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Group, Subgroup, and Person-Specific Symptom Associations in Individuals at Different Levels of Risk for Psychosis: A Combination of Theory-based and Data-driven Approaches

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Introduction: **Dynamics between symptoms may reveal insights into mechanisms underlying the development of psychosis. We combined a top-down (theory-based) and bottom-up (data-driven) approach to examine which symptom dynamics arise on group-level, on subgroup levels, and on individual levels in early clinical stages. We compared data-driven subgroups to theory-based subgroups, and explored how the data-driven subgroups differed from each other.** ***Methods:*** **Data came from $N = 96$ individuals at risk for psychosis divided over four subgroups ($n_1 = 25$, $n_2 = 27$, $n_3 = 24$, $n_4 = 20$). Each subsequent subgroup represented a higher risk for psychosis (clinical stages 0-1b). All individuals completed 90 days of daily diaries, totaling 8640 observations. Confirmatory Subgrouping Group Iterative Multiple Model Estimation (CS-GIMME) and subgrouping (S-)-GIMME were used to examine group-level associations, respectively, theory-based and data-driven subgroups associations, and individual-specific associations between daily reports of depression, anxiety, stress, irritation, psychosis, and confidence.** ***Results:*** **One contemporaneous group path between depression and confidence was identified. CS-GIMME identified several subgroup-specific paths and some paths that overlapped with other subgroups. S-GIMME identified two data-driven subgroups, with one subgroup reporting more psychopathology and lower social functioning. This subgroup contained most individuals from the higher stages and those with more severe psychopathology from the lower stages, and shared more connections between symptoms.** ***Discussion:*** **Although subgroup-specific paths were recovered, no clear ordering of symptom patterns was found between different early clinical stages. Theory-based subgrouping distinguished individuals based on psychotic severity, whereas data-driven subgrouping distinguished individuals based on overall psychopathological severity. Future work should compare the predictive value of both methods.**

Key words: clinical staging/CS-GIMME/S-GIMME/diary data/intensive longitudinal data analyses

Introduction

"In minor things we differ,
in major we're the same"
Maya Angelou

Although relatively rare, psychotic disorders can impose a large burden on affected individuals, friends and family, and society.[1,2] Intervention at an early stage of developing psychosis may improve prognosis.[3] This requires early identification of individuals with subclinical psychotic symptoms, before the onset of a full-blown psychosis. The clinical staging model does this by proposing that mental illness, including psychosis, does not emerge abruptly but rather develops gradually through different stages of illness severity, ranging from stage 0 (increased risk of psychotic or severe mood disorder without current symptoms) to stage 4 (severe, chronic, or unremitting illness).[4] Understanding what drives progression through stages may drastically improve our ability to detect and treat individuals along the psychosis continuum. One

possible driving force may be found in the interaction of symptoms. Symptom interactions can be interpreted from a network theory of psychopathology, which assumes that psychopathology arises as a direct consequence of interactions between symptoms (eg, sad mood → sleep problems → concentration loss → sad mood).[5] These interactions can be visualized in a network where symptoms are called "nodes" and the statistical relations between these nodes are called "edges."[6] Most research on symptom dynamics in psychosis has focused on individuals in later illness stages, after the first episode of psychosis.[7–9] However, the dynamics between symptoms may reveal important insights into underlying mechanisms especially in early stages of illness development, because illness expression in these stages is thought to be more volatile.[10,11]

Group-based symptom dynamics may not be generalizable to the individual in studies on symptom dynamics.[12–15] Using group-based data to draw conclusions about the population at interest is therefore suboptimal, as this assumes homogeneity in a population while heterogeneity is more plausible.[16,17] Assessing individual symptom dynamics requires intensive longitudinal data. In previous work, we modeled individual symptom networks based on diary data and compared characteristics of these individual networks between subgroups representing different early clinical stages of psychosis (van der Tuin et al, under review). While we did not find differences in network connectivity and symptom strength between the subgroups, we did find large individual differences. While acknowledging differences between individuals, it seems also reasonable to expect that not every individual has a 100% unique pattern of symptom interactions and that some similarities between individuals exist; this would be expressed in the existence of subgroups. The extent to which dynamics between symptoms reflect universal, subgroup- or person-specific processes remains an intriguing open question.

