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Original article

Negative symptom configuration in patients with first episode affective psychosis: findings from the 1-year follow-up of the "Parma Early Psychosis" program

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Abstract. *Background and aim:* Evidence on discrete dimensions underlining negative symptoms in First Episode Affective Psychosis (FEAP) may be useful for their treatment strategy, but is still relatively scarce. Aim of this study was to examine the negative symptom configuration in patients with FEAP using both exploratory and confirmatory factor analysis methods on the Positive And Negative Syndrome Scale (PANSS). *Methods:* Seventy-eight participants, aged 13-35 years, completed the PANSS within the "Parma Early Psychosis" (Pr-EP) program, a specialized protocol of early detection and intervention in psychosis implemented since January 2013 in all public adolescent and adult mental health services of the Parma Department of Mental Health (Northern Italy). *Results:* A 3-factor model (i.e. "Alogia", "Social Withdrawal" and "Motor/Affective Expression Poverty" domains) was identified. As an alternative, a 2-factor solution previously proposed in patients with first episode schizophrenia (always within the Pr-EP program) also showed good fit indices in our FEAP sample. *Conclusions:* Our results suggest the crucial importance of identifying discrete negative symptom domains already at the onset of affective psychosis in order to implement specific early intervention strategies aiming to improve prognosis and long-term outcomes also in this young FEAP help-seeking population.

Key words: Affective Psychosis, Early Psychosis, Factor Analysis, First Episode Psychosis, Negative Symptoms.

Introduction

In recent years, evidence on outcome indicators in First Episode Psychosis (FEP) showed that negative symptoms are significantly correlated with functioning decline and poor prognosis (1). Factor analysis research in advanced stages of *schizophrenia* reported that the negative symptom structure is not a unidimensional construct (2). In contrast, multidimensional models frequently proved to be more appropriate (3), although the exact number of factors that best describes negative symptom configuration in schizophrenia is still debated (4).

Empirical evidence also reported that negative symptoms are most prevalent in, but not exclusive of schizophrenia (5). In this respect, a previous study on negative symptoms as first clinical presentation in FEP showed similar factor configurations in both schizophrenia and non-schizophrenia spectrum disorders (6). Specifically, using the "Scale for the Assessment of Negative Symptoms" (SANS) (7) in a clinical sample of 437 FEP subjects, the authors identified a 3-factor model including the following domains: (a) "*Diminished Expression*" (combining items from the SANS "Affective Flattening" subscale together with the "Poverty of Speech" item), (b) "*Inattention/Alogia*"

(including items from SANS "Inattention" and "Alogia" subscales) and (c) "*Social Amotivation*" (combining SANS "Anhedonia-Asociality" and "Avolition/Apathy" subscale items).

To date, research on negative symptoms remains preferentially in schizophrenia and studies in non-schizophrenia FEP are still scarce (8). This is a serious deficiency given the increasing number of research populations inclusive of FEP other than schizophrenia. A more in-depth knowledge on negative symptom structure is also important to orientate future research in non-schizophrenia FEP patients, especially on their long-term outcome predictors and quality of life.

The *aim* of this research was thus to examine the negative symptom configuration in FEP patients with affective psychosis using the negative symptom items of the Positive And Negative Syndrome Scale (PANSS) (9) and to investigate any relevant associations of the emerging factors with functioning and psychopathology.

Methods

Participants

All the participants (n = 78) were young help-seeking individuals recruited through the "Parma Early Psychosis" (Pr-EP) program between January 2013 and December 2019 (for details on the Pr-EP program, see Leuci et al., 2019) (10).

Inclusion criteria of this research were: (a) specialist help-seeking; (b) age between 12 and 35 years; (c) presence of First Episode Affective Psychosis (FEAP) within the following DSM-IV-TR diagnoses: bipolar disorder with psychotic features or major depressive disorder with psychotic features (11); and (d) a Duration of Untreated Psychosis (DUP, defined as the time interval [in weeks] between the onset of psychotic symptoms and the first prescription of antipsychotics) (12) < 2 years. A DUP threshold of < 2 years was chosen because it is usually considered the limit to start a specialized care protocol within the "Early Intervention in Psychosis" (EIP) paradigm (13).

Exclusion criteria were: (a) history of past psychosis episode according to the DSM-IV-TR criteria (11); (b) previous exposure to antipsychotic medication; (c) known intellectual disability (i.e. Intelligence Quotient < 70); (d) current DSM-IV-TR substance dependence (11); and (e) neurological disorders or any other medical condition manifested with psychiatric symptoms. In this research, past exposure to antipsychotics (i.e. before the Pr-EP enrollment) was considered as an equivalent of past psychotic episode in accordance with the FEP criteria developed by Yung et al (2005) (14), defining the psychosis threshold as essentially that at which antipsychotics would probably be started in the common clinical practice.

