



Symptom dimensions stability over time in recent onset psychosis: A prospective study

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ABSTRACT

Background: The factorial structure of schizophrenia symptoms has been much debated but little is known on its degree of unicity, specificity as well as its dynamic over time. Symptom differentiation is a phenomenon according to which patients' symptoms could differentiate from one another during illness to form more independent, distinct dimensions. On the contrary, symptom dedifferentiation is an increase in the correlations between those symptoms over time. The goal of this study was to investigate symptom differentiation or dedifferentiation over time in recent onset psychosis using the Positive and Negative Syndrome Scale.

Methods: A confirmatory factor analysis model based on the consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia was estimated on seven different time points over a three-year period. A general factor capturing common variance between every symptom was also included. Explained common variance was computed for the general factor and each specific factor.

Results: Three hundred and sixty-two recent onset psychosis patients were assessed. Results showed no evidence for either symptom differentiation or dedifferentiation over time. Specific symptoms accounted for >70 % of the variance suggesting a high degree of specificity of the symptomatology.

Conclusions: Overall, this study adds support for a highly multidimensional approach to clinical symptom assessment with an explicit focus on depression. The premise behind the staging approach being inherently one-dimensional, implications for further research is discussed.

1. Introduction

The Positive and Negative Syndrome Scale (PANSS) is a 30-item rating scale designed by Kay et al. (1987) to assess dimensions of schizophrenia symptoms. The original structure posited a three-domain organisation: Positive Symptoms (7 items), Negative Symptoms (7 items), and General Psychopathology (16 items). Other variants have been proposed involving additional factors (Emsley et al., 2003; Van den Oord et al., 2006) but no single model has achieved a broad consensus (van der Gaag et al., 2006; Wallwork et al., 2012). In an attempt to reach a consensus structure, a factor analytic study guided by a broad overview of the literature has suggested that a five-factor model better

captures the PANSS structure in schizophrenia samples (Wallwork et al., 2012). In this study, smaller groupings of items represent Positive and Negative symptoms whereas three other factors consistently emerge and are referred to as Disorganized/Concrete, Excited and Depressed (Wallwork et al., 2012). This model has proved influential in schizophrenia and neuroscience research (Rodriguez-Jimenez et al., 2013; van der Gaag et al., 2006; Wallwork et al., 2012; Ye et al., 2021) and the original study has been widely cited to date. Although the existence of an even better model remains an open question, this consensus model already has the advantage of improving comparability between studies.

Although it is apparently the most extensively studied aspect, the question of the number of factors is not the only important issue when it

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comes to the dimensionality of schizophrenia symptoms. Its dynamic over the course of illness is little known. Additionally, the quantification of the degree of generality and specificity of symptoms is an issue that has not been addressed much so far. While factor analytic studies suggest schizophrenia symptoms are definitively multidimensional (Malla et al., 1993; Stefanovics et al., 2014; Wallwork et al., 2012) and need to be accounted for by more than three factors, the different dimensions may be more or less correlated with each other.

The concept of differentiation and dedifferentiation originated in developmental cognitive psychology (Baltes et al., 1999; Garrett, 1946; Mella et al., 2016; Morse, 1993). This hypothesis states that there is more resemblance across various cognitive functions in children and in older adults than in young adults, where greater specificity is observed because the cognitive functions are more differentiated (Mella et al., 2016). When cognitive functions tend to vary together (i.e. more resemblance), this is reflected in increasing positive correlations between different scores. This tendency towards generality can be modelled through a general factor with factor analysis.

