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DIFFERENCE OF SYMPTOMS NETWORKS IN EARLY AND LATE PHASE SCHIZOPHRENIA; A CROSS-SECTIONAL NETWORK ANALYSIS

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SUMMARY

***Objective**: The functional remission or recovery of schizophrenia patients is a challenging task which relies on pharmacotherapy but also on the timing of psychotherapy and other therapeutic interventions. The study aimed to assess the difference in strength and structure of symptoms networks between early and late phase schizophrenia. Our secondary objective was to check whether the overall, positive, negative, and general symptoms severity change over the course of treatment and disorder.*

***Methods**: This nested cross-sectional analysis combined the samples from two studies performed during 2014-2016 at University Psychiatric Hospital Vrapče, Zagreb, Croatia on the consecutive sample of men 30-60 years old diagnosed with schizophrenia, 85 of them in the early (≤5 years from diagnosis), and 143 in the late phase of the illness. The study was funded by the project: "Biomarkers in schizophrenia - integration of complementary methods in longitudinal follow up of FEP patients".*

***Results**: Median (IQR) age of the participant in the early phase was 36 (32-45) years and in the late phase 44 (38-49) years. Patients in the early phase had significantly higher odds for being in the symptomatic remission compared to the patients in the late-phase schizophrenia (OR=2.11; 95% CI 1.09-4.09) and had 10% less pronounced negative symptoms. The global strength, density, and structure of the symptoms network were not significantly different between the two study groups.*

***Conclusions**: Negative symptoms severity change with the course of illness and differ from the early to the late phase of schizophrenia. However, the overall network of psychotic symptoms is relatively stable, and overall strengths or density and the partial relationship between particular symptoms do not change significantly. The observed worsening of negative symptoms is probably at least partially caused by the lack of clear guidelines and effective treatment options aimed specifically toward negative symptoms.*

***Key words:** schizophrenia - psychosis - PANSS - networks - symptoms*

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INTRODUCTION

People diagnosed with schizophrenia have an elevated risk of dying (Walker et al. 2015) and up to 20 years shorter life expectancy than the general population (Hjorthoj et al. 2017). This is partially associated with the fact that as much as 30% to 66% of patients do not satisfactorily respond to the acute antipsychotic treatment and do not achieve symptomatic remission (Samara et al. 2018, Jurišić et al. 2020). Functional remission or recovery is an even more demanding objective. Prognosis and response to treatment are generally better in patients with better premorbid functioning, more severe initial symptoms (Samara et al. 2018), with acute onset of the disorder (Kanahara et al. 2013), better adherence to the therapy, which was recognized as the main relapse risk factor, and the lower severity of negative and excitement symptoms (Valencia et al. 2015, Austin et al. 2013). Although the prognosis is obviously associated with the structure of psychotic symptoms, the studies of new antipsychotics' efficacy on negative and affective symptoms are inconsistent, methodologically heterogeneous, and sometimes of insufficient quality (Möller & Czobor 2015). Similarly, the majority of psychosocial treatments and research focus on positive symptoms as well (Elis et al. 2013). In brief, we lack the understanding of the pathogenesis of negative symptoms and, consequently, the evidence-based treatment guidelines and effective treatment options (Remington et al. 2016, Jurišić et al. 2020). One of the prerogatives of such understanding is to understand the relation of individual symptoms and symptoms groups. The lack of valid evidence for the exclusive relations between particular schizophrenia symptoms, their overlap between different disorders, definition (classification/diagnosis), and differential diagnosis of particular mental disorders based on the unproven assumption about the distinct latent cause, common, and unique pathogenesis and their categorical, discrete nature (Owen et al. 2016, Silić et al. 2019) led to the formulation of the new theory of mental disorders (Borsboom 2017) which was applied to the problem of psychosis and schizophrenia as well (van Rooijen et al. 2017, Isvoranu et al. 2017, Isvoranu et al. 2016, Murphy et al. 2018, Bak et al. 2016, Galderisi et al. 2018, Klippel et al. 2018, Vukojević & Silić 2018). The network theory of mental disorders postulates that the majority of psychiatric symptoms have no common cause in the underlying mental disorder, but that they cause each other in the complex networks that we recognized as the mental disorder (Borsboom 2017). Besides very promising theoretical advances, one of the important clinical implications is that a particular symptom may remain unchanged in severity after the treatment, but that its role in the total psychopathological network

may be altered (Esfahlani et al. 2017). Or that even the effective lowering of the severity of a particular symptom may do only a small good for the patient if this symptom is still highly central or influential to other symptoms. A study by Esfahlani et al. showed that in the schizophrenia-treatment-responsive patients, the most central symptoms after the treatment with antipsychotics were N1. Blunted affect, P4. Excitement and N3. Poor rapport (Esfahlani et al. 2017). The study authors concluded that: "When antipsychotics do have beneficial effects on these (three) specific symptoms, this leads to a spreading effect and improvement in positive and other symptoms as well." (Esfahlani et al. 2017). This insight, and the compatible finding by Galderisi et al. about the higher betweenness centrality of the functional capacity (Galderisi et al. 2018), was the main motive for our study. Antipsychotics, although relatively effective on positive symptoms, have no consistent, reliable, and satisfactory effect on negative and cognitive symptoms (Owen et al. 2016). These symptoms are more important for functional recovery, and some of them may be responsive to some psychological and social interventions. Our idea was first to check the centrality and impact of particular symptoms by the analysis presented in this paper, and then to use this knowledge in designing the new randomized control trial of the psychodynamic, supportive group psychotherapy aimed to specific negative symptoms.

