Symptom Trajectories in Psychotic Episodes

Zeno Kupper and Wolfgang Tschacher

Whereas the cross-sectional structure of schizophrenic symptoms has been studied extensively, little is known about the development of symptoms during acute episodes. In this study, symptom trajectories of 46 schizophrenia spectrum patients were examined based on daily observation during an average treatment period of 104 days. A novel time series approach was used to identify initial phases of response and other descriptive features of the trajectories. The results yielded five dynamical factors: (1) overall level of positive symptoms, (2) duration of nonspecific response, (3) slope of response in all symptom domains, (4) enduring negative symptoms, and (5) duration of response regarding psychoticity. Compared to patients with an acute schizophrenia-like psychotic disorder, schizophrenia and schizoaffective disorder patients ranked higher in factor 4 (enduring negative symptoms). They tended towards a lower level of positive symptoms and showed a less prominent response to treatment. The examination of a subsample of 19 patients with relapse indicated a prolonged duration of initial treatment response regarding psychoticity. The results support the validity of this approach for the description of symptom trajectories.

IN MENTAL DISORDERS, frequent changes can be observed in signs and symptoms. These fluctuations may even be a hallmark of mental disorders,[1] which can be understood as an expression of complex dynamical systems.[2] Although the frequent changes observed in symptoms and functional impairment constitute a promising field for empirical research[3-8], relatively few empirical studies have focused on the time course of symptoms in schizophrenia. In current research, schizophrenic psychopathology is predominantly analyzed regarding its predictive value and its correlates using few or even just one assessment.[9-11] Correspondingly, the cross-sectional structure of schizophrenic symptoms has been studied extensively.[12-16] There is, however, little information about the longitudinal development of symptom dimensions. One of the rare longitudinal studies[17] found a relative independence of positive and negative symptom domains over a 10-year period. Yet, little is known about the development of symptoms before, during, and after acute episodes. This scarcity of fine-grained longitudinal research is in contrast to the theoretical reasoning on the development of different symptom domains, e.g., the distinction of primary and secondary negative symptoms[18], and the hypotheses concerning the evolution of different symptoms over prodromal, acute, and residual phases.[19-21] Therefore, the evolution of symptoms should not be reduced to a simple pre-post difference, but captured as symptom trajectories by frequent observation. In their study, Czobor and Volavka[22] produce evidence that positive and negative symptom trajectories are closely associated during the first 3 weeks of haloperidol treatment in acutely exacerbated chronic schizophrenia patients. Still, as the authors note, a lack of information concerning the development of symptoms over the course of more than a few weeks prevails. In a recent review, Garver et al.[23] suggest that different symptom evolutions in response to neuroleptics may be a key to the discovery of subgroups of "schizophrenias." These subgroups seem to differ in both symptoms evolution and etiology. In another study,[24] enduring negative symptoms, defined as a lack of response to neuroleptic treatment over a 4-week period, were found to correlate with biological and neuropsychological variables, residual positive symptoms and a poor 1-year outcome. Although promising, these studies on response to neuroleptic treatment present a rather simplified picture of the symptom trajectories during acute episodes as they rely on a small number of observations, e.g., 4 weekly observations.[22]

In the present study, symptom trajectories of acute psychosis in 46 schizophrenia spectrum patients were examined based on frequent (daily) observation during treatment. A novel time series approach was used to identify initial phases of