Applied to psychotic symptoms, symptom differentiation is a phenomenon according to which patients' symptoms could differentiate from one another during illness, justifying the definition of distinctive dimensions. From being relatively unitary, the organisation would change towards a structure with different groups of specific symptoms that are relatively independent of each other. According to this phenomenon, the contribution of a single general factor should be less important over time (Golay and Lecerf, 2013). In other words, in case of differentiation, the clinical picture would become more heterogeneous over the course of time. On the contrary, symptom dedifferentiation would indicate that correlations between symptoms could increase over time (Golay and Lecerf, 2013; Reinert, 1970). All the different types of symptoms tend to occur (or decrease) together. Dedifferentiation is the emergence or the strengthening of a central and unique core dimension in the organisation of the psychopathology. These modifications would be reflected in a change in the factor structure, where symptoms would tend to saturate more on a single general factor. According to this phenomenon, in case of dedifferentiation, the contribution of the general factor should be more important over time.

This study was designed to investigate possible symptom differentiation or dedifferentiation in recent onset psychosis patients using the Positive and Negative Syndrome Scale over three years of specialized treatment.

2. Material and methods

2.1. Participants

The Treatment and early Intervention in Psychosis Programme (TIPP) is a specialized early psychosis (EP) programme run by Lausanne University Hospital's Department of Psychiatry, in Switzerland (Bauermann et al., 2013). Participants' inclusion criteria are: being aged from 18 to 35, living in the hospital's catchment area (population about 350,000) and meeting the criteria for psychosis as defined by the 'psychosis threshold' subscale in the Comprehensive Assessment of At-Risk Mental States (CAARMS) instrument (Yung et al., 2005). Here psychotic disorder threshold is defined as having frank psychotic symptoms such as delusions, hallucinations and thought disorder persisting for longer than one week, with a frequency of at least 3–6 times a week for longer than 1 h each time or daily for <1 h each time. This is a standard and widely used criterion for first episode psychosis threshold (Nelson et al., 2014).

Patients with drug-induced brief psychotic states, organic brain disease, an IQ < 70, or those on antipsychotic medication for more than six months are referred to other programmes. Patients are referred via e-mail or phone call by their families, general practitioners, emergency psychiatric services, private psychiatrists and/or psychiatric institutions for an initial assessment by the TIPP team. This multidisciplinary team,

including psychiatrists and case management nurses, then ensures the accuracy of inclusion criteria. The TIPP paradigm of care is based on the principles of both case management interventions and assertive community treatment undertaken. Over a three-year period, case managers are available to each patient up to twice a week. In addition, an Intensive Case Management team can provide supplementary support at any time during the treatment period. TIPP case managers remain involved, however, to ensure continuity of care. Patients are seen at least 100 times over the three-year programme, primarily by their case manager but also by a resident physician or an intern in psychiatry. A consultant psychiatrist supervises each case.

All patients treated within the TIPP are assessed at baseline. A specially designed questionnaire (the TIPP Initial Assessment Tool: TIAT; available online (Service of General Psychiatry, 2021)) is completed for all patients enrolled in the programme by case managers. It allows assessment of demographic characteristics and past medical history. Follow-up assessments exploring various aspects of treatment and co-morbidities as well as evolution of psychopathology and functional level are conducted by a psychologist and by case managers after 2, 6, 12, 18, 24, 30 and 36 months of treatment.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. This study was approved by the Human Research Ethics Committee of the Canton of Vaud (CER-VD; protocol #2020-00272). The data generated by the follow-up of all patients were used in the study if the latter did not explicitly object to the use of their data for research purposes. Only four patients refused the use of their clinical data for research.

2.2. Clinical assessments

Detailed evaluation of past medical history, demographic characteristics, exposure to adverse life events as well as symptoms and functioning were performed by case managers (CM) and a psychologist, through semi-structured interviews and a questionnaire. Psychopathology levels were scored at each assessment with the Positive and Negative Syndrome Scale (Kay et al., 1987) which grade items on a 1–7 severity scale. A psychologist, who was not involved in patients' treatment and had received standardized training prior to the study, conducted the symptom assessment. For the PANSS, inter-rater agreement standards (Kay et al., 1991) were confirmed through training with video-taped interviews and consensus reference ratings. Diagnosis results from an expert consensus at 18 and 36 months of treatment, based on the DSM-IV criteria. In this study, we used the latest consensus diagnostic available. Insight into illness was evaluated as complete, partial or absent by the CM (Conus et al., 2007). Socio-economic status (SES) was subdivided into low, intermediate and high on the basis of the parents occupation (Chandola and Jenkinson, 2000).

