exploratory analyses

First, the self-reported cognitive bias scale consisted of two items, which correlated negatively. Hence, we analysed each item separately to examine if it preceded subsequent momentary psychotic symptoms in the EviBaS intervention (equivalent to analyses for hypotheses 3). Neither item predicted subsequent momentary psychotic symptoms (p's ≥ .359). Second, the 'psychotic symptoms' scale (auditory verbal hallucinations and paranoia) displayed insufficient internal consistency. Exploratory analyses with auditory verbal hallucinations and paranoia as separate outcomes indicated that the effect of worry consisted mainly of an effect on paranoia (b = 0.116, SE = .044, t = 2.608, p = .009) rather than auditory verbal hallucinations (b = 0.035, SE = .034, t = 1.031, p = .303).

Quality of sleep preceded both paranoia ($b = -0.104$, SE = .041, $t = 2.529$, $p = .012$) and auditory verbal hallucinations ($b = -0.087$, $SE = .032$, $t = 2.736$, $p = .006$). Negative affect, which failed to predict composite psychotic symptoms, predicted paranoia ($b = 0.058$, $SE = .023$, $t = 2.484$, $p = .013$), while there was no effect on auditory verbal hallucinations ($b = -0.011$, $SE = .017$, $t = 0.651$, $p = .516$). Third, we addressed the poor internal consistency of the composite score of precursors (negative affect, worry, self-esteem, self-reported cognitive biases, and quality of sleep). Note that we summarized these precursors to reduce the number of confirmatory tests and we did expect poor internal consistency. We repeated the analyses using single precursors instead of the composite score in separate models. No group x time interactions reached significance (all p's $\geq .411$) replicating our initial findings that group allocation did not affect the course of precursors. Following up hypothesis 2, we examined if each individual precursor (instead of the composite score) preceded subsequent momentary psychotic symptoms differently when compared between groups (immediate vs. delayed access). None of the group x precursor interactions reached significance (all p's $\geq .084$), replicating our initial findings that the effect of precursors on subsequent psychotic symptoms did not differ between groups.

Discussion

We conducted registered longitudinal mixed model analyses on data obtained from a randomized controlled trial (Rüegg, Moritz, Berger, Lüdtke, & Westermann, 2018) and a secondary track of the trial to identify mechanisms of psychotic symptom fluctuations during a psychological online intervention for people with psychosis. By analysing brief intermediate assessments, we were able to compare the course of presumed symptom precursors (worry, negative affect, self-esteem, self-reported cognitive biases, and quality of sleep) between groups, and to examine each precursor's association with subsequent psychotic symptoms. There were no group differences, neither regarding the course of precursors, nor regarding their effect on subsequent psychotic symptoms. However, during the EviBaS intervention we found that momentary worry and quality of sleep predicted subsequent psychotic symptoms (auditory verbal hallucinations and paranoia) across the entire sample. When participants experienced more worry or worse sleep than usual while using the EviBaS intervention, they reported more severe psychotic symptoms upon the next assessment. Exploratory analyses with separate outcomes (due to the poor internal consistency of psychotic symptoms) replicated these findings, showing that fluctuations of quality of sleep preceded both auditory hallucinations and paranoia whereas fluctuations of worry preceded paranoia. Within-participant effects during the intervention in the absence of group effects indicate that the intervention did not improve worry or quality of sleep consistently and persistently across participants, but when fluctuations of worry or quality of sleep occurred, these fluctuations preceded subsequent symptoms. We cannot make the causal inference that worry or sleep led to momentary psychotic symptoms during the intervention. Further, we cannot conclude that the effectiveness of the EviBaS intervention relied on its capacity to reduce worry or sleep problems. We can gain confidence, though, that worry and quality of sleep represent important mechanisms of symptom fluctuations and hence treatment targets in interventions for people with psychosis. It seems worthwhile to monitor worrying and quality of sleep during treatment as these variables could indicate upcoming change of psychotic symptoms. Interestingly, the modules addressing worrying and sleep problems

had lower completion rates compared to other modules of the intervention. It is possible that this finding hints at a discrepancy between the importance of these variables as symptom precursors and their perceived importance by patients (and or perceived changeability).

The effects of worry and quality of sleep on psychotic symptoms occurred although assessments were several days apart over a period of 8 weeks. Hence, one can speculate that worry and quality of sleep, established precursors in previous ESM trials (Hartley et al., 2014; Kasanova et al., 2019), generalize to longer assessment periods. This finding can help to expand our knowledge about the temporal reach of ESM effects. Whereas effects of momentary negative affect or momentary self-esteem could be limited to few hours, worrying and sleep problems could be candidate processes in the prediction of events lying further away, such as relapse or treatment response.

The absence of group differences regarding the course of composite precursors over time was unexpected given the intervention's focus on improving these precursors. This null result was particularly surprising in the light of the intervention's overall effectiveness in the reduction of positive symptoms of psychosis (Westermann et al., 2020). One might argue that the intervention's effect on psychotic symptoms was hence independent of within-participant improvements of precursor symptoms, which would partly contradict the rationale of the intervention. Possibly, the intervention's efficacy mainly relied on directly targeting psychotic symptoms.

Another unexpected finding was that neither negative affect, nor self-esteem, nor self-reported cognitive biases served as precursors of subsequent psychotic symptoms during the intervention despite being well-established precursors of psychotic symptoms in ESM studies (Lüdtke et al., 2017; So et al., 2018; Udachina et al., 2014). The null effect of self-reported cognitive biases on subsequent psychotic symptoms should be interpreted with great caution as our two-item self-report scale was not internally consistent. However, even if it had been, the scale would nonetheless differ from experimental paradigms such as the beads task (Ross, McKay, Coltheart, & Langdon, 2015). Even established self-report scales show no correlation (CBQp; Peters et al., 2014) or only moderate correlation with the beads task (DACOBS; van der Gaag et al., 2013). This inconsistency of self-report and objective measures could be due to the lack of metacognitive awareness of cognitive deficits and biases in psychosis (Peters et al., 2014). An alternative explanation would be that certain experimental tasks measure something other than self-report scales as indicated by research on objective versus subjective effort in schizophrenia (Kreis, Moritz, & Pfuhl, 2020).

The non-significant association of negative affect with subsequent psychotic symptoms was surprising as well, considering the body of research consistently showing lagged effects of negative affect on psychotic symptoms within the same day (Ben-Zeev et al., 2011; Lüdtke et al., 2017; So et al., 2018). This finding is again subject to caution due to the insufficient internal consistency of the outcome variable 'psychotic symptoms'. Exploratory analyses indicated that negative affect might predict paranoia but not auditory verbal hallucinations, which coincides with findings that negative affect relates to paranoid thinking specifically (Freeman, Dunn, et al., 2013). Despite this methodological concern, it is possible that current negative affect influences psychotic symptoms only within the same day – not across several days. This interpretation fits the empirical finding that negative emotions fluctuate intensely throughout the day in people with psychosis (Myin-Germeys, Delespaul, & deVries, 2000). Consequently, effects on subsequent psychotic symptoms are likely to be short-term and transient due to the temporal variability of negative affect. In contrast, worry could be more stable, meaning

that it fluctuates at a slower rate thus making it a better precursor of treatment progress during interventions such as EviBaS. Conceptually, worrying represents both a momentary action as well as a more trait-like thinking style (i.e., a 'worry thinking style'; Freeman & Garety, 2014). This could explain why worrying functions as a precursor both of psychotic symptoms within the same day (Hartley et al., 2014) and of symptom fluctuations during treatment assessed several days later.

Finally, momentary self-esteem did not precede psychotic symptoms, contradicting findings by Udachina et al. (2014). Comparable to negative affect, momentary self-esteem could be highly unstable in people with psychosis as suggested by the revised Attribution–Self-Representation Cycle model of paranoia (as reviewed by Murphy, Bentall, Freeman, O'Rourke, & Hutton, 2018), which would predict only short-term associations with subsequent symptoms. The model proposes that instead of restoring stable self-esteem, externalizing attributions lead to highly unstable self-esteem. Consistent with these predictions the moment-to-moment variability of self-esteem predicts trait paranoia more than the overall level of self-esteem (Thewissen, Bentall, Lecomte, van Os, & Myin-Germeys, 2008). Preliminarily, our findings suggest that self-esteem is not suited as a precursor of infrequently monitored treatment progress, possibly due to its instability impeding far-reaching predictions.

Worry and quality of sleep as potential mechanisms of symptom fluctuations

Worry is associated with paranoia in experimental (Martinelli, Cavanagh, & Dudley, 2013) and ESM trials (Hartley et al., 2014). Further, treating worry leads to improved persecutory delusions in people with psychosis mediated by change in worrying (Freeman, Dunn, et al., 2015). Freeman, Dunn, et al. (2015) discuss that their mediator analysis cannot determine the direction of associations beyond doubt. Our longitudinal design supports the hypothesis that alterations of worry precede paranoia during psychological interventions. Freeman, Dunn, et al. (2015) assume a causal relationship of worry with paranoia in particular. Albeit exploratory, our results support this notion inasmuch as we found associations of worry with subsequent paranoia only but not auditory verbal hallucinations. From a theoretical point of view, worrying is conceptually very similar to paranoia. As Freeman and Garety phrased it 'worry brings implausible ideas to mind, keeps them there, and increases the distress that they cause' (Freeman & Garety, 2014, p. 1180).

Quality of sleep was another significant predictor of subsequent momentary psychotic symptoms in our study preceding both paranoia and auditory verbal hallucinations in exploratory analyses. As for worry, we cannot conclude that quality of sleep causally led to subsequent symptoms but, again, we gain confidence that quality of sleep represents a worthwhile treatment target as it indicates upcoming symptom change. This conclusion coincides with cross-sectional (Koyanagi & Stickley, 2015), experimental (Petrovsky et al., 2014; Reeve et al., 2018), ESM- (Kasanova et al., 2019; Mulligan et al., 2016), and interventional trials in healthy participants (Freeman et al., 2017). So far, preliminary clinical trials in patients have not yielded significant effects of sleep interventions on psychotic symptoms as secondary outcomes (Freeman, Waite, et al., 2015; Hwang et al., 2019) so that effects of sleep interventions on clinical psychotic symptoms await to be established. How sleep contributes to psychotic symptoms is not entirely clear. Negative affect could mediate the effect of quality of sleep (Kasanova et al., 2019; Rehman, Gumley, & Biello, 2018) or induced sleep loss (Reeve et al., 2018) on paranoia. Further, sleep influences several neural processes (Krause et al., 2017) but also psychological outcomes,

such as quality of life, emotion regulation, or cognitive functioning (Faiola et al., 2018; Grezellschak, Jansen, & Westermann, 2017; Harvey, 2009). In sum, sleep is consistently associated with psychotic symptoms but potential pathways are manifold and await further elaboration.

The effects of worry and sleep on psychotic symptoms are not exclusive to people with psychosis. Harvey (2008) describes insomnia as a transdiagnostic process, and both worry (Bell & O'Driscoll, 2018) and sleep (Hennig & Lincoln, 2018) are associated with paranoia in general population samples, indicating that associations between worry/sleep and subclinical psychotic symptoms could be universal. Furthermore, 30% of our sample fulfilled the criteria of a current depressive disorder, corroborating findings that comorbid depression is highly prevalent in people with schizophrenia (Buckley, Miller, Lehrer, & Castle, 2009). Future studies should examine whether comorbid depression moderates the association between psychotic symptoms and worrying or quality of sleep.

