Zooming in on the development of psychotic experiences

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General introduction

"He wrote on a piece of paper with his pencil. Psychosis: out of touch with reality. Since then, I have been trying to find out what reality is, so that I can touch it."
- Jeanette Winterson, author.

Psychotic disorders are characterized by the presence of hallucinations and/or delusions, with impaired reality testing being at the core (1). Psychotic disorders can impose a large burden on those affected, their friends and family as well as society at large (2,3). Once developed, psychotic disorders come with high levels of comorbidity and increased mortality (3,4). Psychotic disorders are relatively rare, affecting approximately 3% of the population (5). However, psychosis can also manifest outside the clinical range. A substantially larger proportion of the adult population, 5 to 8%, report subclinical expressions of psychosis, typically termed psychotic experiences (PEs). PEs are commonly defined as hallucinations, delusions, or paranoia at subclinical levels, which occur in the general population (6,7) and are often less distressing than true psychotic symptoms (2). It is not yet fully understood how and why some individuals move from having PEs to clinical psychotic symptoms. The aim of this thesis is to increase our understanding of the early development of psychosis by using daily diary data.

In this chapter I first discuss how a widely used model, the clinical staging model, aids in categorizing and identifying individuals who are at risk to develop psychosis. Second, I discuss how diary data can offer novel perspectives and insights in these early clinical stages. Third, I describe the dataset that was used throughout this thesis. Fourth, I discuss several applications of daily diary data, more specifically, multilevel methods and the symptom network theory. I end this introduction with a short description per chapter.

Clinical staging

PEs exist along a continuum of severity, with mild, non-distressing unusual perceptual experiences or overvalued beliefs on one end of this continuum and clinical psychotic disorders on the other. The clinical staging model for psychosis acknowledges this continuum by defining different stages of illness severity, ranging from stage 0 to stage 4 (8). Individuals in stage 0 are asymptomatic but at increased risk for psychosis. This can either be a genetic risk or a psychometric risk, with the latter indicating that these individuals score relatively high on a questionnaire for PEs. Individuals in stage 1 are in the so-called 'prodromal stage'. This stage is divided in stage 1a, capturing individuals with mild/nonspecific symptoms, and stage 1b, capturing individuals with moderate symptoms who are considered at Ultra-High Risk (UHR) or Clinical High Risk (CHR) for psychosis.

Individuals in stage 2 have been diagnosed with a first episode of psychotic illness. Individuals in stage 3 are in incomplete remission/recurrence, and individuals in stage 4 have severe and persistent illness (8). Progression through the stages is not inevitable (9). Rather, individuals can either progress, persist or remit in stages (10). The early clinical stages are characterized by a broad trans-diagnostic symptom pattern, with symptomatology becoming more crystallized (i.e., domain-specific) in the later stages (9,11). Shah et al., (12) found that 32% of individuals with a first episode of psychosis had broad early symptoms like depression, anxiety and low functioning rather than specific PEs before their psychosis diagnosis. In addition, Lee et al. (13) found that individuals with subthreshold non-psychotic symptoms, classified as having clinical risk syndromes for nonpsychotic mental disorders, had an increased risk of developing a psychotic disorder. Together, this highlights the importance of looking at a broad, transdiagnostic spectrum of symptoms when understanding risk stages of psychosis. Importantly, psychotic disorder is not the only clinical outcome of early stages for psychosis as they can also develop into other mental illnesses like anxiety or depression (10,14,15). The combination of a broad transdiagnostic symptom pattern in the early stages and a pluripotent trajectory is illustrated in *figure* 1.