A statistical approach well-suited to explore this question is Group Iterative Multiple Model Estimation (GIMME).[18] GIMME allows for identification of dynamics of the total group and dynamics that are unique to the individual. GIMME has two extensions; confirmatory subgrouping GIMME (CS-GIMME)[19] and subgrouping GIMME (S-GIMME),[17] which both allow for taking into account the potential existence of subgroups. Put simply, CS-GIMME uses a confirmatory approach where subgroups are predefined based on theory, and S-GIMME uses an exploratory approach where subgroups are formed based on similar data patterns. In the context of clinical staging, CS-GIMME, therefore, offers the possibility to examine the extent to which symptom dynamics are similar or different in individuals across different clinical stages: it allows us to explore which dynamics between symptoms are general (ie, apply to most individuals who are generally "at-risk" for psychosis), which dynamics are more stage specific (ie, apply only to individuals in the same clinical stage), and which dynamics are individual-specific. In addition, subgroups formed in S-GIMME (=data-driven) can be compared to subgroups based on the clinical staging model (=theory-based). GIMME was developed originally for fMRI research.[18] More recently, the approach has also been used in psychopathological research, including personality disorders[20–22] and depression.[23] To the best of our knowledge, this is the first study that applies S-GIMME and CS-GIMME in the context of (risk for) psychosis with daily diary data.[19]

This study aimed to examine symptom dynamics in individuals in different early clinical stages for psychosis. We used data from the Mapping Individual Routes of Risk and Resilience (Mirorr) study.[24] The Mirorr sample contains four theory-based subgroups (TB-subgroups), consisting of individuals with different levels of risk for psychosis according to the clinical staging model (stage 0–1b). The Mirorr study includes a daily diary study of 90 days on experiences of symptoms from multiple psychopathological domains and factors of risk and resilience. First, we examined which connections between symptoms arose on group-level, a priori defined TB-subgroup-level, and individual-level, using CS-GIMME. Second, we adopted a data-driven approach to determine subgroups based on shared symptom dynamics (as opposed to being predefined according to the clinical staging model), using S-GIMME. These data-driven subgroups (DD-subgroups) were compared to the TB-subgroups. In other words, we investigated whether grouping individuals based on severity of psychotic symptoms (clinical staging model) and based on connections between symptoms (symptom dynamics) would lead to similar clustering of individuals. Third, we explored whether the DD-subgroups differed regarding: age, gender, psychopathology, well-being, and social functioning.

We preregistered our analytic plan after data collection but prior to data analyses (see https://osf.io/jw3uk/ for our preregistration). Regarding the first aim, we hypothesized that GIMME would recover paths at group-level, meaning that these paths are general to the whole sample. This would be in line with the observation that early clinical stages have similarities.[25] In addition, based on subgroup allocation according to the clinical staging model[3] we hypothesized that GIMME would recover paths that are specific for the different subgroups. Finally, we hypothesized that GIMME would recover individual-level paths (ie, paths that are specific for one individual), as we expected that the heterogeneity within the sample would not be fully explained by general or subgroup patterns.[13] This is a first exploratory study and thus we did not have hypotheses about specific paths that would be recovered. Because the other two research aims were exploratory in nature, we had no clear a priori hypotheses.

Methods

Participants and Study Design

Baseline data of the Mirorr study were used (N = 96). Mirorr combined a daily diary study with three yearly follow-up measurements on mental health and functioning in individuals at risk for psychosis. The sample consisted of four subgroups representing different early clinical stages; subgroup 1 represented stage 0 with the lowest risk, subgroup 2 stage 1a with mild psychotic symptoms, subgroup 3 stage 1a with moderate psychotic symptoms, and subgroup 4 represented individuals at Ultra-High Risk (UHR) for psychosis (figure 1).

Inclusion criteria were: age between 18 and 35 years, ability to read and speak Dutch fluently and to follow the research procedures, and providing informed consent. Exclusion criteria were: a history of/or current psychotic episode according to the Diagnostic and Statistical manual of Mental Disorders 4 (DMS-4) criteria, significant hearing or visual problem impairments, and pregnancy.

Baseline measurements involved cross-sectional questionnaires on symptomatology, functioning, need for care, and risk and protective factors, and a 90-day diary study on the daily experience of psychopathological symptoms, emotions, functioning, and stress. For the diary study, participants received a text message with a link to the questionnaire on their smartphone at a fixed time each evening (based on their personal preference), resulting in one measurement per day. A reminder was send after 30 min and a 90-minute window was allowed for responding.

Data from the diary study were used to construct symptom networks in GIMME. For more details about participants, design and procedure, see Booij et al[24] and Wigman et al (under review).

Measures

Demographic Characterization. Age, gender, and education level are described per and across the four subgroups.

Cross-sectional Questionnaires. General psychopathology was measured with the Dutch Symptom Checklist Revised (SCL-90-R[26]). The SCL-90 consists of 90 items, scored on a 5-point Likert-scale (not at all—very much), concerning psychological symptoms in the past week. The Dutch SCL-90 has high reliability (ω = .98)[27] and excellent internal consistency in our sample (Cronbachs α = .98).

Social functioning was measured with the Groningse Vragenlijst voor Social Gedrag (GVSG[28]). The GVSG is a Dutch self-report questionnaire assessing social functioning in nine social domains. Five domains assess interpersonal relationships (parents, partners, children <15, children >15, and friends) and four domains assess social role functioning in education, paid or unpaid work, household chores, and leisure time. The GVSG consists of 45 questions scored on a 4-point Likert scale. Only person-specific relevant domains are used to calculate the total score.