All FEAP patients (and their parents, if minors) agreed to participate to the research and gave their written informed consent to the psychopathological evaluation prior to their inclusion in the study. Local relevant ethical approvals were obtained for the research (AVEN Ethics Committee: protocol n. 36102/09.09.2019). The current research has also been conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki – as revised in 2008) for experiments including humans. The data that support the findings of this research are available on request from the corresponding author. The data are not publicly available due to privacy/ethical restrictions.

Measures

The psychopathological evaluation included the PANSS (9) and the Global Assessment of Functioning (GAF) scale (11). The assessment was conducted by trained Pr-EP team members, who undergone regular supervision sessions and scoring workshops to ensure inter-rater reliability for the administered psychometric instruments.

The *PANSS* (9) is a 30-item clinical interview widely used to assess the severity of psychotic symptoms in the full spectrum of psychosis (15). The original "Negative Symptoms" subscale included the following 7 items: "Blunted Affect", "Emotional Withdrawal", "Poor Rapport", "Passive/Apathetic Social Withdrawal", "Difficulty in Abstract Thinking", "Lack of Spontaneity and Flow of Conversation", and "Stereotyped Thinking". In this research, we used the authorized Italian version of the PANSS (16),

showing good psychometric properties in Italian FEP populations (17).

Factor analysis studies in schizophrenia has not yet unanimously identified a comprehensive set of PANSS items that should be unquestionably included in the negative symptom domain (18). In this respect, an interesting item response analysis research reported that together with the 7 items of the original PANSS "Negative Symptoms" subscale, other two items included in the "General Psychopathology" domain (i.e. "Disturbance of Volition" and "Active Social Avoidance") contributed in a psychometrically meaningful way to the construct of a negative syndrome in psychosis research (19). Thus, in the present study this integrated 9-item negative symptom set (with the addition of the PANSS "Motor Retardation" item, traditionally included in the Marder's "Negative Symptom Factor" [NSF]) (20) was considered for Exploratory Factor Analysis (EFA).

The *GAF* (11) is a scale commonly used to rate clinical, psychopathological and socio-occupational functioning. High scores are related to a better functioning. In the present research, we used the Italian version of the GAF included in the DSM-IV-TR (21), showing good psychometric properties in Italian FEP samples (22).

Procedures and statistical analysis

The axis-I diagnosis was made by two trained Pr-EP team members using the Structured Clinical Interview for DSM-IV-TR axis I Disorders (SCID-I) (23). Psychometric instruments for clinical assessment were administered at baseline and after 12 months of follow-up.

Data were analyzed using the Statistical Package for Social Science (SPSS) for Windows - version 15.0 (24) and the R "Lavaan" software package for structural equation modeling (25). All tests were two-tailed with significance level set at 0.05. Frequencies and percentages were used to represent categorical parameters. Mean ± standard deviation was calculated for describing continuous parameters.

An *EFA* was first performed to thoroughly examine PANSS negative symptom configuration at baseline in FEAP participants. In order to extract a suitable factor model from our dataset, we used a Principal Component Analysis (PCA) with varimax rotation (26). To evaluate the factorability, a statistical significance of Bartlett's Test of Sphericity ($p < 0.05$) and a Kaiser-Meyer-Olkin (KMO) value of more than 0.70 were accepted (27). Moreover, item loading values were considered as relevant if greater than 0.50 for each factor (28). According to Kline (2000) (26), significant item loadings on more than one factor were not retained unless there was a coherent theoretical or practical rationale for retaining that on the robust loading factor. For the EFA emerging factor solution, a Confirmatory Factor Analysis (CFA) was then performed both at baseline and after 1 year of follow-up to confirm its goodness of fit in our FEAP group.

Furthermore, *CFA* was also carried out to compare fit indices of the EFA emerging factor model with other two negative symptom configurations previously identified with the PANSS in schizophrenia research (4, 15). Specifically, as convergent evidence in advanced stages of schizophrenia (prominently based on the SANS) had reported that a 2-factor solution fitted negative symptoms better than a one-factor model (29), factor analysis studies investigated the replicability of this dichothomy with the PANSS. In this respect, Jang et al. (2016) (15) confirmed the goodness of fit of a 2-factor configuration including "*Expressive Deficits*" (i.e. PANSS "Blunted Affect", "Poor Rapport", "Lack of Spontaneity and Flow of Conversation" and "Motor Retardation" items) and "*Experiential Deficits*" (i.e. PANSS "Emotional Withdrawal", "Passive/Apathetic Social Withdrawal" and "Active Social Avoidance" items) domains. However, in a sample of 147 young patients with First Episode Schizophrenia (FES) (recruited within the Pr-EP Program), Pelizza et al. (2020) (4) did not replicate the Jang's 2-factor model, suggesting its non-generalizability in early stages of schizophrenia. In contrast, always starting from the same PANSS 7 negative symptom item set used by Jang et al. (2016) (15), the authors proposed a different bipartite configuration combining a more motor-emotional "Expressive Deficits" domain (including PANSS "Blunted Affect", "Emotional Withdrawal" and "Motor Retardation" items) together with a more defined "Asociality" dimension (composed of PANSS "Passive/Apathetic Social Withdrawal", "Active Social

Avoidance", "Poor Rapport" and "Lack of Spontaneity and Flow of Conversation" items).