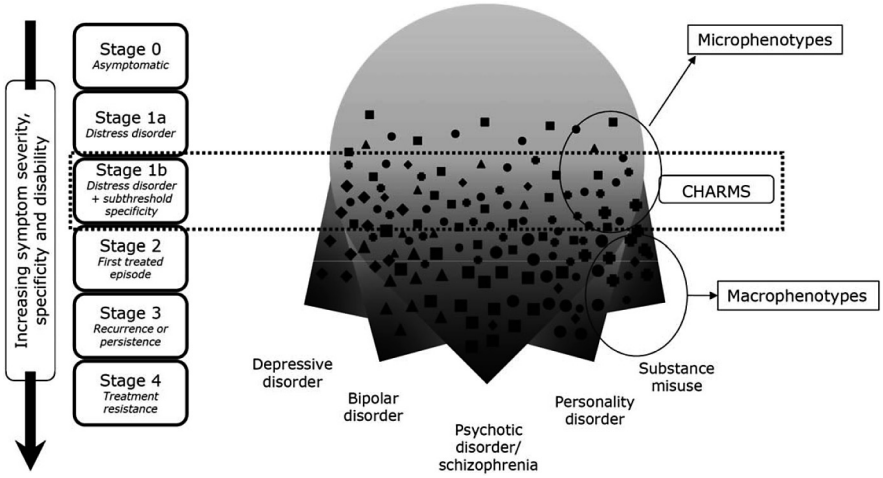

Figure 1: "New transdiagnostic Clinical High At Risk Mental State (CHARMS) paradigm in the context of clinical staging. The shapes represent different types of symptoms". *Note:* reprinted from "Beyond the "at risk mental state" concept: transitioning to transdiagnostic psychiatry", by McGorry et al. 2018, *World Psychiatry, 17(2)*:133-142.

A fundamental goal of the clinical staging model is to prevent progression and promote remission through the clinical stages by prioritizing timely detection and early interventions (16). The clinical staging model can aid in selecting treatments that are stage specific. Clinical staging models are often used in medicine, for example in individuals with cancer. The progression of the cancer, i.e., the stage of cancer, determines the treatment options for a patient. Individuals in later, more advanced stages, receive more aggressive treatment, while individuals in earlier stages can be treated with less invasive treatments. Thus, treatment is tailored to the individual situation, finding a balance between over- and undertreating. The goal of cancer treatment is first and foremost, when possible, survival, but a second important goal is to retain quality of life. This highlights that treatment should be proportional to the illness stage of an individual: over-treatment may lead to unwanted side effects impacting quality of life, and under-treatment may lead to progression of the disease. A similar approach is suited for psychiatric illness, in which treatment in the later stages is also often more intense (i.e., anti-psychotic medication) than in the earlier stages (e.g., behavioral therapy). The typically used diagnostic system, and consequently also the treatment system, often focuses on the chronic and persistent phases of mental illness. This potentially leads to overtreatment of individuals who do present with mental health problems but are located along the early stages (17). An additional consequence is that interventions for those in the early stages are scarce. This has inspired the early detection and treatment paradigm (8). Research has shown that intervention in the early clinical stages of psychosis can be less invasive and is often more effective (8). This highlights the importance of identifying individuals in the early clinical stages of psychosis.

To understand whether treatment is proportional, it is important to identify an individuals' risk to progress to more severe clinical stages (17). The development of psychosis is complex and there is still much to learn about why some individuals progress through the clinical stages while others do not (10). While the risk of transition to a first episode of psychosis for those at UHR has been estimated between 25% (18) and 33% (19) in meta-analyses, little is known about who of the UHR individuals transition and why.

Diary data

One way of increasing our understanding of the complex development of psychosis through subsequent clinical stages may be through changing the level at which we investigate psychosis development. Traditionally, psychotic severity is assessed cross-sectionally with questionnaires about symptom levels and functioning, and

with clinical interviews. These instruments often use the previous week or month as timeframe of reference. However, most experiences fluctuate within- and between days rather than over months (20,21) and assessments at a wider timeframe provide limited insight into how individuals experience symptoms and how these symptoms impact individuals' functioning in daily life. Diary measurements that focus on how symptoms unfold and relate to each other over time can be a way forward. The use of diary measurements in research is not new. In 1913, Bevans used a repeated survey design to assess how working men spent their spare time (22). Diary studies in psychological research emerged later. In 1977, Csikszentmihalyi, Larson & Prescott (23), published a paper in which they examined interpersonal contacts and interaction quality among adolescents. This was the early beginning of the experience sampling method to investigate daily experiences of participants in their natural lives (24). Over recent years, the opportunity to collect such intensive longitudinal data has greatly improved by the introduction of smartphones and smartwatches (25).