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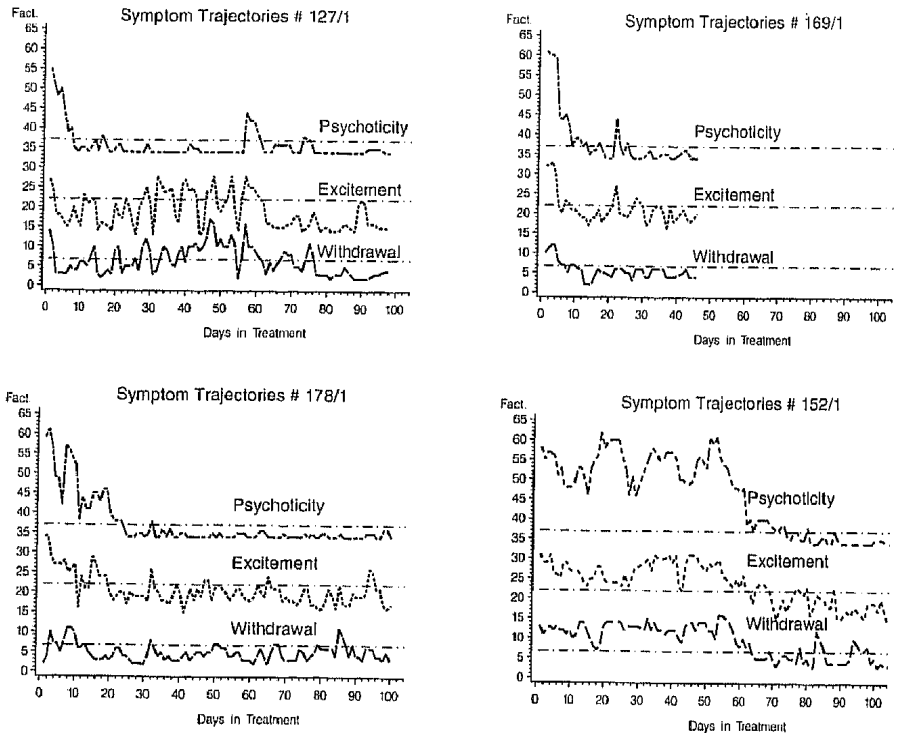

Fig 1. Symptom trajectories in four patients over the course of treatment: factor scores for psychoticity, excitement, and withdrawal. Note: for display, a constant was added to "excitement" (+ 10) and to "psychoticity" (+ 30).

response and other descriptive features of the trajectories in order to address the following questions: (1) How can symptoms trajectories in a variety of symptoms be summarized? And which changes in symptoms go together? (2) Which differences in symptom trajectories can be found on comparing patients with ICD-10 diagnosis of schizophrenia with patients diagnosed as suffering from acute schizophrenia-like psychotic disorder? (3) Which changes in symptom trajectories across episodes occur for patients with relapse?

METHOD

Subjects

Symptom trajectories of 46 schizophrenia spectrum patients were studied during treatment in the therapeutic community "Soteria Bern" in Bern, Switzerland.[25] Upon admission, patients consented to participate in ongoing research. The mean age of the patients was 24.7 years (SD 5.6). Eighteen of 46 patients (39%) were female. The mean observation period was 104 days (SD 57), documented by daily ratings. Patients had a mean of 2.5 (SD 2.9) previous admissions. The sample was selected on the grounds of the following three criteria. First, for methodological reasons, the minimum observation period was 20 days; shorter treatment episodes were excluded. Second, only patients were included who had received an ICD-10 diagnosis of schizophrenia (F20), schizoaffective disorder (F25), or acute schizophrenia-like psychotic disorder (F23.2). Third, in the main part of the analyses, only the first documented stay in the treatment setting of each of the 46 patients was considered.

Instruments

Ratings of patients' symptomatology were performed daily by the staff of the Soteria Bern. To our knowledge, no standardized scales exist for this purpose. We therefore chose to apply the Ciompi-Tschacher (CT) rating scale, which was developed especially for frequent multivariate ratings of psychotic symptoms, based on a univariate scale described elsewhere.[3,8] The rating scale used in the present study was composed of nine Likert scales assessing hallucinations, delusions, derealization, confusion, anxiety, ambivalence, tension, depression, and negative symptoms. In previous research work, using a sample of 61 symptom courses ($n > 5{,}000$ daily observations), a principal components analysis with subsequent varimax rotation gave evidence of three factors that accounted for 73% of the total variance.[26,27] These three factors can be understood as "symptom domains." The symptom domain "psychoticity" consisted of the ratings for hallucinations, delusions, derealization, and confusion; "excitement" consisted of anxiety, ambivalence, and tension; and "withdrawal" consisted of depression and negative symptoms. Thus, each course was represented by three time series, describing the trajectories of the symptom domains psychoticity, excitement, and withdrawal. The symptom trajectories of four patients are displayed in Fig 1.

