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Staging of Schizophrenia With the Use of PANSS: An International Multi-Center Study

Konstantinos N. Fountoulakis, Elena Dragioti, Antonis T. Theofilidis, Tobias Wikilund, Xenofon Atmatzidis, Ioannis Nimatoudis, Erik Thys, Martien Wampers, Luchezar Hranov, Trayana Hristova, Daniil Aptalidis, Roumen Milev, Felicia Iftene, Filip Spaniel, Pavel Knytl, Petra Furstova, Tiina From, Henry Karlsson, Maija Walta, Raimo K. R. Salokangas, Jean-Michel Azorin, Justine Bouniard, Julie Montant, Georg Juckel, Ida S. Haussleiter, Athanasios Douzenis, Ioannis Michopoulos, Panagiotis Ferentinos, Nikolaos Smyrnis, Leonidas Mantonakis, Zsófia Nemes, Xenia Gonda, Dora Vajda, Anita Juhasz, Amresh Shrivastava, John Waddington, Maurizio Pompili, Anna Comparelli, Valentina Corigliano, Elmars Rancans, Alvydas Navickas, Jan Hilbig, Laurynas Bukelskis, Lidija Injac Stevovic, Sanja Vodopic, Oluyomi Esan, Oluremi Oladele, Christopher Osunbote, Janusz K. Rybakowski, Pawel Wojciak, Klaudia Domowicz, Maria Luisa Figueira, Ludgero Linhares, Joana Crawford, Anca-Livia Panfil, Daria Smirnova, Olga Izmailova, Dusica Lecic-Tosevski, Henk Temmingh, Fleur Howells, Julio Bobes, Maria Paz Garcia-Portilla, Leticia García-Alvarez, Gamze Erzin, Hasan Karadağ, Avinash De Sousa, Anuja Bendre, Cyril Hoschl, Cristina Bredicean, Ion Papava, Olivera Vukovic, Bojana Pejuskovic, Vincent Russell, Loukas Athanasiadis, Anastasia Konsta, Dan Stein, Michael Berk, Olivia Dean, Rajiv Tandon, Siegfried Kasper, Marc De Hert.

3rd Department of Psychiatry, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Greece (Drs Fountoulakis, Theofilidis, and Nimatoudis); Department of Medical and Health Sciences (IMH), Faculty of Health Sciences, Linköping University, Linköping, Sweden (Drs Dragioti, Wikilund, and Atmatzidis); Hallunda Psychiatric Outpatient Clinic, Stockholm Psychiatric Southwest Clinic, Karolinska Huddinge University Hospital, Sweden (Drs Dragioti, Wikilund, and Atmatzidis); University Psychiatric Centre KU Leuven, Kortenberg and

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Main Outcomes

1. The general 5-factor solution of the PANSS is confirmed but with different loadings of individual items
2. Schizophrenia could be characterized by the presence of 4 main stages with substages. Each stage is predominantly characterized by a different clinical feature (stage 1: psychosis; stages 2a and 2b: excitement and hostility; stages 3a and 3b: depression and anxiety; stages 4a and 4b: neurocognitive decline)
3. The model was identical for males and females
4. More than 85% of patients can be attributed a stage on the basis of a PANSS-based algorithm

Limitations

1. Cross-sectional study design with the utilization of limited demographic and clinical info or treatment resistance status
2. Neurocognition was assessed on the basis of the therapist's clinical impression
3. Study sample was not epidemiologically selected; represents those patients with at least less than ideal remission who remained in contact with mental health services for several years
4. The method for the identification of stages falls in the grey zone between quantitative and qualitative methodology and both the method and its results are open to debate
5. Although antipsychotic medication is believed to influence only positive psychotic symptoms, their effect on the model remains to be studied specifically

Department of Neurosciences KU, Leuven, Belgium (Drs Thys, Wampers, and De Hert); University Multiprofile Hospital for Active Treatment in Neurology and Psychiatry "Sveti Naum", Sofia, Bulgaria (Drs Hranov, Hristova, and Aptalidis); Department of Psychiatry, Queen's University, Providence Care Hospital, Kingston, Ontario, Canada (Drs Milev and Iftene); National Institute of Mental Health, Klecany, Czech Republic (Drs Spaniel, Knytl, Furstova, and Hoschl); Department of Psychiatry, University of Turku, Turku, Finland (Drs From, Karlsson, Walta, and Salokangas); Department of Psychiatry, Sainte Marguerite University Hospital, Marseille, France (Drs Azorin, Bouniard, and Montant); Timone Institute of Neuroscience, CNRS and Aix-Marseille University, Marseille, France (Drs Azorin, Bouniard, and Montant); Department of Psychiatry, Ruhr University Bochum, LWL-University Hospital, Bochum, Germany (Drs Juckel and Haussleiter); 2nd Department of Psychiatry, National and Kapodistrian University of Athens, Athens, Greece (Drs Douzenis, Michopoulos, and Ferentinos); Department of Psychiatry, National and Kapodistrian University of Athens School of Medicine, Eginition Hospital, Athens, Greece (Drs Smyrnis and Mantonakis); Nyírő Gyula Hospital, Budapest, Hungary (Dr Nemes); Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary (Drs Gonda, Vajda, and Juhasz); Western University, London Ontario, Canada (Dr Shrivastava); Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland (Dr Waddington); Department of Neurosciences, Mental Health and Sensory Organs, Suicide Prevention Center, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy (Drs Pompili, Comparelli, and Corigliano); Department of Psychiatry and Narcology, Riga Stradins University, Riga, Latvia (Dr Rancans); Clinic of Psychiatric, Faculty of Medicine, Vilnius University, Vilnius, Lithuania (Drs Navickas, Hilbig, and Bukelskis); Psychosocial Rehabilitation Department of the Vilnius Mental Health Center, Department for Psychosis Treatment of the Vilnius Mental Health Center, Vilnius, Lithuania (Drs Navickas, Hilbig, and Bukelskis); Clinical Department of Psychiatry, Clinical Centre of Montenegro, Podgorica, Montenegro, Department of Psychiatry, School of Medicine, University of Montenegro, Dzona Dzeksona bb, Podgorica, Montenegro; Clinical Department of Neurology, Clinical Centre of Montenegro, Dzona Dzeksona bb, Podgorica, Montenegro (Drs Stevovic and Vodopic); Department of Psychiatry, College of Medicine, University of Ibadan, Nigeria (Drs Esan, Oladele, and Osunbote); Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland (Drs Rybakowski, Wojciak, and Domowicz); Department of Psychiatry and Mental Health, Santa Maria University Hospital, Lisbon, Portugal (Drs Figueira, Linhares, and Crawford); University of Medicine and Pharmacy of Târgu Mures, Romania (Dr Panfil); Samara State Medical University, Department of Psychiatry, Samara Psychiatric Hospital, Inpatient Unit, Russia (Drs Smirnova and Izmailova); Institute of Mental Health, Belgrade, Serbia; Serbian Academy of Sciences and Arts, Belgrade, Serbia (Dr Lecic-Tosevski); Department of Psychiatry and Mental Health, University of Cape Town Cape Town, Western Cape, South Africa (Drs Temmingh and Howells); Department of Psychiatry, University of Oviedo and Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Oviedo, Spain (Drs Bobes, Garcia-Portilla, and García-Alvarez); Psychiatry Department,

Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey (Drs Erzin and Karadağ); Department of Psychiatry Lokmanya Tilak Municipal Medical College Mumbai, India (Drs Sousa and Bendre); University of Medicine and Pharmacy of Timisoara, Romania (Drs Bredicean and Papava); Institute of Mental Health, School of Medicine, University of Belgrade, Belgrade, Serbia (Dr Vukovic); Department of Psychiatry, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland (Drs Pejuskovic and Russell); 1st Department of Psychiatry, Faculty of Medicine, School of Health Sciences, Aristotle University of Thessaloniki, Greece (Drs Athanasiadis and Konsta); MRC Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa (Dr Stein); Deakin University, IMPACT Strategic Research Centre, School of Medicine, Barwon Health, Geelong, Australia and Orygen, The National Centre of Excellence in Youth Mental Health and the Centre for Youth Mental Health, the Florey Institute for Neuroscience and Mental Health and the Department of Psychiatry, University of Melbourne, Parkville, Australia (Dr Berk); Deakin University, School of Medicine, IMPACT Strategic Research Centre, Barwon Health, Geelong, Australia (Dr Dean); Department of Psychiatry, University of Florida, ***, FL (Dr Tandon); Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria (Dr Kasper).

Correspondence to: Konstantinos N. Fountoulakis, 6, Odysseos str (1st Parodos Ampelonon str.), 55535 Pylaia Thessaloniki, Greece (kfount@med.auth.gr).