To evaluate the adequacy of these 2-factor models in our FEAP group, we used the robust weighted least squares (WLSMV) estimator, which does not assume normally distributed parameters and offers the best option for modeling ordinal data (as the PANSS items are) (30). Four common fit indices to evaluate the goodness of fit of the overall models were used: Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA) and Standardized Root Mean Square Residual (SRMR). The following general rules of thumb were considered to assess the results: TLI and CFI > 0.90 (accepted fit), RMSEA < 0.08 (accepted fit) and SRMR < 0.08 (good fit) (31).

Finally, in FEAP participants Spearman's correlation coefficients of EFA emerging factor scores with baseline functioning (i.e. GAF) and other baseline clinical characteristics usually associated with secondary negative symptoms (i.e. depression, anxiety, positive symptoms and antipsychotic side effects) (32) were also performed, using the Bonferroni correction to revise p-value for multiple testing (33).

Results

Over the course of the study, 78 young FEAP patients (40 [51.2%] males; 66 [84.6%] white Caucasian; mean age at entry = 26.40 ± 6.41 years) were consecutively recruited within the Pr-EP protocol. Clinical and sociodemographic characteristics are shown in the Table 1.

The total sample included 53 (67.9%) individuals with DSM-IV-TR bipolar psychosis (i.e. manic or mixed episode with psychotic features) and 25 (32.1%) with major depressive disorders with psychotic features. As of December 2019, all the FEAP participants completed the 1-year follow-up period.

EFA 1

The KMO measure of sampling adequacy was 0.755 and the Bartlett's Test of Sphericity was statistically significant (p = 0.000), suggesting the EFA appropriateness for our dataset.

In the current study, a suitable 3-factor negative symptom solution was identified, explaining 72.2% of the total variance. In details, a first factor explaining 25.6% of the variance included PANSS "Difficulty in Abstract Thinking", "Lack of Spontaneity and Flow of Conversation" and "Stereotyped Thinking" items (Table 2). A second factor explaining 23.8% of the variance was composed of PANSS "Passive/Apathetic Social Withdrawal" and "Active Social Avoidance" items. Finally, a third factor explaining 22.8% of the variance included PANSS "Blunted Affect", "Emotional Withdrawal", "Disturbance of Volition" and "Motor Retardation" items. The PANSS item N3 ("Poor Rapport") was represented in both first and second domain, suggesting an overall factor non-specificity.

CFA 1

A CFA was then performed to confirm the goodness of fit of the emerging EFA tripartite solution at baseline and after 1 year of follow-up (Table 3). At baseline, fit indices were: CFI = 0.981, TLI = 0.969, RMSEA = 0.132 and SRMR = 0.079. After the 12-month follow-up period, CFI was 0.985, TLI was 0.977, RMSEA was 0.154 and SRMR was 0.103. Specifically, the PANSS item G13 ("Disturbance of Volition") was not adequately represented in both CFA models (respectively, $\lambda = 0.362$ at baseline and $\lambda = 0.484$ after 1 year of follow-up).

Table 1. Sociodemographic and clinical characteristics of FEP patients with affective psychosis (n = 78).

Variable	
Gender (males)	40 (51.2%)
Ethnic group (white Caucasian)	66 (84.6%)
Mother tongue (Italian)	64 (82.1%)
Age at entry	26.40 ± 6.41
Education (in years)	12.15 ± 2.71
DUP (in weeks)	47.60 ± 42.42

Legend - Frequencies (percentages) and mean ± standard deviation are reported; DUP = Duration of Untreated Psychosis.

Table 2. Principal component analyses (PCA) with varimax rotation on PANSS negative symptom items in FEP patients with affective psychosis (n = 78).

PANSS items	Factor 1 ("Alogia")	Factor 2 ("Social Withdrawal")	Factor 3 ("Motor/Affective Expression Poverty")
% variance explained	25.6	23.8	22.8
N1 Blunted Affect	-.020	.194	**.869**
N2 Emotional Withdrawal	-.143	.414	**.817**
N3 Poor Rapport	.543	.559	.057
N4 Passive/Apathetic Social Withdrawal	.204	**.886**	.201
N5 Difficulty in Abstract Thinking	**.865**	.266	.161
N6 Lack of Spontaneity/Flow of Conversation	**.677**	.436	.214
N7 Stereotyped Thinking	**.913**	.038	.035
G7 Motor Retardation	.268	.009	**.643**
G13 Disturbance of Volition	.245	-.194	**.573**
G16 Active Social Avoidance	.185	**.877**	-.015
PANSS items (EFA using the 8 negative symptom item set [i.e. without PANSS items N3 and G13 items])	Factor 1 ("Alogia")	Factor 2 ("Social Withdrawal")	Factor 3 ("Motor/Affective Expression Poverty")
% variance explained	29.3	25.3	26.4
N1 Blunted Affect	.033	.130	**.896**
N2 Emotional Withdrawal	-.095	.404	**.821**
N4 Passive/Apathetic Social Withdrawal	.231	**.878**	.234
N5 Difficulty in Abstract Thinking	**.881**	.270	.116
N6 Lack of Spontaneity/Flow of Conversation	**.701**	.434	.193
N7 Stereotyped Thinking	**.923**	.034	-.015
G7 Motor Retardation	.348	-.143	**.727**
G16 Active Social Avoidance	.194	**.889**	.010