The primary objective of our study was to assess the change of schizophrenia symptoms network strength and structure between the early (≤5 years from the diagnosis) and late (>5 years from diagnosis) schizophrenia. Our secondary objective was to check whether the overall, positive, negative, and general symptoms severity change over the course of treatment and disorder.

METHODS

Study design

In order to increase the generalizability and reliability of our results, we performed this single-center, nested cross-sectional analysis combining two comparable samples from the same population obtained from the two studies performed at University Psychiatric Hospital Vrapče, Zagreb. The first sample was obtained from the cross-sectional study: "Impact of self-stigma and insight of illness on depression and suicidality in patients with schizophrenia" designed by Domagoj Vidović and performed during 2014. The second sample was nested within the baseline measurement of the randomized controlled trial: "Group supportive psychotherapy efficacy in the treatment of schizophrenia" designed by Nataša Đuran and performed during 2015 and 2016. Both studies were performed for the needs of the principal investigators' Ph.D. thesis. Two study protocols were approved by the Ethics Committee of the University Psychiatric Hospital Vrapče, Zagreb, and all participants signed the informed consent form to confirm they understood the important parameters of the studies and were willing to participate. Both studies complied with the World Medical Association Declaration of Helsinki (World Medical Association 2013). In both studies, the anonymity of participants was presserved by assigning them the numeric codes at enrollment. Signed informed consents were kept separately from the data collection instruments.

Study population

The first study targeted population was patients of both genders, with the preserved legal and work capacity, 25-45 years old, with the diagnosis of schizophrenia (ICD-10: F20) established and confirmed by two independent clinicians in accordance with ICD-10 and DSM-IV diagnostic criteria. At the time of enrollment, the DSM-V diagnostic criteria were published, but the authors of the study concluded that the diagnosis would remain the same in all cases, even if they had used DSM-V instead. From this first study, we used the sample of men 30-45 years old. The second study targeted population was hospitalized men 30-60 years old diagnosed with schizophrenia and treated with the 2nd generation antipsychotics. Exclusion criteria in both studies were suicidality and alcohol or drug dependence in comorbidity. The needed sample sizes were estimated for both studies before the data enrollment. We used just the rule-of-thumb to estimate the minimum of 5 participants per variable for this analysis. With 30 PANSS items, we estimated that the usable minimal sample size would be n=150. Finally, we used the pooled sample of 228 participants. In both studies, a consecutive sample was selected in order of the patient's arrival to the exam or the hospitalization.

Outcomes

The primary outcome was Positive and negative syndrome scale (PANSS) individual items' partial polychoric correlations (Kay et al. 1987). PANSS contains 30 items measuring different schizophrenia symptoms severity on the scales ranging from 1, meaning that symptom is absent, to 7, meaning that symptoms are "extreme". PANSS is structured into three subscales: positive symptoms (items P1 to P7), negative symptoms (items N1 to N7), and general symptoms (items G1 to G16). Our secondary outcomes were these three subscales scores and the proportion of patients achieving symptomatic remission. We defined the symptomatic remission according to The Remission in Schizophrenia Working Group (Andreasen et al. 2005) as the sum of eight PANSS items (Kay et al. 1987) lower than 21 and no result on any particular item >3. The eight items were: P1. Delusions, P2. Conceptual disorganization, P3. Hallucinatory behavior, N1. Blunted affect, N4. Passive/apathetic social withdrawal, N6. Lack of spontaneity, G5. Mannerisms/posturing, G9. Unusual thought content.

Independent variable

The independent variable was the duration of schizophrenia dichotomized into "early (≤5 years from the diagnosis), and "late" (>5 years from the diagnosis). Data on the duration of the disorder from the diagnosis was obtained from the hospital medical records.

Statistical analysis

In the analysis of our primary outcome, we used Epskamp and Fried's R package: boot net to estimate the partial correlation networks of PANSS items measuring the severity of symptoms in early and late schizophrenia. To lower the false-positive partial correlations between symptoms, we used the least absolute shrinkage and selection operator (lasso) with the extended Bayesian Information Criterion (EBIC) for the selection of the shrinkage parameter and a tuning parameter γ=0.25. Arrangement of symptoms (nodes) on the network charts was based on the Fruchterman-Reingold algorithm to position the more partially correlated symptoms closer to each other. We estimated the importance of each PANSS item by calculating strength, closeness, and betweenness centrality indices using Epskamp and Kossakowski's R package qgraph. The strength centrality measure is calculated as the sum of the weighted connections of the particular PANSS item with all other items indicating how strongly each symptom is directly connected to all other symptoms. Closeness centrality measure is the average distance between a particular PANSS item to all other items indicating how strongly each symptom is indirectly connected to all other symptoms through other symptoms. The betweenness centrality measure indicates how important is the particular symptom on the average path between two other symptoms. We assessed the accuracy of partial correlations between symptoms by bootstrap confidence intervals, the stability of centrality indices by correlation stability coefficient of 0.7, and the difference between symptoms' weights and centrality indices by bootstrap test. To compare the invariance of the symptoms networks' structure in early and late schizophrenia, invariance of edge strengths, and invariance of the global symptoms networks' strengths, we used van Borkulo's NetworkComparisonTest. (van Borkulo et al. 2017) In the analysis of our secondary outcome, we calculated the mean difference in overall PANSS score and three PANS subscales of positive, negative, and general symptoms with their 95% confidence intervals and the difference relative to the mean score in the schizophrenia late-phase group. We calculated the significance of the difference using a Student's t-test for independent samples and equal variances not assumed. As the measure of the standardized effect size, we calculated the Hedges' g. We corrected the p values for multiple testing effect using the sequential Holm-Bonferroni method, set the level of all significance tests at two-tailed $p<0.05$, and all confidence intervals at 95%. We performed statistical data analysis using the R Core Team (R: A language and environment for statistical computing).