Psychological well-being was measured with the Flourishing Scale (FS[29]). The FS is a short self-report questionnaire measuring psychological well-being on several domains ranging from social relationships to having

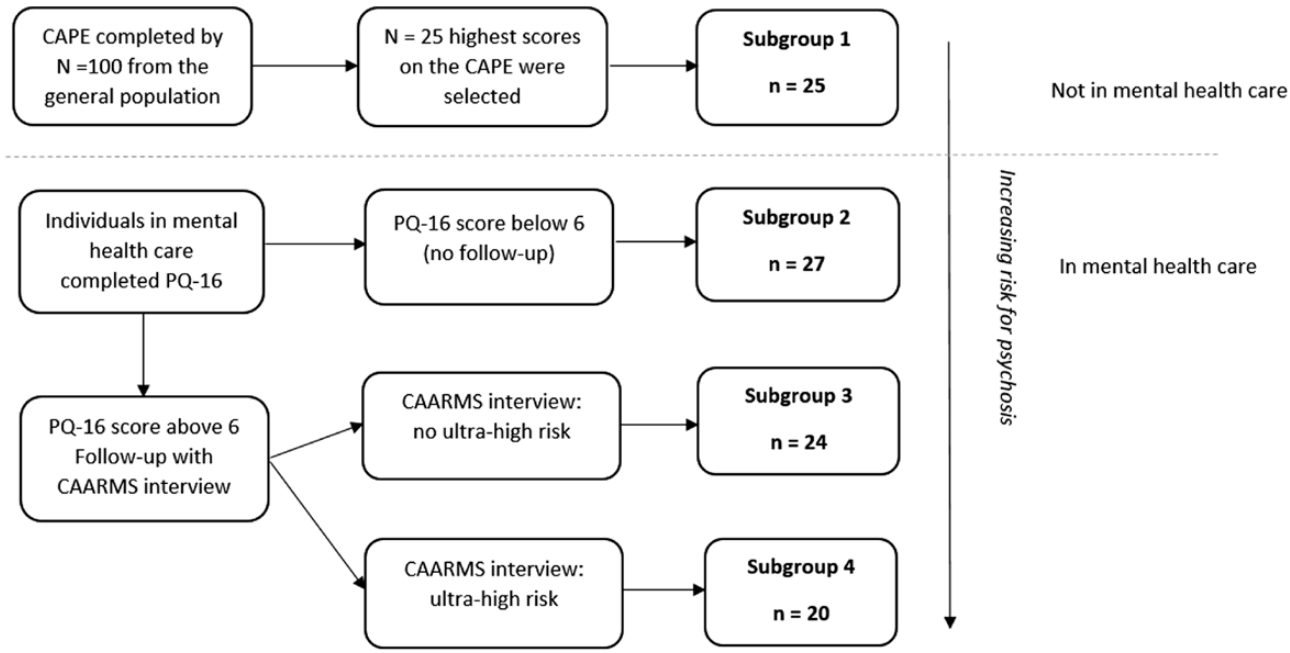

Fig. 1. Allocation of individuals to the 4 TB-subgroups.

a purpose in life. The FS has 8 items which are scored on a 7-point Likert scale. The FS has good reliability and validity,[29] and had good internal consistency in our sample (Cronbachs α = .86).

Subclinical psychotic experiences were measured with the Community Assessment of Psychic Experiences (CAPE[30]) self-report questionnaire. The CAPE consists of 42 questions scored on a 4-point Likert scale on both frequency and distress of psychotic experiences. The CAPE has good reliability and validity,[30] and had good internal consistency in our sample (Cronbachs α = .89).

The number and type of *psychiatric diagnoses* was assessed with the mini-SCAN.[31] The mini-SCAN is a valid[32] and relatively short semi-structured clinical interview for assessing psychiatric diagnoses.

Diary Items. Diary assessments consisted of 80 items covering a broad range of feelings and experiences that are typical for, among others (subclinical) psychosis, depression, anxiety, mania, obsessive-compulsive behavior, and anger. For this study, we selected 16 items and categorized them into six domains: irritation (eg, I felt irritated today), stress (how stressed were you today), depression (eg, I felt down today), psychosis (eg, I felt suspicious today), anxiety (eg, I felt anxious today), and confidence (eg, I felt confident today) (supplementary table 1). Items were scored on a 100-point Visual Analogue Scale (VAS) ranging from "not at all" to "very much." Item scores were averaged per domain resulting in one score per domain. The domain scores were used as nodes in the analyses.