Legend – PANSS = Positive And Negative Syndrome Scale; FEP = First Episode Psychosis. Results are in bold if that item loaded most strongly into the corresponding component and was greater than 0.50.

EFA 2

Based on these factor analysis results, we decided to replicate an EFA considering all the previous PANSS negative symptom item set with the exception of PANSS N3 ("Poor Rapport) and G13 ("Disturbance of Volition") items, in order to improve the factor model appropriateness for our dataset. Our precedent EFA tripartite solution was substantially confirmed, with a KMO measure of sampling adequacy of 0.701 and a statistically significant Bartlett's Test of Sphericity (p = 0.000), which explained 80.9% of the total variance. The first and second factors were perfectly replicated with an explained variance respectively of 29.3% and 25.3% (Table 4). The third factor explaining 26.4% of the variance included all the precedent PANSS components with the exception of the "Disturbance of Volition" item.

CFA 2

In order to confirm the goodness of fit of this new tripartite negative symptom configuration, CFA was replicated at baseline and after 12 months of follow-up (Table 5). At baseline, better fit indices were observed (i.e. CFI = 0.982, TLI = 0.973, RMSEA = 0.109, SRMR = 0.078). After the 1-year follow-up period, better fit indices were also found (i.e. CFI = 0.990, TLI = 0.984, RMSEA = 0.151, SRMR = 0.078).

Table 3. Fit indices obtained in both baseline and 1-year follow-up CFA for the EFA emerging tripartite factor solution identified using the complete PANSS 10 negative symptom item set in our FEP patients with affective psychosis (n = 78).

Fit indices (baseline [T0])	3-factor negative symptom model		Accepted values
X^2	44.424 (p = 0.007)		p > 0.05
CFI	0.981		≥ 0.90
TLI	0.969		≥ 0.90
RMSEA	0.132		≤ 0.08
SRMR	0.079		≤ 0.08
PANSS (λ)	Factor 1	Factor 2	Factor 3
N5	.994	.000	.000
N6	.817	.000	.000
N7	.812	.000	.000
N4	.000	.999	.000
G16	.000	.770	.000
N1	.000	.000	.872
N2	.000	.000	.899
G7	.000	.000	.588
G13	.000	.000	.362
Fit indices (1-year assessment time [T1])	3-factor negative symptom model		Accepted values
X^2	55.288 (p = 0.000)		p > 0.05
CFI	0.985		≥ 0.90
TLI	0.977		≥ 0.90
RMSEA	0.154		≤ 0.08
SRMR	0.103		≤ 0.08
PANSS (λ)	Factor 1	Factor 2	Factor 3
N5	.985	.000	.000
N6	.855	.000	.000
N7	.938	.000	.000
N4	.000	.998	.000
G16	.000	.920	.000
N1	.000	.000	.999
N2	.000	.000	.847
G7	.000	.000	.600
G13	.000	.000	.485

Legend – CFA = Confirmatory Factor Analysis; PANSS = Positive And Negative Syndrome Scale; EFA = Exploratory Factor Analysis; FEP = First Episode Psychosis; X^2 = Chi-square value; p = statistical value; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index; RMSEA = Root Mean Square Error of Approximation; SRMR = Standardized Root Mean Square Residual. Item loading values (λ) are also reported.

The baseline PANSS "Depression" item subscore showed relevant positive correlations with the second and the third factor scores of this EFA tripartite configuration (Table 4). The third domain also had a significant positive correlation with the baseline PANSS "Anxiety" subscore. For the first factor, no relevant association was found.

CFA3

In our dataset, CFA fit indices were also calculated to assess the goodness of fit of the 2-factor negative symptom solutions identified by Jang et a. (2016) (15) and by Pelizza et al. (2020) (4) within schizophrenia research (Table 6). For the Jang's model, baseline fit indices were inadequate (i.e. CFI = 0.867, TLI = 0.785, RMSEA = 0.317, SRMR = 0.198).

For the bipartite configuration proposed by Pelizza et al. (2020) (4) in FES patients, CFA fit indices were adequate both at baseline and after 12 months of follow-up (i.e. respectively, CFI = 0.992, TLI = 0.987, RMSEA = 0.077, SRMR = 0.066; and CFI = 0.994, TLI = 0.990, RMSEA = 0.121, SRMR = 0.076) (Table 6), also appearing slightly better than those emerged in our EFA 3-factor configurations.