Table 1. Participants' characteristics

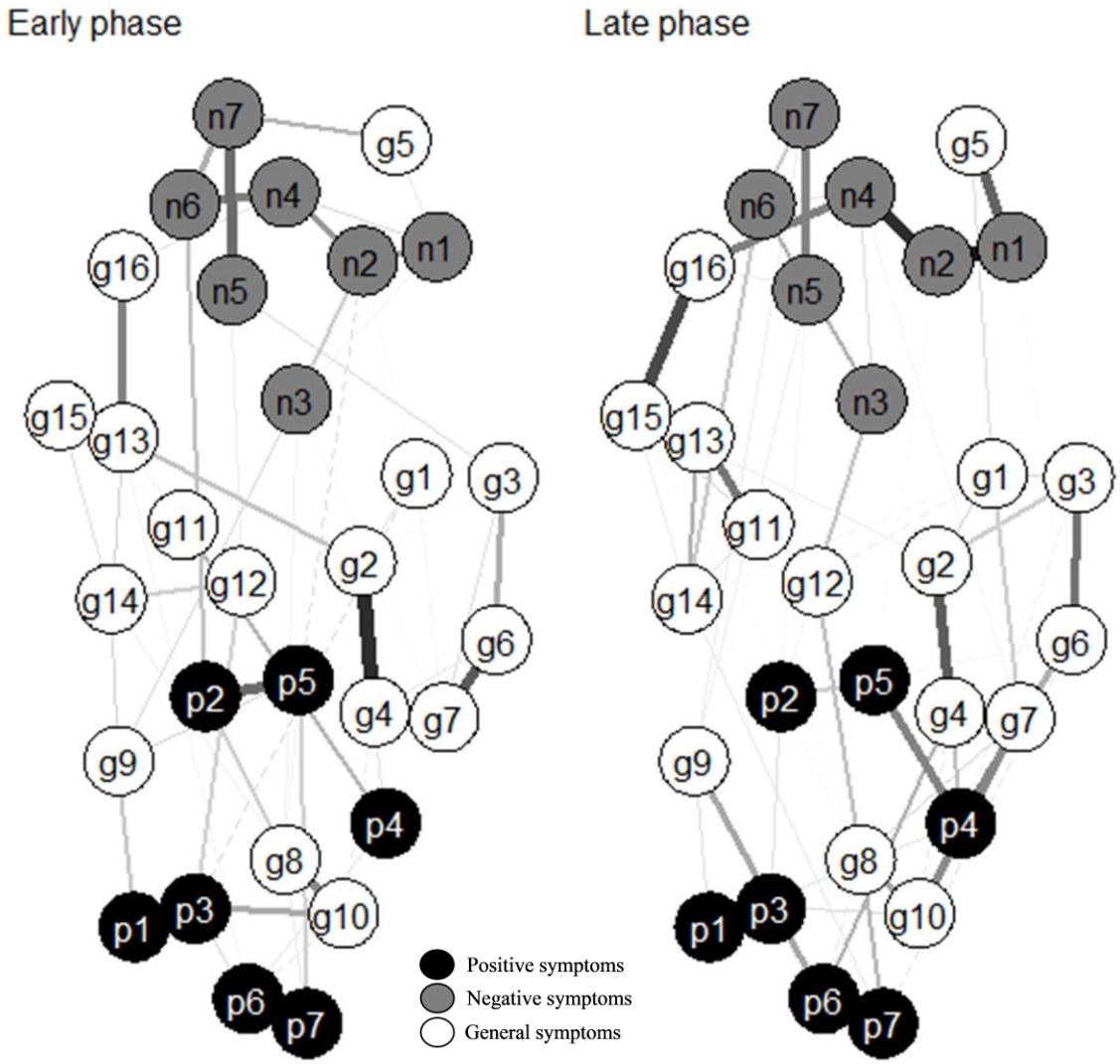
Sociodemographic characteristics	Early-phase (n=85)		Late-phase (n=143)	
Age (years), median (IQR)	36	(32-45)	44	(38-49)
Education				
primary	12	(14.1)	27	(18.9)
secondary	64	(75.3)	107	(74.8)
university	9	(10.6)	9	(6.3)
In steady relationship	11	(12.9)	17	(11.9)
Having children	15	(17.6)	24	(16.8)
Number of household members				
single	8	(9.4)	24	(16.8)
with other people	77	(90.6)	119	(83.2)
Working status				
employed	33	(38.8)	24	(16.8)
unemployed or retired	52	(61.2)	119	(83.2)
Clinical characteristics				
Age at illness onset (years), median (IQR)	34	(30-43)	27	(23-33)
Duration of illness since diagnosis (years), median (IQR)	1	(1-3)	13	(9-19)
Number of previous psychiatric hospitalizations, median (IQR)	1	(0-3)	7	(3-11)
Symptomatic remission*	28	(32.9)	27	(18.9)