Statistical Analyses

Symptom Network Construction. Confirmatory Subgrouping Group Iterative Multiple Model Estimation (CS-GIMME) and Subgrouping-GIMME (S-GIMME)[33] were used to construct symptom networks, using the R package "gimme."[34] GIMME incorporates unified structural equation models (uSEMs[35]), through which it can model group-level, subgroup-level, and individual-level symptoms networks. uSEMs are structural vector autoregressive (VAR) models that regress variables on itself and all other variables in the model at the same time point (contemporaneous paths) and the previous time point (temporal paths).[17] Note that GIMME estimates directions of contemporaneous paths but that these directions cannot be interpreted in causal or temporal terms; the contemporaneous directions are merely statistical prerequisites to estimate temporal associations.[18] Therefore, even though GIMME provided directions of contemporaneous paths and we showed them in the symptom network figures, we did not report or interpreted these otherwise.

For both CS-GIMME and S-GIMME, default settings from the gimme-package[34] were used: autoregressive (AR) paths were freed,[36] subgroups were based on the Walktrap algorithm, and the significance criteria for pruning of paths was set with a Bonferroni correction at $\alpha = .05/N$.[16] These default settings were chosen as previous studies have shown that they reliably recover true effects.[16,17,36–38] The group-level-criterion was set at 75%,[18,39] meaning that to be included in the group-level network, adding an edge should improve model fit for at least 75% of the sample. Setting the group-level network criterion high might aid the recovery of subgroup-paths as these are based on individual-level paths that remain after searching for group-level paths.[17] The subgroup-level network criterion was set at 51%, because subgroups can be rather small and a higher subgroup-level threshold could lead to suboptimal subgroup identification (eg, if 5 out of 7 persons in a subgroup share a path this would be missed by the 75% threshold). Both the group-level threshold of 75% and subgroup-level threshold of 51% are recommended in the literature.[18,39]

First, we performed CS-GIMME with predefined TB-subgroups. Group-level, subgroup-level, and individual-level paths were examined. Second, we performed S-GIMME and compared DD-subgroups identified by S-GIMME to the TB-subgroups by assessing the distribution of individuals from the four TB-subgroups over the recovered DD-subgroups. Next, we assessed which other factors were associated with DD-subgroup membership by performing a Multivariate Analysis of Variance (MANOVA) (inference criterion: $P < .05$) with DD-subgroup as the independent variable and age, gender, well-being, social functioning, and general psychopathology as dependent variables.

Assumptions. GIMME assumptions of normality, stationarity, model-fit, and white noise were checked. Due to a severe violation of the normality assumption, we performed a Copula transformation[40] per item per individual. More information about GIMME assumption checks and how these were handled are provided in supplementary appendix A. All assumptions for the MANOVA were checked and none were violated.

Missing Data. We tested six different imputation strategies on our dataset. We chose exponential moving average, as this strategy performed best. For the detailed procedure see supplementary appendix B.

Power Considerations. The power of GIMME is dependent on both the number of individuals and the number of measurements per individual. Simulation studies have shown that subgrouping GIMME provides reliable results with as few as 25 individuals in the total group,[17] and is robust with observations as few as 60 observations per individual.[36] With 90 time points per individual and 96 individuals, we have sufficient power to accurately detect and recover paths.

Results

Confirmatory Subgrouping GIMME (table 1)

Group-level Results: Paths Shared by the Large Majority. CS-GIMME identified one contemporaneous group-level path between depression and confidence. This path was significant for 85 individuals (89%) with an average magnitude (beta-coefficient) of −0.50 (sd = 0.23). For all individuals, except one, this path was negative, indicating that feeling depressed was associated with less confidence within the same day.

Subgroup-level Results: Stage-specific Paths (table 2). GIMME identified several contemporaneous subgroup paths, which were mainly positive (95% on average). Several subgroup-level paths were unique for certain stages. For Subgroup 1, this was an association between psychosis and irritation. Subgroup 2 included two unique associations: between stress and irritation, and between depression and stress. In Subgroup 4, we saw three unique associations: between anxiety and depression, between depression and irritation, and between psychosis and anxiety. Subgroup 3 did not have any unique subgroup paths. All other subgroup paths were shared by two or more subgroups (table 2).

Individual-level Results: Heterogeneity Between Individuals. Fit indices showed good fit for all individuals (mean: CFI = .98, NNFI = .97, RMSEA = .04, SRMR = .06). On an average, individuals had 9.0 significant estimated paths, and this number did not differ significantly between the subgroups ($F(3,92) = .22$, $P = .89$). There were no completely shared data patterns between all individuals, in other words, none of the 96 individuals in our sample had exactly the same combination of paths as anyone else in this sample.

