Transdiagnostic phenotyping of psychopathology in a help-seeking population (PhenoNetz) - a study protocol for an experience sampling study

Marlene Rosen[1#]*, Linda T. Betz[1]*, Christian Montag[2], Christopher Kannen[2], Joseph Kambeitz[1]

[1] Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital of Cologne, Cologne, Germany

[2] Institute of Psychology and Education, Ulm University, Ulm, Germany

[#] Corresponding Author

E-mail: marlene.rosen@uk-koeln.de

* These authors contributed equally to this work.

Metadata

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Competing interests

The authors declare that no competing interests exist.

Data availability

All relevant data from this study will be made available upon study completion.

Abstract

Background: Prevention in psychiatry provides a promising way to address the burden by mental illness. However, established approaches focus on specific diagnoses and do not address the heterogeneity and manifold potential outcomes of help-seeking populations that present at early recognition services. Thus, novel preventive approaches have been suggested, focusing on a broad transdiagnostic risk syndrome associated with different mental disorders. Conceptualizing such a pluripotent risk syndrome from a network perspective of interacting symptoms allows transdiagnostic investigations beyond binary disease categories. Furthermore, modern technologies such as smartphones facilitate the application of Experience Sampling Methods (ESM). A combination of ESM with network analyses provides valid insights beyond established assessment instruments.

Methods: We will examine n = 75 individuals (age 18-40 years) of the help-seeking population of the Cologne early recognition centre (FETZ). For a maximally naturalistic sample, only minimal exclusion criteria will be applied. We will collect data for 14 days utilizing a mobile application to assess ten transdiagnostic symptoms, i.e., depressive, anxiety and psychotic symptoms as well as distress level. These data will allow to build both personalized and group symptom network models. Additionally, we will explore associations between symptom networks and sociodemographic, risk and resilience factors, as well as psychosocial functioning.

Discussion: Our study will provide insights about feasibility and utility of ESM in a help-seeking population. Providing a first explorative phenotyping of the proposed broad transdiagnostic risk syndrome, this study will contribute to innovation of early recognition in psychiatry. Results will help to pave the way for prevention and targeted early intervention in a broader patient group and thus, enable greater intended effects in alleviating the burden of

psychiatric disorders. In particular, individual insights provided by our study design are important in the context of precision medicine as well as for patients' own self-management.

Introduction

Prevention and early intervention in psychiatry provide promising ways to address the immense burden of mental illness [1–3]. The currently established prevention approach implemented in early recognition services focuses on risk syndromes developed for predicting specific diagnoses (e.g. psychosis [4,5]). However, the majority of help-seeking patients who present at early recognition services are not covered by these specific risk syndromes, as they do not fulfill respective criteria which indicate increased risk qualifying for targeted intervention [4,6]. Help-seeking populations rather present with a mixture of various symptoms [7] such as depressive, anxious and psychotic symptoms. Depressive and anxiety symptoms have proven to be among the main reasons why individuals seek help [8], whereas psychotic symptoms are of interest as they are most burdensome for affected individuals as well as for the health care system, despite their rather low prevalence [9]. These symptoms are shared across different diagnoses [10–12] and appear in help-seeking patients with sub-threshold, risk-syndromes and full-threshold disorders [13]. Furthermore, full-threshold disorders such as mild depression may also represent a risk status for other, more severe mental illnesses, such as severe recurring depression [14]. Taken together, help-seeking populations are much more heterogeneous than defined in specific risk syndromes. In turn, those patients who fulfill criteria of a specific risk syndrome may remain or remit in risk state, develop manifold potential outcomes [15] or show other unfavorable outcomes such as persisting deficits in psychosocial functioning [16]. To date, it is unclear why a high number of disease specific risk-syndromes are associated with other disorders (multifinality) and why various risk factors seem to pave the way to the same disorders (equifinality of divergent trajectories) [17–19].