2.3. Statistical analysis

A multigroup confirmatory factor analysis (CFA) model was estimated on the PANSS items for the 2, 6, 12, 18, 24, 30 and 36 month time points. It was structured using a bi-factor configuration (Golay and Lecerf, 2011) including one general factor (F_g) and five specific factors modelled following Wallwork et al. proposal based on their factor analytic study (Wallwork et al., 2012). The bi-factor configuration allows to estimate the share of the general and group components respectively (Golay and Lecerf, 2011; Jennrich and Bentler, 2012). The P1, P3, P5 and G9 items were placed on the Positive factor, the N1, N2, N3, N4, N6 and G7 items were placed on the Negative Factor, the P2, N5 and G11 items were placed on the Disorganized/concrete factor, the P4, P7, G8 and G14 items were placed on the Excited factor and the G2, G3 and G6 items were placed on the Depressed factor. All items were also placed on F_g . Following the bi-factor configuration, all factors correlation were

fixed to zero (Golay and Lecerf, 2011) (Fig. 1). To ensure that the factors retain the same meaning over time, the factor loadings were constrained to be equal across measurement occasions (metric level invariance).

The explained common variance (ECV) was computed for all five specific factor (F_{1-5}) and the general factor (F_g) on the basis of the factor standardized loadings (λ) using the following formula: $ECV(F_k) =$

$$\frac{(\sum \lambda_{Fk}^2)}{(\sum \lambda_{F1}^2) + (\sum \lambda_{F2}^2) + (\sum \lambda_{F3}^2) + (\sum \lambda_{F4}^2) + (\sum \lambda_{F5}^2) + (\sum \lambda_{Fg}^2)} \quad (\text{Bentler, 2009; Reise et al., 2013}).$$

It is important to bear in mind that factor analysis assesses the proportion of variance of the total psychopathology explained by each factor and does not assess changes in symptom severity in these domains over time.

Given the potentially non-normal nature of the PANSS items, models were estimated using Maximum Likelihood estimation with Robust standard errors (MLR). The relationship between time and the ECV of each factor was evaluated using Pearson's correlations. All statistical analyses were performed using the Mplus statistical package version 8.3 and SPSS version 25.

3. Results

The final sample (Table 1) consisted of 362 patients (Mean age = 24.75; SD = 4.79), and included a majority of male (66.6 %). Among these patients, 55.8 % met diagnostic criteria for schizophrenia, 9.4 % for schizoaffective disorder, 13.0 % for schizophreniform or brief psychotic disorder, 8.0 % for bipolar disorder, 3.6 % for depression with psychotic features, and 10.2 % for other psychotic disorders.

ECV of the PANSS items across three years are presented on Fig. 2. The ECV of the general factor was relatively stable in time and accounted for between 26.7 % and 30.6 % of the variance (28.2 % on average; Table 2). In other words, the lion's share of the variance was accounted for by specific independent factors.

The positive and negative factors appear to be the two other most important factors with regard to the proportion of ECV, each accounting for slightly <20 % of the variance. Correlation between time and ECV revealed that no factor changed in ECV over time.

4. Discussion

To our knowledge, this is the first study investigating the differentiation and dedifferentiation of psychotic symptoms over time in recent onset psychosis patients. Results showed no evidence for these phenomena when studying its dynamic over three years of treatment.

Table 1
Demographic and baseline factors related to inclusion in the study.