Discussion

Main aim of this research was to investigate negative symptom configuration in FEAP individuals using the PANSS. To the best of our knowledge, no previous study specifically examining discrete negative symptom dimensions in FEAP was reported in the literature to date.

In the current study, *EFA* results found that a 3-factor solution was suitable for our data set, explaining more than 80% of the total variance of PANSS negative symptom structure at first presentation in FEAP patients. In this tripartite configuration, a first factor (including PANSS "Difficulty in Abstract Thinking", "Lack Of Spontaneity and Flow of Conversation" and "Stereotyped Thinking" items) corresponds to a pure "*Alogia*" domain, specifically combining diminished fluidity and productivity in the verbal interactional process with a difficulty in proceeding beyond concrete thinking in problem-solving tasks and a decreased speech spontaneity/flexibility (as evidenced in rigid and repetitious thought content) (9).

Table 4. Spearman's correlations of EFA factor subscores (emerged within the reduced 8 negative symptom item set) with baseline functioning (i.e. GAF score) and other relevant clinical and psychopathological characteristics in FEP patients with affective psychosis (n =78).

PANSS negative symptom factor subscores	GAF score	PANSS "Positive Symptoms" score	PANSS "Depression" item score	PANSS "Anxiety" item score	Equivalent dose of Clorphromazine (mg)	PANSS "Conceptual Disorganization" item
PANSS factor 1	-0.067	0.082	0.267	0.133	0.089	0.210
PANSS factor 2	-0.143	-0.23	0.421*	0.272	0.046	0.176
PANSS factor 3	-0.220	0.083	0.595*	0.317**	-0.082	0.214

*Legend – EFA = Exploratory Factor Analysis; GAF = Global Assessment of Functioning; FEP = First Episode Psychosis; PANSS = Positive and Negative Syndrome Scale. Bonferroni corrected p-value: *p < 0.001; **p < 0.01. Spearman's rank correlation coefficient (ρ) values are reported.*

Table 5. Fit indices obtained in both baseline and 1-year follow-up CFA for the EFA emerging tripartite factor solution identified using the reduced PANSS 8 negative symptom item set in our FEP patients with affective psychosis (n = 78).

Fit indices (baseline [T0])	3-factor negative symptom model		Accepted values
X^2	44.424 (p = 0.007)		p > 0.05
CFI	0.982		≥ 0.90
TLI	0.973		≥ 0.90
RMSEA	0.109		≤ 0.08
SRMR	0.078		≤ 0.08
PANSS (λ)	Factor 1	Factor 2	Factor 3
N5	.993	.000	.000
N6	.816	.000	.000
N7	.813	.000	.000
N4	.000	.999	.000
G16	.000	.774	.000
N1	.000	.000	.875
N2	.000	.000	.895
G7	.000	.000	.586
Fit indices (1-year assessment time [T1])	3-factor negative symptom model		Accepted values
X^2	55.288 (p = 0.000)		p > 0.05
CFI	0.990		≥ 0.90
TLI	0.984		≥ 0.90
RMSEA	0.151		≤ 0.08
SRMR	0.078		≤ 0.08
PANSS (λ)	Factor 1	Factor 2	Factor 3
N5	.985	.000	.000
N6	.856	.000	.000
N7	.938	.000	.000
N4	.000	.999	.000
G16	.000	.926	.000
N1	.000	.000	.999
N2	.000	.000	.829
G7	.000	.000	.567

Legend – CFA = Confirmatory Factor Analysis; PANSS = Positive And Negative Syndrome Scale; EFA = Exploratory Factor Analysis; FEP = First Episode Psychosis; X^2 = Chi-square value; p = statistical value; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index; RMSEA = Root Mean Square Error of Approximation; SRMR = Standardized Root Mean Square Residual. Item loading values (λ) are also reported

Table 6. Fit indices obtained in the CFAs using the PANSS 2-factor negative symptom solutions previously identified in schizophrenia research by Jang et al. (2016) and by Pelizza et al. (2020) within our FEP patients with affective psychosis (n =78).

Fit indices (Jang's model)	2-factor negative symptom model	Accepted values
X^2	106.939 (p = 0.000)	p > 0.05
CFI	0.867	≥ 0.90
TLI	0.785	≥ 0.90
RMSEA	0.317	≤ 0.08
SRMR	0.198	≤ 0.08
Fit indices (Pelizza's model) (baseline [T0])	2-factor negative symptom model	Accepted values
X^2	18.611 (p = 0.136)	p > 0.05
CFI	0.992	≥ 0.90
TLI	0.987	≥ 0.90
RMSEA	0.077	≤ 0.08
SRMR	0.066	≤ 0.08
Fit indices (Pelizza's model) (1-year follow-up assesment time [T1])	2-factor negative symptom model	Accepted values
X^2	24.435 (p = 0.027)	p > 0.05
CFI	0.994	≥ 0.90
TLI	0.990	≥ 0.90
RMSEA	0.121	≤ 0.08
SRMR	0.076	≤ 0.08

Legend – CFA = Confirmatory Factor Analysis; PANSS = Positive And Negative Syndrome Scale; FEP = First Episode Psychosis; X2 = Chi-square value; p = statistical value; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index; RMSEA = Root Mean Square Error of Approximation; SRMR = Standardized Root Mean Square Residual.