Thus, there is a growing call for a new approach for prevention in psychiatry assuming a broad transdiagnostic risk syndrome. This broad transdiagnostic risk syndrome

represents an early shared pathway to different psychiatric disorders [20], in keeping with accumulating evidence about transdiagnostic phenomena in psychiatry such as distress, which is discussed as a mediating and triggering factor in mental illness [21–25]. However, insights into the structure of psychopathology of this proposed transdiagnostic risk syndrome, i.e., interactions of symptoms of a heterogeneous help-seeking population, as well as associations with risk and resilience factors and psychosocial functioning, is lacking so far.

Conceptualizing the transdiagnostic risk syndrome from a network perspective allows investigations beyond binary disease categories. The network approach considers and, thus, enables to assess the complex dysfunctional process of a psychopathological state as a dynamic system of connected, interacting and maintaining symptoms [26,27]. Moreover, the impact of individual and environmental factors on these personalized dynamic systems can be assessed.

Particularly in combination with experience sampling methods (ESM), network analyses enable insights beyond those obtained by standard established assessment instruments. ESM allows for valid insights into psychopathology in daily life by assessing targeted phenomena repeatedly during the course of the day within a specific time period. Thereby, ESM guarantees high reliability, eliminating biases resulting from false memory or aggregation processes of experience over a longer time period [28]. Feasibility and acceptance of such high frequent assessments is facilitated by modern technologies such as smartphones (see [29] and [30]). The intensive time-series data resulting from ESM provide insights not only on group, but also on individual level, offering a promising gateway into understanding psychopathology as a set of person-specific dynamic processes [27,31]. These unique insights are crucial for precision medicine as they reveal processes and symptoms most relevant to each individual, which may serve as potential target points for personalized interventions [32]. In addition, learning about specific individual processes underlying their

mental states can improve self-management of individuals, reinforcing a sense of participation in one's own care [33,34]. So far, utility and potential of ESM in psychiatry were exclusively tested in the context of specific psychiatric diseases and not yet systematically in a help-seeking population of a psychiatric early recognition center. The combination of ESM with network analyses allows for an informative transdiagnostic phenotyping in this population, and provides a still missing characterization of the proposed transdiagnostic risk syndrome. The results can form the basis for future preventive approaches targeting a broad pluripotent risk syndrome. This represents a promising way to address a larger proportion of the help-seeking population than current diagnosis-specific strategies.

Methods

Aim

This study aims at an explorative transdiagnostic phenotyping of a help-seeking population of an early recognition center for mental disorders using innovative, intensive longitudinal data collection via a smartphone app. A better understanding of relevant psychopathology in this burdened population is of great relevance, given the lack of adequate interventions [35]. Combining ESM with network analyses allows for unique insights into yet under-researched early transdiagnostic psychopathological processes, as well as their association with risk, resilience, and psychosocial functioning.

Setting and participants

100 participants will be recruited from the help-seeking population presenting at the early recognition center of mental disorders at the University Hospital of Cologne (FETZ) (fetz.uk-koeln.de), with an expected drop-out rate of 25%, leading to a total of 75 participants in the final sample. The FETZ offers specialist diagnostics for the early recognition of mental

disorders, with a focus on severe mental illness, in particular psychotic disorders, and is a first contact point for people aged 18 to 40 years that have noticed changes in their experience and behaviour. Most patients find out about the FETZ through internet research or are referred to by healthcare practitioners.

For a naturalistic characterization of the help-seeking population presenting at the FETZ using ESM, we will not impose specific inclusion criteria for participation in the PhenoNetz-study. Likewise, to ensure validity of the obtained data, only a minor part of help-seeking participants will be excluded based on the following criteria:

- acute suicidal thoughts
- IQ ≤ 70
- age > 40 years
- known previous illness of the central nervous system, as well as untreated unstable somatic illnesses with known effects on the central nervous system (e.g. untreated hypothyreosis)
- insufficient knowledge of the German language