Limitations

First, the regression-based design does not permit causal interpretations. Second, the validity of the self-reported cognitive biases assessment was insufficient. Third, analyses in this study were nomothetic despite appearing idiographic at first sight (Piccirillo & Rodebaugh, 2019). Although our focus lied on within-participant effects, we examined 'fixed effects' across participants instead of individual symptom trajectories. Fourth, the proportion of female participants in our sample (60%) was higher than in comparable face-to-face psychotherapy trials for people with psychosis (e.g., 44%; Lincoln et al., 2012). However, the unequal gender distribution is not surprising when considering that online interventions for other disorders, such as depression, seem to attract female users particularly (e.g., 67% female participants in Karyotaki et al., 2018). Nonetheless, the gender distribution limits the generalizability of our findings beyond online interventions.

Conclusions

Worry and quality of sleep are potential mechanisms of symptom variability and hence treatment targets in the context of online interventions for psychosis. While effects of worry might be limited to paranoia, quality of sleep appears to affect auditory verbal hallucinations as well. From a methodological point of view, our results show how participant-mean-centred longitudinal analyses represent an informative addition to group comparisons in randomized controlled trials. For clinicians, it seems promising to monitor worrying and sleep problems during treatment as indicators of both positive and negative treatment progression. Future studies should examine the effects of worrying and quality of sleep on symptoms other than auditory hallucinations and paranoia, such as negative symptoms.

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Conflict of interest

All authors declare no conflict of interest.

Author contributions

Thies Lüdtke (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft); Gerit Pfuhl (Conceptualization; Investigation; Methodology; Project administration; Supervision; Writing – review & editing); Steffen Moritz (Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing); Nina Lee Rüegg (Conceptualization; Data curation; Investigation; Project administration; Writing – review & editing); Thomas Berger (Conceptualization; Funding acquisition; Investigation; Project administration; Resources; Supervision; Writing – review & editing); Stefan Westermann (Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing – review & editing).

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Paper 3

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ORIGINAL RESEARCH
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Mindfulness Mediates the Effect of a Psychological Online Intervention for Psychosis on Self-Reported Hallucinations: A Secondary Analysis of Voice Hearers From the EviBaS Trial

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Background: Psychological online interventions (POIs) could represent a promising approach to narrow the treatment gap in psychosis but it remains unclear whether improving mindfulness functions as a mechanism of change in POIs. For the present study, we examined if mindfulness mediates the effect of a comprehensive POI on distressing (auditory) hallucinations.

Methods: We conducted a secondary analysis on voice hearers (n = 55) from a randomized controlled trial evaluating a POI for psychosis (EviBaS; trial registration NCT02974400, clinicaltrials.gov). The POI includes a module on mindfulness and we only considered POI participants in our analyses who completed the mindfulness module (n = 16).

Results: Participants who completed the mindfulness module reported higher mindfulness (p = 0.015) and lower hallucinations (p = 0.001) at post assessment, compared to controls, but there was no effect on distress by voices (p = 0.598). Mindfulness mediated the POI's effect on hallucinations (b = −1.618, LLCI = −3.747, ULCI = −0.054) but not on distress by voices (b = −0.057, LLCI = −0.640, ULCI = 0.915).

Limitations and Discussion: Completion of the mindfulness module was not randomized. Hence, we cannot draw causal inferences. Even if we assumed causality, it remains unclear which contents of the POI could have resulted in increased mindfulness and reduced hallucinations, as participants completed other modules as well. In addition,

confounding variables could explain the mediation and the sample size was small. Nonetheless, the overall pattern of results indicates that the POI is likely to improve mindfulness, and that increased mindfulness could partially explain the POI's efficacy.

Keywords: mindfulness-based intervention, auditory verbal hallucinations, mediation analysis, schizophrenia, internet intervention

INTRODUCTION

Approximately 40% of patients with psychosis do not receive treatment consistently (1). Psychological online interventions (POIs) could help to narrow this treatment gap. Barak et al. (2) describe such interventions as a "primarily self-guided intervention program that is executed by means of a prescriptive online program operated through a website and used by consumers seeking health- and mental-health related assistance" (p. 5). For depression and anxiety, meta-analyses indicate that POIs are effective (3, 4), so it seems promising to develop POIs for psychosis as well. So far, POIs for people with psychosis are scarce [e.g., (5)], but pilot studies and study protocols indicate that they are receiving increasing attention [e.g, HORYZON; (6, 7)].

POI approaches for psychosis differ in their scope to ameliorate psychotic symptoms and associated burden. While some interventions provide peer-to-peer networks or offer online platforms to share experiences (7, 8), another promising approach is to address potential psychological precursors of psychosis to alter psychotic symptoms indirectly. Studies have identified a variety of such precursors, mostly negative behavioral, cognitive, or affective states, such as sleep disturbances (9), worry (10), and depression (11). Theoretical models suggest that these variables are causal factors contributing to psychosis (12). There have been first attempts to address some precursors online [e.g., depression; (13)] but many other potential precursors have not yet received attention. One of them is mindfulness. Mindfulness could represent a functional coping strategy in psychosis that might be particularly effective in reducing the distress caused by auditory verbal hallucinations (AVHs) by promoting a nonjudgmental observation of sensory experiences.

Approximately three in four people with schizophrenia or schizoaffective disorder experience AVHs once in their life (14). Not only are AVHs common, they also cause considerable distress (15). From a cognitive behavioral perspective, AVHs reflect false external attributions of internal processes rather than purely perceptual phenomena (16), and beliefs about the voices cause negative affective consequences rather than their frequency. A person who hears voices twice as often does not necessarily suffer twice as much (17). Hence, cognitive behavioral therapy for psychosis (CBTp) aims at reducing distress and disturbance caused by voices rather than their frequency. Face-to-face CBTp has proven successful for the treatment of psychotic symptoms in general (18) and for voices specifically (19). Despite CBTp's success, there is room for improvement in the psychological treatment of psychosis and AVHs in view of small effect sizes on overall positive symptoms (g = 0.16) in comparative trials (18). Mindfulness-based exercises could effectively add to the effects of CBTp as they provide patients with tools that go beyond the ones of CBTp and that could be particularly useful to reduce distress and disturbance caused by voices. Traditionally, CBTp aimed at identifying automatic thoughts and reevaluating them (20). This approach emphasized the importance of thoughts and their impact on feelings and actions. Mindfulness-based interventions, on the other hand, try to reduce a thought's impact by not engaging with it at all. Instead of challenging a thought or a sensation, detached mindfulness helps to let such thoughts or experiences pass. So-called third-wave CBTp interventions illustrate how mindfulness-based exercises can complement CBTp (20).

Mindfulness is a diverse concept, which encompasses components such as decentering, awareness, and acceptance. As reviewed by Kabat-Zinn (21), mindfulness, which has its origins in Buddhist meditation techniques, can be subsumed as "moment-to-moment, nonjudgmental awareness". Kabat-Zinn (22) shaped the definition of mindfulness as "paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally" (p. 4). In the following, we refer to this definition of mindfulness. A common denominator of all mindfulness interventions is their goal to embrace present experiences in a nonjudgmental way without avoiding or suppressing them (23) thereby reducing distress, for example, elicited by AVHs (24). From a theoretical point of view, mindfulness helps people who experience AVHs to be aware of the sensation without letting the sensation define oneself. Basic research supports this notion: Mindfulness is negatively correlated with hallucinations and associated distress (25). Experiential avoidance (i.e., the attempt to avoid thoughts, feelings, memories or sensations) precedes psychotic symptoms in studies with longitudinal designs (26). Its counterpart, the mindfulness-based emotion regulation strategy "experiential acceptance," appears to be superior to other emotion regulation strategies, such as reappraisal (24). In people with depression, mindfulness seems to be particularly effective at reducing worry and rumination (27), processes that are common precursors of psychosis (28).

Findings from "offline" treatment studies emphasize the potential of mindfulness-based interventions. A meta-analysis found that mindfulness-based interventions are effective at reducing hospitalization rates but also negative and affective symptoms, at a small to moderate effect size (23). A second meta-analysis encompassing both mindfulness and acceptance-based interventions found small to moderate short-term effects on total psychotic symptoms and positive symptoms, but not on negative

symptoms of schizophrenia (29). The authors also report moderate evidence for lower hospitalization rates and shorter duration of hospitalization (29). Louise et al. (30) found no effect of mindfulness-based interventions on distress, positive, or negative symptoms of schizophrenia but only on depressive symptoms. Finally, participants perceive mindfulness-based interventions as safe and meaningful, leading to low dropout rates and high satisfaction (23, 25).

To date, it remains unclear whether the findings from mindfulness-based face-to-face interventions are transferable to internet-based interventions for psychosis. Furthermore, we do not know which role mindfulness plays in the effectiveness of CBT-based POIs in general, especially regarding AVHs. Possibly, improving mindfulness is an important mechanism of action in treating psychotic symptoms, such as AVHs. Considering the accumulating evidence for the effectiveness of mindfulness-based interventions and the possible benefits of online interventions for psychosis, we expect that POIs for psychosis with mindfulness components represent a promising approach. Hence, our group has developed a comprehensive CBT-based POI for psychosis, which encompasses a module on mindfulness [(31); Westermann et al.[1]]. While the POI covers the treatment of several putative precursors of psychotic symptoms, in this secondary paper, we focus on its effects on mindfulness, distressing AVHs, and general hallucinatory experiences. From a theoretical point of view, we expected that mindfulness is particularly effective at reducing distress associated with AVHs, so we included people reporting lifetime AVHs in our analyses. In addition, we only considered participants from the treatment group who used the mindfulness module of our POI. As our POI is not a purely mindfulness-based intervention, we cannot evaluate its mindfulness components directly, but we evaluate whether mindfulness acts as a mechanism of change. We hypothesized that (a) the overall POI reduces distress elicited by voices and (b) that changes of mindfulness mediate this effect.

METHODS

We conducted a secondary analysis on a subgroup of lifetime voice hearers obtained from the EviBaS trial [(31); Westermann et al.[1]]. The EviBaS trial is a preregistered (NCT02974400, clinicaltrials.gov) multicenter parallel group single-blind randomized controlled superiority trial with an allocation ratio of 1:1 comparing a waitlist control group to a POI for people with psychosis. The POI addresses persecutory delusions and AVHs, as well as presumed precursors of psychotic symptoms in web-based modules that participants can access via an internet browser. The POI includes modules on mindfulness (which we focus on in this paper), worry and rumination, social competence, self-worth, depression, sleep, and metacognitive biases, such as "jumping to conclusions" (32). An introductory module explains the rationale of the POI while a closing module provides information and worksheets on relapse. Each module contains both educational components as well as exercises, in which participants apply what they have learned to their own experiences. A smartphone application accompanies the POI and provides exercises for everyday life. Participants used their private computers and smartphones to access the POI and the application.

At baseline, participants completed an online assessment consisting of self-report questionnaires as well as a diagnostic interview via telephone conducted by trained personnel. When participants fulfilled eligibility criteria, we randomly allocated them to the waitlist control group or the intervention group using a web-based randomization tool (Random.org, RRID: SCR_008544). Participants from the intervention group received access to the POI for 8 weeks. After this period, all participants completed a post assessment, again consisting of a telephone interview and online self-report questionnaires. We did not provide any active treatment for the control group during the waiting period but one of the inclusion criteria was that all participants received either antipsychotics, psychotherapeutic treatment or (at least monthly) psychiatric consultations, or a combination of both. After the waiting period, participants from the waitlist group had access to the intervention, but this does not affect the data of this study.