Data are presented as number (percentage) of participants if not stated otherwise
Abbreviations: IQR = interquartile range; * Remission was defined according to The Remission in Schizophrenia Working Group (23) as the sum of eight PANSS items (22) lower than 21 and no result on any particular item >3.
Eight items were: P1. Delusions; P2. Conceptual disorganization; P3. Hallucinatory behavior; N1. Blunted affect; N4. Passive/apathetic social withdrawal; N6. Lack of spontaneity; G5. Mannerisms/posturing; G9. Unusual thought content

Table 2. Severity of symptoms

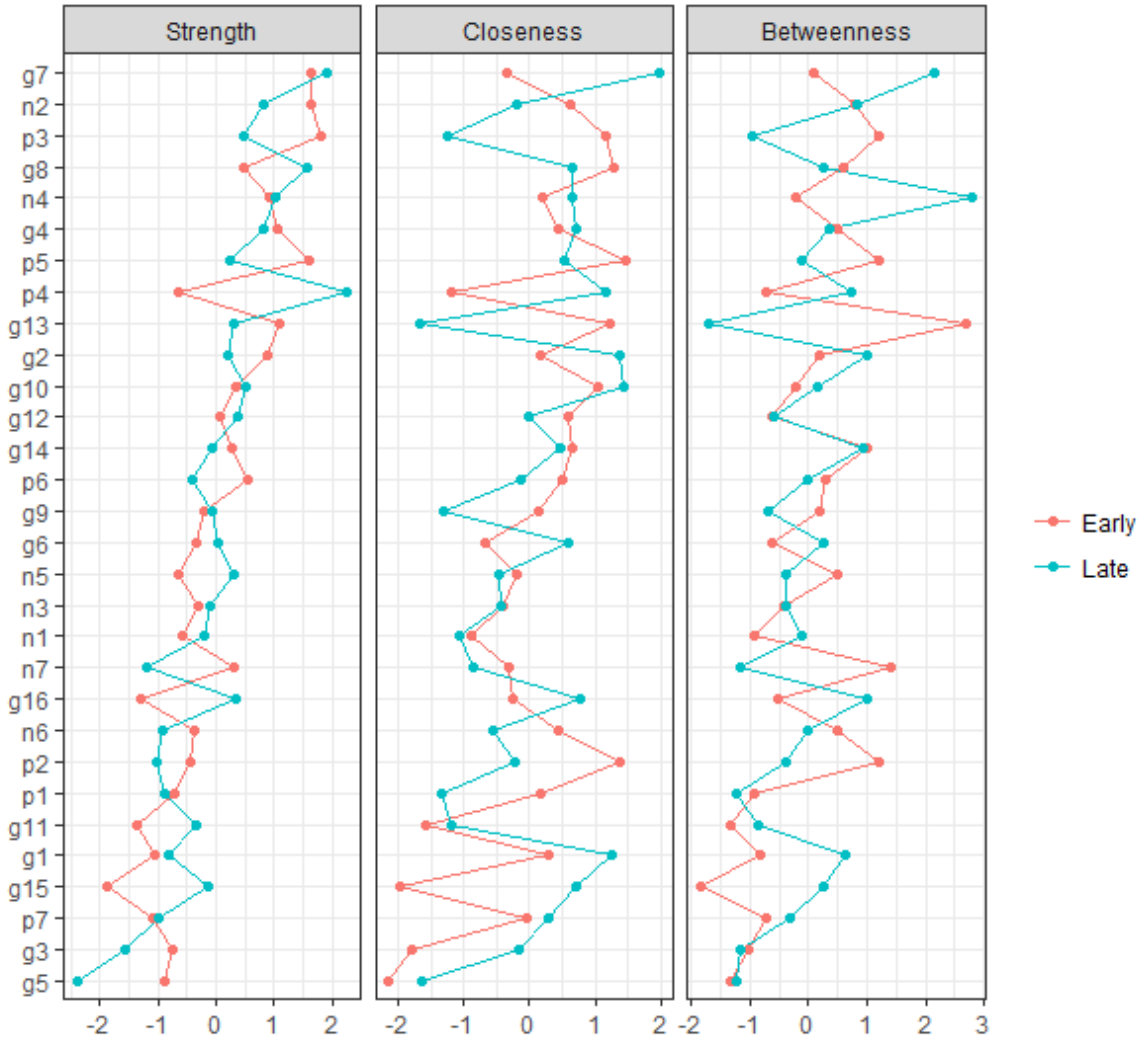
	Early-phase (n=85)		Late-phase (n=143)		Δ	(95% CI)	Δ%	p	p_{corr}	g
PANSS overall score	78	(17.1)	83	(14.5)	-5.1	(-9.5 to -0.7)	-6%	0.022	0.066	0.32
PANSS subscales scores										
Positive symptoms	17	(4.9)	18	(4.5)	-0.5	(-1.8 to 0.8)	-3%	0.429	0.429	0.21
Negative symptoms	20	(5.9)	23	(5.1)	-2.3	(-3.9 to -0.8)	-10%	0.003	0.012	0.55
General symptoms	41	(9.2)	43	(7.3)	-2.3	(-4.6 to 0.1)	-5%	0.055	0.110	0.25