In the present study the internal consistency of the three symptom domains as expressed by Cronbach's coefficient alpha was $\alpha = 0.87$ for psychoticity (four items), $\alpha = 0.76$ for excitement (three items), and $\alpha = 0.72$ for withdrawal (two items). Given the small number of items in the symptom do-

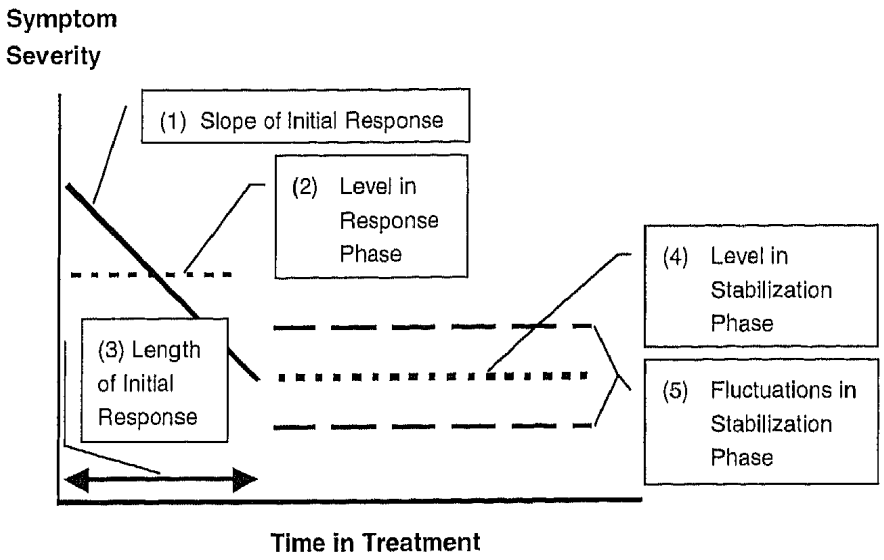

Fig 2. Schematic plot of the five parameters used to describe the symptom trajectories.

mains, the alpha values indicate a moderate to high internal consistency. Interrater reliability was assessed in the treatment setting by an extensive test under naturalistic conditions. Reliability was calculated using intraclass correlations (ICC).[28] The formula for random sets was used. Average interrater reliability was ICC = 0.71 for the sum of all symptom ratings, ICC = 0.60 for psychoticity, ICC = 0.66 for excitement, and ICC = 0.58 for withdrawal. These values are valid for the reliability of one single observation, but the reliability of the parameters for describing the trajectories used in this study (means, slopes, etc.) is much higher, since the average number of observations used in the estimation of parameters is more than 50. The validity of the daily ratings was assessed by comparing averaged daily ratings with Positive and Negative Syndrome Scale (PANSS)[29] scores in 25 randomly selected patients. Daily ratings were averaged across a period of 1, 2, and 4 weeks prior to the date of the respective PANSS interview. Correlation between these averaged daily ratings and PANSS scores in general ranged from moderate to high, supporting the validity of the daily ratings. The symptom domain psychoticity correlated with the PANSS positive score for all three time periods (Pearson's r = .60 for 1 preceding week, r = .63 for 2 weeks, and r = .76 for 4 weeks). Psychoticity was best described by PANSS P1 delusions (r = .64/.71/.76). The symptom domain withdrawal correlated with the PANSS negative score (r = .62/.61/.57) and was found to correspond especially to the PANSS items "emotional withdrawal" N2 (r = .73/.70/.67), "passive social withdrawal" N4 (r = .69/.67/.66), and "lack of spontaneity" N6 (r = 68/.71/.67). The symptom domain excitement correlated moderately with both the PANSS general psychopathology score (r = 50/.52/.43) and the PANSS positive symptoms score (r = .45/.45./.35).