A second factor (including PANSS "Passive/Apathetic Social Withdrawal" and "Active Social Avoidance" items) reflects a "*Social Withdrawal*" domain, including passivity/apathy in social interactions together with diminished active social involvement related to unwarranted fear, hostility and distrust (9).

Finally, a third factor (combining PANSS "Blunted Affect", "Emotional Withdrawal" and "Motor Retardation" items) identifies a "*Motor/Affective Expression Poverty*" dimension, including affective indifference to life's events, a reduction in the behavioral aspects of emotion expression (i.e. facial mimic, gestures and voice tone) and slowing in movement and speech (9).

In comparison with the tripartite model identified by Lyne et al. (2013) (6) with the SANS in a FEP population with non-schizophrenia spectrum disorders, our 3-factor configuration only replicated the "Inattention/Alogia" domain. Indeed, the first factor ("Diminished Expression") lost the SANS "Poverty of Speech" item, exclusively maintaining its purely affective behavioral components. Similarly, the third dimension ("Social Amotivation") lost its motivational attributes, while maintaining its asociality aspects.

In the current research, CFA results overall confirm adequate fit indices for our EFA emerging tripartite configuration both at baseline and after 1 year of follow-up, supporting the exclusion of the PANSS "Poor Rapport" and "Disturbance of Volition" items from the model because of their factor non-specificity or inappropriateness. Moreover, correlations of the EFA emerging factors with baseline clinical characteristics usually associated with secondary negative symptoms notably showed no association with positive symptoms, functioning and daily dose of antipsychotics. In contrast, "Social Withdrawal" and "Motor/Affective Expression Poverty" had relevant correlations with baseline depression and anxiety. These findings confirm that a secondary component of negative symptoms is relevant in FEAP patients, having a significant impact on psychopathological outcomes already at their first clinical presentation. Therefore, an in-depth assessment and treatment of such secondary negative symptom aspects are clinically considerable (34).

In the present study, CFA results also allowed to compare the goodness of fit of our EFA configuration with those identified by Jang et al. (2016) (15) in advanced stages of schizophrenia and by Pelizza et al. (2020) (4) in FES. Specifically, the Jang's 2-factor model showed worse fit indices than our tripartite negative symptom solution, failing to find an adequate correspondence in our dataset. Specifically, the "Expressive Deficits" domain lost the PANSS "Poor Rapport" item (which showed a factor non-speicificity in our model) and its poverty of speech (which aggregated in the "Alogia" dimension in our EFA). In this respect, alogia seems to be an independent, unitary domain already during the first episode of a psychosis other than FES. Within schizophrenia research, several authors suggested that alogia is not conceptually

related to negative symptoms, often presenting relevant correlations with disorganization and/or cognitive deficits (35). However, in our tripartite model, no association of "Alogia" domain with the PANSS "Disorganization" item was found (Table 4).

Similarly, the Jang's "Experiential Deficits" dimension equally failed to find a correspondence in our 3-factor configuration, specifically losing its emotional withdrawal component, which aggregated in the "Motor/Affective Expression Poverty" domain in our EFA. In FEAP, this result suggests to differentiate in FEAP a social withdrawal (with its diminished social drive) from an emotional withdrawal, aggregating in a more general domain including affective expression deficits in our EFA.

As an alternative, the Pelizza's 2-factor solution identified in FES patients (always within the Pr-EP program) equally showed good CFA fit indices both at baseline and after 12 months of follow-up. These findings are substantially comparable (even slightly better) with those reported in our EFA emerging tripartite configuration. In comparison to this model identified in early schizophrenia, our "Motor/Affective Expression Poverty" perfectly replicated the "Expressive Deficits" dimension. In this respect, in order to avoid any conceptual overlapping of negative symptoms with disorganization and/or cognitive deficits emerged in schizophrenia research, the PANSS "Difficulty in Abstract Thinking" and "Stereotyped Thinking" items was excluded from the negative symptom set using for the EFA in FES patients (4). For this reason, no specific "Alogia" domain was in the FES 2-factor negative symptom model and the PANSS "Lack of Spontaneity and Flow of Conversation" item aggregated in the "Asociality" dimension. However, further studies in larger FEAP populations replicating the comparison of CFA fit indices between these two different negative symptom solutions are needed.