ABSTRACT

Introduction: A specific clinically relevant staging model for schizophrenia has not yet been developed. The aim of the current study was to evaluate the factor structure of the PANSS and develop such a staging method.
Methods: Twenty-nine centers from 25 countries contributed 2358 patients aged 37.21±11.87 years with schizophrenia. Analysis of covariance, Exploratory Factor Analysis, Discriminant Function Analysis, and inspection of resultant plots were performed.
Results: Exploratory Factor Analysis returned 5 factors explaining 59% of the variance (positive, negative, excitement/hostility, depression/anxiety, and neurocognition). The staging model included 4 main stages with substages that were predominantly characterized by a single domain of symptoms (stage 1: positive; stages 2a and 2b: excitement/hostility; stage 3a and 3b: depression/anxiety; stage 4a and 4b: neurocognition). There were no differences between sexes. The Discriminant Function Analysis developed an algorithm that correctly classified >85% of patients.
Discussion: This study elaborates a 5-factor solution and a clinical staging method for patients with schizophrenia. It is the largest study to address these issues among patients who are more likely to remain affiliated with mental health services for prolonged periods of time.

Keywords: illness course, outcome, schizophrenia, staging

Introduction

Schizophrenia is a chronic and complex disorder. Its diagnosis is made according to the Diagnostic and Statistical Manual of Mental Disorders (which is currently in its 5th Edition) and is based on polythetic criteria (APA, 2000, 2013). This means it is officially accepted that it is common for patients to present with highly varying and commonly comorbid pictures of psychopathology (Keshavan et al., 2008; Lang et al., 2013). The observation that patients often do not correspond to the identified subtypes as defined by previous versions of the DSM but instead present with mixed symptoms and syndromes not only leads to the abandoning of subtypes but also adds variability in etiology and pathobiology as well as uncertainty concerning treatment and prognosis (Lang et al., 2013).

Several models were developed to gain insight into the structure of the clinical picture and the psychopathology of schizophrenia. So far, the most widely used model is the pyramidal model, developed by Stanley Kay and colleagues and based on ratings of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987, 1988; Kay, 1990; Kay and Sevy, 1990; Kay and Sandyk, 1991). The pyramid is made by poles corresponding to positive, negative, and depressive symptomatology that create a triangular base. According to this model, excitement symptoms constitute a separate vertical axis (Figure 1) (Kay and Sevy, 1990).

Overall, the 5-factor model value has been repeatedly shown across various studies (Marder et al., 1997; Lykouras et al., 2000; Wolthaus et al., 2000; Emsley et al., 2003; Fresan et al., 2005; Monteiro et al., 2008; Llorca et al., 2012; Wallwork et al., 2012; Stochl et al., 2014; Wu et al., 2015), although there are data suggesting that even more multifaceted and complex models may be valid as well (Peralta and Cuesta, 1994; Nakaya et al., 1999a, 1999b; Emsley et al., 2003; Van den Oord et al., 2006; Walsh-Messinger et al., 2018). The 5-factor model manifests significant variety among the dimensions identified by different authors, there does not seem to exist adequate fit (van der Gaag et al., 2006), and maybe the most important inconsistency concerns the most appropriate item composition of the proposed PANSS models (White et al., 1997; Lykouras et al., 2000; White, 2005; van der Gaag et al., 2006). Nevertheless, the PANSS and associated

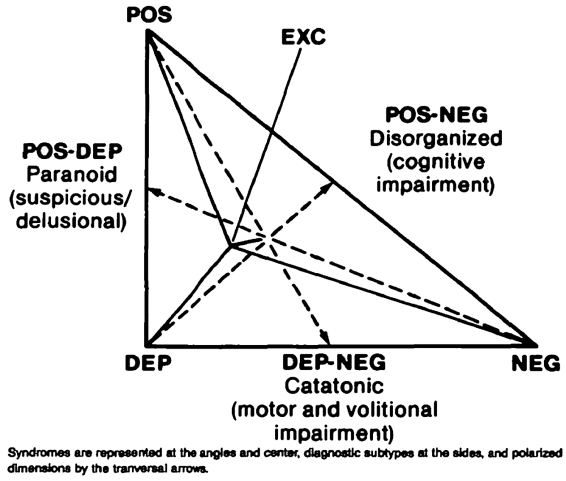

Figure 1. The classic 5-factor model of Stanley Kay and colleagues.

models are used extensively in psychiatric research to assess diagnostic and treatment efficacy (Lindenmayer et al., 1986; Marder et al., 1997; Bunk et al., 1999; Lykouras et al., 2000; Emsley et al., 2003, 2007; Monteiro et al., 2008; Citrome et al., 2011; Llorca et al., 2012; Wallwork et al., 2012; Stochl et al., 2014; Wu et al., 2015).

There are several possible explanations for the observed variability in PANSS factors, and they mainly include contributing factors such as age and sex (Pandurangi et al., 1994; Leung and Chue, 2000; Hayashi et al., 2002; Emmerson et al., 2009; Walsh-Messinger et al., 2018). According to many authors, age could serve as a proxy of staging. A number of studies have reported the presence of significant associations of stage of illness with course, outcome, prognosis, and treatment response (Nakaya et al., 1999a, 1999b; Emsley et al., 2007; Cuesta et al., 2012; Hill et al., 2012). The effect of socio-cultural factors as well as intrinsic factors pertaining to the specific diagnostic and conceptual approaches of individual researchers and research centers could exert a major contributing effect towards significant heterogeneity of the results (Khan et al., 2013a, 2013b), but these issues are not adequately studied (Dollfus and Petit, 1995; Nakaya et al., 1999a, 1999b; Hayashi et al., 2002; Walsh-Messinger et al., 2018).

It is evident that there is a need for an empirically derived and comprehensive model. Such a model should take into account the specific stage of the illness in combination with gender- and age-specific signs and symptoms as well as socio-cultural characteristics. If such an approach eventually appears, it could add to our understanding of schizophrenia and improve diagnostic accuracy and patient management. During the last decades, the research has focused on the staging of mental disorders (Fava and Kellner, 1993; Agius et al., 2010; McGorry et al., 2010). In this frame, a 5-stage model (i.e., prodromal, acute psychotic episode, residual, and prechronic and chronic phases) has been proposed based on the course of schizophrenia (Fava and Kellner, 1993). Other authors have proposed 3 to 8 stages based on the development of the illness over time (Agius et al., 2010; McGorry et al., 2010). The main idea is that clinical staging could permit better targeting of treatment and could also significantly improve the individualized balance of potential risks and benefits (Wojciak et al., 2016). In spite of these pressing needs, to date there is no easily applicable and reliable clinical tool available for the identification of stages in patients with schizophrenia.

The primary aim of the current study was to empirically devise a staging approach (according to an approximation based on illness duration) using the PANSS model in a very large sample of stabilized patients with schizophrenia of varying ages. A second aim was also to explore the pattern and quality of psychopathology especially between the sexes, since better understanding of the clinical picture could facilitate attempts at staging.

MATERIALS AND METHODS

Study Sample

The study population included patients with a DSM-IV or DSM-5 diagnosis of schizophrenia (APA, 2000, 2013), including first-episode patients. There was much effort to exclude organic mental disorders, and more specifically dementia of any kind, according to the clinical judgment of the investigators. Participants were either inpatients prior to discharge or outpatients and were collected in a number of clinical settings, including academic units, clinics, and hospitals across different countries.

Eligible patients were stabilized and all were treated with medication based on their therapists' judgment. There were no interventions associated with the current study. Patients were excluded if they had a coexisting diagnosis of substance abuse or dependence or a concurrent medical or neurological disorder according to their medical records.

All clinical evaluations were performed by trained psychiatrists before clinic or hospital discharge. The study obtained approval by the Research Ethical Committee of the Aristotle University Medical School, Thessaloniki, Greece and the other participating centers. Informed consent was obtained from all patients after a detailed description of the study procedures.

Twenty-nine centers from 25 countries around the world participated in the study and contributed a total of 2358 patients (Table 1).

Measurements

The study collected socio-demographic information on patients with schizophrenia (age and sex) together with assessment using the PANSS (Kay et al., 1987, 1988; Kay, 1990; Kay and Sevy, 1990; Kay and Sandyk, 1991). The PANSS is a 30-item rating scale developed by Kay and colleagues (Kay et al., 1987) to assess dimensions of schizophrenia symptoms and their severity. Items were initially compacted to resolve 3 scales: positive (7 items), negative (7 items), and general psychopathology (GP) (16 items). In this study we used the modified version, which includes 4 dimensions: positive, negative, GP, and excited symptoms (Kay and Sevy, 1990). Trained interviewers administered the PANSS during structured clinical interviews and scored items on a scale from 1 (asymptomatic) to 7 (extremely symptomatic).