With the improved opportunity to collect intensive longitudinal data, there has been a steep increase in research that uses this kind of data to assess all sorts of psychological phenomena. Several terms have been used to describe intensive longitudinal data, all referring to measurements that are recorded multiple times over a relatively short measurement period. An umbrella term that covers a wide range of methods to study people in their natural environment is ambulatory assessments (26). There are also terms that refer to slightly different or more specific forms of intensive longitudinal data. Methods that focus on momentary experiences (e.g., at this moment, how sad do you feel?) usually have a high frequency of questions per day (e.g., 7-10 times a day) and are called 'ecological momentary assessments' (27) or the 'experience sampling method' (23). Both terms are often used interchangeably in the literature. Another way of measuring daily life is asking how people felt in the period between measurements (e.g., since the last beep, how sad did you feel?), one or multiple times a day. Thus, there are some differences between the methods in terms of recall period and frequency, with each their own merits and drawbacks. The data used in this thesis comes from a study that assessed experiences, thoughts and emotions once a day at the end of each day for a period of 90 days. As such, this study can be considered a daily diary study. An advantage of daily diary studies is that the burden on participants is relatively low with only one measurement per day. Consequently, it is possible to measure participants over longer periods of time.

The use of intensive longitudinal data offers new and exciting possibilities to better understand mechanisms underlying the early development of psychosis. There are several advantages of intensive longitudinal data over cross-sectional measurements. First, because a person is assessed multiple times over time,

it offers the possibility to assess processes within individuals. Second, it offers the possibility to assess differences between individuals' temporal symptom patterns and the amount of between-individual variation. Even within diagnoses, there is considerable heterogeneity between individuals in the presentation of psychopathological symptoms (28), which makes the generalizability of group results to individual persons low (29-33). In addition, cross-sectional group studies cannot inform us sufficiently on within-person processes (33). Using intensive longitudinal data can give new insights in how symptom patterns may play out within individuals in the early clinical stages for psychosis and how people may differ herein.

One important reason for the need to better understand underlying mechanisms in the early clinical stages is that this might improve the possibility to predict who progresses and who does not. This will also help in identifying those who can benefit most from early intervention. Our current ability to identify those at most risk to progress to more severe illness is limited and should be improved (10,18,34). Often, the risk of transitioning to psychosis has been investigated using questionnaires and interviews, but they have only moderate predictive capacity (35,36). More recently, risk calculators have been introduced to increase prediction accuracy (37,38). Another way to increase prediction accuracy might be through the use of intensive longitudinal data by assessing symptoms in daily life rather than fixed characteristics or retrospective measurements over the past week or month. However, given the burden of collecting intensive longitudinal data, it should first be established whether such data have *added* value over that of cross-sectional data in the prediction of course and outcome of risk states.

The dataset

Throughout the whole thesis, the dataset from the *Mapping Individual Routes of Risk and Resilience* (Mirorr) study was used. Mirorr was designed to investigate the patterns of experiences, symptoms and behaviors in daily life to better understand the manifestation, course, and outcome of early psychopathological experiences, in particular PEs. The Mirorr study combined two daily diary periods of 90 days each with 3 yearly follow-up measurements on a broad spectrum of mental health, risk and protective factors and social functioning. *Figure 2* shows the study design of the Mirorr study. For the diary assessment, participants completed an online diary once a day for 90 days. They received a link to the questionnaire each evening on their smartphone that was to be completed within 1.5 hours, with reminders sent every 30 minutes. The diary questionnaire consisted of 80 closed-ended items covering a broad range of transdiagnostic experiences typical for psychosis, depression, anxiety, mania, obsessive compulsive behavior

symptoms, anger symptoms, and functioning, as well as risk and protective factors. Note that, in line with other literature, we referred to these experiences as symptoms, but that the items in fact represent daily experiences of psychopathological symptoms (e.g., today I felt down). The diary study was repeated at 1-year follow-up. At baseline, 1-year follow-up, 2-year follow-up, and 3-year follow-up, several questionnaires on psychopathology, well-being, functioning, and risk and protective factors were administered.