Data are presented as mean (standard deviation) if not stated otherwise; Abbreviations: Δ = mean difference; CI = confidence interval of the mean difference; Δ% = mean difference relative to the score in late-phase group; p = statistical significance of the difference calculated using Student's t-test for independent groups and equal variances not assumed; p_{corr} = statistical significance corrected using the sequential Holm-Bonferroni correction; g = Hedges's g given as the standardized effect size



Abbreviations: p1. Delusions, p2. Conceptual disorganization, p3. Hallucinatory behavior, p4. Excitement, p5. Grandiosity, p6. Suspiciousness/persecution, p7. Hostility, n1. Blunted affect, n2. Emotional withdrawal, n3. Poor rapport, n4. Passive/apathetic social withdrawal, n5. Difficulty in abstract thinking, n6. Lack of spontaneity & flow of conversation, n7. Stereotyped thinking, g1. Somatic concern, g2. Anxiety, g3. Guilt feelings, g4. Tension, g5. Mannerisms & posturing, g6. Depression, g7. Motor retardation, g8. Uncooperativeness, g9. Unusual thought content, g10. Disorientation, g11. Poor attention, g12. Lack of judgement & insight, g13. Disturbance of volition, g14. Poor impulse control, g15. Preoccupation, g16. Active social avoidance

Figure 1. EBICglasso regularized cross-sectional networks of symptoms in early (≤5 years from diagnosis) and late phase of schizophrenia; solid lines represent positive and dotted lines negative associations adjusted for all other symptoms, the line thickness represents the size of the partial polychoric correlations; tuning parameter γ=0.25; n(early phase)=85; n(late phase)=143



Abbreviations: p1. Delusions, p2. Conceptual disorganization, p3. Hallucinatory behavior, p4. Excitement, p5. Grandiosity, p6. Suspiciousness/persecution, p7. Hostility, n1. Blunted affect, n2. Emotional withdrawal, n3. Poor rapport, n4. Passive/apathetic social withdrawal, n5. Difficulty in abstract thinking, n6. Lack of spontaneity & flow of conversation, n7. Stereotyped thinking, g1. Somatic concern, g2. Anxiety, g3. Guilt feelings, g4. Tension, g5. Mannerisms & posturing, g6. Depression, g7. Motor retardation, g8. Uncooperativeness, g9. Unusual thought content, g10. Disorientation, g11. Poor attention, g12. Lack of judgement & insight, g13. Disturbance of volition, g14. Poor impulse control, g15. Preoccupation, g16. Active social avoidance

Figure 2. Symptoms' centrality indices in early and late phase schizophrenia

RESULTS

We used the data from 228 men diagnosed with schizophrenia, 85 of them in the early phase defined as ≤five years from the diagnosis, with the median (IQR) age of 36 (32-45), and 143 in the late phase, with the median (IQR) age of 44 (38-49). Two populations were comparable regarding a steady relationship and having children (Table 1). Patients in the early phase schizophrenia were somewhat better educated, more often living in the household with other family members or other people, and were markedly more often employed. They had significantly higher odds for being in the symptomatic remission compared to the patients in the late-phase schizophrenia (OR=2.11; 95% CI 1.09-4.09; p=0.024) (Table 1). After the correction for multiple testing using the sequential Holm-Bonferroni method, the two study groups significantly differ only in the negative symptoms PANSS subscale score (Table 2). Patients in the early phase had 10% less pronounced negative symptoms than the patients in the late phase, after the adjustment for multiple testing. The N1., Blunted affect, was significantly lower in the early phase group (Table 3). Patients in the early phase had a moderate or more severe blunted affect in 24/85 (28.2%) of cases, compared to 69/143 (48.3%) of the patients in the late phase (OR=0.42; 95% CI 0.23-0.78; p=0.003). Two networks are presented in Figure 1. The number of symptoms with partial polychoric correlations >0 was 158 in the early and 182 in the late phase group. The global strength was 14.04 in early and 13.45 in the late schizophrenia, and this difference of S=0.59 was not significant

(p=0.813). The difference in the two networks structure was not significant neither (M=0.22; p=0.939). The largest difference between early and late schizophrenia in the symptoms, with the most direct connections with other symptoms, was observed in the case of P4. Excitement, as it was more central in the late phase schizophrenia network (Figure 2). In the late phase of the disorder P4. Excitement was directly partially correlated to P5. Grandiosity; G7. Motor retardation; G10. Disorientation, and to a lesser extent, to G4. Tension. In early-phase schizophrenia, P4. Excitement had a weaker partial correlation with P5. Grandiosity. Regarding the closeness centrality indicating the indirect partial correlations between symptoms, we observed the largest difference between early and late phases in cases of G13. Disturbance of volition and P3. Hallucinatory behavior, which were more central in the early phase; and in G7. Motor retardation and P4. Excitement, which were more central in the late phase. The largest difference in the betweenness centrality was found in cases of G13. Disturbance of volition, which was more central in the early, and in N4. Passive/ apathetic social withdrawal, which was more central in the late phase of schizophrenia.