Duration of the illness was defined as time since the first development of clear psychotic symptoms. This was achieved in a heterogeneous way; for some patients, very precise data were available while for others the information came from interviewing the patients and their families.

Definition of First Episode of Schizophrenia Patients

The term first episode psychosis was first used in the context of schizophrenia (Targum, 1983), but today it includes a broad spectrum of psychotic disorders. There is no consensus in the literature concerning the exact nature and the criteria to define

Table 1. Composition of the study sample in terms of country of origin, sex, and first episode of schizophrenia (FES) status

	Total study sample (n = 2358)					FES-E (n = 484)			FES-M (n = 61)			FES-L (n = 57)			non-FES (n = 1756)		
			M		F	M		F	M		F	M		F	M		F
Country	n	%	n	%	n	n	%	n	n	%	n	n	%	n	n	%	n
Belgium	365	15.48	246	67.40	119	8	61.54	5	2	100.00	0	0		0	236	67.43	114
Bulgaria	31	1.31	17	54.84	14	0		0	0		0	0		0	17	54.84	14
Canada	30	1.27	15	50.00	15	0	0.00	1	0		0	0		0	15	51.72	14
Czech Rep	556	23.58	302	54.32	254	188	55.46	151	22	53.66	19	18	46.15	21	74	54.01	63
Finland	10	0.42	4	40.00	6	0		0	0		0	0		0	4	40.00	6
France	69	2.93	47	68.12	22	0	0.00	1	0		0	0		0	47	69.12	21
Germany	56	2.37	40	71.43	16	4	80.00	1	0		0	0	0.00	1	36	72.00	14
Greece	184	7.80	112	60.87	72	9	56.25	7	1	100.00	0	2	100.00	0	100	60.61	65
Hungary	108	4.58	51	47.22	57	6	54.55	5	1	100.00	0	1	100.00	0	43	45.26	52
India	47	1.99	30	63.83	17	2	100.00	0	1	33.33	2	0	0.00	2	27	67.50	13
Ireland	98	4.16	80	81.63	18	46	82.14	10	0		0	0		0	34	80.95	8
Italy	50	2.12	33	66.00	17	6	54.55	5	0		0	0		0	27	69.23	12
Latvia	74	3.14	30	40.54	44	0	0.00	1	0	0.00	1	1	50.00	1	29	41.43	41
Lithuania	50	2.12	27	54.00	23	1	50.00	1	0		0	0		0	26	54.17	22
Montenegro	50	2.12	24	48.00	26	1	100.00	0	0	0.00	1	0		0	23	47.92	25
Nigeria	93	3.94	43	46.24	50	0		0	0		0	0		0	43	46.24	50
Poland	55	2.33	28	50.91	27	3	33.33	6	0		0	0		0	25	54.35	21
Portugal	18	0.76	7	38.89	11	0		0	1	100.00	0	0		0	6	35.29	11
Romania	37	1.57	18	48.65	19	0	0.00	1	0		0	0		0	18	50.00	18
Russia	50	2.12	47	94.00	3	0		0	0		0	0		0	47	94.00	3
Serbia	50	2.12	45	90.00	5	0		0	1	100.00	0	1	50.00	1	43	91.49	4
South Africa	71	3.01	58	81.69	13	5	100.00	0	2	100.00	0	6	100.00	0	45	77.59	13
Spain	60	2.54	40	66.67	20	3	50.00	3	4	66.67	2	0	0.00	2	33	71.74	13
Sweden	39	1.65	21	53.85	18	0		0	0		0	0		0	21	53.85	18
Turkey	107	4.54	64	59.81	43	3	75.00	1	1	100.00	0	0		0	60	58.82	42
Total	2358	100.00	1429	60.60	929	285	58.88	199	36	59.01	25	29	50.87	28	1079	61.44	677

Abbreviations: F, females; FES-L, late group with duration of more than 3 years; FES-M, middle group with duration between 18 months and 3 years; M, males; non-FES, patients who are not during their FES; sFES-E, Early group of no more than 18 months of illness duration (n = 484).

first episode psychosis (Keshavan and Schooler, 1992; Taylor and Perera, 2015). First episode schizophrenia (FES) emerged with the development of early intervention programs, but the benchmark for the beginning of this first episode remains undefined (Breitborde et al., 2009). In our study sample it concerns the first experience of symptoms by the patient (Farde et al., 1990), which we regard as the most appropriate method since the patient may have experienced a significant period of untreated psychosis prior to reaching services or have made previous, unsuccessful attempts to access treatment (Lincoln et al., 1998).

While the literature frequently deals with the issue of defining the onset of the first episode, less has been discussed concerning until when it should be considered to be a real "first episode," since many patients never remit and experience a single chronic episode throughout their lives. While FES with several years duration might not be conceptually valid, since chronicity is evident in the absence of remission, patients are still experiencing their first and single psychotic episode. Since refractory patients number approximately 23% and the majority (approximately 84%) of them are already refractory during their first episode, this subgroup would correspond to 20% of our FES patients and likely includes those whose FES lasts more than 18 months (Demjaha et al., 2017).

Among the 602 patients who were initially considered as experiencing FES, 484 (80.39%) had a duration of illness since onset of no more than 18 months, 523 (86.87%) of no more than 2 years, 545 (90.53%) of no more than 3 years, 558 (92.69%) of no more than 4 years, and 568 (94.35%) of no more than 5 years. Thirty-four (5.65%) had an illness duration of more than 5 years. Therefore, the FES sample was split into an early group with duration of illness no longer than 18 months (FES-E; n = 484), a middle group with a duration between 18 months and 3 years (FES-M, n = 61), and a late group with a duration longer than 3 years (FES-L, n = 57).

Data Analyses

Demographic and PANSS data were calculated as frequencies (%), means, SDs, and range. ANCOVA was performed on an exploratory basis to examine for differences between groups. Correlations were assessed with the calculation of the Pearson R.

The methodology included two phases. During the first phase, exploratory factor analysis (EFA) was performed using a principal component analysis (PCA) with varimax normalized rotation, and the factors were selected on the basis of an eigenvalue >1 (Dziuban and Shirkey, 1974), which is the standard for such an analysis. The cut-off of loading values to group individual items under specific factors was chosen in an arbitrary way but by taking into consideration the need to attribute every item to a factor and as few as possible under 2 or more factors. This was done by choosing the loadings >0.40. If 2 items cross-loaded to more than 1 factor with loadings >0.40, then all those were chosen and the item was considered to load on multiple factors. If only loadings below 0.40 existed, then all those >0.30 were chosen and the item was considered to load on multiple factors. PCA was also used to examine the stability of the extracted factor structure between the 2 sexes and in FES patients. The aim was to recognize reliable and valid latent structures concerning this specific study sample and to compare these with findings in the literature.

The second phase included an attempt to explore the presence of stages. There is no external gold standard, and in a previous study age was used as a proxy because duration of illness was unavailable for that study sample (Dragioti et al., 2017). In the current study sample, duration of illness correlates moderately with age (R = 0.45). Staging was approached by plotting the factor scores (obtained during the first phase) vs duration of illness and the identification of points in illness development with a shift in the curve of any factor score. The lines were smoothed with the use of weight distances with least squares method. This procedure fits a curve to the data by calculating a polynomial (second-order) regression for each value on the X variable scale to determine the corresponding Y value such that the influence of the individual data points on the regression (i.e., the weight, see the stiffness option on the plot fitting dialog) decreases with their distance from the particular X value. This approach provides a sensitive method for revealing nonsalient overall patterns of data. Due to measurement error, such patterns can be hard to identify by simply looking at the scatterplot, although if revealed, they may turn out to be interpretable and reliable, and thus the method could be used to identify patterns so as to develop quantitative models since the smoothing procedure often consists of segments that cannot easily be described by 1 function (Strutz, 2016). This is essentially an optical method and it has many subjective elements. As such it is open to debate.

The third phase concerned the attribution of a specific stage to all the subjects of the study sample and testing for differences between stages. The exact method will be described together with the respective results since its description prerequires knowledge of the results. The fourth phase included discriminant function analysis with stages as grouping variable and all the individual PANSS items as predictors

Finally linear regression analysis was used to develop functions that will allow to calculate factor scores (dependent variables) from the classic PANNS subscale scores (P, N, GP, EC; used as independent variables). These functions could allow the staging of patients whose data are available only in the forms of PANSS subscales and also could allow the characterization of study samples whose PANSS scores are reported only as means of the classic PANSS subscales.