Here, we report results from a subsample of the EviBaS trial consisting of participants who reported lifetime AVHs. In addition, we drew a subset from the participants allocated to the POI, namely those who, inter alia, used the mindfulness module (see **Figure 1** for a flow chart).

Recruitment

The EviBaS trial took place in Germany and Switzerland. Local ethics committees have approved of the study (Cantonal Ethics Committee Bern, ID 03/14; German Society for Psychology, ID SM052015_CH). We recruited through a database of former participants with schizophrenia spectrum diagnoses. In addition, we advertised the study online and by contacting psychiatric institutions in Switzerland and Germany.

In accordance with the Declaration of Helsinki, participants gave informed consent prior to participation online. Eligibility criteria were an age of 18 years or older, access to the internet, sufficient command of the German language, a lifetime diagnosis of a nonaffective psychotic disorder (confirmed by trained study personnel in a diagnostic telephone interview), current positive symptoms of psychosis (delusions, suspiciousness, or hallucinations), and antipsychotic or psychotherapeutic treatment/psychiatric consultations (at least monthly), or both. We verified the diagnosis of a psychotic disorder as well as current positive symptoms in a diagnostic interview. We requested participants to fill in an emergency plan, a document listing contact persons that participants could reach out to in case of an emergency during their participation in the study. Exclusion criteria were acute suicidality, an acute danger towards others, or a diagnosis of a neurological disease of the central nervous system.

[1] Westermann, S., Rüegg, N., Lüdtke, T., Moritz, S., & Berger, T. (under review). Internet-Based Self-Help for Psychosis: Findings from a Randomized Controlled Trial.

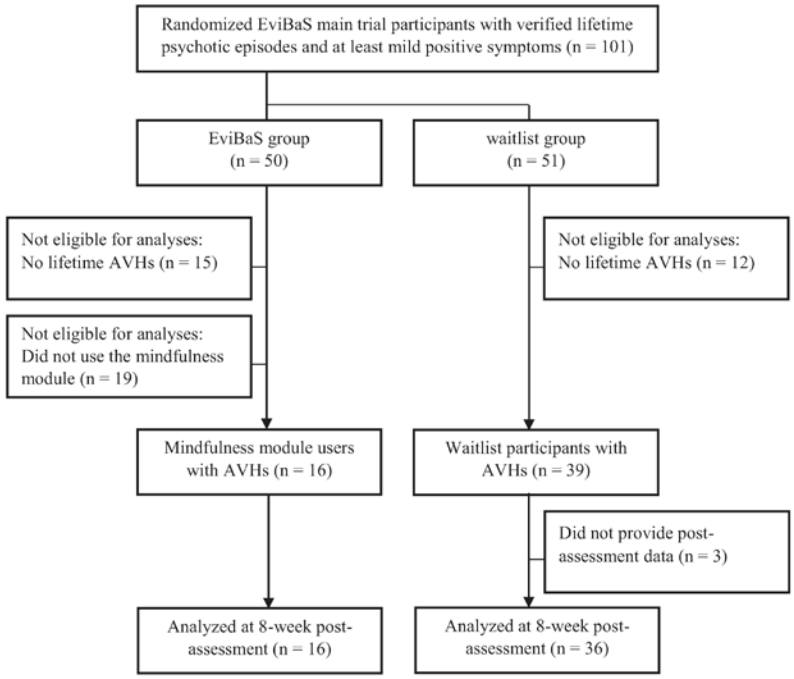

FIGURE 1 | Flow chart depicting the selection of participants for the secondary analyses presented here.

The Mindfulness Intervention

Apart from an introductory module, which was mandatory, participants could decide whether they would like to work through a certain module of the POI or not. For this paper, we only analyzed participants who worked on the mindfulness module. **Figure 2** shows a screenshot from the mindfulness module. The mindfulness module consisted of 24 web pages, which contained text, pictures, and audio files. We made clear that the aim of the mindfulness module was to improve mindfulness and there was no cover story. The first 13 pages of the module provided psychoeducation on mindfulness, such as historical origins, effects of mindfulness on psychological health, as well as presumed associations with psychosis. The remaining 11 pages included mindfulness exercises, such as breathing exercises, the "S.T.O.P." exercise (stop, take a mindful breath, observe what your feelings, thoughts etc., proceed your activity), and the "body scan" exercise. Participants received instructions via text, or via audio files, recorded by a psychotherapist. The whole mindfulness module took approximately 1 hour to complete. Participants could, however, repeat exercises if they wished to do so. Trained and supervised psychology students ("moderators") guided participants throughout the POI. Moderators provided feedback once or twice per week via private messages and offered assistance.

Measures

Rüegg et al. (31) provide a detailed description of all outcome measures included in the EviBaS trial. In the following, for the sake of brevity, we focus on outcomes relevant for the secondary analyses presented here. As in previous studies of our group [e.g., (33)], we report participants' cumulated antipsychotic dosages instead of chlorpromazine equivalent values at baseline. The cumulated antipsychotic dosage indicates the percentage of the maximum dosage of a certain antipsychotic drug. We chose this metric because chlorpromazine equivalents have faced criticism regarding their validity for second generation antipsychotics (34) as their effectiveness appears to be related to different types of receptors instead of just dopamine (35). In addition, we hoped that the percentage of the maximum dosage would be easily accessible to the reader.

Psychopathology

We used the German version (36) of the Mini International Neuropsychiatric Interview [MINI; (37)] to verify the diagnosis of a nonaffective psychotic episode, as well as comorbid diagnoses, via telephone. The MINI is a structured interview with good specificity (37). To assess psychotic symptom severity, we used the Positive and Negative Syndrome Scale [PANSS; (38)]. The PANSS measures positive, negative, and global symptoms of schizophrenia on 30 items rated on 7-point

scales. Higher scores reflect more severe symptoms. The PANSS shows good psychometric properties (39). Participants were only eligible to participate if they received a score of three or higher on at least one of the items P1 (delusions), P3 (hallucinations), or P6 (suspiciousness/persecutory delusions).

Mindfulness

We measured mindfulness using the Mindful Attention and Awareness Scale [MAAS; (40)]. On 6-point Likert scales, the MAAS measures participants' ability to mindfully experience the current moment. The German version of the MAAS shows a good internal consistency of $\alpha = 0.83$, good test-retest reliability of $r = 0.82$, and correlations with subjective well-being (41). Higher scores reflect more mindfulness.

AVHs

We used a subset of items from the Delusion and Voices Self-Assessment (DV-SA; 42) to measure self-reported distress caused by AVHs. We calculated the self-generated subscale "distress by voices" consisting of the items "distress", "obedience", "control", "interference with relationships", and "interference with activities". Higher scores reflect more severe symptoms. The original voices scale shows good internal consistency of $\alpha = 0.83$. Test-retest reliability ranged from 0.86 to 0.96 (42). To our knowledge, there is no German version of the DV-SA. Our group translated the scale for the EviBaS trial. We chose the respective items of the distress by voices subscale based on theoretical considerations. With $\alpha = 0.83$, the internal consistency of the newly created "distress by voices" subscale was good in our sample ($n = 55$). Because conclusions based on a nonvalidated subscale of the DV-SA are limited, we included another measure of hallucinations as well, which is well established and validated. The German adaption (43) of the Launay Slade Hallucination Scale Revised [LSHS-R; (44)] shows good internal consistency in the general population ($\alpha = 0.83$) and in patients with psychosis ($\alpha = 0.87$). On 12 items, the LSHS-R measures both subclinical as well as pathological hallucinatory experiences on 5-point Likert scales. Higher scores reflect more severe symptoms.

FIGURE 2 | Translated web browser screenshot of the mindfulness intervention depicting the "inner smile" exercise.

Statistical Analyses

We used SPSS 25® (SPSS, RRID: SCR_002865) for all analyses. For the mediation analysis, we used the PROCESS® macro provided by Andrew Hayes (45). All significance tests were two-sided with a significance level of $p = 0.05$. We report effect sizes as η^2_p with $\eta^2_p = 0.01$ as small, $\eta^2_p = 0.06$ as medium, and $\eta^2_p = 0.14$ as large effects. We compared groups at baseline using *t*-tests and χ^2-tests. We conducted ANCOVAs to examine baseline-corrected posttreatment group effects of mindfulness, distress by voices, and hallucinations. Apart from baseline scores, ANCOVAs did not include additional covariates. Post hoc, however, we repeated analyses with gender as an additional covariate to account for unequal gender distributions. To answer the question whether mindfulness functions as a mechanism of change, we conducted a mediation analysis with group allocation as the independent variable, posttreatment distress by voices as the outcome, pre-post change scores of mindfulness as the mediator, and baseline distress by voices as a covariate. We repeated the analysis with LSHS-R hallucination scores instead of distress by voices. For PROCESS® analyses, we report robust bootstrap confidence intervals based on a resampling procedure with 5,000 samples (LLCI = lower level confidence interval, ULCI = upper level confidence interval). We report complete cases analyses, which include participants who completed the post assessment of respective outcomes (n = 52; 95%).

RESULTS

Retention, Adherence, and Baseline Characteristics

Between December 2016 and May 2018, we recruited a sample of n = 101 participants in the EviBaS trial, which was below the targeted sample size of 140 (based on a power calculation assuming an at least medium-sized effect in the main trial; see Westermann et al.[1]). Possibly, the extensive and hence demanding baseline assessment impeded the recruitment process. Out of n = 7,237 persons who visited a study website to obtain information about the trial, n = 746 gave informed consent to participate and began to complete the online assessment. In total, n = 140 potential participants finished the baseline questionnaires as well as the telephone interview and were diagnosed with a schizophrenia-spectrum disorder, of which n = 101 participants fulfilled the inclusion criterion of at least mild symptoms on the PANSS items P1, P3, or P6 (see Westermann et al.[1]). Missing the target sample size led to reduced power. This applies particularly to the secondary analyses presented here, given that we only analyzed a subgroup of participants. For the analyses presented here, we drew a subset of participants who reported lifetime AVHs and who used the mindfulness module, if allocated to the POI (54%). That is, we excluded POI participants from analyses, if they did not use the mindfulness module. Consequently, the group sizes of the POI group (n = 16) and the waitlist group (n = 39) are unequal. **Table 1** displays sample characteristics. The distribution of women and men differed significantly between groups, with a higher proportion of women in the POI group compared to the waitlist group. With PANSS total scores of roughly 65, our sample could be described as mildly to moderately ill (46). We present adherence for the mindfulness module only (for information on overall adherence to the POI, see Westermann et al.[1]). The mean time spent in the module was 74 min (SD = 53 min). The distribution was skewed with one person spending much time in the mindfulness module (256 min), as indicated by a lower median of 61 min.

Effects of Group Allocation on Mindfulness, Distress by Voices, and Hallucinations

We examined assumptions before all analyses. According to visual inspection, the assumption of normality within groups was violated for distress by voices due to several low scores and hence a skewed distribution. All other assumptions were met. We conducted three separate ANCOVAs examining the group effect on distress by voices (DV-SA-subscale), mindfulness (MAAS), and hallucinations (LSHS-R) at postassessment (see **Table 2**). Group allocation did not influence distress by voices. Relative to controls, posttreatment mindfulness was significantly higher in the POI group, while LSHS-R hallucinations were significantly lower. In exploratory complete cases analyses, we compared waitlist participants to intervention group participants who did not use the mindfulness module (n = 19), and found no effects (all p's > 0.478).