DISCUSSION

Key findings and literature comparison

Our study indicated the difference in the severity of negative symptoms between the early and the late phase of schizophrenia. However, we did not find significant differences in the symptoms networks' strength, density, or structure. Our finding that only 20-30% of patients achieve the symptomatic remission is congruent with the large individual-patient meta-analysis of randomized controlled trials performed this year on the sample of 6221 patients diagnosed with schizophrenia (Samara et al. 2018). Still, our finding of the significant increase in the mean severity of negative symptoms seems to contradict the conclusions of some other studies (Ortiz et al. 2017, Ventura et al. 2015). However, the difference in negative symptoms in our study between the early and late phases was relatively small, and our network analysis did not indicate strength or structural changes between the negative symptoms. Both mentioned studies were performed on the samples of both genders, while participants in our study were only men. The worsening of negative symptoms that we observed, as well as their long term stability and relatively stable association with some important indicators of the functional recovery that was observed by Ventura et al. (Ventura et al. 2015), basically point to the same direction: the lack of clear guidance and effective therapeutic options for the treatment of negative symptoms. Such stability may imply, as Ortiz et al. concluded, that the negative symptoms are not (only) the consequence of the long-term illness, antipsychotic treatment, a higher number of psychiatric hospitalizations, social and functional difficulties, but indeed the primary and stable schizophrenia feature (Ortiz et al. 2017). Many other studies concluded the same (Owen et al. 2016).

Limitations and strengths of the study

The first limitation was determined by our study design. It was a cross-sectional analysis of two subpopulations defined by the duration of schizophrenia from the diagnosis to the time of the enrollment. Therefore, we could not observe the changes in symptoms structures by the course of the illness and treatment. Second, the cut off we used to define "early-phase" or "late-phase" schizophrenia was arbitrary. The cut off at the 5th year from diagnosis is often used, but there was no evidence that it is the optimal one. Furthermore, the course of illness and the therapy are natural quantitative/temporal variables and dichotomization results in the loss of information. We were aware of this limitation during the planning phase, but the overall available sample size prevented us from using a more precise division, while (un)availability of proper statistical methods prevented us from using this variable in its natural, quantitative form. Third, consecutive samples used in the two studies we combined are more vulnerable to the selection bias when compared to the random samples. As the severity of the symptoms is associated with the frequency of control visits and hospitalization rates, the consecutive samples of patients diagnosed with schizophrenia may over-represent the patients with a more severe disorder, and thus lower the representativeness of our samples and analysis for the general population of patients diagnosed with schizophrenia. A more serious bias would emerge if patients with more severe positive symptoms are more likely to be hospitalized and have higher frequencies of control exams than patients with primary negative symptoms. In such cases, the so-caused bias might jeopardize the internal validity of our findings on the strength and structure of the positive and negative symptoms networks. The fourth limitation would be regarding the PANSS scale, as it was administered only once, and the assessment was not independently validated.

The strength of this study lies in the homogeneity of our participants, as they were all middle-aged men and thereby excluding biases regarding sex differences. They were also comparable regarding their education, relationship status, and having children. Furthermore, we established that the development of negative symptoms is progressing with the course of the illness. As a final point, we showed that therapeutic interventions have a place in the treatment of negative symptoms and that this notion is time-correlated. Early start with adequate medical treatment, including new pharmacotherapeutic solutions and different psychotherapeutic modalities, is a crucial factor in the long term remission and social reintegration of these patients.