Our findings raises non-neglectable clinical issues: (1) the different psychopathological relevance and specificity of the negative symptom factor models identified in FEP populations with affective psychosis in comparison with those proposed in advanced stages of schizophrenia; and (2) the legitimacy and rationale of adopting a unitary, trans-nosological factor model of negative symptoms in different stages of psychosis rather than a time course or a spectrum specific one. Indeed, a purely dimensional model of negative symptoms in patients with psychosis is probably too simplistic and equivocal. As an alternative, a categorical or hybrid (dimensional-categorical) solution should be considered. About this, a current line of research showed that negative symptoms in schizophrenia spectrum disorders could be consistent with a categorical-dimensional structure, in which dimensional variation existed within categorical negative symptom subgroup (for details, see latent variable mixture models categorically distinguishing deficit from non-deficit forms of negative symptoms) (36). Finally, an in-depth evaluation of the subjective experience of negative symptoms could further elucidate any other psychopathological specificity in negative symptomatology between schizophrenia and non-schizophrenia spectrum disorders.

Limitations

Several limitations of this study should also be acknowledged. First, we examined FEP individuals evaluated in a real-world, non-academic setting, primarily engaged in the identification of optimal clinical care pathways in standard community mental health services. Therefore, the majority of the enrolled participants (n = 75 [97.4%]) were already taking antipsychotics at baseline assessment and the generalizability of our results is limited to this kind of population. The results are thus not generalizable to individuals in different illness course (such as subjects with long-term medication or FEP help-seekers who are not on antipsychotic treatment) and with FEP other than affective psychosis.

Second, our analysis was conducted on data collected within an EIP protocol that did not specifically focus on negative symptoms. In particular, the assessment of major psychopathology was performed with the PANSS (a scale frequently used in FEP populations to measure psychosis psychopathology), which was originally composed of only 7 negative symptoms and is less articulated than the SANS. Thus, further studies using the SANS or more specific psychometric instruments for assessing negative symptomatology (e.g. the Brief Negative Symptom Scale BNSS]) (37) in FEAP are needed. However, given the widespread

use of the PANSS in FEP populations, our factor analysis results have the potential to be replicated in analogous samples and offer an important lead to further explore the emerging structure of negative symptoms in early psychosis other than schizophrenia. This is of primary clinical importance, since research in this topic is still scarce and negative symptoms have relevant, long-term prognostic impact.

Another weakness was the limited sample size of our FEAP participants. Therefore, further perspective studies on larger FEAP populations are needed.

Conclusions

Our results suggest that a 3-factor model adequately fit the negative symptomatology in FEAP patients. As an alternative, a 2-factor solution previously identified by Pelizza et al. (2020) (4) in young help-seekers with FES seems to be equally adequate, suggesting similar discrete negative symptom dimensions in different FEP diagnoses (i.e. FEAP and FES). Over and above the details of the factor solutions, a purely dimensional model of negative symptoms in patients in different stages of psychosis could be partially equivocal. Consequently, the recent trend toward conceptualizing the structure of negative symptoms as trans-nosographically uniform across psychosis probably does not adequately capture the clinical complexity of negative symptomatology, and invite further research in this field.

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References

1. Gee B, Hodgekins J, Fowler D et al. The course of negative symptom in first episode psychosis and the relationship with social recovery. Schizophr Res 2016; 174: 165-71.
2. Blanchard JJ, Cohen AS. The structure of negative symptoms within schizophrenia: implications for assessment. Schizophr Bull 2006; 32: 238-45.
3. Ahmed AO, Kirkpatrick B, Galderisi S, Mucci A, Rossi A, Bertolino A. Cross-cultural validation of the 5-factor structure of negative symptoms in schizophrenia. Schizophr Bull 2019; 45: 305-14.
4. Pelizza L, Landi G, Pellegrini C et al. Negative symptom configuration in first episode schizophrenia: findings from the "Parma Early Psychosis" program. Nord J Psychiatry 2020; 74: 251-8.
5. Pelizza L, Azzali S, Paterlini F et al. Characterization of young people with first episode psychosis or at ultra-high risk: the Reggio Emilia At-Risk Mental States (ReARMS) program. Riv Psichiatr 2019; 54: 254-63.
6. Lyne J, Renwick L, Grant T, Kinsella A, McCarthy P, Malone K. Scale for the Assessment of Negative Symptoms structure in first episode psychosis. Psychiatry Res 2013; 210: 1191-7.
7. Andreasen NC. Negative symptoms in schizophrenia: definition and reliability. Arch Gen Psychiatry 1982; 39: 784-8.
8. Dollfus S, Lyne J. Negative symptoms: history of the concept and their position in diagnosis of schizophrenia. Schizophr Res 2017; 186: 3-7.
9. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13: 261-76.
10. Leuci E, Quattrone E, Pellegrini P, Pelizza L. The "Parma-Early Psychosis" program: general description and process analysis after 5 years of clinical activity. Early Interv Psychiatry 2020; 14: 356-64.
11. American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders, IV edition, Text Revision (DSM-IV-TR). APA Press, Washington, DC, 2000.
12. Ran MS, Xiao Y, Chui CHK et al. Duration of untreated psyhosis (DUP) and outcome of people with schizophrenia in rural China: 14-year follow-up. Psychiatry Res 2018; 267: 340-5.
13. Landi G, Leuci E, Quattrone E et al. The 'Parma-Early Psychosis' programme: characterization of help-seekers with first episode psychosis. Early Interv Psychiatry, https://doi.org/10.1111/eip.12968.