RESULTS

Sociodemographic Characteristics

The study population consisted of 2358 patients: 929 females (39.40%) and 1429 males (60.60%) aged 37.21 ± 11.87 years (range 16–81 years) with the DSM-IV or -5 diagnosis of schizophrenia (APA, 2000, 2013). Among these, 602 (25.53%) were in their first episode (mean duration 1.20 ± 2.48 years). Thirty-four of them were chronic patients whose first episode never resolved and had a duration >5 years. Their age at onset was 26.16 ± 8.07 years and their illness duration was 11.05 ± 10.93 years (range 0–54). They were either inpatients (prior to release) or outpatients and were collected in a number of clinical settings including academic units and mental hospitals from different countries (Table 1).

EFA of PANSS

The PCA model resulted in 5 factors based on eigenvalues above 1. These explained 59% of the total variance (Table 2) in contrast to the model proposed by Kay and Sevy (Kay and Sevy, 1990). Factor complexity was also observed; more than 1 item cross-loaded on more than 1 factor (e.g., items P2, N5, and N7).

The first factor included items N1 through N7, G7, G13, G15, and G16 corresponding to a negative domain; the second factor included items P1, P2, P3,P5, P6, G9, and G12 corresponding to a positive domain; the third factor included items G1, G2, G3, G4, and G6 corresponding to a depression and anxiety domain (general psychopathology); the fourth factor included items P4, P7, G8, and G14 corresponding to an excitement and hostility domain; and the fifth factor included items P2, N5, N7, G5, G10, and G11 corresponding to a neurocognitive domain. The positive and negative domains were abbreviated Po and Ne, respectively, to be easily distinguishable from the classical P and N subscales of the PANSS.

Differences between males and females were minimal (webappendix Table A). Male factor analysis was identical to the results of the whole sample with the exception that G13 and G15 were also included in the neurocognitive domain. In females the positive factor does not include P5, which is allocated to the excitement and hostility domain; the neurocognitive domain does not include items G13 and G15, which belong only to the general psychopathology domain.

To verify the results, centers were randomly allocated into 3 groups. The first group included 976 participants, the second 631, and the third 751 participants. Factor analysis was performed separately with the participants of each center group in order to test the assumption that there could be a center bias in the results. The results are shown in webappendix Table B and suggest a 5-factor solution for the first and second groups and a 6-factor solution for the third group of centers. While the overall structure seems stable, some variability among these 3 factor models exists, suggesting the presence of a minor center bias.

Differences Among Subgroups

ANCOVA with sex as grouping variable, standard PANSS subscales as dependent variables, and age and duration of illness as covariates returned a significant effect for sex (Wilks = 0.984, F = 9.59, Effect df = 4, Error df = 2351, $P < .001$) as well as for age (Wilks = 0.994, F = 3.26, Effect df = 4, Error df = 2351, $P < .011$) and duration (Wilks = 0.975, F = 14.99, Effect df = 4, Error df = 2351, $P < .001$). The results were different when the factor scores of the current PCA were used as dependent variables; there was a significant effect for sex (Wilks = 0.986, F = 6.82, Effect df = 5, Error df = 2350, $P < .001$) and duration (Wilks = 0.961, F = 18.97, Effect df = 5, Error df = 2350, $P < .001$) but not for age (Wilks = 0.997, F = 1.22, Effect df = 5, Error df = 2350, $P = .297$). The Scheffe post hoc test revealed significant differences between the 2 sexes in the N subscale ($P < .001$) and the Ne ($P < .001$) and DA factor scores ($P = .004$), suggesting that females had fewer negative symptoms but more depression and anxiety (Table 3).

Although the classical subscales, factor scores, and domain scores are highly intercorrelated with R values ranging between 0.8 and 0.9, the behavior of these different rating methods is quite different and the scale scores are closer to reality.

The use of ANCOVA to test for differences between FES-E and non-FES patients (with age and duration as covariates) returned significant effects when the classical PANSS subscales were used for FES (Wilks = 0.987, F = 7.48, Effect df = 4, Error df = 2233, $P < .001$) as well as for age (Wilks = 0.991, F = 4.97, Effect df = 4, Error df = 2233, $P = .001$) and duration (Wilks = 0.975, F = 14.13, Effect df = 4, Error df = 2233, $P < .001$). The Scheffe post hoc test returned significant differences only concerning the N subscale between FES-E and non-FES patients ($P < .001$). When the factor scores

Table 2. Factor Analysis With the Use of the Total Study Sample

	Factor 1 Ne	Factor 2 Po	Factor 3 DA	Factor 4 EH	Factor 5 Ncog
P1 Delusions	0.10	*0.87*	0.18	0.11	0.05
P2 Conceptual disorganization	0.23	*0.47*	0.10	0.16	*0.56*
P3 Hallucinatory behavior	0.13	*0.68*	0.18	0.03	0.13
P4 Excitement	−0.16	*0.31*	0.24	*0.55*	0.34
P5 Grandiosity	−0.14	*0.46*	0.02	0.26	0.20
P6 Suspiciousness/persecution	0.18	*0.70*	0.21	0.30	−0.13
P7 Hostility	0.11	*0.24*	0.07	*0.81*	0.01
N1 Blunted affect	*0.80*	0.04	0.07	−0.03	0.14
N2 Emotional withdrawal	*0.85*	0.09	0.07	0.04	0.09
N3 Poor rapport	*0.79*	0.10	−0.05	0.22	0.12
N4 Passive/apathetic social withdrawal	*0.80*	0.11	0.18	0.04	0.07
N5 Difficulty in abstract thinking	*0.46*	*0.23*	−0.12	0.01	*0.48*
N6 Lack of spontaneity & flow of conversation	*0.79*	0.01	0.03	0.02	*0.23*
N7 Stereotyped thinking	*0.45*	*0.31*	0.15	0.12	*0.44*
G1 Somatic concern	0.06	*0.23*	*0.47*	0.02	*0.21*
G2 Anxiety	0.13	*0.18*	*0.74*	0.13	0.10
G3 Guilt feelings	0.04	*0.07*	*0.68*	0.01	0.03
G4 Tension	0.11	*0.17*	*0.64*	*0.31*	*0.23*
G5 Mannerisms & posturing	*0.31*	0.04	*0.21*	0.10	*0.55*
G6 Depression	*0.30*	0.01	*0.71*	0.05	−0.06
G7 Motor retardation	*0.62*	−0.05	*0.32*	−0.03	*0.25*
G8 Uncooperativeness	*0.25*	*0.18*	*0.07*	*0.75*	*0.17*
G9 Unusual thought content	0.08	*0.70*	*0.18*	*0.15*	*0.34*
G10 Disorientation	0.13	*0.11*	*0.03*	*0.24*	*0.62*
G11 Poor attention	*0.31*	*0.19*	*0.24*	*0.23*	*0.53*
G12 Lack of judgment & insight	*0.24*	*0.58*	−0.12	*0.29*	*0.24*
G13 Disturbance of volition	*0.52*	*0.04*	*0.25*	*0.16*	*0.39*
G14 Poor impulse control	*0.07*	*0.16*	*0.16*	*0.72*	*0.29*
G15 Preoccupation	*0.43*	*0.31*	*0.26*	*0.16*	*0.31*
G16 Active social avoidance	*0.64*	*0.23*	*0.26*	*0.18*	−0.01
Explained variance	5.56	3.66	2.89	2.72	2.70
Proportion of total	19%	12%	10%	9%	9%
Total variance explained					59%

Abbreviations: DA, depression/anxiety; EH, excitement/hostility; Ncog, neurocognitive impairment; Ne, negative; Po, positive.
When males and females were used in separate factor analyses, the differences were negligible. In italics are items mainly loading to each factor.