Table 3. Particular PANSS items severity

	Early-phase (n=85)		Late-phase (n=143)		Δ	(95% CI)	Δ%	p	p_{corr}	g
Positive symptoms										
P1. Delusions	2.6	(1.16)	2.7	(1.02)	-0.10	(-0.40 to 0.20)	-4%	0.523	>0.999	0.09
P2. Conceptual disorganization	2.5	(0.93)	2.8	(0.87)	-0.34	(-0.59 to -0.10)	-12%	0.007	0.168	0.33
P3. Hallucinatory behavior	2.1	(1.16)	2.2	(0.99)	-0.16	(-0.46 to 0.14)	-7%	0.283	>0.999	0.09
P4. Excitement	2.8	(1.00)	2.7	(1.02)	0.17	(-10 to 0.45)	7%	0.212	>0.999	0.10
P5. Grandiosity	2.0	(1.09)	2.3	(1.07)	-0.34	(-0.64 to -0.05)	-15%	0.020	0.460	0.28
P6. Suspiciousness/persecution	3.0	(1.03)	2.8	(0.98)	0.17	(-0.10 to 0.44)	6%	0.221	>0.999	0.20
P7. Hostility	2.3	(1.01)	2.2	(0.95)	0.13	(-0.18 to 0.36)	6%	0.089	>0.999	0.10
Negative symptoms										
N1. Blunted affect	2.9	(1.05)	3.5	(1.01)	-0.62	(-0.90 to -0.35)	-18%	<0.001	0.030	0.58
N2. Emotional withdrawal	3.0	(0.97)	3.4	(0.95)	-0.41	(-0.67 to -0.15)	-12%	0.002	0.058	0.42
N3. Poor rapport	2.5	(1.14)	3.0	(1.05)	-0.45	(-0.75 to -0.15)	-15%	0.003	0.078	0.46
N4. Passive/apathetic social withdrawal	3.1	(1.01)	3.3	(0.97)	-0.16	(-0.43 to 0.11)	-5%	0.234	>0.999	0.20
N5. Difficulty in abstract thinking	3.2	(1.10)	3.4	(0.94)	-0.20	(-0.48 to 0.08)	-6%	0.166	>0.999	0.20
N6. Lack of spontaneity & flow of conversation	2.8	(1.18)	3.1	(1.03)	-0.26	(-0.56 to 0.05)	-8%	0.096	>0.999	0.27
N7. Stereotyped thinking	2.8	(1.15)	3.1	(0.97)	-0.24	(-0.53 to 0.06)	-8%	0.112	>0.999	0.29
General symptoms										
G1. Somatic concern	2.4	(1.23)	2.5	(1.02)	-0.11	(-0.43 to 0.20)	-4%	0.477	>0.999	0.09
G2. Anxiety	3.2	(0.91)	3.0	(0.78)	0.14	(-0.10 to 0.37)	5%	0.253	>0.999	0.24
G3. Guilt feelings	2.4	(1.16)	2.6	(0.88)	-0.14	(-0.42 to 0.15)	-5%	0.352	>0.999	0.20
G4. Tension	3.3	(0.96)	3.1	(0.75)	0.23	(-0.01 to 0.47)	7%	0.063	>0.999	0.24
G5. Mannerisms & posturing	2.6	(1.16)	3.1	(1.03)	-0.47	(-0.77 to -0.17)	-15%	0.002	0.056	0.46
G6. Depression	2.6	(1.14)	2.7	(1.09)	-0.12	(-0.42 to 0.19)	-4%	0.452	>0.999	0.09
G7. Motor retardation	2.1	(1.05)	2.6	(0.96)	-0.43	(-0.70 to -0.15)	-17%	0.003	0.075	0.50
G8. Uncooperativeness	2.0	(0.93)	2.3	(1.01)	-0.26	(-0.52 to -0.00)	-11%	0.047	>0.999	0.30
G9. Unusual thought content	2.4	(0.91)	2.8	(0.89)	-0.39	(-0.63 to -0.15)	-14%	0.002	0.054	0.44
G10. Disorientation	1.5	(0.78)	1.5	(0.66)	-0.08	(-0.28 to 0.12)	-5%	0.444	>0.999	0.00
G11. Poor attention	2.5	(0.95)	2.7	(0.84)	-0.18	(-0.42 to 0.07)	-7%	0.156	>0.999	0.23
G12. Lack of judgement & insight	3.0	(1.02)	3.1	(1.06)	-0.09	(-0.37 to 0.19)	-3%	0.531	>0.999	0.10
G13. Disturbance of volition	2.9	(1.11)	2.9	(1.00)	-0.04	(-0.33 to 0.24)	-1%	0.766	0.766	0.00
G14. Poor impulse control	2.5	(1.01)	2.7	(0.98)	-0.22	(-0.49 to 0.05)	-8%	0.114	>0.999	0.20
G15. Preoccupation	2.6	(0.84)	2.7	(0.97)	-0.06	(-0.30 to 0.18)	-2%	0.609	>0.999	0.11
G16. Active social avoidance	2.8	(0.99)	2.9	(1.20)	-0.06	(-0.35 to 0.23)	-2%	0.694	>0.999	0.09

Data are presented as mean (standard deviation) if not stated otherwise

Abbreviations: Δ = mean difference; CI = confidence interval of the mean difference; Δ% = mean difference relative to the score in late-phase group; p = statistical significance of the difference calculated using Student's t-test for independent groups and equal variances not assumed; p_{corr} = statistical significance corrected using the sequential Holm-Bonferroni correction; g = Hedges's g given as the standardized effect size

Implications for practice and research

The findings of our study once again point out the importance of negative symptoms for the overall recovery in schizophrenia patients. It is of most importance that clinicians, as well as researchers, find a way to effectively treat the negative symptoms as their remission is crucial for a full recovery and social integration. Whether it is a new antipsychotic treatment or clear guidelines aimed specifically toward negative symptoms, the need for such action is immense. As the underlying psychopathological mechanisms aren't clear yet the search for an effective treatment should be oriented to psychotherapeutic interventions and the development of clear guidelines on how and when to implement certain therapeutic modalities. As schizophrenia is turning out to be a multifactorial disease, maybe it is time to start treating it in more than one way.

CONCLUSION

Our study has shown that negative symptoms severity change with the course of illness and differs from the early phase to the late phase of schizophrenia. However, the overall network of psychotic symptoms is relatively stable, and overall strengths or density and the partial relationship between particular symptoms do not change significantly. The observed worsening of negative symptoms is probably at least partially caused by the lack of clear guidelines and effective treatment options aimed specifically toward negative symptoms.

Conflict of interest: None to declare.

Contribution of individual authors:

Nataša Đuran, Neven Henigsberg & Vlado Jukić designed the study.

Nataša Đuran, Domagoj Vidović & Vlado Jukić defined the criteria for each group, checked all the characteristics of the participants and defined the outcomes and analytic approaches.

Jelena Sušac & Dina Bošnjak collected the data of the participants.

Žarko Bajić did the data analysis.

Žarko Bajić & Vlado Jukić assisted with the interpretation of the data.

Jelena Sušac & Dina Bošnjak did the literature search.

Nataša Đuran, Jakša Vukojević & Žarko Bajić wrote the first draft of the manuscript.

Domagoj Vidović & Neven Henigsberg provided valuable inputs during the writing process.

All authors have approved the final version of the manuscript.