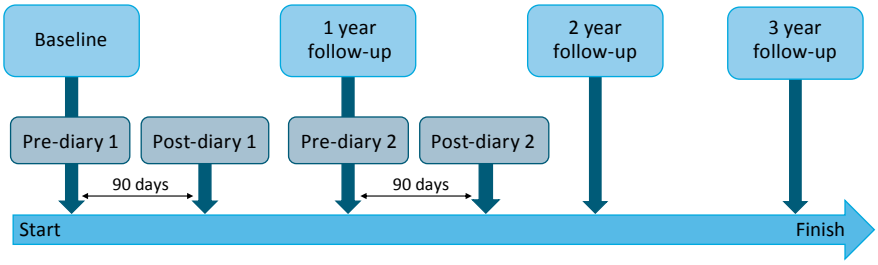

Figure 2: Design of the Mapping Individual Routes of Risk and Resilience (Mirorr) study.

Mirorr consists of 96 individuals aged 18-35 years, distributed along the early stages of the psychosis continuum (stage 0- stage 1b). Individuals were allocated to four subgroups based on their level of PEs (*Figure 3)*, representing clinical stage 0 (subgroup 1), stage 1a with low symptoms (subgroup 2), stage 1a with mild symptoms (subgroup 3), and stage 1b, individuals at UHR for psychosis (subgroup 4). The subgroups are further described in **Chapter 2**, where we provided an in-dept characterization of the Mirorr participants using baseline measurements and daily diary data.

Applications of intensive longitudinal data

Intensive longitudinal data involves multiple measurements for each individual over time. Such data can be analyzed in multiple ways with different statistical techniques, depending on the aim of the research. With intensive longitudinal data collected in multiple individuals, symptom dynamics can be modeled at the individual level or at the group level. Multilevel models are well suited to investigate the dynamics between two variables by assessing the between- and within-day associations while taking individual differences into account. When investigating more than two variables simultaneously, the dynamics between these variables can be modelled as networks of symptoms. Symptom networks can be modelled

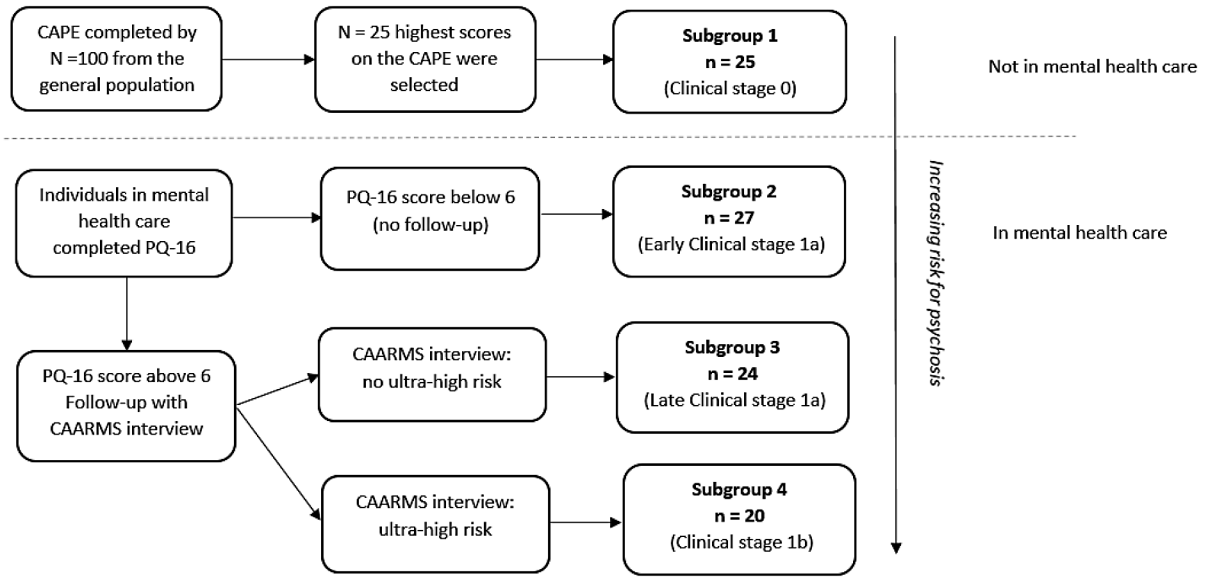

Figure 3: Allocation of participants to the four subgroups of the Mapping Individual Routes of Risk and Resilience (Mirorr) study. Abbreviations: CAPE; Community Assessment for Psychic Experiences, PQ-16; Prodromal Questionnaire 16, CAARMS; Comprehensive Assessment of At Risk Mental States.

by using vector autoregressive models. I will discuss these applications and the theory behind these in more detail in the next paragraphs.