Mindfulness as a Mediator of Group Differences

Group allocation did not influence distress by voices at postassessment. Nonetheless, we conducted the mediation analysis to identify a possible suppression effect (47). However, there was no mediation. The group effect on distress by voices remained nonsignificant (direct effect: $b = -0.309$, SE = 0.756, t = 0.409, p = 0.685). The nonexistent mediation was confirmed by the bootstrap confidence interval of the indirect effect (indirect effect: $b = -0.057$, LLCI = −0.640, ULCI = 0.915).

As there was a significant positive effect of the intervention on LSHS-R hallucinations, we examined whether increased mindfulness would mediate this effect, which was the case. Adding mindfulness change scores as a mediator reduced the group difference of posttreatment hallucinations but it remained significant (direct effect: $b = -5.600$, SE = 2.052, t = 2.729, p = 0.009). The bootstrap confidence interval of the indirect effect confirmed a significant mediation (indirect effect: $b = -1.618$, LLCI = −3.747, ULCI = −0.054). The unstandardized coefficient of the indirect effect indicates that mindfulness accounted for 1.618 points of the group difference in LSHS-R score at posttreatment. Because of the unexpected baseline group differences regarding gender (i.e., the proportion of women was higher in the POI group compared to the waitlist group), we decided to repeat the analyses with gender as a covariate. We found that the direction and significance of effects remained unchanged.

TABLE 1 | Baseline characteristics.

Characteristics	waitlist (n = 39)	POI (n = 16)	Statistics
Demographics			
Age in years, mean (SD)	41.36 (9.25)	41.69 (9.88)	t (53) = 0.12, p = 0.907
Education in years, mean (SD)	11.59 (1.77)	11.69 (1.30)	t (53) = 0.20, p = 0.843
Gender, proportion female (%)	18/39 (46%)	13/16 (81%)	χ^2 (1) = 5.68, p = 0.017*
Clinical variables			
PANSS total, mean (SD)	67.10 (15.45)	61.63 (19.16)	t (53) = 1.11, p = 0.271
PANSS positive, mean (SD)	15.36 (4.93)	14.88 (4.81)	t (53) = 0.33, p = 0.741
PANSS negative, mean (SD)	12.62 (4.35)	11.00 (4.62)	t (53) = 1.23, p = 0.225
PANSS global, mean (SD)	29.08 (7.16)	26.69 (8.87)	t (53) = 1.05, p = 0.300
MINI: current major depressive episode (%)	12/39 (31%)	6/16 (38%)	χ^2 (1) = 0.23, p = 0.629
MINI: current psychotic disorder (%)	24/39 (62%)	11/16 (69%)	χ^2 (1) = 0.26, p = 0.614
Taking antipsychotics (%)	34/39 (87%)	11/16 (69%)	χ^2 (1) = 2.59, p = 0.108
Cumulated antipsychotic dosage, mean (SD)	46.50 (38.41)	36.13 (44.58)	t (50) = 0.86, p = 0.396
Completing post assessment online (%)	35/39 (90%)	16/16 (100%)	χ^2 (1) = 1.77, p = 0.183
Outcome variables at baseline			
DV-SA distress by voices, mean (SD)	3.92 (3.94)	3.31 (4.13)	t (53) = 0.52, p = 0.609
MAAS mindfulness, mean (SD)	3.84 (0.91)	3.50 (1.12)	t (53) = 1.18, p = 0.244
LSHS-R hallucinations	17.97 (11.35)	20.69 (12.35)	t (53) = 0.79, p = 0.436

*Cumulated antipsychotic dosage = The sum of the dosages of a participant's antipsychotic drugs divided by the maximum dosage of each drug; e.g., if the maximum dosage of a drug is 20 mg per day and a participant takes 10 mg of that drug, this equals a score of 50%. MINI, Mini International Neuropsychiatric Interview. Distress by voices = sum score of items 4, 7, 8, 9, and 10 from the Delusion and Voices Self-Assessment (DV-SA) questionnaire. The cumulated antipsychotic dosage was not available for all participants, hence the lower df. *p < 0.05.*

DISCUSSION

We conducted a secondary analysis with a subsample from the EviBaS trial [(31); Westermann et al.[1]], consisting of people with psychosis who reported lifetime AVHs. As our focus was on mindfulness, we only analyzed POI participants who used the mindfulness module. We hypothesized that the POI and its mindfulness components would lead to reduced distress by voices and increased mindfulness at postassessment when compared to a waitlist control condition. In addition, we hypothesized that an increase of mindfulness would mediate the effect on distress by voices. To account for methodological concerns regarding the self-generated and nonvalidated distress by voices scale, we also examined the group effect on hallucinations measured with the LSHS-R and conducted the mediation analysis accordingly.

Contrary to our expectations, distress by voices at postassessment did not differ between groups. However, LSHS-R hallucinations and self-reported mindfulness differed between groups at postassessment, both in favor of the POI group. There was a significant mediation of the group effect on posttreatment hallucinations. Increased mindfulness explained a significant proportion of the group difference in posttreatment hallucination scores. After adjusting for the mediator, the direct effect remained significant. Therefore, mindfulness explains the effect only partly.

We did not evaluate a purely mindfulness-based intervention. Although we only analyzed data from participants who used the mindfulness module, those participants also used other modules of the intervention. Hence, we cannot draw causal conclusions regarding the effect of the mindfulness-exercises within our comprehensive POI for psychosis. Nonetheless, the pattern of results indicates that mindfulness functions as a mechanism of change in our POI. Firstly, the mediation analysis showed that an increase of mindfulness accounted for a significant portion of the group effect on hallucinations. This result indicates that the POI partly reduced hallucinations by increasing mindfulness. Secondly, at post assessment, POI participants reported higher self-reported mindfulness compared to a waitlist control condition. Considered separately, each individual result suffers from methodological limitations (see limitations). Taken together, however, the consistent pattern of results indicates that mindfulness played an important role in the effectiveness of the POI, despite the fact that our design does not allow causal conclusions.

We chose the outcome "distress by voices" based on theoretical considerations. Although we examined a sample of people with AVHs, many participants did not experience stress elicited by voices and hence, there was little to no room for improvement for most participants. The broader outcome "hallucinatory experiences" measured with the validated LSHS-R scale, however, captured experiences of a much larger proportion of participants, making it more suitable as an outcome measure. Due to the methodological concerns of the "distress by voices" scale, we argue that our study does not allow

TABLE 2 | Complete cases ANCOVAs showing the baseline corrected effect of group allocation on distress by voices, mindfulness, and Launay Slade Hallucination Scale Revised (LSHS-R) hallucinations (n = 52).

Outcome	Adjusted means waitlist (SE)	Adjusted means POI (SE)	Complete cases ANCOVAs
Distress by voices	3.38 (0.38)	3.02 (0.58)	F (1; 49) = 0.281, p = 0.598, η^2_p = 0.006
Mindfulness	3.83 (0.10)	4.28 (0.15)	F (1; 49) = 6.346, p = 0.015*, η^2_p = 0.115
Hallucinations	16.78 (1.09)	9.56 (1.64)	F (1; 49) = 13.360, p = 0.001*, η^2_p = 0.214

*POI, psychological online intervention; all ANCOVA models include the baseline values of the respective outcome as covariates. *p < 0.05*

drawing definite conclusions regarding the POIs effect on distress by voices. The finding does coincide with a previous study, though. In a randomized controlled trial conducted by Gottlieb et al. (5), the web-based program "coping with voices" resulted in significantly greater increases of social functioning compared to usual care but there was no effect on the severity of auditory hallucinations (5). There are important differences between our study and the one conducted by Gottlieb et al. (5), such as a slightly different outcome (clinician rated auditory hallucinations vs. self-reported hallucination-associated stress) or the strength of the control condition (waitlist vs. usual outpatient care). Nonetheless, the results are comparable and indicate no effect of web-based interventions/POIs on AVHs specifically.

As described above, the main reason to include the LSHS-R scale was to account for methodological shortcomings of our self-generated "distress by voices" scale. From a theoretical point of view, however, we would have expected effects on distress, only. The effect on overall hallucinatory experiences was surprising but could partly be due to properties of the LSHS-R scale. Firstly, the scale measures experiences that are present in the general population (48). Hence, the items were "easier", which resulted in more room for improvement. Secondly, and more importantly, several items from the scale measure experiences, which show large overlap with mindfulness-related processes. For example, the first item of the scale captures difficulties in concentrating, which can be interpreted as a lack of mindfulness: "No matter how hard I try to concentrate, unrelated thoughts always creep into my mind" (48). Our mindfulness module specifically aimed at improving a person's ability to mindfully experience the current moment without distractions.

Limitations and Future Directions

Firstly, we did not evaluate a purely mindfulness-based but a comprehensive POI, which addresses mindfulness among other factors. Hence, we cannot conclude that the specific module was responsible for the positive effects on mindfulness or hallucinations. We excluded participants who did not use the mindfulness module but our participants did not use the mindfulness module exclusively. It is unlikely that administering the mindfulness module as a stand-alone intervention would have yielded similar results. From a therapist's point of view, however, increased mindfulness and reduced hallucination severity are desirable outcomes, irrespective of which exercise of the POI accounted for it. Secondly, usage of the mindfulness module was nonrandomized and adherence low with almost 50% of the intervention group not using the mindfulness module. As completion of the mindfulness module depended on participants' own preference, it is likely that a selection bias resulted in a highly motivated and hence not representative subsample of participants. This also becomes apparent in a significantly higher proportion of female participants in the subgroup completing the mindfulness module. Female gender is associated with higher adherence in online interventions (49). Controlling for gender, however, did not affect results in our analyses. Analyzing only the subgroup of participants who completed the mindfulness module resulted in a selective and a small POI sample ($n = 16$). Statistical analyses with small sample sizes are accompanied by low power, which might partly explain why we did not find effects on distress by voices. At the same time, small sample sizes increase the risk of overestimating effect sizes, which might have affected the significant group differences. Thirdly, we relied on self-report measures instead of clinician-rated scales to measure mindfulness. Self-report measures have faced severe criticism in mindfulness research (50). The same criticism applies to the measurement of voice hearing and associated distress. A clinician-rated instrument, such as the psychotic symptom rating scales [PSYRATS; (51)], would have led to findings that are more durable. Fourthly, the mediation analysis does not allow concluding that increased mindfulness causally led to a reduction of hallucinations. Possibly, a third variable explains the mediation, such as mindfulness-associated affect: Mindfulness predicts positive affect in psychosis (52), while negative affect predicts psychotic symptoms, such as paranoia (53). Therefore, it is possible that not mindfulness but associated affective changes accounted for the effects in our study. Fifthly, participants were aware that the intervention aimed at improving mindfulness. Positive effects on self-reported mindfulness could hence reflect a social desirability bias. Finally, as mentioned before, findings based on the distress by voices scale are questionable. We did not validate the scale *a priori* and the distribution of scores was not normal in groups, limiting the informative value of the ANCOVA.