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References

1. *Austin SF, Mors O, Secher RG, Hjorthøj CR, Albert N, Bertelsen M, et al: Predictors of recovery in first episode psychosis: the OPUS cohort at 10 year follow-up. Schizophr Res 2013; 150:163–8*
2. *Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR: Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry 2005; 162:441–9*
3. *Bak M, Drukker M, Hasmi L, van Os J: Correction: An n=1 Clinical Network Analysis of Symptoms and Treatment in Psychosis. PLoS One 2016; 11:e0165762*
4. *Van Borkulo CD, Boschloo L, Kossakowski J, Tio P, Schoevers RA, Borsboom D, Waldorp LJ: Comparing network structures on three aspects: A permutation test. Manuscript submitted for publication 2017; 10*
5. *Borsboom D: A network theory of mental disorders. World Psychiatry 2017; 16:5–13*
6. *Elis O, Caponigro JM, Kring AM: Psychosocial treatments for negative symptoms in schizophrenia: current practices and future directions. Clin Psychol Rev 2013; 33:914–28*
7. *Esfahlani FZ, Sayama H, Visser KF, Strauss GP: Sensitivity of the Positive and Negative Syndrome Scale (PANSS) in Detecting Treatment Effects via Network Analysis. Innov Clin Neurosci 2017; 14:59–67*
8. *Galderisi S, Rucci P, Kirkpatrick B, Mucci A, Gibertoni D, Rocca P, et al: Interplay Among Psychopathologic Variables, Personal Resources, Context-Related Factors, and Real-life Functioning in Individuals With Schizophrenia: A Network Analysis. JAMA psychiatry 2018; 75:396–404*
9. *Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M: Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. The Lancet Psychiatry 2017; 4:295-301*
10. *Isvoranu A-M, Borsboom D, van Os J, Guloksuz S: A Network Approach to Environmental Impact in Psychotic Disorder: Brief Theoretical Framework. Schizophr Bull 2016; 42:870–3*
11. *Isvoranu A-M, van Borkulo CD, Boyette L-L, Wigman JTW, Vinkers CH, Borsboom D, et al: A Network Approach to Psychosis: Pathways Between Childhood Trauma and Psychotic Symptoms. Schizophr Bull 2017; 43:187–96*
12. *Jurišić D, Ćavar I, Sesar A, Sesar I, Vukojević J, Ćurković M: New insights into schizophrenia: a look at the eye and related structures. Psychiatr Danub 2020; 32:60-9*

13. Kanahara N, Yoshida T, Oda Y, Yamanaka H, Moriyama T, Hayashi H, et al: Onset Pattern and Long-Term Prognosis in Schizophrenia: 10-Year Longitudinal Follow-Up Study. PLoS One 2013; 8:e67273
14. Kay SR, Fiszbein A, Opler LA: The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13:261–76
15. Klippel A, Viechtbauer W, Reininghaus U, Wigman J, van Borkulo C, MERGE, et al: The Cascade of Stress: A Network Approach to Explore Differential Dynamics in Populations Varying in Risk for Psychosis. Schizophr Bull 2018; 44:328–37
16. Möller H-J, Czobor P: Pharmacological treatment of negative symptoms in schizophrenia. Eur Arch Psychiatry Clin Neurosci 2015; 265:567–78
17. Murphy J, McBride O, Fried E, Shevlin M: Distress, Impairment and the Extended Psychosis Phenotype: A Network Analysis of Psychotic Experiences in an US General Population Sample. Schizophr Bull 2018; 44:768–77
18. Owen MJ, Sawa A. Mortensen PB: Schizophrenia Lancet 2016; 388:86-97
19. Ortiz BB, Eden FDM, de Souza ASR, Teciano CA, de Lima DM, Noto C, et al: New evidence in support of staging approaches in schizophrenia: Differences in clinical profiles between first episode, early stage, and late stage. Compr Psychiatry 2017; 73:93–6
20. Remington G, Foussias G, Fervaha G, Agid O, Takeuchi H, Lee J, et al: Treating Negative Symptoms in Schizophrenia: an Update. Curr Treat options psychiatry 2016; 3:133–50
21. van Rooijen G, Isvoranu A-M, Meijer CJ, van Borkulo CD, Ruhé HG, de Haan L, et al: A symptom network structure of the psychosis spectrum. Schizophr Res 2017; 189:75–83
22. Samara MT, Nikolakopoulou A, Salanti G, Leucht S: How many patients with schizophrenia do not respond to antipsychotic drugs in the short term? An analysis based on individual patient data from randomized controlled trials. Schizophrenia bulletin 2019; 45:639-46
23. Silić A, Vukojević J, Čulo I, Falak H: Hikikomori silent epidemic: a case study. Research in Psychotherapy: Psychopathology, Process and Outcome 2019; 22
24. Valencia M, Fresán A, Barak Y, Juárez F, Escamilla R, Saracco R: Predicting functional remission in patients with schizophrenia: a cross-sectional study of symptomatic remission, psychosocial remission, functioning, and clinical outcome. Neuropsychiatr Dis Treat 2015; 11:2339–48
25. Ventura J, Subotnik KL, Gitlin MJ, Gretchen-Doorly D, Ered A, Villa KF, et al: Negative symptoms and functioning during the first year after a recent onset of schizophrenia and 8 years later. Schizophr Res 2015; 161:407–13
26. Vukojević J, Silić A: The future of psychiatry and the story of two worlds. Asian journal of psychiatry 2018; 35:3
27. Walker ER, McGee RE, Druss BG: Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA psychiatry 2015; 72:334–41
28. World Medical Association: World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310:2191–4

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