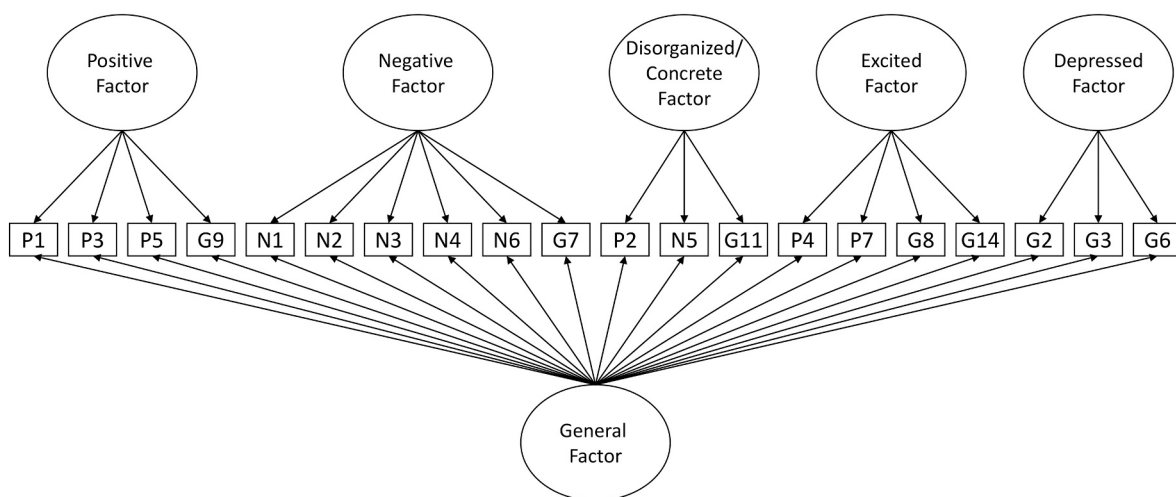
	Included N = 362	Not Included N = 99	Statistic	p- Value
Age in y, mean (SD)	24.75 (4.79)	23.99 (4.38)	t(459) = -1.422	0.156
Sex, male, % (N)	66.6 (241)	70.7 (70)	$\chi^2(1) = 0.605$	0.437
SES, % (N)			U = 16,425.000	0.173
Low	20.4 (74)	33.3 (33)		
Intermediate	44.2 (160)	31.3 (31)		
High	35.4 (128)	35.4 (128)		
GAF baseline, mean (SD)	39.93 (16.00)	41.94 (16.79)	t(412) = -1.014	0.311
Insight at presentation, % (N)			U = 12,694.000	<0.001
Absent	28.3 (98)	43.2 (41)		
Partial	47.1 (163)	48.4 (46)		
Complete	24.6 (85)	8.4 (8)		
DUP in weeks, median (IQR)	10.71 (62.43)	18.00 (59.00)	U = 16,148.00	0.132
Age of onset in y, mean (SD)	23.29 (5.29)	22.99 (4.54)	t(459) = -0.515	0.607
Diagnosis, % (N)			Fisher's exact test	0.628
Schizophrenia	55.8 (202)	57.6 (57)		
Schizophreniform/ BPE.	13.0 (47)	18.2 (18)		
Schizoaffective disorder	9.4 (34)	9.1 (9)		
Major depression ^a	3.6 (13)	3.0 (3)		
Biopolar disorder	8.0 (29)	4.0 (4)		
Others	10.2 (37)	8.1 (8)		

Note. SES: socio-economic status, GAF: Global Assessment of Functioning, DUP: duration of untreated psychosis, IQR: interquartile range, SD: standard deviation, BPE: brief psychotic episode.

^a With psychotic features.

Results showed that specific symptoms accounted for >70 % of the variance reinforcing the idea of a high specificity of the symptomatology. These results have both theoretical and clinical implications. From a theoretical standpoint, it first confirms that the structure of psychotic symptoms stays in a similar multidimensional and highly specific configuration over a relatively long period. Addressing this multidimensionality and evolution over time is important to promote sustainable recovery (Borsboom, 2008; McGorry et al., 2008).

This study has implications for clinical assessment and for the



With metric invariance (factor loadings constrained to be equal across measurement occasions)

Fig. 1. PANSS' items and factor configuration.