Table 3. Means and SD of the Classical PANSS Subscales and Factor Scores According to the Current Factor Analysis in the Various Study Sample Groups

							FES patients n = 602							
	Total sample n = 2358		Males n = 1429		Females n = 929		FES-E (n = 484)		FES-M (n = 61)		FES-L (n = 57)		Non-FES Patients (n = 1756)	
Scores	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Classical subscales														
PANSS-P	14.86	6.35	14.99	6.24	14.67	6.52	15.21	6.69	13.62	6.07	14.91	7.61	14.81	6.22
PANSS-N	18.12	7.45	18.78	7.45	17.11	7.34	16.84	6.86	16.38	7.34	15.56	6.58	18.62	7.57
PANSS-GP	31.40	10.72	31.50	10.67	31.26	10.79	31.13	10.00	29.02	9.12	27.67	8.94	31.69	10.98
PANSS-EC	8.89	4.15	8.88	4.03	8.89	4.33	8.72	4.39	7.95	2.91	8.49	5.11	8.98	4.08
Factor scores														
Po	0.00	1.00	0.01	1.01	−0.02	0.98	0.14	1.01	−0.06	1.12	0.11	1.22	−0.04	0.98
Ne	0.00	1.00	0.08	1.00	−0.13	0.99	−0.13	1.02	−0.20	1.07	−0.43	0.93	0.06	0.99
DA	0.00	1.00	−0.05	0.99	0.07	1.01	−0.05	0.88	−0.13	0.70	−0.26	0.86	0.03	1.04
EH	0.00	1.00	−0.01	0.98	0.02	1.03	0.00	1.04	−0.17	0.70	0.09	1.38	0.00	0.98
Ncog	0.00	1.00	0.02	1.01	−0.03	0.99	−0.06	0.92	−0.04	0.81	−0.12	0.91	0.02	1.03

According to ANCOVA analyses, there were differences between the 2 sexes in the N subscale ($P < .001$) and the N ($P < .001$) and DA factor scores ($P = .004$). There were also differences only concerning the N subscale ($P < .001$) and concerning the P and N factor scores between FES-E and non-FES patients (both at $P < .001$).
Abbreviations: DA, Depression/anxiety; EC, excitement component; EH, excitement/hostility; GP, general psychopathology; N, negative subscale of the PANSS (classic); Ncog, neurocognitive impairment; Ne, negative factor; P, positive subscale of the PANSS (classic); Po, positive factor.

were used there was a significant effect for FES (Wilks = 0.987, F = 5.76, Effect df = 5, Error df = 2232, P < .001) as well as for duration (Wilks = 0.955, F = 21.25, Effect df = 5, Error df = 2232, P = .001) but not for age (Wilks = 0.995, F = 2.14, Effect df = 5, Error df = 2232, P = .058). The Scheffe post hoc test returned significant differences concerning the Po and Ne factor scores between FES-E and non-FES patients (both at P < .001). The respective means and SDs are shown in Table 3.

Identification of Illness Stages

The plot of factor scores vs duration of illness is shown in Figure 2. As described in the Methods section, the identification of stages was done with the inspection of the plot. Therefore it inherently has subjective biases and is open to discussion, but still it reflects a fair interpretation of the picture.

In Figure 2 it is obvious that the factor scores (their lines are smoothed with the distance weighted least squares method) are not monotonous but they change through time and a different factor emerges as duration increases.

The points that define stage change are those that mark a change in the pattern of symptoms. In this way, 4 distinct major stages can be identified: Stage 1 lasts 3 years on average. During this stage, positive symptoms (Po) are dominant but they tend to remit with the passage of the time. During the same time, negative symptoms (Ne) as well as depression and anxiety (DA) are stable, but excitement and hostility (EH) increases and the stage ends when they replace positive symptoms as the dominant symptomatology.

Stage 2 lasts 9 years on average. During this stage, EH are dominant and continue to increase. Po symptoms tend to remit further and stabilize, while Ne symptoms, DA, and the neurocognitive deficit (Ncog) start to increase and the stage ends when depression and anxiety overrun excitement and hostility as the dominant feature in the symptomatology.. It can be divided into 2 substages: Stage 2a lasts 3 years on average. During this period, Po symptoms tend to remit further while EH continue to increase. Additionally, during this phase, Ne symptoms as well as DA start to increase and the substage ends when they exceed positive symptoms. The Ncog is stable. Stage 2b lasts 6 years on average. During this stage, EH and Po symptoms stabilize, Ne symptoms and DA continue to rise, and Ncog impairment also starts to rise. The substage ends when DA exceed EH as the dominant feature in symptomatology.

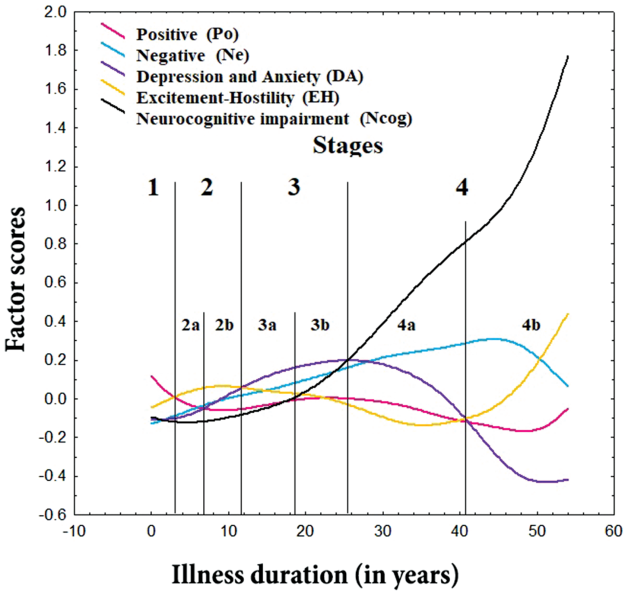

Figure 2. Plot of factor scores (y-axis) vs duration of illness (x-axis) and identification of stages

Stage 3 lasts 13 years on average. During this period, DA is the dominant feature and continues to rise slowly; at the end of the period, they reach a zenith. Ne symptoms and Ncog deficit continue to rise, and the stage ends when Ncog exceeds DA as the dominant feature. It can be divided into 2 substages of roughly equal duration: In Stage 3a, EH continues to decline but is still a prominent component of the clinical picture. This substage ends when Ne and Po symptoms and Ncog overrun it. During Stage 3b, EH together with Po symptoms contribute least to psychopathology, which is dominated by DA, Neg symptoms, and Ncog impairment.

Stage 4, the final stage, is characterized by an exponential increase in Ncog deficit and on average starts 25 years after illness onset. It can be divided into 2 sub stages. Stage 4a lasts 15 years on average and is characterized by a robust increase in Ncog impairment and a less robust increase in Ne symptoms. The other symptom clusters decline. Decreases in DA are prominent and the substage ends when they contribute least to the clinical picture. Stage 4b starts approximately 40 years after illness onset and is characterized by a prominent Ncog deficit that dominates the clinical picture. Ne symptoms decline and are replaced by EH as the second most important element.

The plotting of factor scores against duration separately for males and females suggested the presence of the same stages (webappendix Figure A). The only difference was that the first and second stages appeared to be shorter and occurred earlier in females, but differences were not significant.

There seems to be some effect of country/center since there was a difference between duration of illness among countries. There was a significant correlation (P < .05) between the percentage of cases classified in each stage by country and the mean duration of illness by country concerning stages 1 (R = −0.43) and 4 (R = 0.48). Both findings were eliminated when Sweden was taken out of the analysis. The related data are shown in webappendix Table H and webappenxix Figure B. The use of ANCOVA with country as grouping variable, duration of illness as covariate, and factor scores as dependent variables showed significant differences among countries concerning all factor scores (Wilks' Lambda: 0.5059; F(120,11446) = 14.1827; P < .001). Approximately two-thirds of countries differed from each other concerning each factor score, and each one of them differed from 1 to 8 others but no clear pattern of differences was present.

Development of a Method to Identify Stage of Illness for the Individual Patient

The identification of illness stages was based on factor scores as described in the previous section. Therefore, the first step to stage an individual patient is to calculate her/his factor score. The calculation of this score can be achieved by using factor score coefficients that are provided in webappendix Table C. The distribution of patients in the various stages is shown in Table 4, and the characteristics of each stage in terms of age, age at onset, duration of illness and factor scores and the relationship between them are shown in Tables 5 and 6.

The specific criteria utilized to group patients into stages are shown in Table 5. More than one-half of the patients (55%) fulfill these strict criteria, while the rest fall into grey zones

Table 4. Distribution of the Patients in the Different Stages

							FES patients							
	Total sample		Males		Females		FES-E		FES-M		FES-L		Non-FES	
Stage	n	%	n	%	n	%	n	%	n	%	n	%	n	%
1	510	21.63	312	21.83	198	21.31	124	25.62	16	26.23	18	31.58	352	20.05
2	643	27.27	388	27.15	255	27.45	143	29.55	15	24.59	17	29.82	468	26.65
2a	295	12.51	182	12.74	113	12.16	72	14.88	4	6.56	6	10.53	213	12.13
2b	348	14.76	206	14.42	142	15.29	71	14.67	11	18.03	11	19.30	255	14.52
3	613	26.00	354	24.77	259	27.88	116	23.97	16	26.23	10	17.54	471	26.82
3a	295	12.51	165	11.55	130	13.99	58	11.98	9	14.75	6	10.53	222	12.64
3b	318	13.49	189	13.23	129	13.89	58	11.98	7	11.48	4	7.02	249	14.18
4	592	25.11	375	26.24	217	23.36	101	20.87	14	22.95	12	21.05	465	26.48
4a	344	14.59	215	15.05	129	13.89	61	12.60	6	9.84	8	14.04	269	15.32
4b	248	10.52	160	11.20	88	9.47	40	8.26	8	13.11	4	7.02	196	11.16

FES, first episode of schizophrenia; FES-E, early group of no more than 18 months of illness duration; FES-L, late group with duration of more than 3 years; FES-M, middle group with duration between 18 months and 3 years; non-FES, patients not in their first episode.