Procedure and materials

All patients presenting at the FETZ not fulfilling any of the listed exclusion criteria will be addressed either directly in the FETZ or via telephone or e-mail (given permission to contact was obtained by the clinical personnel at the FETZ) and informed about background, goal, design, risks and benefits, as well as data security aspects of the study. Additional open questions will be answered directly by one of the primary investigators (MR, LB). In case of willingness to participate, written informed consent will be provided by all participants prior to their participation in the study. Participants will be compensated with 40€ for their participation. Participants can withdraw from the study at any time without negative

consequences. The study was approved by the Institutional Review Board of the University of Cologne, Faculty of Medicine (reference number 20-1092).

Figure 1 illustrates the study design. During baseline assessment, data on socio-demographics, medication, substance use, psychopathology including psychosocial functioning as well as risk- and resilience factors will be assessed through both observer- and self-ratings (table 2). All data will be collected via Research electronic data capture (RedCap [36]). In the baseline assessment, the mobile application used for ESM data collection in the study, the *insightsapp* [37] (figure 2a), will be installed on the personal smartphones of the participants. As the *insightsapp* only runs on Android, participants with personal smartphones using other operating systems (e.g., iOS) will be equipped with a study smartphone. Participants will be encouraged to complete as many surveys as possible without compromising their personal safety (e.g., while driving).