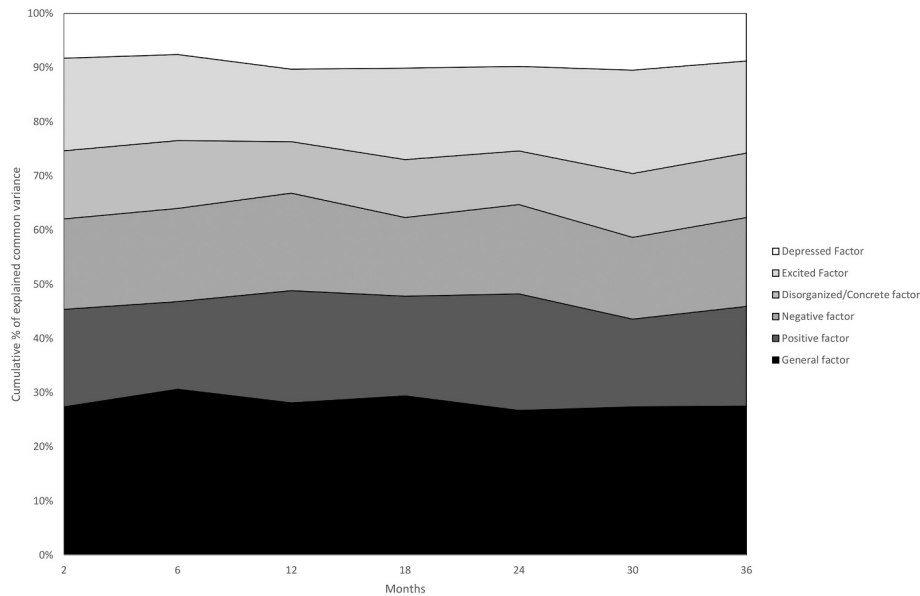


Fig. 2. Explained common variance of the PANSS factors across three years.

Table 2

Explained common variance (ECV) of the PANSS factors across three years.

ECV (%)	2 months	6 months	12 months	18 months	24 months	30 months	36 months
General factor	27.4	30.6	28.1	29.4	26.7	27.4	27.5
Positive factor	18.0	16.2	20.7	18.4	21.5	16.2	18.4
Negative factor	16.7	17.2	18.0	14.5	16.5	15.1	16.4
Disorganized/concrete factor	12.6	12.5	9.5	10.7	9.9	11.8	11.9
Excited factor	17.1	15.9	13.4	16.9	15.6	19.1	17.0
Depressed factor	8.3	7.6	10.3	10.1	9.8	10.5	8.8
Number of observations (total = 1212)	182	195	188	183	178	146	140

concept of staging in psychosis. Clinical staging is based on the principle that psychiatric illnesses progress over time through successive stages marked by symptoms of increased clarity and intensity (Baumann et al., 2015; Hickie et al., 2013; McGorry et al., 2010; McGorry and Van Os, 2013; Scott et al., 2013). Within this framework, mechanisms and early markers of illness can be used to define an illness stage allowing the adjustment of safer and more proportionate treatments (Baumann et al., 2015). It can be argued that the premise behind the staging approach is inherently one-dimensional in nature. Concepts such as chronic illness, remission, unique or multiple relapses indeed relate to symptoms in general. Given the highly specific nature of symptoms highlighted in the present study, the staging approach should evolve to fully embrace this multidimensional organisation of psychopathology. Indeed, recent clinical staging concepts are beginning to call for a distinction between “disease progression” (worsening of the syndrome itself) and “disease extension” (spreading of the syndrome to have wider reaching effects on multiple outcomes) (Carpenter et al., 2019). The frequent comorbidity between mood and psychotic symptoms for instance, is an illustration of the need for a multidimensional concept. Of course, terms such as “depressive relapse”, “excitation remission” or “chronic negative symptoms” may blur the staging model to some degree but may also reintroduce a necessary nuance to the concept.