Procedures

Descriptive parameters for the symptom courses. Compared to rehabilitation courses, symptom trajectories during acute episodes seem to follow a less linear course pattern. In rehabilitation courses, functioning of schizophrenia patients has been described in terms of the level (mean), the direction of change (slope of a linear trend), and the amount of fluctuation around this linear trend (root mean square error).[6] This type of description has shown to be both discriminative between clinical subgroups and informative regarding the outcome of rehabilitation. The main response to treatment during acute episodes, however, takes place in the first few weeks and treatment induced changes tend to decrease dramatically or even cease thereafter.[22,23] Essentially, this implies that linear trends may not be appropriate to fully characterize such courses. Therefore, the approach chosen in this study was to discriminate between a "response phase" and a "stabilization phase." The response phase, always starting at day 1 and lasting up to an individually varying point in time (e.g., day 25), was modeled as a linear trend, whereas the remaining time in treatment (e.g., day 26 to day 40) was modeled as a stationary stabilization phase. In order to describe the symptom courses, a total of five "trajectory parameters" were chosen: (1) slope of initial response; (2) level of symptoms (mean) in the response phase; (3) length (duration in days) of the initial response; (4) level of symptoms (mean) during the stabilization phase; and (5) fluctuations (standard deviation) during the stabilization phase. Figure 2 depicts the five trajectory parameters estimated for each variable.

To prevent a biased estimation of trends, a possible serial dependency of the data needed to be considered. Since in previous studies[3,8] symptom courses during psychotic episodes have been found to be autocorrelated, the linear trends in the response phase were estimated including a maximum-likelihood estimation of autocorrelation in the fluctuations around the trend (using the procedure AUTOREG from the SAS/ETS statistical software package[30]).

A crucial step in the analysis was to determine the length of the response phase, which was accomplished using an automated iterative procedure: starting from day 10 to the end of the series, the ratio of variance explained by a linear trend was estimated for any possible length of the response phase. Subsequently, the length of the response phase was chosen as to yield a maximum ratio of explained variance. It seems that this

procedure closely approaches an intuitive differentiation between the response and stabilization phases that is given in response to visual inspection of diagramed series. Unlike other approaches,[22] the iterative procedure can approximate a nonlinear change while preserving the scales of symptoms and time, thus providing a more descriptive approach and facilitating the interpretation of results.

Factor analysis of trajectory parameters. The five trajectory parameters, as defined previously, were calculated individually for the three symptom domains of psychoticity, excitement, and withdrawal, resulting in a total of 15 descriptive parameters for the symptom trajectories in each patient. These parameters where then examined by means of factor analysis to answer the question as to how changes in the different symptom domains were interrelated. A principal components analysis (PCA) with varimax rotation was used to determine dynamical factors summarizing the symptom trajectories.

Differences between diagnostic subgroups. In order to explore differences in diagnostic subgroups, patients with disorders diagnosed as acute schizophrenia-like psychosis (n = 22) were compared with patients suffering from schizophrenia and schizoaffective disorder (n = 24). As a hypothesis, compared to schizophrenia courses, courses diagnosed as acute schizophrenia-like psychosis should be characterized by a faster and more pronounced improvement in symptoms.

Stability and change in patients with repeated admissions. In patients showing repeated admissions to Soteria Bern (n = 19), the first and the last observed stay were compared by means of correlations and paired *t* tests. As the sample size is small and no previous studies of this type exist, this analysis is explorative. Trait-like dynamical factors, reflecting an individually stable pattern of change during psychotic episodes, may correlate between first and last episodes. Other dynamical factors may be subject to changes in mean, indicating chronicity or other developments of the disorder.

RESULTS

Treatment Response

The duration of the initial trend-like improvement (response phase) was similar in all three symptom domains. Median values were 17.5 days (mean = 26.4, SD 29.1) for psychoticity, 14.5 days (mean = 26.7, SD 26.7) for excitement, and 15.5 days (mean = 27.0, SD 27.1) for withdrawal. The skewness of the distributions and the large standard deviations reflect that most patients got better within 2 weeks, while a small group of patients took considerably longer to improve. In comparison with the averaged values for psychoticity, excitement and withdrawal during the first 7 days, averaged values of the last 7 days suggested a highly significant improvement in all three symptom domains ($t = 4.53$, $df = 45$, $P < .0001$ for psychoticity, $t = 4.54$, $df = 45$, $P < .0001$ for excitement, and $t = 4.34$, $df = 45$, $P < .0001$ for withdrawal). The mean effect sizes were d = -0.73 for psychoticity, d = -1.02 for excitement, and d = -0.84 for withdrawal, expressing significant reduction in symptom severity.