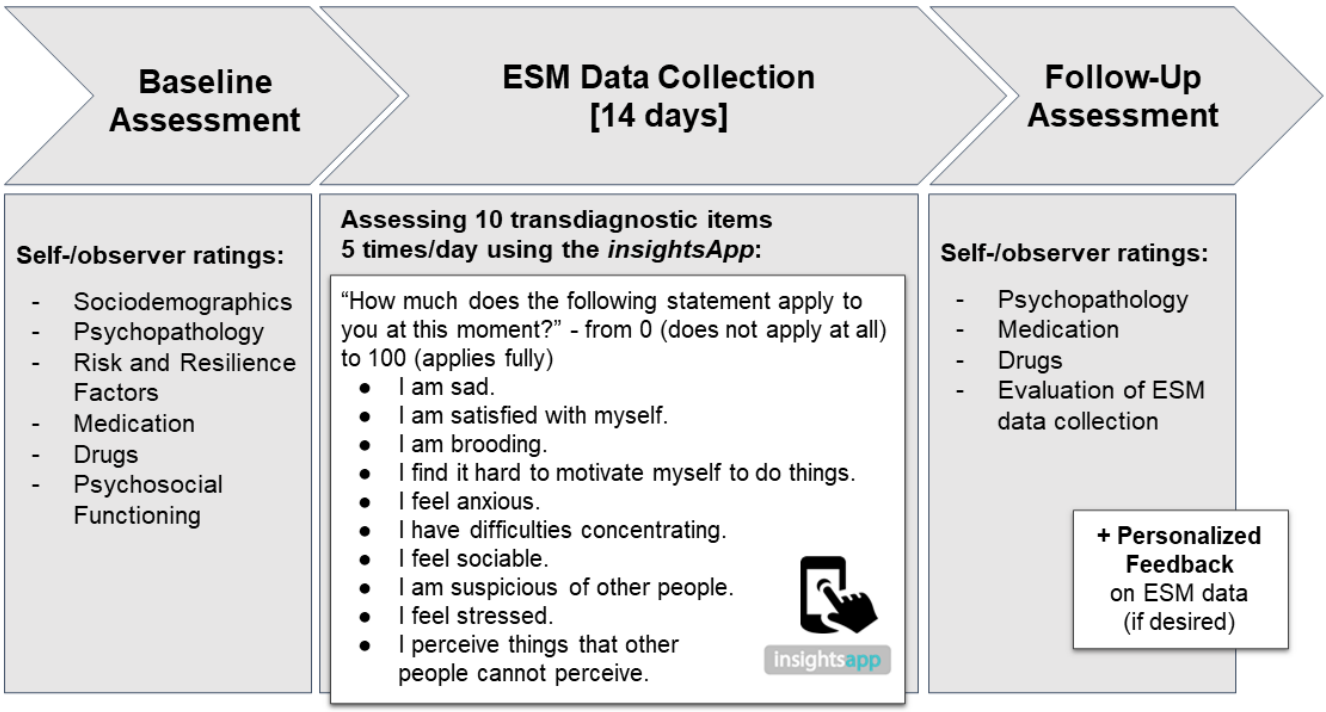

Figure 1. Study design of the PhenoNetz-study. Participants included will undergo baseline assessment with self- and observer ratings, followed by a 14-day-ESM data collection period. In the subsequent follow-up assessment, selected self- and observer ratings will be collected again. If desired, the participants will receive personalized feedback on their ESM data after the two weeks of ESM data collection, such that the feedback does not interfere with ESM data collection.