Despite the methodological concerns of this secondary analysis, our results indicate that mindfulness-based exercises complement CBT-based POIs effectively. Even if we cannot examine the unequivocal contribution of the POI's mindfulness exercises, our mediation analysis indicates that adding mindfulness exercises to CBT-based POI's is a promising approach. In addition, participants with psychosis wish for the treatment of a broad range of treatment targets other than positive symptoms of psychosis (54) and mindfulness-based interventions are well accepted (23). Consequently, we argue that POIs for psychosis could benefit from adding mindfulness exercises in the treatment of hallucinations and that mindfulness represents a worthwhile outcome in POI studies. However, our secondary analysis does not allow causal conclusions, as usage of the mindfulness module was voluntary and not randomized. In order to draw causal inferences about mindfulness-based POIs on voice related stress, we need further randomized controlled trials evaluating purely mindfulness-based POIs with appropriate clinician-rated outcome measures. In addition, the small sample size limits the reliability of the estimated effects. Hence, there is a need for sufficiently powered future studies to replicate our preliminary findings.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Kantonale Ethikkommission für die Forschung, Murtenstrasse 31, 3010 Bern, Switzerland and Ethik-Kommission der DGPs, Universität Trier, Fachbereich I Psychologie, D-54286 Trier, Germany. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

TL and HP-K contributed equally to the development of the design, data acquisition, data analysis, interpretation of the data, and drafting of the manuscript. SW, SM, and NR contributed to the design, data acquisition, data analysis, and data interpretation. They critically revised the manuscript, and provided important intellectual input. TB critically revised the manuscript, provided important, intellectual input, contributed to the development of the design, and data acquisition. All authors approve of the content of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Paper 4 (in preparation)

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Aberrant Salience Predicts Fluctuations of Paranoia but not Relapse During a 1-Year Experience Sampling Study in People With Psychosis

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Abstract

Identifying novel and reliable early warning signs could help to reduce the high risk of relapse in psychosis. Here, we examined whether short-term symptom predictors from Experience Sampling Method (ESM) studies represent worthwhile candidate relapse predictors. We conducted a one-week ESM assessment period (10 assessments per day) followed by a one-year Follow Up period (bi-weekly online assessments) to measure short- and long-term fluctuations of negative affect (i.e., anxiety, sadness, worry, and self-esteem), aberrant salience, paranoia, and auditory verbal hallucinations. In addition, we assessed relapse in bi-monthly online assessments (e.g., hospitalization, symptom deterioration, suicidal tendencies). Using linear and logistic mixed models, we examined predictors of psychotic symptoms and relapse. Thirty participants with verified psychotic disorders provided 1194 ESM- and 416 Follow Up assessments. Negative affect (b = 0.184, $p_{corr.}$ = .003) and aberrant salience (b = 0.187, p_{corr} < .001) predicted subsequent paranoia in ESM assessments, but only aberrant salience remained a significant predictor in bi-weekly Follow Up assessments (b = 0.366, p_{corr} < .001). None of the examined variables predicted relapse, possibly due to the low number of people who relapsed (n = 13, 43%). To our knowledge, this is the first study to compare ESM and Follow Up assessment periods directly in order to identify novel relapse predictors, such as aberrant salience. Our results suggest that patients should monitor changes of aberrant salience as a warning sign of long-term fluctuations of paranoia, presumably reflecting underlying dopaminergic processes.

Keywords: schizophrenia, psychotic symptoms, Ecological Momentary Assessment, auditory verbal hallucinations, negative affect

General Scientific Summary

We examined whether negative emotions (e.g., sadness, anxiety), as well as the unusual feeling that something unimportant suddenly catches one's attention, are warning signs of paranoia, voice hearing, and potentially even psychotic relapses over a one-year study period. Although no variable predicted relapse, the unusual feeling that unimportant things appear significant did predict paranoia two weeks later, indicating that it is promising for people with psychosis to monitor this feeling of *aberrant salience* in order to anticipate and potentially prevent the worsening of symptoms before they occur.

Aberrant Salience Predicts Fluctuations of Paranoia but not Relapse During a One-Year Experience Sampling Study in People With Psychosis

As early as 1919, Kraepelin believed that *dementia praecox*, as he termed schizophrenia, would inevitably deteriorate (for a review on the history of relapse research, see Taylor & Jauhar, 2019). Although Kraepelins view appears exaggerated today, relapse rates are indisputably high. They range from 49% within 3 years (Pelayo-Teran et al., 2017) to 82% within 5 years (Robinson et al., 1999). Consequently, it comes as no surprise that there is an extensive body of research on predictors of psychotic relapse (e.g., Lecomte et al., 2019). Although studies are numerous, only a fraction examined time-variant predictors, such as prodromal symptoms that forecast relapse, in prospective repeated-measures studies. Unlike stable predictors of relapse (e.g., age of psychosis onset; Pelayo-Teran et al., 2017), time-variant predictors help people with psychosis and caregivers to gauge the risk of an upcoming relapse at any given time. Eisner et al. (2013) reviewed the sensitivity and specificity of prodromal symptoms, also referred to as *early signs* of relapse (e.g., anxiety, dysphoria, or insomnia). Sensitivity ranged from 10% to 80% (median = 61%) and specificity ranged from 38% to 100% (median = 81%). The largest reviewed study incorporated 339 outpatients in up to bi-weekly diagnostic meetings over a period of two years (Gaebel & Riesbeck, 2007). Trouble sleeping was the most sensitive prodromal symptom (sensitivity = 39%, specificity = 78%), followed by being tense and nervous (sensitivity = 37%, specificity = 79%), exemplifying that the predictive validity of prodromal symptoms is modest at most (Eisner et al., 2013). Recently, a new approach emerged, which relies on collecting *passive* smartphone data to detect anomalous behavior to predict relapses (Barnett et al., 2018; Buck et al., 2019). For example, the number and duration of outgoing calls and the number of total text messages predicted relapse in one study (Buck et al., 2019). These passive approaches are promising

but preliminary so far (Buck et al., 2019). In sum, there is room for improvement in the prediction of relapse using time-variant predictors.

One way to improve the prediction of relapse is to identify novel and reliable relapse predictors. For the present study, we focused on self-reported predictors rather than passive smartphone data because self-report predictors have the advantage that participants can monitor them on their own, without having to rely on an algorithm or an external person who monitors the data. Hence, self-report predictors promote participants' autonomy, a concept that received increasing attention recently, for example in interventions for psychosis (Westermann et al., 2020). In order to identify candidate predictors, we drew on the so-called Experience Sampling Method (ESM; Myin-Germeys et al., 2018). ESM studies aim at identifying moment-to-moment fluctuations of psychotic symptoms and their predictors while relying on frequent ecologically valid assessments conducted mostly via handheld computers or smartphones. Usually, ESM studies encompass short assessment periods of up to 10 measurements per day for approximately one week, meaning that they examine micro fluctuations of symptoms. If applied to longer assessment periods, however, predictors derived from ESM studies have the potential to add to the prediction of relapse, assuming that ESM effects generalize to longer assessment periods. In fact, there is considerable overlap of short-term ESM predictors and early signs of relapse. In ESM studies, sleep problems (Kasanova et al., 2020), but also negative affective states, such as anxiety or depressed mood (Ben-Zeev et al., 2011; Ludtke et al., 2017) predict upcoming micro-fluctuations of symptoms. All of these variables likewise serve as warning signs of relapse (e.g., Gaebel & Riesbeck, 2007).

The evident overlap of ESM- and relapse predictors suggests that short-term ESM processes represent micro-level equivalents of long-term mechanisms of relapse. Feeling anxious, for example, precedes subsequent paranoia few hours later (Ludtke et al., 2017) but

likewise predicts relapse one week later (Gaebel & Riesbeck, 2007). Although relapse and paranoia are different outcomes, it is possible that the underlying process is the same, in that anxiety predicts subsequent paranoia (which can be part of a psychotic relapse). The isolated effect on specific symptoms, such as paranoia, could be one of the reasons why established early signs of relapse show only moderate predictive validity. It is possible that certain warning signs consistently precede psychotic symptoms but these symptoms do not necessarily lead to relapse (Herz & Lamberti, 1995). Thus, we assume that ESM-based predictor-symptom associations generalize to long-term assessment periods, explaining the overlap of ESM-based predictors and early signs of relapse. In addition, we assume that further ESM studies can inform us about future, so far uninvestigated, warning signs of relapse.

In the present study, we tested the aforementioned assumptions by directly comparing a one-week ESM assessment period to a one-year Follow Up period in the same sample. This procedure enabled us to examine whether short-term ESM effects on paranoia and hallucinations generalize to long-term assessment periods, potentially granting insight into underlying processes of relapse formation. If ESM-based variables can predict a worsening of paranoia two weeks in advance, people with psychosis can target these predictors or seek help in order to avert these symptoms. As our overarching goal was to improve the prediction of relapse, we examined the same ESM-based variables as predictors of full-blown relapse as well.

To identify candidate precursors for the present study, we drew on established symptom predictors from ESM trials. We chose aberrant salience, defined as the attribution of novelty and significance to stimuli that are not inherently significant (Kapur, 2003), as well as negative affect (i.e., sadness, anxiety, low self-esteem, and worrying), the latter overlapping with established warning signs of relapse (e.g., Gaebel & Riesbeck, 2007). Aberrant salience

has great potential to improve the prediction of long-term symptom fluctuations and relapse as it has a strong theoretical foundation (Kapur, 2003), is introspectively accessible (Cicero et al., 2010), and reliably associated with psychotic symptoms in ESM-studies (Reininghaus et al., 2016; So et al., 2018). Due to its theoretical (Kapur, 2003) and empirical (for a review see Miyata, 2019) associations with dopamine functioning, aberrant salience may signal subsequent symptom fluctuations or relapses through underlying changes within the dopamine system. Further, aberrant salience could be a psychosis-specific relapse predictor rather than an unspecific prodromal symptom, such as sleep problems (Gaebel & Riesbeck, 2007), as it is a construct specifically tied to psychosis.

We hypothesized that aberrant salience, as well as negative affect (i.e., sadness, anxiety, low self-esteem, and worrying) predicts subsequent psychotic symptoms in a one-week ESM phase as well as a one-year Follow Up phase. Further, we hypothesized that aberrant salience, negative affect, extreme levels of affect, quality of sleep and adherence to medication predicts subsequent psychotic relapse (measured bi-monthly), and that participants could anticipate an upcoming relapse.

Method

Recruitment

We recruited participants from Hamburg, Germany, and surrounding areas between March 2018 and May 2019. We reached out to former participants, who consented to receive study invitations, and contacted psychiatric wards of local hospitals, self-help groups, and assisted living facilities. In addition, we advertised the study on the internet, via leaflets, posters, and within a local newspaper.

Inclusion criteria were age (18–65 years), sufficient command of the German language, a verbal IQ of 85 or higher according to a verbal intelligence test (Schmidt & Metzler, 1992), and a non-affective psychotic disorder according to a clinician-administered

interview (MINI; Lecrubier et al., 1997). We excluded participants if they reported a diagnosis of dementia or a severe neurological disease, and if they fulfilled the diagnostic criteria of a severe substance use disorder or high suicidality according to the MINI. Finally, we excluded participants who refused to fill in an *emergency plan*, a document listing contact persons whom participants could reach out to in case of suicidal thoughts, psychotic relapse, or other crises.

Trial Design and Procedure

The ethics committee of the German Psychological Association approved the study (ID: SM082017) and all participants provided written informed consent prior to participation. We conducted the study in accordance with the Declaration of Helsinki and we prospectively registered the analysis plan (osf.io/em6v9, registered September 12, 2018). Participants received up to 70 € of compensation. Figure 1 depicts the trial design.