Factor Analysis of Trajectory Parameters

The factor analysis yielded five factors accounting for 76% of the total variance (Table 1). These factors can be termed "dynamical factors" as they summarize the symptom trajectories during treated psychotic episodes. These are: factor 1—overall level of positive symptoms; factor 2—duration of nonspecific response (initial trend-like treatment response regarding excitement and negative symptoms); factor 3—slope of response (in all symptom domains); factor 4—enduring negative symptoms; and factor 5—duration of response in psychoticity.

Figure 3 translates the numerical results of Table 1 into a symbolic summary of these five dynamical factors. The symbols depict the temporal features analogous to Fig 2: tilted lines show trends, lines with double arrows represent the length of initial responses, single lines stand for the means during the response and stabilization phase respectively, whereas double lines represent fluctuations during the stabilization phase. Solely temporal features showing factor loadings of 0.5 or higher are included in Fig 3.

Differences Between Diagnostic Subgroups

A significant overall difference in the dynamical factors showed between the schizophrenia subgroup (n = 24) and the schizophrenia-like psychosis subgroup (n = 22, multivariate analysis of variance [MANOVA], $F(4, 41) = 3.46$, $P < .05$; Table 2). When compared to patients with schizophrenia-like psychosis, schizophrenia and schizoaffective disorder patients showed higher scores in factor 4 (enduring negative symptoms) and tended to be lower in factor 1 (overall level of positive symptoms). Furthermore, factor 3 (slope of response) indicated a less prominent improvement during the first, trend-like phase of the courses for the schizophrenia patients.

Table 3 presents the results from a subsample (n = 19) of the same patients observed during a later psychotic episode, resulting in repeated admission. The first and last treatment course of each

Table 1. Five Factors Representing the Dynamics of Symptoms During Treated Psychotic Episodes

	Factor 1: Overall Level of Positive Symptoms	Factor 2: Duration of Nonspecific Response	Factor 3: Slope of Response	Factor 4: Enduring Negative Symptoms	Factor 5: Duration of Response in Psychoticity
Psychoticity					
Level in response phase	0.60	(−0.45)	(−0.47)		
Slope of initial response			0.88		
Length of initial response					0.72
Mean in stabilization phase	0.61	(−0.49)			(−0.32)
Fluctuations	0.60	−0.58			
Excitement					
Level in response phase	0.85				
Slope of initial response			0.84		
Length of initial response		−0.84			
Mean in stabilization phase	0.79				
Fluctuations	(0.45)			0.61	
Withdrawal					
Level in response phase				0.54	0.62
Slope of initial response			0.70		
Length of initial response		−0.84			
Mean in stabilization phase				0.87	
Fluctuations				0.89	
Eigenvalue	3.48	2.99	2.08	1.66	1.26
Variance explained	23%	20%	14%	11%	8%
Cumulative	23%	43%	57%	68%	76%

NOTE. Factor loadings of 0.30 and higher are shown; values between 0.30 and 0.50 are given in parentheses.

patient were compared. The overall level of positive symptoms as expressed by factor 1 tended to an increase in patients showing repeated admissions to the treatment setting (t = -1.95, P = .068, two-tailed). Equally, in later episodes there was a prolonged treatment response as measured by factor 5 (t = -2.67, P = .016). These two results suggest an increased symptom severity and may indicate chronicity in these patients with multiple admissions. Furthermore, only factor 5 tended to be associated between first and last episode (r = 0.41, P = .08).

DISCUSSION

The purpose of the present study was to explore temporal relationships between different domains of daily assessed symptoms in acute schizophrenia. Symptom domains of psychoticity, excitement, and