14. Yung AR, Yuen YP, McGorry PD et al. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. Aust N Z J Psychiatry 2005; 39: 964-71.
15. Jang SK, Choi HI, Park S, Jaekal E, Lee GY, Cho YI. A two-factor model better explains heterogeneity in negative symptoms: evidence from the Positive and Negative Syndrome Scale. Front Psychol 2016; 7: 707.
16. Pancheri P, Brugnoli R, Carilli L, Delle Chiaie R, Marconi PL, Petrucci RM. Valutazione dimensionale della sintomatologia schizofrenica: validazione della versione italiana della Scala per la Valutazione dei Sintomi Positivi e Negativi (PANNS). G Ital Psicopatol 1995; 1: 60-75.
17. Poletti M, Pelizza L, Azzali S et al. Clinical high risk for psychosis in childhood and adolescence: findings from the 2-year follow-up of the ReARMS project. Eur Child Adolesc Psychiatry 2018; 28: 957-71.
18. Shafer A, Dazzi F. Meta-analysis of the Positive And Negative Syndrome Scale (PANSS) factor structure. J Psychiatr Res 2019; 115: 113-20.
19. Khan A, Lindenmayer A, Opler M, Yavorsky C, Rothman B, Lucic L. A new integrated negative symptom structure of the Positive and Negative Syndrome Scale (PANSS) in schizophrenia using item response analysis. Schizophr Res 2013; 150: 185-96.
20. Marder SR, Daniel DG, Alphs L, Awad AG, Keefe RSE. Methodological issues in negative symptom trials. Schizophr Bull 2011; 37: 250-4.
21. Andreoli V, Cassano GB, Rossi R. DSM-IV-TR: manuale diagnostico e statistico dei disturbi mentali, IV Edizione, Text Revision. Masson, Milano, 2007.
22. Pelizza L, Azzali S, Garlassi S, et al. Adolescents at ultra-high risk of psychosis in Italian neuropsychiatry services: prevalence, psychopathology and transition rate. Eur Child Adolesc Psychiatry 2018; 27: 725-37.
23. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR axis I Disorders (SCID-I). New York State Psychiatric Institute, New York, NY, 2002.
24. SPSS Inc. Statistical Package for Social Science (SPSS) for Windows, version 15.0. SPSS Inc. Press, Chicago, IL, 2010.
25. Rosseel Y. Lavaan: an R package for structural equation modeling. J Stat Software 2012; 48: 1-36.
26. Kline P. Handbook of psychological testing, 2nd Edition. Routledge, London, 2000.
27. Marsh HW, Morin AJ, Parker PD, Kaur G. Exploratory structural equation modeling: an integration of the best features of exploratory and confirmatory factor analysis. Ann Rev Clin Psychol 2014; 10: 85-110.
28. Hair J, Anderson R, Tatham W, Black W. Multivariate data analysis, 5th Edition. Prentice Hall International, London, 1998.
29. Galderisi S, Farden A, Kaiser S. Dissecting negative symptoms of schizophrenia: history, assessment, pathophysiological mechanisms and treatment. Schizophr Res 2017; 186: 1-2.
30. Brown TA. Confirmatory factor analysis for applied research, 2nd Edition. The Guilford Press, New York, NY, 2015.
31. Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct Equ Model 1999; 6: 1-55.
32. Kirkpatrick B, Buchanan RW, McKenney PD, Alphs LD, Carpenter WT. The schedule for the deficit syndrome: an instrument for research in schizophrenia. Psychiatry Res 1989; 30: 119-23.
33. Bonferroni CE. Teoria statistica delle classi e calcolo delle probabilità. Pubblicazioni del Regio Istituto Superiore di Scienze Economiche e Commerciali di Firenze, Firenze, 1936.
34. Kirschner M, Aleman A, Kaiser S. Secondary negative symptoms: a review of mechanisms, assessment and treatment. Schizophr Res 2017; 186: 29-38.
35. Galderisi S, Mucci A, Buchanan RW, Arango C. Negative symptoms of schizophrenia: new developments and unanswered research questions. Lancet Psychiatry 2018; 5: 664-77.
36. Ahmed AO, Strauss GP, Buchanan RW, Kirkpatrick B, Carpenter WT. Schizophrenia heterogeneity revised: clinical, cognitive, and psychosocial correlates of statistically-derived negative symptoms subgroups. J Psychiatr Res 2018; 97: 8-15.
37. Kirkpatrick B, Strauss GP, Nguyen L et al. The Brief Negative Symptom Scale: psychometric properties. Schizophr Bull 2011; 37: 300-5.

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