Figure 1

Overview of the trial design.

1. Baseline		- Face-to-face meeting, ca. 2 hrs. duration - Interview: MINI, PANSS - Questionnaires: CAPE, BSI-18…
ESM Period started directly after the Baseline assessment		
2. ESM	 min. distance	- 70 scheduled assessments, 10 per day for 7 days, 98 sec. duration - ESM Items: paranoia, verbal hallucinations, aberrant salience, negative affect…
Post-ESM assessment took place when participants returned smartphone after ca. 7 days		
3. Post-ESM		- Face-to-face meeting, ca 20 min. duration - Questionnaire: Experiences ESM - Instructions Follow Ups
Follow Ups started ca. one week after the Post-ESM assessment		
4. Follow Up	 distance	- 24 scheduled assessments, bi-weekly for one year, 13 min. duration - ESM items (identical to ESM) - Follow Up items: Sleep, adherence, relapse-expectation… - Bi-monthly, relapse assessment, 43 min. duration: Hospitalization, increased care & 25% CAPE increase, self-injury, suicidal ideation, violence, clinical deterioration

Baseline Assessment

At baseline, we conducted a structured clinical interview (MINI and PANSS; for a description, see measures section) to examine the severity of psychotic symptoms as well as inclusion and exclusion criteria.

ESM Assessment Phase

Participants received a smartphone (Motorola G3, 5-inch screen) and a user manual at the end of the baseline assessment. The experimenter explained functions of the smartphone and the items. Participants completed as many practice trials as necessary to ensure comprehension. We used a password-secured program to lock all functions of the smartphone

except for the ESM program *movisensXS* (movisens GmbH, Karlsruhe, Germany). The alarms for the ESM assessments occurred randomly ten times per day between 9:00 a.m. and 9:00 p.m. with a minimum distance of 30 minutes between them. In addition, participants could activate ESM assessments manually when they wanted to catch up on a missed assessment or if they currently experienced symptoms. To reduce burden, participants could change the loudness of the alarm as long as they notice it. We informed them that they should not answer the phone when it would result in safety risks or severe disturbances. After the ESM assessment phase, participants returned the smartphone and completed a questionnaire on their ESM experience (Post-ESM assessment). Of note, the design and parts of the items were based on a previous study (Westermann et al., 2017) but the participants of the current and the preceding study were sampled independently.

Follow Up Phase

Over the course of one year, participants completed bi-weekly Follow Up assessments online (QuestBack Unipark®) on their private computers, using a link that we sent them via email. Study personnel sent reminder emails if participants did not respond within two days after the invitation. If participants skipped several consecutive assessments, we contacted them via telephone. We matched responses from the same participant using an anonymous code. Every two months, the Follow Up questionnaire included an extensive relapse assessment.

Measures

Baseline Measures

We report participants' cumulated antipsychotic dosages, defined as the dosage of a certain drug divided by its maximum dosage, cumulated across drugs. We chose this index because chlorpromazine equivalents have faced criticism (Danivas & Venkatasubramanian, 2013). We administered the Mini International Neuropsychiatric Interview, Version 7.0.2

(MINI; Lecrubier et al., 1997) to confirm relevant disorders, and the Positive and Negative Syndrome Scale to assess psychotic symptom severity (PANSS; Kay et al., 1987). Study personnel received extensive training for the MINI and the PANSS, including several attendances of interviews by the principal investigator, interviews with supervision, and continuous debriefings and supervision during the study. We included the Community Assessment of Psychic Experiences (CAPE; Stefanis et al., 2017) as a self-report measure of psychotic and global symptom deterioration during relapse assessments.

ESM Assessments (7 Days, 10 Times per Day)

The ESM smartphone assessments consisted of 17 items, rated on visual analogue scales. Here, we only present items that are relevant for the present study. Please find the complete list of items in the preregistered report (osf.io/em6v9). We assessed emotional valence (I feel very pleasant – very unpleasant) and arousal (very excited – very unexcited). In addition, single items assessed anxiety (“I feel anxious” based on Kramer et al., 2014), self-esteem (“I feel worthless”, based on Rosenberg, 1965), worrying (“At the moment, my worries overwhelm me”, based on Stober & Bittencourt, 1998), and sadness (“I feel sad”, self-generated). To reduce the number of confirmatory tests, we aggregated anxiety, self-esteem, worrying, and sadness to a *negative affect* scale. In the proper meaning, the scale consists of not only affective states but also cognitions (e.g., a worry thinking style; Freeman & Garety, 2014) but for the sake of brevity, we refer to it as *negative affect* throughout. Two items captured psychotic symptoms, “I feel suspicious”, adapted from previous ESM trials (Kramer et al., 2014; So et al., 2018) and the self-generated item “I hear voices that no one else can hear”. We analyzed paranoia and auditory verbal hallucinations as separate outcomes instead of using a composite score because we expected differential effects of predictors on each outcome based on a recent study (Lüdtke et al., in press). This was a deviation from the preregistered analysis plan. We included five out of seven items of the *increased significance*

subscale of the aberrant salience inventory (Cicero et al., 2010). We chose items 27, 21, 1, 16, and 5 based on their factor loadings (Cicero et al., 2010). We adapted the items slightly to capture current aberrant salience using the same visual analogue scale as the other items (e.g., “Do certain trivial things suddenly seem especially important or significant to you?”).

Follow Ups (One Year, Bi-Weekly)

Follow Up assessments included the aforementioned ESM items rated on the same visual analogue scales. Additionally, we assessed quality of sleep (“I would describe the quality of my sleep as >good<”) and medication adherence, (“How much of the prescribed medication did you take in the past two weeks?”), the latter rated on a visual analogue scale ranging from 0% to 100%. The remaining items on drug abuse and alcohol abuse were not relevant for the present analyses.

Relapse Assessments (One Year, Bi-Monthly)

We assessed relapse using a binary variable based on criteria proposed by Csernansky et al. (2002). Relapse could either be absent (none of the criteria fulfilled) or present (at least one criterion fulfilled). Relapse criteria were as follows. *Hospitalization*: Participants reported hospital admissions within the previous two months, including dates and the reason for hospitalization, which we inspected manually. *Increased psychiatric care and 25% increase of CAPE total score*: We asked participants “Compared to the start of the study, did the psychiatric or psychological care that you received increase within the last 2 months?” accompanied by an explanation of what increased psychiatric or psychological care means. Additionally, we calculated the difference of the CAPE total score compared to baseline to detect increases of at least 25%. *Deliberate self-injury*: We assessed deliberate self-injury using the item “Please state if you deliberately injured yourself in the past week; if yes how often” from the Borderline Symptom List (BSL-23; Bohus et al., 2009). *Suicidal ideation*: We used the suicide item from the Beck Depression Inventory-II (Beck et al., 1996). *Violence*

towards others or property damage: The item “Has there been a situation in the past 2 weeks where you physically attacked another person or where you destroyed the property of others?” was self-generated. *Clinical deterioration*: We included the Brief Symptom Rating Scale (BSI-18; Derogatis & Fitzpatrick, 2004) as a measure of overall clinical deterioration (50% increase compared to baseline).

Participants’ Relapse Expectations (One Year, Bi-Weekly)

We used the self-generated item “Do you think that you might experience a relapse in the near future?” to examine relapse expectations (we provided an explanation of relapse). Response options were “rather yes”, “rather no”, and “I don’t know”.

Statistical Analyses

Power

We aimed for a target sample size of $n = 40$ participants based on previous studies in the field (see trial registration for a detailed description; Identifier osf.io/em6v9). We failed to reach the target sample size by 25% resulting in a sample of $n = 30$ participants.

Reliability

We report the momentary Cronbach’s α at the first completed ESM assessment, corresponding to the classical cross-sectional internal consistency. As the momentary Cronbach’s α does not account for the nested structure of the data, we computed two additional indices of multilevel reliability proposed by Bonito et al. (2012). The occasion level reliability describes the consistency of responses across the items, whereas the person level reliability describes the reliability of a person’s mean response across occasions (Nezlek, 2017).

Lagged Regression Analyses

All confirmatory analyses represent variants of mixed models, which account for the nested structure of repeated measurements clustered within participants. We did not impute

missing values because mixed models are flexible in handling missing data (Twisk, 2019, p. 150). We person-mean centered all time-variant predictor variables (e.g., aberrant salience) separately for ESM and Follow Up assessments by computing the within-person mean and subtracting it from each value. All models included random intercepts but no random slopes. 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 interaction of precursor and assessment type. The interaction term indicated whether the effect of the respective precursor on subsequent symptoms differed between ESM and Follow Up assessments. The statistical models on relapse were variants of logistic mixed models with relapse (yes/no) as the outcome and different predictor variables (adherence to medication, quality of sleep, negative affect, and aberrant salience) measured at least one week and up to four weeks prior to the outcome. The logistic mixed model relied on a binomial probability distribution and a logit link function. We used two-sided tests and conventional *p*-values of .05 and applied the Benjamini and Hochberg correction to control for the false discovery rate (FDR) due to multiple tests in linear models (Benjamini & Hochberg, 1995).

Results

Sample Characteristics and Adherence

See Table 1 for sample characteristics. A PANSS total score of approximately 45 indicated that participants were rather healthy (Leucht et al., 2005). Nonetheless, 40% had a current psychotic episode.

Thirty participants fulfilled the inclusion criteria, completed the baseline assessment and differing proportions of the ESM assessments. The ESM period encompassed 70 planned assessments but the assessments did not terminate automatically after 7 days. Instead, assessments continued until the experimenter deactivated the smartphone. For two

participants, the ESM assessment period significantly exceeded 7 days. One participant kept the smartphone for 19 days because they encountered technical difficulties and asked for an extension of the assessment period. Another participant got sick during participation, resulting in a period of 28 days until they returned the smartphone. Without these two outliers, the mean number of ESM assessment days was *M* = 7.43 days (*SD* = 1.32), with a median and mode of 7 days. On average, participants provided 57.07 ESM assessments (range: 8 to 105), resulting in 1712 data points. We only considered data points in the analyses if they were not less than 10 minutes and not more than 4 hours apart, resulting in 1194 valid data points (70%).

Twenty-eight participants completed at least one Follow Up assessment, resulting in 554 Follow Up assessments, corresponding to *M* = 18.47 assessments on average (*SD* = 8.78; median = 23.5). If each participant had provided all 24 assessments, there would have been 744 assessments. As for the ESM assessments, we used a time criterion to identify valid data, resulting in 416 analyzed data points (75%).

Table 1

Sample characteristics at baseline (n = 30)

Characteristics	*M* (*SD*) or proportion (%)
Demographics	
Age in years	42.87 (12.11)
Gender female	16/30 (53%)
At least 11 years of education	22/30 (73%)
Clinical variables	
Diagnosis of current psychotic episode	12/30 (40%)
Taking antipsychotic medication	25/30 (83%)
Cumulated antipsychotic dosage	56.38 (38.22)
PANSS total score	45.59 (14.31)
PANSS positive	13.03 (7.22)
PANSS negative	11.00 (5.17)

Note. *SD* = Standard Deviation. All participants fulfilled criteria of a lifetime psychotic episode according to the MINI interview. PANSS positive and negative subscales calculated according to the 5-factor solution by Vandergaag et al. (2006). Cumulated antipsychotic dosage refers to the percentage of the maximum dosage of the antipsychotic drugs that a participant received.