Subgrouping (Data-driven) GIMME

In the first step, we used four theory-based subgroups (TB-subgroups) in CS-GIMME. In contrast, in this step S-GIMME identified two data-driven subgroups (DD-subgroups) in contrast to the four TB-subgroups. DD-subgroup 1 comprised 25 individuals and Subgroup 2 comprised 55 individuals. Additionally, 6 individuals did

Table 1. Demographics and Clinical Functioning per TB-subgroup[41]

	Subgroup 1 *N* = 25	Subgroup 2 *N* = 27	Subgroup 3 *N* = 24	Subgroup 4 *N* = 20	Total group *N* = 96	Difference[†]
Cross-sectional measurements						
Demographic						
Age Mean (SD)	23.3 (3.38)	24.8 (3.95)	26.1 (4.12)	24.8 (5.28)	24.7 (4.20)	ns
Gender (% Female)	80.0	74.1	70.8	80.0	76.0	ns
Completed education[‡]						
Low (%)	4.0	18.5	8.3	30.0	14.5	ns
Middle (%)	56.0	51.9	58.3	50.0	54.2	ns
High (%)	40.0	25.9	29.2	20.0	29.2	ns
Other (%)	0	4.0	4.0	0	2.1	
Clinical functioning						
SCL-90 Mean (SD)	141.44 (38.24)	173.78 (45.08)	211.04 (56.09)	232.50 (57.29)	186.91 (59.34)	4,3,2 > 1; 4,3 > 2
GVSG Mean (SD)	15.33 (1.83)	14.60 (1.71)	13.20 (2.35)	13.00 (1.61)	14.27 (1.89)	3,4 < 1; 3< 2
FS Mean (SD)	42.12 (7.75)	35.44 (8.68)	33.33 (8.39)	32.05 (9.05)	35.95 (9.17)	4,3,2 < 1
CAPE Mean (SD)						
Total	60.9 (9.61)	67.5 (11.2)	77.3 (15.3)	75.4 (17.2)	69.9 (14.72)	4,3 > 1
Positive symptoms	23.5 (3.79)	22.7 (2.23)	26.3 (5.09)	26.2 (5.26)	24.6 (4.44)	4,3 > 2,1
Negative symptoms	23.8 (5.14)	28.0 (6.77)	32.5 (7.77)	31.0 (9.37)	28.7 (7.91)	4,3,2 > 1
Depressive symptoms	13.6 (3.29)	16.9 (4.78)	18.5 (5.39)	17.7 (5.36)	16.6 (5.03)	4,3,2 > 1
Mini-SCAN	.36 (.57)	1.22 (.85)	2.04 (1.27)	2.15 (1.27)	1.40 (1.23)	4,3,2 > 1
diagnoses Mean no. (SD)						4,3 > 2
Diary items per domain (median (IQR))						
Irritation	11.87 (12.46)	13.47 (18.89)	24.12 (27.18)	41.42 (21.77)	19.08 (31.63)	4,3 > 1; 4 > 2
Stress	22.43 (13.03)	29.92 (20.62)	44.55 (23.57)	48.78 (30.87)	29.90 (26.53)	4,3 > 1; 4 > 2
Depression	16.55 (5.94)	25.72 (26.05)	27.27 (26.82)	47.43 (29.46)	25.34 (27.80)	4,3,2 > 1; 4 > 2,3
Psychosis	6.40 (3.74)	6.56 (6.67)	6.98 (11.27)	22.92 (14.90)	7.83 (9.68)	4 > 3,2,1
Anxiety	8.41 (7.06)	21.88 (21.09)	19.31 (42.53)	36.16 (22.62)	17.86 (28.26)	4,3,2 > 1; 4 > 2
Confidence	63.32 (18.70)	44.58 (15.53)	49.66 (22.47)	46.21 (20.19)	49.86 (23.23)	4,3,2 < 1

Note:
[†]Significant difference $P < .05$, ns = not significant
[‡] Low = primary education or lower secondary education, Medium = upper secondary education, High = university/college education.[36]

Table 2. Detected Group and Subgroup Paths for CS-GIMME and S-GIMME.

		Mean beta (SD)[†]	% Significant[‡]
CS-GIMME[a]			
Subgroup 1	Depression—Confidence*	−.49 (.19)	88%
	Depression—Anxiety	.34 (.20)	84%
	Irritation—Depression	.34 (.17)	80%
	Psychosis—Irritation	.28 (.17)	64%
Subgroup 2	Depression—Confidence *	−.53 (.20)	93%
	Anxiety—Stress	.49 (.26)	93%
	Stress—Irritation	.24 (.15)	63%
	Depression—Stress	.21 (.25)	44%
Subgroup 3	Depression—Confidence *	−.49 (.29)	88%
	Irritation—Depression	.47 (.41)	75%
	Anxiety—Stress	.36 (.25)	83%
	Depression—Anxiety	.46 (.48)	75%
Subgroup 4	Depression—Confidence *	−.48 (.25)	85%
	Anxiety—Stress	.39 (.20)	80%
	Anxiety—Depression	.42 (.28)	75%
	Depression—Irritation	.42 (.34)	75%
	Psychosis—Anxiety	.35 (.17)	75%
S-GIMME[a]			
Subgroup 1	Depression—Confidence *	−.50 (.17)	92%
Subgroup 2	Depression—Confidence *	−.51 (.24)	91%
	Irritation—Depression	.54 (.31)	95%
	Depression—Anxiety	.47 (.34)	89%
	Anxiety—Stress	.43 (.26)	87%
	Psychosis—Irritation	.28 (.34)	73%