Multilevel methods

Intensive longitudinal data offers the opportunity to investigate how specific symptoms are associated with each other on a daily basis. This can be both temporally, e.g., how anxiety at the previous day (t-1) influences depression the current day (t), and contemporaneously, e.g., how anxiety the current day (t) influences depression the current day (t). This way, we can explore how daily fluctuations in one symptom relate to daily fluctuations in another symptom. Such information helps to elucidate underlying processes in mental health. These associations can be estimated through multilevel models. Multilevel models can be used when variables vary at more than one level. In intensive longitudinal data, one individual is repeatedly measured over time. Here, the time measurement (level 1) is nested within individuals (level 2). Multilevel models take into account that there is dependency among measurements within individuals. With multilevel models, daily dynamic relationships between a broad range of symptoms can be modeled both within- and between individuals. In this thesis we used multilevel modeling to assess the association between daily assessments of PEs and risk (**Chapter 3)** and protective **(Chapter 4)** factors for such experiences in individuals in early clinical stages. In addition, we assessed whether these associations reflected stage-specific or more general mechanisms.

Symptom networks

Another option offered by intensive longitudinal data is to create individual symptom networks. Recently, a shift in research has been made to acknowledge the dynamic nature of symptoms more, both within and across clinical stages (10,21). To resume the analogy of cancer, it is reasonable to expect that a brain tumor causes headache, fatigue and nausea. Thus, one underlying cause (i.e., the tumor), causes all symptoms. Removing the tumor is expected to, in time, alleviate all symptoms. For over decades, this common cause model has also been applied in the field of psychiatry (39). So, for example, in the case of depression, the common cause model assumes a pathogenetic pathway: 'the depression' causes other symptoms such as sad mood, sleep problems and concentration. However, this overlooks the fact that symptoms can directly and mutually influence each other. For example, sad mood may cause sleep problems and concentration loss, but sleep problems can also cause sad mood and concentration loss. In psychiatry, finding common pathogenetic pathways has proven to be very difficult (40-42). Perhaps psychopathology should be approached differently (10). A theory that explicitly acknowledges the interdependencies among psychopathological

symptoms is the symptom network theory (43). The network theory states that psychopathology develops due to interactions between symptoms rather than as flowing from one underlying cause (40,43). Networks of symptoms can be visualized in network graphs in which symptoms are called 'nodes' and connections between them 'edges'. Networks provide an intuitive representation of how psychopathology arises and how symptoms can influence each other; as such, they offer a novel way of thinking about and understanding psychopathology. Symptom networks can be constructed based on cross-sectional group data or on (individual) time series data. Symptom networks based on cross-sectional group data provide a network in which the connections represent co-occurrence of symptoms in a group of individuals. While this may be informative for certain research questions, it neglects the dynamic and fluctuating nature of symptom expression (20,21). In addition, results found at group level do not necessarily translate to associations found over time and within individuals (29-33,44). Therefore, in this thesis, we exclusively focus on symptom networks created with daily diary data, which provides us with the valuable opportunity to study the dynamic relationship between symptoms at an individual level. These individual symptom networks can be investigated in several ways.

Vector Autoregressive models. Individual symptom networks can be created through Vector Autoregressive (VAR) analyses. A VAR model is a multivariate autoregressive model that regresses variables over a specified set of time lags on themselves and all other variables of the multivariate system (45,46). VAR models can be used to investigate temporal relationships over subsequent time points as well as contemporaneous relationships within one time point. Ideally, both temporal and contemporaneous associations are assessed, as contemporaneous associations might capture temporal associations that happen within a shorter time frame than the measurement window (47). In temporal networks, the directionality of edges can be estimated due to the temporal dependencies. In other words, it can be estimated which variables influence which from timepoint t-1 to timepoint t. This is in contrast to contemporaneous networks, in which no edge direction can be estimated because the associations are estimated at the same time point. The rate and strength of temporal or contemporaneous edges that are returned by the VAR is dependent on a) the sampling rate of measurements and b) the timeframe in which symptoms unfold.