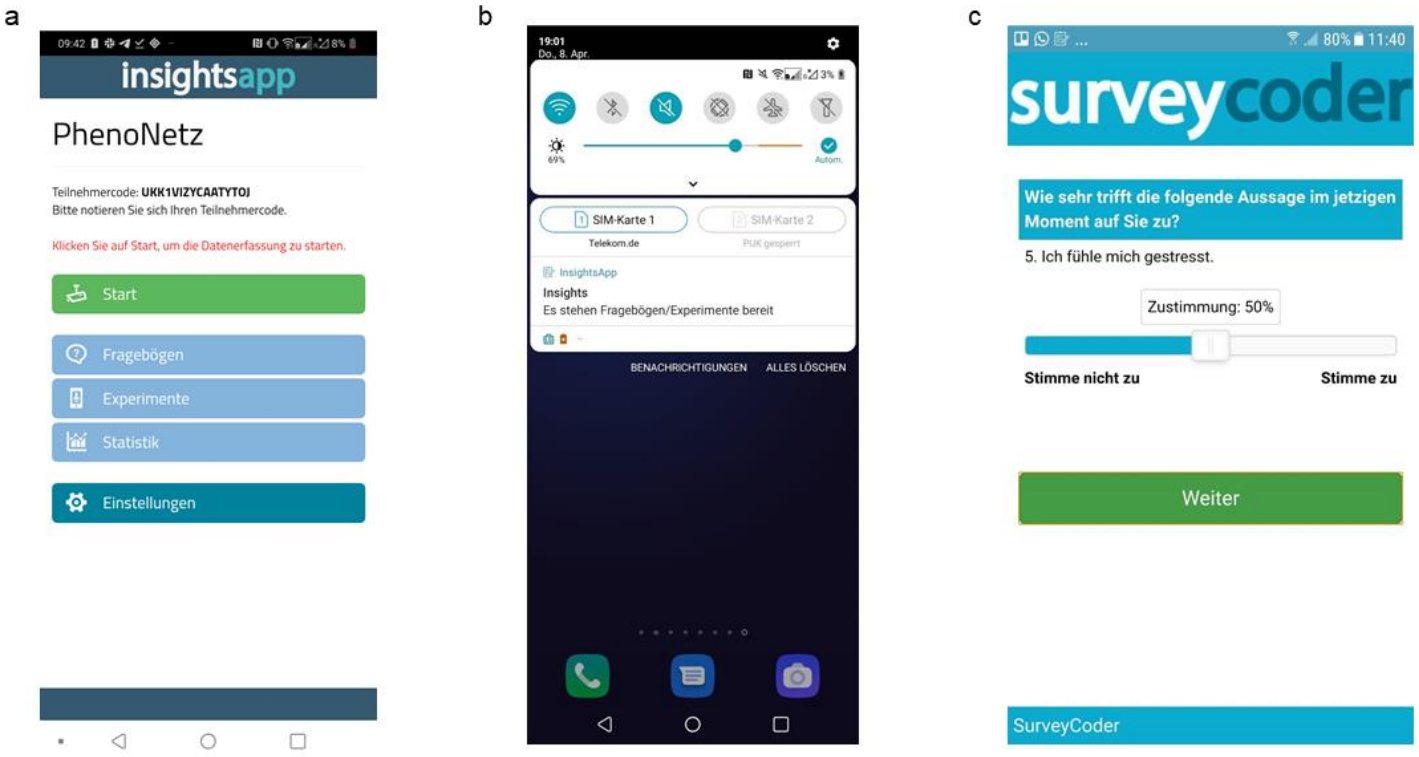

Figure 2. Layout of the *insightsapp.* (a) Main menu. (b) In-app reminder. (c) Visual analogue scale for answering transdiagnostic items.

Table 2. Constructs with scales assessed at the baseline and follow-up assessments (before and after the ESM period, respectively) of the PhenoNetz-study.

Construct	Questionnaire	Self- vs observer-rating	Baseline assessment	Follow-up assessment
sociodemographics	-	Observer rating	x	-
psychopathology				
diagnostic classification	Structured Clinical Interview for DSM-5 (SCID) [38]	Observer rating	x	-
current substance use	analogous to PRONIA study [39]	Observer rating	x	x
current medication	analogous to PRONIA study [39]	Observer rating		x
depression	Beck Depression Inventory (BDI-II) [40]	Self rating	x	x
anxiety	State and Trait Anxiety Inventory (STAI) [41]	Self rating	x	x
social phobia	Social Phobia Inventory (SPIN) [42]	Self rating	x	x
psychotic symptoms	Community Assessment of Psychic Experience (CAPE) [43]	Self rating	x	x
quality of life	WHO Quality of Life Questionnaire (WHOQOL) [44]	Self rating	x	x
risk- and resilience				
childhood trauma	Childhood Trauma Questionnaire (CTQ) [45]	Self rating	x	-
bullying	Bullying Scale (BS) [46]	Self rating	x	-
resilience	Resilience Scale for Adults (RSA) [47]	Self rating	x	-

coping	Coping Inventory for Stressful Situations (CISS-24) [48]	Self rating	x	-
personality	NEO – Five Factor Inventory (NEO-FFI) [49]	Self rating	x	-
attachment	Attachment Style Questionnaire (ASQ) [50]	Self rating	x	-
expressed emotion	Level of Expressed Emotion Scale (LEE) [51]	Self rating	x	-
social support	Multidimensional Scale of Perceived Social Support (MSPSS) [52]	Self rating	x	-
introspection	Self-reflection and insight scale (SRIS) [53,54]	Self rating	x	x
self-efficacy	Skala zur allgemeinen Selbstwirksamkeitserwar-tung (SWE) [55]	Self rating	x	-
psychosocial functioning	Global Functioning Social and Role Scales (GF: Social and Role) [56]	Observer rating	x	-
Experience with ESM period	adapted from [57]	Self rating	-	x

Using ESM, potentially relevant transdiagnostic (subthreshold) symptoms such as sadness, anxiety, psychotic experiences und stress will be recorded (table 3). Items are based on previous studies and questionnaires, given the lack of standardized ESM assessment in clinical populations. In-app reminders will be sent out five times a day at fixed time points: 9:30h, 12:30h, 15:30h, 18:30h, 21:30h for a duration of 14 days (figure 2b). In each survey, participants will be asked how much they endorse a certain feeling or behavior at the time of filling out the survey: “Wie sehr trifft die folgende Aussage im jetzigen Moment auf Sie zu?” (How much does the following statement apply to you at this moment?). Responses will be given on a visual analogue scale (in percent) from “0 = trifft überhaupt nicht zu” (does not apply at all) to “100 = “trifft voll und ganz zu” (applies fully), with a slider that can be moved

in 1-unit increments (figure 2c). Participants will be asked to fill in the items as soon as possible after receiving the in-app reminder, but no later than 60 minutes afterwards. Filling in the items takes about 1-1.5 minutes in total. Similar ESM protocols were deemed acceptable for clinical populations in prior studies [28,57,58]. The *insightsapp* will be used only for the regular active collection of transdiagnostic symptoms by means of the described self-report questions. No personal information (such as name, phone number, etc.) or passive data are accessed, stored or transferred by the *insightsapp*. To maximize the number of completed surveys for every participant, participants will be contacted at least once during the assessment period to assess instruction adherence, identify any concerns associated with the method and help participants with any problems in completing the ESM questionnaire.