Note:
*Group path.
[†]Beta is the mean magnitude.
[‡]Percentage of individuals per subgroup for whom this path was significant.
[a]Note that although GIMME did provide a direction for contemporaneous associations, we did not report these, as directions for contemporaneous paths cannot be interpreted as such.

not fit in either of these subgroups (1 from TB-subgroup 1, 1 from TB-subgroup 2, 1 from TB-subgroup 3 and 3 from TB-subgroup 4) and were excluded from further analyses. Individuals in higher TB-subgroups were more often allocated to DD-subgroup 2 than to DD-subgroup 1 (table 3). Individuals in lower TB-subgroups were approximately evenly distributed across DD-subgroups 1 and 2; post hoc analyses showed that individuals from TB-subgroup 1 and TB-subgroup 2 with more severe psychopathology were more often allocated to DD-subgroup 2 (supplementary table 2). Hence, DD-subgroup 2 included individuals with more severe psychopathology (see also table 4).

Group-level Results: Paths Shared by the Large Majority Individuals. Similar to CS-GIMME, S-GIMME identified one contemporaneous group path between depression and confidence. This path was negative for 98% of the individuals, and significant for 93% of the individuals, with a mean beta-coefficient of −0.51 (sd = 0.22).

Table 3. Distribution of Individuals from Theory-based Subgroups (CS-GIMME) in Data-driven Subgroups (S-GIMME) in Absolute Numbers and Percentages.

	S-GIMME	
	Subgroup 1	Subgroup 2
CS-GIMME		
Subgroup 1	14 (56%)	10 (40%)
Subgroup 2	13 (48%)	13 (48%)
Subgroup 3	6 (25%)	17 (71%)
Subgroup 4	2 (10%)	15 (75%)

Subgroup-levelResults:Data-drivenSubgroups. S-GIMME identified no subgroup paths for subgroup 1 and four contemporaneous subgroup paths for Subgroup 2 (table 2). Note that the ordering of DD-subgroups by S-GIMME is arbitrary. All paths identified by S-GIMME for DD-subgroup 2 overlap with TB-subgroup paths previously identified by CS-GIMME. Path 1 (irritation—depression) and path 2 (depression—anxiety) were also identified in TB-subgroups 1 and 3. Path 3 (anxiety—stress) was identified for TB-subgroups 2, 3, and 4; and path 4 (psychosis—irritation) was identified for TB-subgroup 1 (table 2).

Individual-level Results: Heterogeneity Between Individuals. Fit indices showed good fit for all individuals (mean: CFI = .98, NNFI = .96, RMSEA = .04, SRMR = .06). On an average, 9.1 significant paths were estimated per individual (including group- and subgroup-paths). In Subgroup 1, on an average 8.5 paths were estimated and in Subgroup 2, on an average 9.4 paths; this difference was not significant ($F(1,88) = 2.49$, $P = .12$).

Differences Between the Two DD-subgroups. MANOVA showed that DD-subgroup 2 reported more general psychopathology ($F(1, 88) = 6.65$, $P = .01$) and lower social functioning ($F(1,88) = 5.73$, $P = .02$) than DD-subgroup 1. The two DD-subgroups did not differ in age, gender, or well-being (table 4).

Discussion

We examined daily symptom interactions over 90 days in individuals divided across four theory-based subgroups (TB-subgroups) that represented different early clinical stages of psychosis (stage 0–1b). We focused on symptom interactions on group level, on clinical-stage level, and on individual level. In line with our hypotheses, we found a

Table 4. Demographics and Clinical Functioning per DD-Subgroup.

	Subgroup 1	Subgroup 2	Total group	Difference[†]
	N = 35	*N* = 55	*N* = 90	
Cross-sectional measurements				
Demographic				
Age (mean (SD))	23.9 (3.27)	25.2 (4.47)	24.70 (4.08)	ns
Gender (% Female)	82.9	72.7	76.7	ns
Completed education[‡]				
Low (%)	20	11	14.4	ns
Middle (%)	42.9	58.2	52.2	ns
High (%)	34.3	29.1	31.1	ns
Other (%)	3	2	2	
Clinical functioning				
SCL-90 Mean (SD)	166.91 (58.10)	198.64 (56.11)	186.3 (58.67)	2 > 1
GVSG Mean (SD)	14.71 (1.69)	13.79 (1.84)	14.15 (1.83)	2 < 1
FS Mean (SD)	37.43 (8.92)	35.44 (9.52)	36.21 (9.29)	ns
CAPE Mean (SD)				
Total	67.3 (15.4)	71.5 (14.0)	69.83 (14.61)	ns
Positive symptoms	24.3 (4.12)	25.0 (4.73)	24.71 (4.49)	ns
Negative symptoms	27.4 (8.11)	29.4 (7.58)	28.59 (7.81)	ns
Depressive symptoms	15.6 (4.97)	17.1 (5.03)	16.53 (5.04)	ns
Mini-SCAN diagnoses Mean no. (SD)	1.09 (1.17)	1.56 (1.23)	1.38 (1.22)	2 > 1
Diary items per domain (Median (IQR))				
Irritation	9.29 (14.78)	25.48 (30.06)	19.83 (32.01)	2 > 1
Stress	25.31 (21.36)	34.28 (24.70)	29.71 (27.37)	2 > 1
Depression	19.14 (19.72)	28.48 (26.24)	25.55 (27.07)	ns
Psychosis	5.79 (6.02)	9.02 (15.30)	7.89 (9.46)	2 > 1
Anxiety	9.88 (19.55)	24.35 (35.72)	17.64 (25.90)	2 > 1
Confidence	49.42 (28.79)	50.09 (18.20)	49.76 (22.32)	ns