It is also important to return to the fact that the general factor explained the most variance on average and showed the highest variance explained in absolute terms in all seven measurement occasions in comparison with the five other factors. Its signification could be a summary score of what may be seen as all the different types of symptoms which tend to occur together (Golay and Lecerf, 2011; Jennrich and Bentler, 2012). Following the general factor hypothesis, this factor should indeed be interpreted as a common cause of the symptoms

(Borsboom et al., 2011). This could be wrong because the general factor is not the primary fact observed in this study. The primary fact is the positive correlations between PANSS items which then could be tentatively explained by the general factor. This factor is nothing more than one possible interpretation of that primary fact (Protzko and Colom, 2021). It is also possible to consider a causal systems perspective, which posits that disorders are causal networks consisting of symptoms and direct interactions between them (Borsboom, 2008). The network perspective of psychopathology can also account for the positive correlations between symptoms in the absence of an underlying latent general factor of psychopathology (Borsboom et al., 2011): very different symptoms are mutually interacting, often reciprocally reinforcing, elements of a complex network (Borsboom and Cramer, 2013). In turn, what we consider as general psychopathology is the by-product of complex symptoms interactions and could be seen as an index of the extent of which these reciprocal causal actions do actually occur. How does the general factor or the amount of interaction relate to other characteristics like age, sex, or insight remain to be further studied. From a clinical standpoint, this finding suggest that clinicians should be aware that direct interactions between symptoms may manifest in a variety of contexts and may contribute to transform very narrow and specific troubles into ultimately more general and broad expression of symptoms. We argue that the high specificity of psychopathology can be seen as an opportunity to tailor treatment. Nevertheless, given the importance of general psychopathology, we hypothesize that specific symptoms are not always bound to remain circumscribed over long periods.

A major strength of this study is its prospective design that allowed us to examine symptomatology over a three-year period. Regarding potential limitations, some patients of our highly representative clinical

sample of patients could not be included because data on psychopathology was not available. While patients who were included had slightly higher level of insight, they did not differ on other important variables such as age, gender, socio-economic-status, baseline GAF, diagnosis, age of onset or DUP (Table 1). Insight was however not directly taken into account in the dimensions studied which is a limitation.

Additionally, although we were able to include a large sample of 362 patients, the naturalistic nature of the cohort prevented us from including all sample individuals at each assessment considering some patients either refused or did not attend assessment at various time points. It is difficult to assess the contribution such missing data might have made for the variation in variance explained results. However, our conclusions were not based on the change in severity of symptoms over time but rather on the comparison of the importance of several sources of explanation for inter-individual variations over time. We therefore believe that the impact of potential selection bias should be limited.

Several different models have been proposed for the PANSS and this study was only based on a consensus proposal (Wallwork et al., 2012). However, another PANSS structure may be even more appropriate. Nevertheless, we do not have major reasons to believe this could play a key role in our first conclusion regarding the absence of differentiation/dedifferentiation, but it could ultimately highlight changes over time in additional specific factors (Ye et al., 2021). Finally, because the first PANSS assessment was performed after 2 months in treatment, PANSS data were not available at baseline. This is important because most symptom reduction occurs during the first few weeks of treatment. Therefore, the study is not able to assess differences in the factor structure of the symptom expression of the illness during this short term key period. Furthermore, what happens regarding symptoms during the time elapsing between the onset of full-blown psychosis and initiation of treatment as well as on periods beyond the 3-year follow-up should be assessed in further studies.

In conclusion, results showed no evidence for either symptom differentiation or dedifferentiation over time. Specific symptoms (positive symptoms, negative symptoms, depressed, excited, disorganized/concrete) accounted for >70 % of the variance suggesting a high specificity of the symptomatology. Overall, this study supports the necessity of a highly multidimensional approach to clinical symptom assessment. Our results suggest as well that the staging concept, which is inherently one-dimensional in nature, should evolve in order to fully embrace this multidimensional organisation of psychopathology.

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CRedit authorship contribution statement

PG designed this study. PG analyzed and interpreted the data. PG drafted the first version of the manuscript. JR, LAE, NM, JE, AS and PC critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare no conflict of interest in relation to the subject of the study.

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