Table 3. ESM items assessed in the PhenoNetz-study (along with the English translation).

1.	Ich bin traurig (I am sad).
2.	Ich nehme Dinge wahr, die andere Menschen nicht wahrnehmen können (I perceive things that other people cannot perceive).
3.	Ich habe Schwierigkeiten, mich zu konzentrieren (I have difficulties concentrating).
4.	Ich bin kontaktfreudig (I feel sociable).
5.	Ich fühle mich gestresst (I feel stressed).
6.	Ich bin zufrieden mit mir (I am satisfied with myself).
7.	Ich fühle mich ängstlich (I feel anxious).
8.	Es fällt mir schwer, mich zu Dingen zu motivieren (I find it hard to motivate myself to do things).
9.	Ich bin misstrauisch gegenüber anderen Menschen (I am suspicious of other people).
10.	Ich grüble (I am brooding).

In the follow-up assessment conducted after the 14 days of ESM data collection, data on psychopathology, medication and substance use will be assessed again, referring to the 14 days during which ESM data were collected (table 2). In addition, experiences and strain associated with the ESM data collection will be assessed via a questionnaire translated and adjusted from a previous study conducted in clinical participants [57] (supplementary table S1). If desired, participants will be provided with a personalized feedback report on their ESM data.

Data security

Using a smartphone app installed on the personal smartphone of participants for data assessment requires particular attention to data security (for a broader discussion on ethical concerns regarding digital phenotyping procedures in the psychological and psychiatric sciences see [59,60]). Therefore, subjects must provide additional consent to collect data within the app and grant the necessary permissions to the app on the smartphones (such as being notified by the app about available surveys). The ESM data collected by the *insightsapp* is pseudonymized (16-digit alphanumeric codes) and sent directly to a server hosted and maintained by a professional web hosting service after each survey. Answers to the surveys are only stored temporarily locally on the smartphones and deleted once they are transmitted to the server. To secure the data transfer from the smartphone to the server, both the connection between the *insightsapp* and the backend software on the server is encrypted by the use of a SSL certificate.

Safety

Given that this study is observational, there are no direct risks associated with participation. Previous studies have demonstrated good acceptance of the ESM protocol implemented in this project. Even if participants become more aware of their symptoms due to

high-frequency data collection, this does not have a negative effect in terms of worsening symptoms [28,57,61]. Participants can terminate the ESM data collection at any time without giving reasons. Participants who are acutely suicidal or a danger to others will immediately be presented to the service physician for further assessment. Should this become apparent in a telephone call, participants will be reported to the responsible social psychiatric service.

Data analytic plan

All statistical analyses will be conducted in the *R* language for statistical computing [62]. Descriptive analysis of the sample will include mean, standard deviation, median and interquartile range as appropriate. Participants included in the analysis will be compared to those that dropped out of the study or were excluded due to too little available measurements (< 20 measurements [63,64]) via appropriate classes of permutation tests [65]. Changes in measures that were assessed twice, pre- and post-ESM (see table 2), will be compared via linear mixed modeling. Prior to the analyses of ESM data, we will detrend the ESM data by fitting fixed-effects linear regression models to each ESM item, regressing out a linear trend on time (i.e., general increases/decreases in items over time). We will then generate both within-person group level and individual person networks as described in detail below. These analyses allow us to examine symptom dynamics both within one individual ($n = 1$), as well as averages within multiple individuals ($n > 1$).