Table 5. Characteristic Patterns of Factor Scores Combinations in the Different Stages

Stage/	Po			Ne			DA			EH			Ncog		
substage	Importance	mean	SD	Importance	mean	SD	Importance	mean	SD	Importance	mean	SD	Importance	mean	SD
1	*Highest*	1.22	0.81	Low	0.05	1.03	Low	−0.36	0.78	Middle	−0.37	0.75	Low	−0.28	0.87
2	Middle	−0.38	0.77	Middle	−0.14	1.06	Middle	−0.37	0.70	*Highest*	0.85	1.22	*Lowest*	−0.32	0.84
2a	Middle	0.11	0.78	Middle	0.23	1.19	Middle	−0.62	0.67	*Highest*	1.21	1.39	*Lowest*	−0.31	1.04
2b	Low	−0.79	0.46	Middle	−0.46	0.81	Middle	−0.15	0.66	*Highest*	0.54	0.95	*Lowest*	−0.33	0.61
3	Low	−0.28	0.78	Middle	0.00	0.89	*Highest*	1.10	0.83	Middle-low	−0.27	0.62	Low-middle	−0.29	0.78
3a	Low	−0.27	0.74	Middle	−0.16	0.83	*Highest*	0.97	0.80	Middle	−0.03	0.62	*Lowest*	−0.74	0.61
3b	*Lowest*	−0.29	0.81	Middle	0.15	0.91	*Highest*	1.22	0.85	*Lowest*	−0.50	0.53	Middle	0.13	0.66
4	Low	−0.35	0.70	Middle	0.11	1.00	Middle-low	−0.43	0.72	Low-middle	−0.32	0.64	*Highest*	0.89	0.95
4a	Low	−0.48	0.70	Middle	0.02	0.95	Middle	−0.10	0.62	*Lowest*	−0.44	0.62	*Highest*	0.89	0.93
4b	middle	−0.17	0.66	Middle	0.23	1.05	*Lowest*	−0.89	0.58	Middle-high	−0.16	0.64	*Highest*	0.89	0.98

Abbreviations: DA, depression/anxiety; EH, excitement/hostility; Ncog, neurocognitive impairment; Ne, negative; Po, positive.
Italics mark the determining significance of this particular factor for the specific stage.

between stages, being located on the continuum of these stages classifications.

The DFA returned significant results for the 4 main stages (Wilks' Lambda: 0.1411; $F(90,6958)=71.417$; $P<.001$). However, classification into substages using a single function was less accurate; therefore, a 2-step process seems more appropriate: first to classify into main stages and second to subclassify within that stage. The correct classification of cases according to this method is approximately 90% (webappendix Table D). The discriminant functions for substages are also very efficient with a similar percentage of cases correctly classified (webappendix Tables E–G).

The use of ANCOVA with sex and main stage as grouping factors, age as covariate, and duration of illness as dependent variable indicated no significant sex by stage interaction. Similar results were obtained when substage was used ($P<.1$).

Calculation of Factor Scores From the Classic Subscales Scores

The results of the linear regression analysis with factor scores (Po, Ne, DA, EH, and Ncog) as dependent variables and the classic PANSS subscales (P, N, GP, and EC) as predictors suggested that the calculation of factor scores is possible for some but not for all factors (Table 7).

Discussion

Factor Structure of the PANSS

The current study utilizes probably the largest sample of patients in an effort to develop a staging system for schizophrenia with the use of PANSS ratings alone. Results suggest that PANSS reflects a 5-factor model (Po, Ne, DA, EH, and Ncog), with significant differences in the allocations of individual items compared with the standard structure. There were no differences between males and females concerning the factor structure. However, females had lower Ne and higher DA factor scores.

The literature suggests that the most stable and reliable model that repeats itself across various studies includes 3 dimensions: positive, negative, and disorganization (Peralta and Cuesta, 2001). There seemed to be no effect of sex (Peralta and Cuesta, 1995) or chronicity (Mojtabai, 1999; Peralta and Cuesta, 2000) but there did seem to be effects of education, marital status, and race, with African Americans being significantly less likely than Caucasians to report having a past or current diagnosis of depression or mania (Dixon et al., 2001). However, it is important to bear in mind that the psychometric tools used rather than the clinical picture could essentially determine the outcome since they define whether a particular cluster of symptoms will be detected or not (Peralta and Cuesta, 2001). This is

Table 6. Age, Age at Disease Onset, and Duration of Illness in the Different Stages

	Age				Age at onset				Illness duration			
Stage	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
1	36.06	11.92	16	81	26.29	8.33	12	77	9.77	10.39	0	45
2	36.22	11.24	18	79	26.69	8.45	7	71	9.53	9.72	0	47
2a	36.49	11.52	18	79	27.01	9.29	7	71	9.48	9.97	0	47
2b	35.99	11.00	19	76	26.42	7.67	14	54	9.56	9.52	0	44
3	37.43	10.76	17	74	26.24	7.35	10	59	11.19	10.20	0	40
3a	36.85	10.04	18	65	26.96	7.37	13	53	9.89	9.41	0	40
3b	37.97	11.37	17	74	25.57	7.29	10	59	12.41	10.75	0	39
4	39.07	13.31	17	73	25.39	8.11	7	64	13.68	12.77	0	54
4a	39.60	13.20	17	71	25.43	7.95	10	64	14.17	12.60	0	49
4b	38.33	13.46	18	73	25.33	8.35	7	59	13.00	12.99	0	54
All groups	37.22	11.87	16	81	26.16	8.07	7	77	11.06	10.94	0	54

Table 7. Results of Regression Analysis With Factor Scores (Po, Ne, DA, EH, and Ncog) as Dependent Variables and the Classic PANSS Subscales (P, N, GP, and EC) as Predictors

	P	P	N	P	N	GP	P	N	GP	EC	N	GP	EC
Po	0.813	0.859	−0.130	1.050	–	−0.370	1.290	−0.080	–	−0.630	0.163	0.364	0.282
P-level	<.001	<.001		<.001			<.001				<.001	<.001	<.001
R-square	0.66	0.67		0.72			0.86				0.02	0.13	0.08
Ne	0.106	0.991	−0.240	1.030	−0.190	−0.080	−0.160	1.010	−0.030	−0.090	0.910	0.416	0.102
P-level	<.001	<.001		<.001			<.001				<.001	<.001	<.001
R-square	0.01	0.87		0.87			0.88				0.83	0.17	0.01
DA	0.215	0.215	–	−0.370	−0.490	1.100	−0.290	−0.520	1.220	−0.200	0.060	0.556	0.332
P-level	<.001	<.001		<.001			<.001				<.001	<.001	<.001
R-square	0.04	0.04		0.51			0.52				0.003	0.31	0.11
EH	0.409	0.435	−0.080	0.274	−0.200	0.303	−0.250	0.030	−0.510	1.380	0.075	0.364	0.825
P-level	<.001	<.001		<.001			<.001				<.001	<.001	<.001
R-square	0.17	0.17		0.20			0.85				0.005	0.13	0.68
Ncog	0.229	0.245	0.144	−0.160	–	0.568	−0.130	–	0.602	−0.07	0.295	0.461	0.285
P-level	<.001	<.001		<.001			<.001				<.001	<.001	<.001
R-square	0.05	0.10		0.22			0.23				0.08	0.21	0.08

Abbreviations: DA, depression/anxiety; EH, excitement/hostility; Ncog, neurocognitive impairment; Ne, negative; Po, positive.
The aim was to arrive at reliable functions to calculate factor scores from subscale scores. Overall the results are satisfactory only for some of the factor scores.

also in accord with the observation that the dimensions found in schizophrenia studies are not specific for schizophrenia but rather of psychosis in general, and they apply to the whole spectrum of psychotic illnesses including affective psychoses (Peralta and Cuesta, 2001). It is possible that there are no specific features to characterize schizophrenia; on the contrary there is only a more severe genetic loading and more frequent early insults, which impair neurodevelopment, especially of the medial temporal lobe (Murray et al., 2004).