[†]Significant difference $p < .05$, ns = not significant.
[‡] Low = primary education or lower secondary education, Medium = upper secondary education, High = university/college education.

general path for the majority of individuals at risk for psychosis, several clinical stage-specific paths and a considerable amount of heterogeneity between individuals, expressed in individual-specific paths. In addition, data-driven subgroups (DD-subgroups) based on symptom dynamics differed from the TB-subgroups based on the clinical staging model. The two DD-subgroups that emerged differed from each other in symptom network structure, and in levels of psychopathology and social functioning.

A general process found in the large majority of our sample was that individuals felt less confident when they felt more depressed than usual on the same day. This path highlights the importance of a broader view on psychopathology, expanding the focus from psychopathology to including positive psychology in both research and clinical practice.[42] Previous research in individuals at UHR for psychosis showed that self-esteem has been associated with depressive feelings.[43] Our results indicate that this association can be extended to individuals in lower clinical stages and thus may reflect a general risk factor.

While mean levels of daily-assessed psychopathological symptoms and cross-sectional assessments of psychotic symptoms increase with clinical stage, this difference was not reflected in different symptom dynamics between the subgroups. Although there were several stage-specific paths, we did not see paths involving psychotic experiences more often in higher subgroups, even though the base rates of daily psychotic experiences were rather low in the TB-subgroups 1–3. In fact, only two groups had a subgroup path involving psychotic experiences. Individuals in the general population (TB-subgroup 1) felt more irritated on days they had more psychotic experiences, while individuals who are at UHR for psychosis (TB-subgroup 4) felt more anxious on days they had more psychotic experiences. Possibly, psychotic experiences become more severe and intense in later stages, therefore leading to anxiety rather than irritation. Feelings of anxiety are not uncommon in individuals at UHR for psychosis,[44] and vice versa, psychotic experiences commonly exist in individuals with an anxiety disorder.[45] However, the finding of a daily association between psychotic experiences and anxiety is new and whether this is specific for UHR individuals requires more research. If replicated, this could inform treatment strategies targeting risk for psychosis. Overall,

subgroups had more similarities in symptom dynamics of subgroup paths than differences and no clear ordering of data patterns was found. Thus, differences in symptom dynamics do not clearly distinguish between subsequent clinical stages. Possibly, the differences between the early clinical stages captured in our study were too subtle to detect and differences can only be found when comparing individuals in lower stages with individuals in more advanced stages of illness.

Multiple individual-specific paths remained after estimating group and subgroup paths, indicating a considerable degree of heterogeneity in the sample. Notably, no two individuals in our sample displayed exactly the same pattern of associations. These findings highlight the importance of an individualized approach, both in research and treatment. In addition, only within-days (contemporaneous) and no between-days (temporal) group- and subgroup associations were found. Possibly, this indicates that the influence of symptoms on each other happens within the day, rather than across days.