Internal Consistency

We examined internal consistencies of the negative affect scale as well as the aberrant salience scale. The momentary Cronbach's α values (α = .866 for both scales) as well as the person level consistencies (negative affect: α = .994; aberrant salience: α = .993) were good to excellent. Only the occasion level consistency was insufficient (negative affect: α = .108; aberrant salience: α = .149). We conducted the analyses as planned nonetheless.

Hypothesis Tests

We hypothesized that negative affect and aberrant salience predicts subsequent psychotic symptoms. As shown in Table 2, both scales predicted subsequent paranoia in within-day ESM assessments, but not auditory verbal hallucinations. Next, we examined whether negative affect as well as aberrant salience likewise predicted psychotic symptoms in bi-weekly Follow Up assessments. In Follow Ups, only the effect of aberrant salience on subsequent paranoia remained significant after the FDR correction, indicating that aberrant salience functions 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, indicating that the effect of aberrant salience on paranoia was not different between ESM and Follow Up assessments (b = 0.103, SE = 0.077, t(1167.07) = 1.340, p = .181). The effect of negative affect on subsequent paranoia, on the other hand, 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 short, aberrant salience predicted paranoia within the same day and over the course of weeks, whereas the effect of negative affect was limited to ESM data.

As typical for ESM studies (e.g., Kasanova et al., 2020), we do not provide standardized effect sizes due to the multilevel structure of the data. Nonetheless, the unstandardized effects can be interpreted easily because we used uniform Likert scales. For example, an effect of b = 0.187 indicates that if a person scores one point higher on the 100-point Likert scale for aberrant salience, they score 0.187 higher on the 100-point Likert scale for paranoia approximately two weeks later. This means that an increase of 10 points of aberrant salience corresponds to 1.87 points of paranoia. Consequently, one might argue that effects are rather small. However, given that these small within-person effects can accumulate over time, they can be meaningful nonetheless.

Table 2

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. Precursors 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 (1995).

Occurrences and Prediction of Relapse

Thirteen participants (43%) relapsed at least once during the one-year follow-up period. We counted consecutive reports of relapse that occurred in short succession (≤ 8 weeks distance) as one incidence of relapse. Eight participants relapsed once (62%), one participant relapsed twice (8%), three participants relapsed three times (23%), and one

participant relapsed four times (8%). We examined whether aberrant salience or any of the other candidate precursors predicted the occurrence of relapse. We conducted a logistic mixed model analysis with relapse (no/yes) as the outcome and person-mean centered negative affect, aberrant salience, quality of sleep, and medication adherence as the predictors. The analysis relied on 77 occasions of relapse vs. no relapse. None of the predictor variables reached significance (see Table 3), which was not surprising, given the low number of relapses and thus power. We planned to examine whether participants could anticipate an upcoming relapse but we had to waive the analysis because of insufficient cell counts (there was only one incident of a participant indicating that they expected a relapse). Finally, we calculated a binary *extreme affect* score, which was coded "1" if a participant scored two Standard Deviations above or below person-mean centered emotional valence or arousal (otherwise, it was coded "0"). A chi-square test revealed no association of extreme affect and subsequent relapse (χ^2 (1) = 1.316, p = .350).

Table 3

Logistic mixed model with the outcome relapse (no/yes).

Precursor	Coefficient	SE	*t*	*p*	OR
Intercept	2.286	.5188	4.406	< .001	9.835
Adherence to medication	-.116	.0887	1.309	.195	.890
Quality of sleep	.008	.0163	.476	.636	1.008
Negative affect	-.027	.0293	.916	.363	.973
Aberrant salience scale	.012	.0297	.392	.696	1.012

Note. Precursors are person-mean centered, measured at the occasion prior to the event (relapse vs. no relapse). SE = Standard Error.

Exploratory Analyses

We recently found that worry preceded paranoia several days later during a psychological online intervention for psychosis (Lüdtke et al., in press). We therefore examined worry as a stand-alone predictor of paranoia in the present study as well. Worry was a significant predictor both in ESM (b = 0.093, SE = 0.038, t(760.43) = 2.412, p = .016) and Follow Up assessments (b = 0.094, SE = 0.048, t(388.91) = 1.980, p = .048), which was confirmed by a non-significant interaction of worry and assessment type (b = -0.033, SE = 0.058, t(1171.33) = 0.572, p = .567). Consequently, worry could be another long-term predictor of paranoia, similar to aberrant salience.

Next, we examined the influence of antipsychotic medication on the association of aberrant salience and subsequent paranoia, given that aberrant salience relates to dopaminergic processes (Miyata, 2019). Adding adherence to medication as a covariate changed the effect of aberrant salience on paranoia from b = 0.366 (p < .001) to b = 0.519 (p < .001), which corresponds to a 42% increase. We subsequently examined medication (no/yes) as a moderator of the effect. A significant interaction indicated that the effect of aberrant salience on paranoia was significantly lower when participants were medicated compared to unmedicated participants (interaction coefficient: b = -0.763, SE = 0.158, t(386.08) = 4.827, p < .001). Hence, the effect of aberrant salience depends on medication in two ways. First, it is stronger in people who do not receive antipsychotic medication. Second, adherence to medication is a confounder, meaning that it influences both aberrant salience and paranoia in longitudinal analyses.

Discussion

ESM studies have identified numerous short-term self-report predictors of psychotic symptom fluctuations in assessment periods of few days. Interestingly, these short-term predictors resemble long-term warning signs of psychotic relapse (e.g., depressed mood or compromised sleep). Hence, there is reason to believe that one can draw on ESM-based

predictors to predict long-term symptom fluctuations and potentially relapse. In order to examine whether ESM-based predictors are as effective in long-term assessments as they are in short-term assessments, we compared precursor-symptom associations between a one-week ESM assessment period and a one-year Follow Up period, using the same predictors (aberrant salience, negative affect) and outcomes (paranoia, auditory verbal hallucinations). Only aberrant salience was a significant predictor of subsequent paranoia consistently in ESM and Follow Up assessments. Given this promising result, we expected that aberrant salience also predicts actual relapse. However, contrary to our expectations, we found no effect of aberrant salience or any of the other predictors (adherence to medication, sleep, negative affect) on subsequent relapse. We interpret null findings in relapse prediction with great caution due to insufficient power and consider aberrant salience a very worthwhile candidate precursor in future studies nonetheless. The most evident implication of our study is that it is promising to monitor aberrant salience in bi-weekly intervals because it can signal subsequent increases of paranoia.

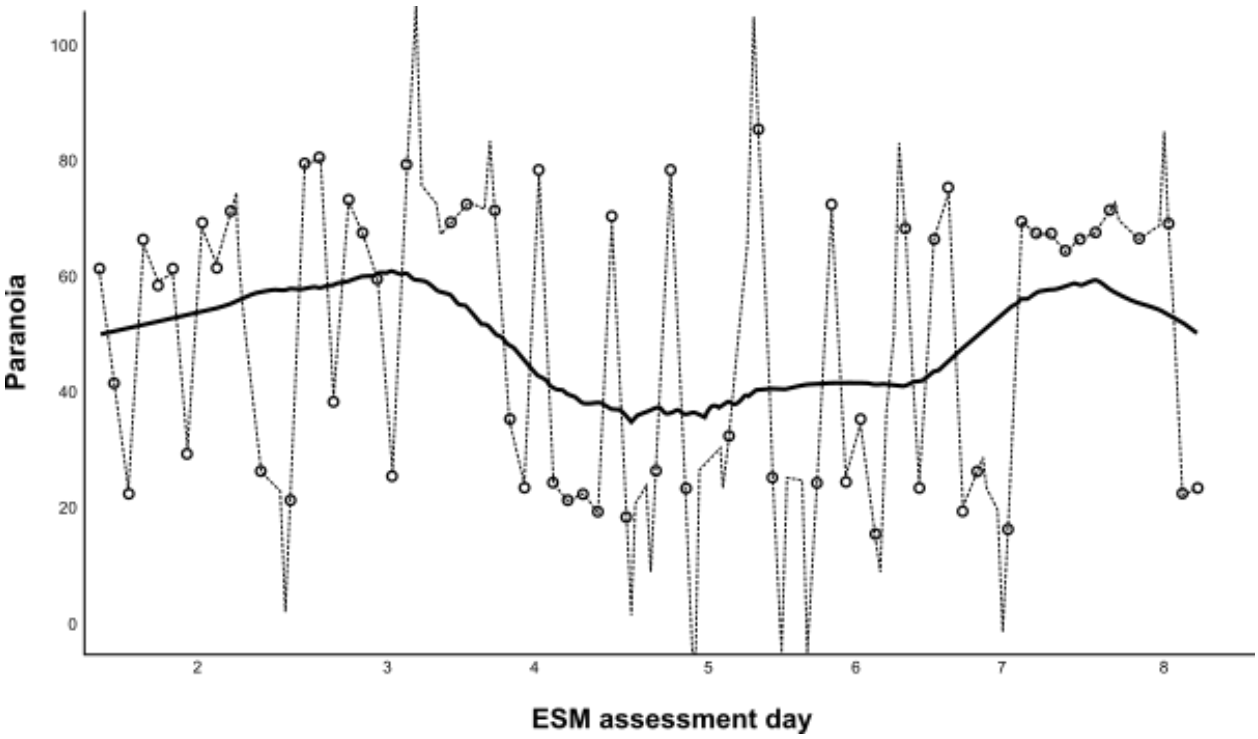
Short- Versus Long-Term Effects of Aberrant Salience

Aberrant salience consistently predicted paranoia irrespective of the distance between predictor and outcome assessment (hours vs. weeks). This result appears counterintuitive at first sight. One might argue that if the effect is short-term, it should be long gone after a couple of hours and if it is long-term, it should not yet be visible after a few hours. As a possible explanation for this contradiction, we propose that short-term and long-term fluctuations co-occur, meaning that variables, such as aberrant salience or paranoia, fluctuate rapidly throughout the day while these rapid fluctuations occur around slower-paced long-term trends. Under the aforementioned assumption, it is possible that ESM assessments capture associations between rapid fluctuations of variables, whereas infrequent Follow Ups capture associations between slower trends of the same variables. For purely descriptive

purposes, we illustrated this assumption graphically based on one-week ESM data from one of our participants (Figure 2 depicts Loess-curves with different degrees of smoothing to visualize rapid vs. slow fluctuations). In the example data depicted in Figure 2, paranoia fluctuates heavily within few hours, but these fluctuations occur around a slower trend of changing paranoia, which only becomes apparent across days. The correspondence of short- and long-term effects of aberrant salience on paranoia implies that it is promising to apply variable sampling rates in clinical practice to obtain high-frequency assessments when needed. For example, participants could change from bi-weekly assessments to frequent ESM assessments if aberrant salience exceeds a certain cut-off.

Figure 2

Exemplary course of paranoia across one week of ESM.



Note. Y-axis displays raw scores from the visual analogue scale for paranoia, ranging from 0–100. Here, we present data from participant no. 6 to illustrate short-term fluctuations around slower-paced trends of paranoia over time.

Aberrant Salience as a Predictor of Long-Term Symptom Fluctuations

To our knowledge, there are no studies on aberrant salience as a predictor of relapse. However, there are studies on the emergence of psychosis (e.g., Freeman et al., 2019) or the transition from *high risk* states to psychosis (e.g., Howes et al., 2020), which acknowledge aberrant salience as a contributing factor. Instruments such as the Schizophrenia Proneness Instrument assesses *basic symptoms* that – in part – resemble aberrant salience. For example, one item captures captivation of attention: “Sometimes an object really seems to stand out from the rest of what I see…” (Schultze-Lutter, 2009, p. 7). A recent feasibility trial found that basic symptoms improve the prediction of psychotic symptoms beyond early signs of relapse in weekly smartphone assessments (Eisner et al., 2019). In sum, aberrant salience and related constructs have not received much attention as predictors of relapse, so far, but results are promising.