Beyond these 3 basic dimensions, the literature suggests that more detailed and complex models could also be valid. There is evidence supporting the existence of 8 major dimensions of psychopathology: psychosis, disorganization, negative, mania, depression, excitement, catatonia, and lack of insight. The dimensional structure of symptoms becomes even more complex if one considers that these large dimensions can be further divided into more elementary components (Peralta and Cuesta, 2001).

The findings of the principal component analysis in the current study support a 5-factor model and are in accordance with some but not all previous studies, some of which suggest more complex models (Nakaya et al., 1999a; Lykouras et al., 2000; Fresan et al., 2005; Van den Oord et al., 2006; van der Gaag et al., 2006; Liemburg et al., 2013; Dragioti et al., 2017; Walsh-Messinger et al., 2018). Overall, the general agreement is that the most stable and reliable models contain 3 dimensions—positive, negative, and disorganization (Peralta and Cuesta, 1994)—though reporting of a supplementary hostility and depression factors is frequent in the literature (Hwu et al., 2002).

Sex differences have been previously reported; males are more likely to display negative symptoms and cognitive deficits with psychomotor abnormalities while females are more likely to display affective symptoms (Pandurangi et al., 1994; Leung and Chue, 2000; Walsh-Messinger et al., 2018). A recent study focusing on sex differences in the symptom structure of the PANSS found differences regarding the manifestation of a depression factor in women and a hostility factor in men (Walsh-Messinger et al., 2018). However, other studies did not find any influence of sex on the factor structure of the PANSS (Hayashi et al., 2002), which is in accordance with the findings of the current study.

The results of the current study are consistent with a previously reported 6-factor solution in a large sample of 500 patients (Van den Oord et al., 2006). That factor structure included negative, positive, excited/activation, anxious-depressed/dysphoric, disorganized/autistic preoccupation, and withdrawal factors but not a cognitive domain. Four of these are comparable to 4 of our factors, but the item synthesis was somewhat different. The participants in the aforementioned study were chronic outpatients or stable inpatients, a sample quite similar to the present study.

They are also in accord with a previous study that allocated several N items in the neurocognitive domain (Galderisi et al., 2013).

Staging

The present analysis also suggests that it is possible to stage patients with the use of the PANSS alone. The "external criterion" used was duration of illness, as defined by age of the patient and age at onset. While neither age nor duration of illness are identical with staging, duration is considered a reasonable proxy, age at onset variance notwithstanding. Age, duration, and number of episodes correlate with each other (Emmerson et al., 2009).

The analysis indicated 4 main stages, each of which (except from the first) is subdivided into 2 substages. Staging was almost identical between males and females. Each stage is characterized by a dominant domain of psychopathology (Po for the first stage, EH for the second, DA for the third, and Ncog for the fourth while the least dominant aspects of psychopathology determine the substages) (Table 5). Stages were not independent of each other, but rather there is a smooth transition from the previous to the next stage, as if along a continuum rather than with discrete steps. Importantly, age and duration of illness played a significant role; however, they were not as determining as one might expect; for example, almost 21% of FES-E patients were classified to the final stage 4 with more than 8% belonging to 4b. This is significantly lower than the respective percentages concerning non-FES patients (26.48% and 11.16%, respectively) but the difference is modest. Concerning stage 1, the picture is reversed. The above suggest that the trajectory of schizophrenia generally follows a homogenous course but speed of progression is highly heterogeneous. On average, changes in specific domains take several years to appear.

This staging proposal has a number of consequences. First, it suggests that the actual psychotic period of schizophrenia does not extend to most of its timeline but rather is restricted to the initial stages. Other clinical components then become more prominent. Whether this constitutes a true illness progression or reflects the results of treatment with antipsychotics that have a primary beneficial effect on positive symptoms is unclear. This however is in partial accordance with the suggestion that after 3 years there is an attenuation in the relapse rate (Wunderink et al., 2013) or possibly a change in their pattern with more frequent and shorter relapses during the early stages, making way for less frequent but more chronic episodes (Andreasen et al., 2013).

Another consequence is that depression and anxiety seem to be predominant for a significant proportion of illness duration, and this length is greater than the time during which positive symptoms predominate. This may help to explain why patients with schizophrenia are often treated with antidepressants and why such treatment may be beneficial not only for depressive symptoms but also for both positive and negative symptomatology (Rummel et al., 2005, 2006; Helfer et al., 2016). The presence of the 3rd stage and the shorter duration of stages 1 and 2 in females raises the question of whether the widely believed better course and outcome of schizophrenia in females is essentially an effect of an earlier occurrence of stage 3 in females. However, this assumption is not supported by the findings of the current study using ANCOVA that duration does not differ between sexes of the same stage of illness.

Stability of the neurocognitive deficit and changes in positive and negative domains during the first 2 stages might explain the failure of studies to identify a relationship between duration of untreated psychosis and neurocognitive function and the heterogeneous results concerning its relationship with positive and negative symptoms (Ho et al., 2003; Compton, 2004; Norman et al., 2005; Perkins et al., 2005; McGlashan, 2006; Barnes et al., 2008; Melle et al., 2008; Primavera et al., 2012; Penttila et al., 2014; Qin et al., 2014; Rund, 2014; Albert et al., 2017; Sullivan et al., 2019). The lack of relationship between duration of untreated psychosis (DUP) and neurocognition is impressive (Bora et al., 2018) but under the current staging model is expected given the worsening of neurocognitive impairment late in the course of the illness. These results are consistent with the presence of rather mild neurocognitive deficits at illness onset that remain stable for decades, in accordance with many previously reports (Bora and Murray, 2014).

An important question is whether stages 2 and 3 actually imply the presence of an affective component that has largely been neglected so far (Fountoulakis et al., 2017a), but in terms of duration it predominates the lives of patients with schizophrenia. Stage 2 is characterized by excitement and hostility, and in females it seems grandiose ideas also have a role. Irritability and uncooperativeness seems to dominate the picture, and it is reasonable to consider the possibility of subthreshold chronic mania without euphoria. The core concepts of schizophrenia and manic depression were developed by Emil Kraepelin, but the existence of intermediate and mixed cases is held by many authors to strongly argue in favor a "unitary psychosis theory" (Einheitspsychose), as conceived in the works of Joseph Guislain (1797–1860), Ernst Albrecht von Zeller (1804–1877), Wilhelm Griesinger (1817–1868), and Heinrich Neumann (1814–1888) and as reflected in the works of contemporary authors (Berrios and Beer, 1994; Angst, 2002; Lake and Hurwitz, 2006; Moller, 2008; Van Os, 2009, 2010, 2011; van Os and Kapur, 2009; van Os and Linscott, 2012). However, the failure of lithium to impact core schizophrenia would argue against this if one assumes that lithium response has some trait biomarker capacity (Leucht et al., 2004).

In 1905 Specht argued that all psychoses were derived from mood abnormalities, which is not in accordance with the current staging model where mood disorder follows psychotic episodes. However, since then, many authors have associated paranoia with depression and delusional guilt, thus questioning the distinction between schizophrenia and psychotic mood disorders (Specht, 1905; Abrams et al., 1974; Pope and Lipinski, 1978; Doran et al., 1986; Lake and Hurwitz, 2006; Maier et al., 2006).

The history of nomenclature and classification can provide us important insights into the staging model of the current paper. Jacob Kasanin (1897–1946) was the first to coin the term schizoaffective psychosis in 1933 (Kasanin, 1933, 1994) to describe a group of psychotic mood disorder patients according to contemporary classification systems. In 1937, Langfeldt described the so-called schizophreniform psychoses with many affective clinical elements and favorable outcome (Langfeldt, 1937), while Kant in 1940 described recovered schizophrenics as having a higher number of affective psychoses among their relatives compared with schizophrenia patients (Kant, 1940). Valuable contributions in nosology were made by Kurt Schneider (1887–1967) who described for the first time concurrent and sequential forms of schizoaffective psychosis (Schneider, 1973; Marneros, 1983; 2003).

Recent research suggests that most patients with schizophrenia will probably experience significant depression. In the current model this corresponds to the third stage and includes approximately 26% of patients on cross-sectional estimate. In the literature, the cross-sectional prevalence of depression in patients with schizophrenia is less than 10%, with lifetime

prevalence up to 75%, although fewer patients experience the full syndrome of depression. It is difficult to assess true depressive symptomatology since many aspects (e.g., motor retardation, social withdrawal) overlap with negative symptomatology. Traditionally, there has been a focus on post-psychotic depression, which is considered to be a result of demoralization and increasing insight following resolution of the psychotic episode (Conley et al., 2007; Buckley et al., 2009). Previous research has identified 3 dimensions of depression (retardation, depressive core symptoms, and accessory depressive symptoms) (Muller et al., 1999).