Network density. Analyses of individual symptom networks provides information at different levels. At the level of the full network, one can see how strongly all nodes are connected to each other. This is reflected in 'network density', which represents the ratio of the number of edges that are actually observed to the total possible number of edges. It has been hypothesized that strongly connected networks pose a vulnerability for developing (more) severe psychopathology, as

one perturbation to the network can activate all other nodes in the network, leading to a state of stable psychopathology (43). Several studies, using both cross-sectional (48-50) and ESM group-level data (51-55), found that groups of individuals with established mental illness have more densely connected networks than groups of individuals from the general population. However, Groen et al. (56) found no differences in network density between a group with persistent depression and a group with reduced symptoms. In addition, network density based on daily diary data (50 days) was not cross-sectionally associated with anxiety and depression (57), but network density based on EMA data collected 9 times per day (for 8 days) was. Thus, findings on the association between network density and psychopathology remain inconclusive and more research is warranted to understand if, and how, network density is associated with psychopathology severity.

Node centrality. At the level of the individual nodes, symptom centrality provides information on the relative importance of individual symptoms within the network (58,59). There are several measures of centrality, with strength/degree, betweenness and closeness being the most popular. As betweenness and closeness are considered less suited for network analyses in psychology, the only centrality index that might provide relatively unbiased information is node strength (60). Thus, in this thesis, when assessing symptom centrality, only strength will be assessed. Strength is defined as how often and strongly a symptom is connected to all other symptoms in the network. In temporal networks, where a direction is given to each edge in the network, one can distinguish between in-strength and out-strength. In-strength indicates how often and strong other symptoms influence the specific node, and out-strength how often and strong the specific node influences other symptoms in the network. It has been argued that nodes with high out-strength may represent important targets for treatment (58,61). McGorry et al. (10) hypothesized that the role of symptoms changes with different at-risk stages for psychopathology, which would be expressed by different centrality indexes in different stages.

Group Iterative Multiple Model Estimation. Previously, I argued that it is important to look at individual dynamics rather than solely at group dynamics, because individuals are likely to differ from each other. On the other hand, it seems logical to expect that individuals do not all differ 100% from one another. As Maya Angelou (American poet) said: “in minor things we differ, in major we are the same”. In other words, some characteristics may be relatively unique, while others may be more common. As Robert Kendell (62) argued, there are three characteristics in human beings: 1) a universal set of characteristics (e.g., possessing a heart), 2) a truly individual set of characteristics (e.g., fingerprints), and 3) a set of characteristics that is shared with some, but not with others (e.g., blue eye color). Thus, in researching symptom dynamics, it can be beneficial to investigate the extent to

which these dynamics are shared or unique. Especially in terms of treatment and prediction, some form of overlap between individuals in terms of subgroups that share characteristics is important to allow for some form of generalization. A statistical approach well-suited to examine this is Group Iterative Multiple Model Estimation (GIMME) (63). GIMME has the ability to create a group network as well as individual networks through an iterative process. It uses structural equation models (uSEMS; (64)), that is, structural VAR models that regress variables on themselves and all other variable in the model at the same time point (the contemporaneous paths) and the previous time points (the temporal paths) (65). GIMME first fits a null network model (i.e., a model with no parameters) for each individual. Second, it fits a group-level model through assessing whether adding a parameter (edge) to the model would improve the model fit for the majority (set at a percentage by the researcher) of the sample. In this way, GIMME first adds edges replicated across all individuals. Third, for the remaining edges, GIMME estimates individual-level models separately for each individual (66). This way, GIMME arrives at a confirmatory model including all group- and individual edges. As Robert Kendell (62) mentioned, there may be subsets of individuals that are more alike than other subsets of individuals. GIMME has an extension to assess exactly this: in addition to modeling group and individual paths, GIMME can model subgroup paths. Subgroups can either be pre-determined based on theory (confirmatory subgrouping-GIMME)(67), or detected by GIMME based on similar data patterns, making it data-driven (subgrouping-GIMME)(65). While there is merit to comparing symptom networks between subgroups created based on clinical stage (i.e., theory-based subgroups), a pitfall is that diagnostic boundaries are known to be arbitrary (68). Often, there are no natural boundaries between mental disorders, as shown by large comorbidities. In addition, there may be considerable overlap between the early stages, as boundaries between them are also arbitrary. A data-driven way to create subgroups based on symptom dynamics may provide new insights into how these stages overlap or represent distinct stages.