Individual networks

For each participant, we will generate both temporal (a directed network displaying symptoms predicting each other across an approximately 3-h lag, while controlling for all other experiences in the model at the prior measurement) and contemporaneous networks (an undirected partial correlation network showing how the 10 assessed transdiagnostic symptoms relate to each other in the same window of measurement, controlling for the previous time point

(temporal effects)). Both contemporaneous and temporal idiographic networks provide important information on potential dynamics between symptoms, emotions and experiences for each participant [34]. These dynamics are indicative of psychopathological mechanisms specific to the individual. Technically, we will z-standardize the data per ESM item, and then use a Graphical Vector Autoregressive (GVAR) model using full information maximum likelihood estimation (FIML) to account for missing data, and stepwise model search to find an optimal model that minimizes some the Bayesian Information Criterion (BIC), thresholding at $\alpha = .01$ for the pruning or addition of individual edges (*R* package 'psychonetrics' [66]). To assess the most central symptoms in the contemporaneous network, we will compute strength centrality, a commonly used index of centrality. For the temporal network (3h lag), In-Strength (how much input a symptom received from other symptoms) and Out-Strength (how much output a symptom provides to other symptoms) values will be calculated. The indices of centrality will be calculated using the *R* package 'qgraph' [67].

Group-level networks

We will mean-center ESM items per person, and then use the multi-level vector autoregressive (mlVAR) *R* package to estimate three group-level network structures including the 10 assessed symptoms, reflecting the average process of all participants: between-subject (undirected partial correlation network between the means of participant's scores, capturing, in general, whether participants high on a given node are also high on other nodes during the two-week course of the study), contemporaneous (an undirected partial correlation network showing how symptoms relate to each other in the same window of measurement, controlling for temporal relationships), and temporal (a directed network displaying symptoms predicting each other across an approximately 3-h lag, while controlling for all other experiences in the model at the prior measurement). See [34,63,64] for a detailed description of methodological

details. Centrality will be assessed using strength centrality in the contemporaneous network, and In-Strength and Out-Strength in the temporal network (*R* package 'qgraph' [67]).

Aims and hypothesis

Our hypotheses will be tested in the following steps:

1. We will compute both group longitudinal (between-person, contemporaneous, temporal) networks and individual longitudinal networks (contemporaneous and temporal; see [34]) as described above. In line with prior clinical research [58], we hypothesize that networks will be highly variable across individuals and show relevant deviations of individual networks from group level networks, showcasing the importance of generating personalized models.

2. We will identify symptom centrality and unique partial correlations among symptoms in each network for each type of network as described above. We hypothesize that on group level, feeling stressed will be the most central symptom in the contemporaneous network and predict other experiences in the temporal network, given that stress experience is frequently discussed as a transdiagnostic factor in psychopathological experiences [22–25].

3. We will evaluate the degree of association between risk factors (e.g. childhood trauma) and network connectivity, assessed by global strength of individual networks (temporal and contemporaneous), in a linear modeling approach. Based on prior research and theoretical considerations [68–70], we hypothesize that risk factors will be associated with an increased network connectivity. Similarly, we hypothesize that poorer psychosocial functioning will be associated with increased network connectivity.

4. We will identify most variable partial correlations (i.e., associations between symptoms that vary the most across participants), most variable central symptoms (i.e. symptoms that vary the

most across participants in their centrality in individual contemporaneous networks, as assessed with strength centrality), and most variable predictive symptoms in individual temporal networks (i.e. symptoms that vary the most across participants in their predictivity in individual temporal networks, as assessed with out-degree strength centrality) and associated them with risk/resilience factors as well as sociodemographic factors in an explorative fashion.

5. We hypothesize that after participation in the study, patients will demonstrate more self-reflection than at baseline, as indicated by significant increases in the self-reflection and insights-scale total score from baseline to follow-up (post-ESM assessment, assessed by linear modeling).