On the other hand, there are limited data on the occurrence of mania in patients with schizophrenia, at least partially because the presence of mania changes the diagnosis. By definition, no patient with schizophrenia ever experiences a manic or hypomanic episode. One group in the 1970s implied that about 95% of their sample of patients diagnosed with paranoid schizophrenia actually suffered from psychotic mania (Abrams et al., 1974). Irritability, excitement, and violence could be explained at least partially as a direct result of a mood disorder. It has been reported that violence during the onset of the illness might be a direct consequence of delusions, while in chronically ill and disabled patients violence is related to the effects of impoverished and constricted lives, with patients having difficulty controlling their impulsive behavior (Taylor, 1985; Walsh et al., 2002). The current staging does not support the reactive nature of excitation, hostility, and irritability. It does not support their relationship to delusions either, since they seem to occur when psychosis is in at least partial remission.

The current paper is probably one of the few to specifically address the issue of staging on the basis of clinical symptoms. It is important to note that our results come from stabilized patients, that is, patients already treated with antipsychotics and in partial remission. It is also known that antipsychotics are efficacious as well against manic-like symptoms, excitation, and hostility, and therefore it could be suggested that more patients with schizophrenia might manifest a more severe form of this kind of symptomatology especially during the acute psychotic episode. Probably as a result of the psychometric tools used (which in most studies are restricted to classic schizophrenia scales such as the PANSS and SAPS/SANS but not young mania rating scale (YMRS)), manic-like symptoms have been identified in only a minority of reports that have studied the factor structure of clinical symptoms of schizophrenia in samples similar to ours (Lorr et al., 1962; Kitamura et al., 1995; Peralta and Cuesta, 1999; Van Os et al., 1999; Fountoulakis et al., 2017a), or in recent-onset cases (van Os et al., 1996; McGorry et al., 1998), but rarely in follow-up studies (Willem Van der Does et al., 1995; Salokangas, 1997). Another limitation of the literature is that there are some subtle features that are not routinely assessed and thus they are incompletely studied. For example, anhedonia, which is considered to constitute an important characteristic of schizophrenia, seems to correspond to an anticipatory but not a consummatory pleasure deficit (Gard et al., 2007).

Probably as some authors suggest, the presence of mood symptoms is predictive of better outcome, but in contrast, core "schizophrenic" symptoms were not predictive of a worse outcome (Astrup and Noreik, 1966; Noreik et al., 1967; Holmboe et al., 1968; Pope and Lipinski, 1978). According to our staging model, this could reflect the different stages of these patients at the time of assessment. It is important to note, however, that a number of latter studies have also disputed the predictive value of mood symptoms (Croughan and Robins, 1974; Welner et al., 1977a, 1977b; Gift et al., 1980; Moller et al., 1982). Emotional processing deficits in schizophrenia are both state and trait dependent (Maat et al., 2015), and there is no evidence for a generalized hedonic deficit in patients with schizophrenia or schizoaffective disorder (Oorschot et al., 2013).

On the other hand, a hierarchical classification of symptoms has been reported. This implies but does not prove a possible causal relationship. For example, formal thought disorder was reported to correlate with mania (Cuesta and Peralta, 2011) and mood symptoms with paranoia (Lake, 2008), but depression was unrelated to the neurocognitive deficit (Escamilla, 2001; Harvey, 2011).

Previous research found that the stage of illness plays an important role in the disorganization factor (Dollfus and Petit, 1995; Nakaya et al., 1999a, 1999b) and this reflects our finding concerning the fourth and final stage where the neurocognitive impairment together with excitement/hostility are the dominant domains in psychopathology. From a clinical point of view, we can infer that at this stage, the burden of illness becomes progressively greater, and this is especially true concerning neurocognitive function as a result of neuroprogression due to chronicity and recurrent psychotic episodes. This finding is in agreement with evidence suggesting that the neurocognitive impairment may constitute a core syndrome of schizophrenia (Lin et al., 2014) and that at least in a significant subgroup of patients it determines the final outcome in old age (Kurtz, 2005).

These results are supported by the concept of staging that assumes a developmental character of the illness (Agius et al., 2010; McGorry et al., 2010; Fountoulakis et al., 2018a, 2018b, 2018c). Additionally, one could say that schizophrenia is characterized by a psychotic, a manic (irritable not euphoric), a depressive, and finally a dementia stage, which is in accord with previous studies that report a strong mood and especially manic component in the psychopathology of schizophrenia (Fountoulakis et al., 2017a). However, the extent to which these results are influenced by current treatment status and selective efficacy of medication of specific clusters of symptoms remains to be determined (Garriga et al., 2016; Fountoulakis, 2017; Fountoulakis et al., 2017b).

Previous efforts to stage schizophrenia arrived at a 3-stages model (Dragioti et al., 2017). These 3 stages suggest that psychosis at initial stages is to some extent limited and allows some kind of insight. At the same time, it also triggers reactive depression and reactive behaviors, including aggression. As the disease progresses, the patient enters a disorganized state where behaviors are largely independent from thought content and the events in the environment. The third stage is characterized by neurocognitive impairment. Thus, these stages of illness seem to reflect a progress from preserved insight and more coherent mental functioning to disorganization and neurocognitive impairment. It also suggests that the sexes differ in terms of the relationship of psychotic features (and especially catatonia) with neurocognition. An important clinical implication is that the PANSS can be a practical tool in schizophrenia patients when screening for clinical stages. It may also be crucial for psychiatrists in allocation of treatment to patients according to sex and stage of illness.

Another interesting finding of the current study is that not only the factor structure of the PANSS but also the staging model is identical in males and females without the presence of any substantial differences. This is in contrast with much of the literature (Pandurangi et al., 1994; Leung and Chue, 2000; Walsh-Messinger et al., 2018) but in accordance with some studies (Hayashi et al., 2002).

Strengths and Limitations of the Current Study

This is the first study to report on the correlation between current symptomatology and duration of the illness and to utilize this relationship to develop a clinically relevant staging model.

The strengths of the current study include the large study sample, which is the largest so far in the literature investigating the factor structure of the PANSS as well as efforts to clinically stage schizophrenia. In contrast to other studies, we did not exclude any basic component of the disease's symptomatology (Kelley et al., 2013; Khan et al., 2013a, 2013b; Fong et al., 2015; Wu et al., 2015). An additional strength is the multi-center and multinational characteristic of the sample. The finding that the results and the models are identical in males and females further strengthen their reliability and probably their validity.

The most important limitation of the study is that it utilized a cross-sectional design with the use of limited demographic and clinical information or treatment resistance status of the patients, and these were combined with lack of long-term follow-up of patients and in the absence of an external golden standard. This absence was intentional and intrinsic to a design that aimed to stage patients on the basis of their current clinical picture alone and with only illness duration as an additional clue. This was chosen as an approach because anamnestic data are not reliable in contrast to the assessment of the present state. For a similar reason only stabilized patients were included. To develop a staging method easily applicable in the everyday clinical practice, the neurocognitive function was assessed only on the basis of the clinical judgment of the rater and in the frame of PANSS scoring rather than with sophisticated neuropsychological assessment. Also in elderly patients the presence of a comorbid underlying vascular or Alzheimer's pathology cannot be ruled out. It is important to mention that the current staging proposal is based on group means not on individual patient trajectories.

There were differences among countries and centers in terms of age and duration of the disorder as well as in provided health care and benefits. It is unlikely these had a major effect on results; however, such an effect cannot be excluded. The effect of premature mortality and the way survival affected the results especially at later stages is also unknown.

A further limitation is that the study sample was not epidemiologically selected and therefore may not represent the general population of patients with schizophrenia. Instead, it represents those patients with at least less-than-ideal remission who remained in contact with mental health services for several years. It is unclear whether the differences observed among countries were because of this selection method; however, such a nonsystematic heterogeneity among countries is expected and does not seem to determine the overall outcome and results of the study.

Finally, the method for the identification of stages falls in the grey zone between quantitative and qualitative methodology, and both the method and its results are open to debate. Although antipsychotic medication is believed to influence only positive psychotic symptoms, their effect on the model remains to be studied specifically.

CONCLUSION

The current study tested the PANSS-based "pyramidal model" of schizophrenia and arrived at a 5-factor solution that elaborates the literature. It includes positive, negative, anxiety/depression, excitement/hostility, and neurocognition as domains and proposes the rearrangement of individual PANSS items within this framework. It also proposes a 4-stage staging model with additional substages. These stages and substages are well characterized by clinical symptoms and add to our understanding of schizophrenia as a progressive chronic illness.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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All authors contributed equally.

Interest Statement

None pertaining to the current study. Several of the authors have received grants and support from the pharmaceutical industry, but this had no influence on the results and interpretation and the writing of the current study.

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