As proposed by Kapur (2003), aberrant salience emerges as a consequence of a stimulus-unrelated hyperdopaminergic state in the brain. Animal studies and neuroimaging studies in humans support this hypothesis in that dopamine neurons in the midbrain-striatum respond to stimulus salience (for a review, see Miyata, 2019). According to Kapur (2003), antipsychotic medication, which mainly targets dopamine receptors (Wang et al., 2018), is effective because it dampens aberrant salience. Given this theoretical background, we examined the influence of antipsychotic medication on the relationship between aberrant salience and paranoia in exploratory analyses. Medication served as both a moderator and confounder of aberrant salience’s effect on paranoia. These findings are preliminary but they

have important implications. First, aberrant salience as a predictor of paranoia seems to be most potent in unmedicated participants, possibly because antipsychotics dampen salience (Kapur, 2003). Second, our findings suggest that self-reported aberrant salience could be a good indicator of underlying dopaminergic processes, which further strengthens the validity of aberrant salience as a theory-driven predictor of psychotic symptoms. Our exploratory findings also substantiate the importance of persistent antipsychotic medication after remission (Leucht et al., 2012; Pelayo-Teran et al., 2017).

Null Effect of Negative Affect in Follow Up Assessments

Negative affect (i.e., sadness, anxiety, low self-esteem, and worrying) predicted paranoia only during the one-week ESM phase but not during bi-weekly Follow Ups. This result was surprising because it contradicts findings that negative affective states are somewhat successful predictors of relapse (Gaebel & Riesbeck, 2007). Consequently, we have to revise our assumption that the established early signs *anxiety and dysphoria* (Eisner et al., 2013) predict relapse through long-term effects on paranoia, which we would have expected based on short-term ESM studies (Ludtke et al., 2017; So et al., 2018). Instead, there must be other pathways, through which sadness and anxiety predict relapse at least partially. In the following, we discuss how the *randomness* of momentary anxiety, mood, and self-esteem could have been responsible for the lack of long-term effects on paranoia and hallucinations. People with psychosis experience heightened negative affect following stressful events (Myin-Germeys & van Os, 2007), and assuming that stressful events occur randomly, people with psychosis should experience random bursts of negative affect over time. Referring back to Figure 2, this implies that negative affective states do not follow a general long-term trend. Instead, both short- and long-term fluctuations of negative affect could be dependent on random stressors, making negative affect unsuited as a predictor of long-term fluctuations of paranoia. Likewise, self-esteem fluctuates rapidly in people with psychosis, especially in

people with paranoia (Murphy et al., 2018). The Attribution-Self-Representation Cycle Model (Bentall et al., 2001) of self-esteem predicts random fluctuations of negative affect in paranoia, again ruling out the possibility of long-term predictions.

The last item of the negative affect scale captured worry ("my worries overwhelm me"). Unlike mood, anxiety, or self-esteem, worrying represents both a momentary action as well as a more stable *worry thinking style* (Freeman & Garety, 2014), rendering it a suited long-term predictor of paranoia. In hindsight, it was not ideal to add worry to the negative affect scale to reduce the number of confirmatory tests, so we analyzed worry as a stand-alone predictor in exploratory analyses. We found that worrying in fact preceded paranoia consistently in ESM and Follow Up assessments, supporting the presumption that worry represents another worthwhile long-term predictor of paranoia. This result corresponds to a recent finding indicating that worry predicts symptom fluctuations during an online intervention for psychosis (Lüdtke et al., in press). In addition, the result further substantiates the now well-established notion that worry is a primary treatment target in cognitive behavioral face-to-face (Freeman et al., 2015) and online interventions (Westermann et al., 2020) for psychosis. Therefore, null findings regarding the negative affect scale must be interpreted with caution. While momentary sadness, anxiety, and self-esteem might represent purely short-term predictors of paranoia, worry could be another suitable long-term symptom predictor besides aberrant salience.

Limitations and Conclusion

All analyses were regression-based (prohibiting causal conclusions) and relapse analyses relied on a small sample size, thus awaiting replication in future studies. Further, our analyses relied on firm theoretical assumptions regarding the direction of effects, namely negative affect preceding psychotic symptoms. We did not consider the opposite direction although the concept of postpsychotic depression is well established in psychiatry (Moritz et

al., 2019) and studies indicate that depressive symptoms serve as both a predictor and an outcome of paranoia (Moritz et al., 2017).

To conclude, our study was a first attempt to improve the prediction of relapse using predictors and methods derived from ESM research. It was optimistic to assume that any ESM-derived predictor generalizes to long-term assessments but at least some ESM-based variables (i.e., aberrant salience in our study) are worthwhile candidates of long-term symptom fluctuations and possibly relapse.

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Appendix

Complete list of measured constructs of study 4 (ESM Study)

ESM Study – Baseline assessment

TARGET	MEASURE
DEMOGRAPHICS	Self-generated questionnaire assessing gender, age, nationality, marital status, housing situation, education, occupation, diagnoses, begin of psychotic disorder, number of psychotic episodes, number of hospitalizations, antipsychotic medication, adherence to antipsychotic medication, other psychopharmacological medication, status of treatment
DEPRESSION	Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001)
PSYCHOTIC SYMPTOMS	Community Assessment of Psychic Experiences (CAPE; Stefanis et al., 2002)
ACCEPTANCE / PSYCHOLOGICAL FLEXIBILITY	The acceptance and Action Questionnaire-II (AAQ-2; Bond et al., 2011)
SUSCEPTIBILITY TO PSEUDO-PROFOUND STATEMETNS	Bullshit receptivity scale (Pennycook et al., 2015)
POSITIVE AND NEGATIVE AFFECT	Positive and negative affect schedule (PANAS; Watson et al., 1988)
EMOTION REGULATION	Emotion regulation questionnaire (ERQ; Gross & John, 2003)
GENERAL SYMPTOMS	Brief Symptom Rating Scale (BSI-18; Derogatis & Fitzpatrick, 2004a)

ESM Study – ESM Smartphone assessments

TARGET	MEASURE
VALENCE OF AFFECT	Self-generated visual analogue scale item ranging from pleasant to unpleasant
AROUSAL OF AFFECT	Self-generated visual analogue scale item ranging from relaxed to tense
SYMPTOM DISTRESS	Self-generated visual analogue scale item ranging from not distressed to distressed by symptoms
ANXIETY	Self-generated visual analogue scale item ranging from “not at all” to “completely”
SELF-WORTH	Self-generated visual analogue scale item ranging from “not at all” to “completely”
SADNESS	Self-generated visual analogue scale item ranging from “not at all” to “completely”
ANGER	Self-generated visual analogue scale item ranging from “not at all” to “completely”
COMPANY	Participants could indicate who they were with at the moment (e.g., friends or family)
PLACE	Participants could indicate where they were (e.g., at home)
ACTIVITY	Participants could indicate what they were doing currently (e.g, working)
PARANOIA	Visual analogue scale item ranging from “not at all” to “completely”
WORRY	Visual analogue scale item ranging from “not at all” to “completely”
JTC	Visual analogue scale item ranging from “not at all” to “completely”
VOICE HEARING	Self-generated visual analogue scale item ranging from “not at all” to “completely”
ABERRANT SALIENCE	Five visual analogue scale items ranging from “not at all” to “completely”

ESM Study – Follow Up Assessments

TARGET	MEASURE
VALENCE OF AFFECT	Self-generated visual analogue scale item ranging from pleasant to unpleasant
AROUSAL OF AFFECT	Self-generated visual analogue scale item ranging from relaxed to tense
SYMPTOM DISTRESS	Self-generated visual analogue scale item ranging from not distressed to distressed by symptoms
ANXIETY	Self-generated visual analogue scale item ranging from “not at all” to “completely”
SELF-WORTH	Self-generated visual analogue scale item ranging from “not at all” to “completely”
SADNESS	Self-generated visual analogue scale item ranging from “not at all” to “completely”
ANGER	Self-generated visual analogue scale item ranging from “not at all” to “completely”
COMPANY	Participants could indicate who they were with at the moment (e.g., friends or family)
PLACE	Participants could indicate where they were (e.g., at home)
ACTIVITY	Participants could indicate what they were doing currently (e.g, working)
PARANOIA	Visual analogue scale item ranging from “not at all” to “completely”
WORRY	Visual analogue scale item ranging from “not at all” to “completely”
JTC	Visual analogue scale item ranging from “not at all” to “completely”
VOICE HEARING	Self-generated visual analogue scale item ranging from “not at all” to “completely”
ABERRANT SALIENCE	Five visual analogue scale items ranging from “not at all” to “completely”
SECOND JTC ITEM	Visual analogue scale item ranging from “not at all” to “completely”

SELF-ESTEEM	Visual analogue scale item ranging from “not at all” to “completely”
ABILITY TO USE ABC SCHEMA	Visual analogue scale item ranging from “not at all” to “completely”
DEPRESSION	Visual analogue scale item ranging from “not at all” to “completely”
HAPPINESS	Visual analogue scale item ranging from “not at all” to “completely”
MINDFULNESS	Visual analogue scale item ranging from “not at all” to “completely”
SOCIAL COMPETENCE	Visual analogue scale item ranging from “not at all” to “completely”
QUALITY OF SLEEP	Visual analogue scale item ranging from “not at all” to “completely”
STRESSFUL EVENT	Visual analogue scale item ranging from “not at all” to “completely”
ANTIPSYCHOTIC MEDICATION	Yes/no question
ADHERENCE TO ANTIPSYCHOTIC MEDICATION	Visual analogue scale item ranging from “0%” to “100%”
ALCOHOL CONSUMPTION	Open Answer in text box
AMOUNT OF CIGARETTES	Open Answer in text box
DRUG USE	Yes/no qusetion
FREQUENCY OF DRUG USAGE	Scale ranging from 1 to 14 within past two weeks
RELAPSE EXPECTATION	Rather yes/ I don’t know/ rather no
RELAPSE EXPECTAION RATIONALE	Open Answer in text box

ESM Study – Relapse Assessment (part of Follow Ups)

TARGET	MEASURE
DEPRESSION	Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001)
GENERAL SYMPTOMS	Brief Symptom Rating Scale (BSI-18; Derogatis & Fitzpatrick, 2004a)
PSYCHOTIC SYMPTOMS	Community Assessment of Psychic Experiences (CAPE; Stefanis et al., 2002)
PSYCHOTIC SYMPTOMS	Delusion and Voices Self-Assessment (DV-SA; Pinto et al., 2007)
WORK INABILITY	Open Answer in text box
HOSPITALIZATION	Yes/no item
REASON FOR HOSPITALIZATION	Open Answer in text box
DURATION OF HOSPITALIZATION	Open Answer in text box
INCREASED PSYCHIATRIC CARE	Yes/no item
SUICIDAL TENDENCIES	suicide item from the Beck Depression Inventory-II (BDI-II; Beck et al., 1996)
SELF-HARM	Item from the Borderline Symptom List (BSL-23; Bohus et al., 2009)
VIOLENCE TOWARDS OTHERS	Yes/no item