Required number of ESM observations

Due to the methodological novelty of individualized networks based on intensive time series data, there exist no guidelines on the number of ESM observations required [64]. More observations collected over a longer period of time improves stability and validity of the results; however, this has to be balanced against the feasibility of the integration of the study into the daily lives of the participants. Additionally, the performance of network estimation methods depends on the unknown true network structure—the network equivalent of a true effect size in power analysis [34,64]. In a simulation study [71], for a person-specific network consisting of 8 items, 50 observations were deemed sufficient, i.e. about 6.25 observations per item. In our study, we included 10 items, for which we ideally will obtain 70 observations each, which leaves room for 7 missed surveys (10%) given a target of at least 63 observations. With fewer observations, estimated edges can still be interpreted to represent true edges, but one might miss on estimating other, smaller true edges [34,71].

Sample size

Formal power analyses are not yet worked out for group-level network models based on intensive longitudinal data. Supplementary materials from Epskamp, Waldorp, et al. (2018) report simulation results for mlVAR, showing that mlVAR models are excellent in recovering the fixed effect structures with quite few data, starting at 50 observations. With our targeted sample size of 75, we will surpass this threshold.

Status and timeline of the study

Study recruitment started on November 11, 2020, and is currently ongoing, with an anticipated date of recruitment completion of November 2021.

Discussion

This study aims at an explorative phenotyping of the heterogenous help-seeking population of a psychiatric early recognition center. Applying ESM, we will identify transdiagnostic symptom networks and their association with protective and risk factors, as well as psychosocial functioning. In doing so, we provide a first attempt to validly depict symptoms of the proposed broad transdiagnostic risk syndrome. An explorative phenotyping of the proposed transdiagnostic risk syndrome, combining ESM and network analysis, might provide valuable insights on group- as well as on individual level: Central items and processes might represent anchor points for interventions. Furthermore, insights into potential etiological processes, identified by association with risk factors and resilience factors, might inform prevention strategies. Similarly, etiological processes connected to psychosocial functioning might inform effective interventions for psychosocial disabilities, which are still lacking [35]. Hypotheses about the proposed broad transdiagnostic risk syndrome or effective interventions based on findings of our explorative study might guide future research. Likewise, potential impact of self-monitoring by the high-frequent assessment of ESM needs to be followed by impact studies, testing if ESM could serve as an intervention in help-

seeking populations. Moreover, ESM only represents one powerful element to gain insights into relevant variables collected in everyday life to improve prevention and targeted early intervention [72,73]. Studying the digital footprints left by the human-smartphone interaction (e.g. log in frequency, use of different apps, calling behavior), can provide additional important insights into psychopathological states in help-seeking individuals [74].

Work in this area is deservedly receiving more and more attention [27,32,64], and we believe that this will result in enhanced patient benefit. Our study intends to contribute a milestone towards innovation of personalized early recognition in psychiatry, allowing to help a greater proportion of heterogeneous help-seeking populations [32]. Subsequent impacts on early states and the progress of mental disorders might reduce associated personal, familial, societal, clinical as well as economic burden more effectively.

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Supplementary material for
"Transdiagnostic phenotyping of psychopathology in a help-seeking population (PhenoNetz) - a study protocol for an experience sampling study"

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Table S1. Questionnaire to assess experiences and strain associated with the ESM data collection translated and adjusted from a previous study conducted in clinical participants [1].

	Stimme überhaupt nicht zu	Stimme nicht zu	Weder noch	Stimme zu	Stimme stark zu
Es war mir lästig, jeden Tag fünf mal zehn Fragen zu beantworten.					
Ich war mir meiner Stimmung/ meiner Symptome bewusst.					
Das Beantworten der Fragen in der App hat mir meine Stimmung/ meine Symptome bewusster gemacht.					
Ich habe mich schlechter gefühlt, wenn ich mir meiner Stimmung/ meiner Symptome bewusst war.					
Ich habe mich besser gefühlt, wenn ich mir meiner Stimmung/ meiner Symptome bewusst war.					

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