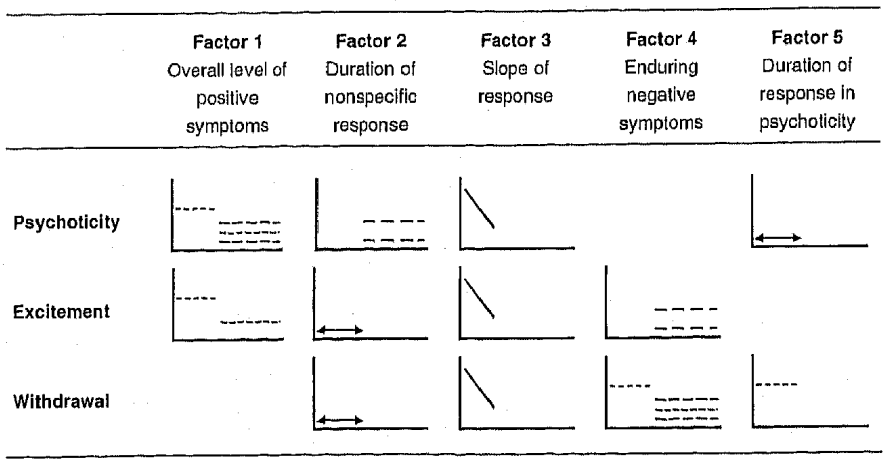

Fig 3. Symbolic summary of five dynamical factors. Note: x-axis is time, y-axis symptom severity. Factors loading > 0.5 are shown.

Table 2. Symptom Trajectories in Diagnostic Subgroups: Schizophrenia Versus Schizophrenia-like Psychosis

	Schizophrenia (F20/F25) (n = 24)		Schizophrenia-like Psychosis (F23) (n = 22)			
	Mean	SD	Mean	SD	*F*	*P*
Factor 1: Overall level of positive symptoms	−0.24	0.97	0.26	0.99	3.1	.09
Factor 2: Duration of nonspecific response	−0.15	1.02	0.17	0.97	1.2	NS
Factor 3: Slope of response	0.24	0.68	−0.27	1.22	3.10	.09
Factor 4: Enduring negative symptoms	0.29	0.85	−0.31	1.08	4.48	.04
Factor 5: Duration of response in psychoticity	−0.06	0.85	0.07	1.16	0.18	NS

NOTE. Overall MANOVA model is significant, $F(4, 41) = 3.46$, $P < .05$.
Abbreviation: NS, not significant.

withdrawal are often found to be cross-sectionally independent.[12-14] The present study, however, investigated the interconnectedness of these symptoms over the time course of psychotic episodes in a relatively small group of patients. As a main result, five dynamical factors representing the trajectories of symptoms were found: factor 1—overall level of positive symptoms; factor 2—duration of nonspecific response; factor 3—slope of initial response; factor 4—enduring negative symptoms; and factor 5—duration of initial treatment response regarding psychoticity. For the present sample, the results show that the symptom domains were both independent *and* interconnected, depending on which temporal aspects of the symptom courses were examined. The rate of initial response, for example, as expressed by the slopes of trends during a first phase, was correlated considerably among the three symptom domains. Regarding their levels of symptoms and the duration of improvement, however, the three symptom domains were partially independent.

The more characteristic symptoms of schizophrenia such as delusions and hallucinations here termed psychoticity, tended towards the same level as symptoms of excitement, both loading on factor 1, "overall level of positive symptoms." Factor 1 reflects the general severity of positive symptoms over the whole course of the episode. For patients with multiple admissions to the treatment setting, this severity of positive symptoms tended to increase over time. Furthermore, the length of initial improvement in the nonspecific symptom domains of excitement and withdrawal were strongly interrelated (factor 2). Hypothetically, the temporal association between these nonspecific symptom domains may suggest common mechanisms for symptoms such as anxiety and depression during psychotic episodes. Moreover, results showed that the rate of initial change in all symptom domains was strongly correlated (factor 3). This dynamical factor may reflect a generalized responsiveness to treatment across symptom domains as found in previous studies.[22,23] There was evidence for enduring negative and depressive (withdrawal) symptoms (factor 4), which, in addition, were higher in patients with schizophrenia compared to patients with a schizophrenia-like psychosis. These results are in line with theoretical distinctions between variable and more stable components of negative symtomatology.[18,19,24] Finally, whereas the time necessary for psychoticity to change was

Table 3. Comparing First and Last Observed Episode in Patients With Multiple Admissions (n = 19)