Our TB-subgroups did not align with the DD-subgroups that were recovered. More specifically, we defined *four* subgroups based on the clinical staging model, with each subgroup representing an increasing risk for psychosis, while *two* DD-subgroups based on similar symptom dynamics were found. The DD-subgroups differed from each other in several ways. First, DD-subgroup 1 had no shared paths, while DD-subgroup 2 had four shared paths. Second, individuals in DD-subgroup 2 had worse social functioning and more psychopathology than DD-subgroup 1. Both TB-subgroups and DD-subgroups differentiated between individuals with different severities of mental health problems as shown by individual scores on psychopathology and social functioning, but interestingly, both methods (theory-based and data-driven) did this differently. TB-subgroup allocation was based on cross-sectional assessments of need for mental healthcare and severity of psychotic experiences, while DD-subgroup allocation was based on the day-to-day dynamics between symptoms. The severe DD-subgroup included individuals with high levels of general psychopathology from all four TB-subgroups; thus the data-driven approach appears to capture individuals across the early clinical stages with more *general psychopathology severity* rather than *psychotic severity*. Both methods might capture different aspects of vulnerability for mental health problems. Recent papers[46,47] have pointed out that early clinical stages are characterized by a transdiagnostic expression of psychopathology and that this crystalizes further into more disorder-specific expressions in later stages. This raises the question to what extent a clinical staging model should be disorder-specific or more general. This is an ongoing discussion in the literature and more research is necessary to get a satisfactory answer to this question. The current manuscript provides relevant information to fuel this discussion by showing that taking a symptom dynamics perspective may shed additional light on how to best cluster individuals. A recent paper by Hasmi et al[48] found that not merely the attenuated psychosis is responsible for the "high risk" in individuals at UHR for psychosis (TB-subgroup 4 in our sample), but rather the combination between attenuated psychosis and another disorder. Possibly, rather than solely the severity of psychotic experiences, the larger psychopathological context is responsible for an increased psychosis risk. Our findings align with this in that, even though the two DD-subgroups did not differ in severity of psychotic experiences, the most severe data-driven subgroup captured those with psychotic experiences in a larger context of more severe general psychopathology. The results of Hasmi et al[48] in combination with our results, suggest that early clinical stages may be characterized more by general psychopathology with a psychotic component rather than psychotic symptoms per se. This could indicate that the way symptoms interact with each other and the level of psychopathology might be more useful in assessing risk and preventing the onset of psychosis than psychotic symptoms as such. However, these results are really preliminary and by no means conclusive. To get an real answer to this question, more research needs to be done. In particular, it remains unknown what method predicts the future course of psychopathology better. In follow-up studies, we aim to investigate whether illness progression is better predicted by TB-subgroup allocation (ie, clinical staging model) or DD-subgroup allocation (ie, more general psychopathology).

One important general consideration when interpreting our results is that we assessed daily experiences of psychopathological symptoms rather than symptoms in the strictest clinical sense. While these might not be 100% corresponding, it seems reasonable to accept that they overlap considerably. This study is unique in its design with daily measures of a broad range of transdiagnostic symptoms over a long period of 90 days in individuals in different clinical stages. It has been repeatedly stressed that a next step in psychological research is to focus more on variation within individuals because symptoms are not static[49] and between individuals, rather than only at group levels.[7,8,10,13,15,50,51] GIMME is a powerful tool to do exactly this: it identifies shared paths between (sub)groups of individuals while allowing for individual variation. The use of CS-GIMME and S-GIMME allowed us to compare symptom dynamics in TB-subgroups to DD-subgroups, enabling us to investigate symptom dynamics in individuals in the early clinical stages of psychosis. Using a daily diary design that assesses symptoms once a day is both a key strength of the current study, enabling us to measure individuals for a long period, and a limitation of this study, because one measurement per day does not allow to detect processes that unfold within shorter time windows. Till date, there is no optimal time window for measuring the interaction between symptoms.[15]

This study also has some limitations. Inherent to our study design and sample with individuals who are at-risk for psychosis, we saw low base rates of daily psychotic experiences, especially in the lower severity groups. The low base rates may have contributed to our limited findings concerning paths involving psychotic experiences in our sample. Mirorr intentionally included individuals with a wide range of diagnoses and thus treatments to reflect the broad range of backgrounds of individuals with psychosis risk. Because of this heterogeneity, we could not statistically compare different treatments. However, a study examining treatment effects systematically did not find effects of imipramine or Mindfulness-Based Cognitive Therapy treatment on the dynamic network connections of mental states,[52] suggesting that the influence of treatment may be limited. Furthermore, it is very complex to perform power analyses on multivariate time-series data, and insufficient work has been done in this area of research. Currently, power analysis tools are being developed for multivariate time series data, but are not available yet for analyses with more than two variables. Although recommendations based on simulation studies suggest that our study should have enough statistical power, more research is required.[53] Additionally, GIMME makes several assumptions about the data and to meet these assumptions, data had to be transformed, which complicated the interpretation of the results in terms of magnitudes. To ease interpretation, we handled transformations in the same way for each individual. In addition, the assumption of white noise (nonautocorrelation between residuals) was not met for nine individuals, potentially leading to less accurate estimates for these individuals. However, visual inspection showed similar deviations between predicted and actual values in these nine individuals and in individuals without violation of the white noise assumption. Therefore, we assume that this violation did not affect the results greatly. Last, in our analyses we set the threshold for detecting group paths to 75% and for subgroup paths to 51%, as recommended in the literature. However, thresholds are always somewhat arbitrary and further research should focus on comparing different thresholds and establishing optimal thresholds for specific sample sizes.

In sum, this study adds new and relevant information to the field of early psychosis by showing that grouping individuals based on symptom dynamics provides different information than grouping them based on severity of psychotic symptoms. Whether grouping information based on symptom dynamics is complementary, superior or inferior to grouping information based on severity of psychopathology in predicting future course of psychopathology is a next step in this line of research.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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Conflict of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this research.

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