Stability of networks. One of the strong merits of diary data is that it captures short-term fluctuations in experiences. However, this more fleeting nature of the constructs that are assessed could also be seen as a drawback. An important question that rises is how stable these patterns are at the level of daily life. In addition, interventions based on symptom network structures are being developed to improve treatment (69,70). This implicitly assumes that symptom network structure is associated with psychopathological severity, and in turn, that individual network structures change alongside changes in psychopathology severity. This is an implicit assumption that has not been tested before.

Predictive value of symptom dynamics. Because symptom dynamics provide different insights in psychopathology, they may potentially improve our ability to

predict the future course of psychopathology. One requirement is that they should outperform commonly used questionnaires, considering the added effort and time investment in collecting diary data for both the patient and clinician/researcher. Several metrics derived from diary data have been proposed as predictors of future psychopathology. One of them is symptom network density as hypothesized by the density hypothesis. Recently, Dejonckheere et al. (71) proposed that more simple metrics from intensive longitudinal data, like the mean and variance of the symptom severity, are better predictors than complex measures like network density. How intensive longitudinal data can aid in the prediction of psychopathology, and whether they outperform cross-sectional questionnaires, remains to be investigated.

Outline of this thesis

With the present thesis I aim to increase our understanding of the early development of psychosis by using daily diary data. Using different methods to analyze daily diary data, I aim to increase insight into mechanisms of how PEs, and more general psychopathology, develop.

Part 1 of this thesis focuses on how individuals in different early clinical stages, each representing different levels of risk for psychosis, differ from each other and how they are alike. In addition, it focuses on how risk- and protective factors are associated with PEs on a daily basis. In **Chapter 2**, we gave an in-dept description of the Mirorr sample that was used throughout the whole thesis. The sample was assessed at baseline with several cross-sectional and 90-day daily diary measures of psychopathology, risk and protective factors and psychosocial functioning. In this chapter, we compared the four subgroups from Mirorr (representing clinical stage 0-1b) on all measures. A prominent known risk factor for the development of psychosis is sleep problems (72,73). As both sleep and PEs are known to fluctuate over time, using intensive longitudinal data and multilevel modeling is well-suited to investigate their associations. In **Chapter 3**, we assessed the dynamic daily association of sleep quality and quantity with Pes, and differences therein between the four subgroups from Mirorr. While most research in psychiatry focuses on risk factors, assessing protective factors might be equally important (74). Therefore, in **Chapter 4**, we adopted the same approach as in Chapter 3, but here focused on the daily association between positive affect, as a potential protective factor, and PEs.

Part 2 of this thesis focuses on applying the symptom network approach to the early development of psychosis and on improving prediction of psychopathology and PEs. To gain more insight in the extent to which symptom dynamics are

stage-specific or more general, we constructed individual symptom networks based on 10 transdiagnostic symptoms in **Chapter 5.** More specifically, we compared symptom network density and node centralities between and within the early clinical stages, and thus also tested the 'density hypothesis' from the network theory. To assess which symptom dynamics are general in the early clinical stages and which are more stage- or individual specific, we applied GIMME in **Chapter 6.** Here we compared theory-based subgroups (the four Mirorr subgroups) to data-driven subgroups based on similar network dynamics. In addition, we compared these data-driven subgroups on psychopathology, well-being and social functioning. In **Chapter 7**, we related changes in psychopathology over the period of 1 year to the stability of diary-based symptom networks. Herewith we tested the implicit assumption that changing network structure would also result in changes in psychopathology severity. In **Chapter 8,** we assessed the added value of daily diary data in the prediction of psychopathology and PEs. For this, we used a stepwise approach in which we first tested the added value of the mean and variance of a 90-day daily diary over that of baseline questionnaires in the prediction of psychopathology and PEs. Second, we assessed the added value of individual symptom network density over that of the baseline questionnaires and the mean and variance of the diary period. In addition, to see whether a shorter diary period resulting in less burden for the patient showed similar results, we repeated the same analyses for diary periods of 7-14- and 30-days.

In **Chapter 9**, I summarize and discuss the main findings described in this thesis. Next, I discuss five lessons that can be learned from this thesis, methodological considerations and clinical implications. I end with concluding remarks on the main message of this thesis.

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