	First Episode Observed		Last Episode Observed		Correlation Between First and Last Episode			
	Mean	SD	Mean	SD	*t*	*P*	*r*	*P*
Factor 1: Overall level of positive symptoms	−0.21	0.78	0.55	1.25	−1.95	.068	−0.38	NS
Factor 2: Duration of nonspecific response	0.20	0.42	0.09	0.83	0.46	NS	−.18	NS
Factor 3: Slope of response	−0.32	1.23	0.07	0.91	−1.26	NS	0.26	NS
Factor 4: Enduring negative symptoms	−0.30	1.03	−0.12	0.98	−0.50	NS	−0.15	NS
Factor 5: Duration of response in psychoticity	−0.25	0.77	0.26	0.77	−2.67	.016	0.41	.08

independent from most other variables, it was related to the level of initial symptoms of withdrawal (factor 5), which could suggest the presence of mechanisms that restrain the remitting of symptoms. Potentially, this factor may be related to chronicity in schizophrenic disorders. For the present, this assumption appears to be supported by the observation that the small number of patients with multiple admissions showed increased scores on this factor. This reflects a slower improvement of psychotic symptoms in their last recorded episode.

The study as a whole, using a novel statistical approach, yields a differentiated view of the temporal evolution of symptoms. By extracting dynamical factors, this explorative approach uncovers temporal dimensions that can be both theoretically and clinically important. However, the results should be evaluated with caution. Due to the relatively small sample size and the fact that factor structures of symptoms are influenced by numerous issues,[31] the dynamical factors found are very likely to represent one among various possible structures. Furthermore, the validity of the results depends on methodological choices that cannot be fully evaluated at this point, mainly due to the lack of similar empirical work. Our two main methodological choices, where (1) the use of the CT rating scale for the daily assessment of symptoms and (2) the statistical approach to describe a response phase and a stabilization phase in the courses. The CT rating scale for the daily assessment of symptoms is relatively novel. The results suggest that the CT rating scale can capture symptom courses in a reliable and differentiated way. The reliability of the parameters used in this study is supported by the fact that all estimations of individual parameters are based on multiple ratings. The second methodological choice of major importance is the distinction between a response phase and a stabilization phase, as well as the individual estimation of the length of the response phase. The distinction seems appropriate, as the results on symptom courses during treatment indicate an initial phase of greater improvement and a later phase of stabilization[22,23]. As for the possibility to generalize to other patient groups and treatment settings, it has to be considered that in the open community-based treatment setting possibly lower doses of medication were used than in traditional hospital based wards.[25] The findings may be limited to the types of psychotic episodes that can be treated in a less coercive, community-based, setting. It can be noted, however, that the main results of this study are compatible with findings from hospital-based settings.[22,23]

So far, few studies have examined the development of symptoms during psychotic episodes. The dynamics of symptoms during schizophrenic episodes, as it was found in the present explorative study, is on the one hand similar to the structure of schizophrenic symptoms found in cross-sectional studies,[12-14] since, for example, the overall levels of positive and negative symptoms were largely independent. The results, though, are also in accordance with the results from the longitudinal study of Czobor and Volavka,[22] who found a close association of change in positive and negative symptoms during 3 weeks of haloperidol treatment of schizophrenic episodes. Consequently, the five dynamical factors found may represent specific temporal relationships between symptom domains that could not be detected using cross-sectional designs or longitudinal studies using few observations.

To summarize, it seems that the approach presented in this study is suitable for describing acute psychotic episodes. Symptom trajectories can yield more information about response to treatment than cross-sectional measurements alone. Symptom trajectories could be predictors of outcome, and they may also be instrumental in the identification of subgroups. A dynamical approach to symptoms includes a three-dimensional view: symptom domain, symptom severity, and symptom evolution in time. Potentially, such an approach may yield additional theoretical and clinical insight into the development and improvement of symptoms or problems, both in schizophrenia and in other mental disorders. The main challenge, in our opinion, is to move the study of symptom courses from being a topic for clinical case descriptions to the level of larger scale quantitative studies. The inclusion, for example, of a highly resolved description of symptom courses could prove fruitful for studies comparing different typical and atypical antipsychotic medications and studies exploring the importance

of functional and structural changes in schizophrenia patients.[23,24] As this type of research is still sparse, we are optimistic about the incremental benefits from dynamical approaches to the symptoms of schizophrenia.

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