NEUROCOGNITIVE PROFILES OF PATIENTS WITH THE FIRST EPISODE OF PSYCHOSIS AND SCHIZOPHRENIA DO NOT DIFFER QUALITATIVELY: A NESTED CROSS-SECTIONAL STUDY

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SUMMARY

Background: The aim of study was to analyze neurocognitive profiles in patients with first-episode psychosis (FEP) and patients with schizophrenia (SCH), and their correlations with other clinical features.

Subjects and methods: We performed a multicentric cross sectional study including 100 FEP and 100 SCH recruited from three Croatian hospitals during 2015-2017. Assessment included a set of neurocognitive tests, psychiatric scales and self-reporting questionnaires. The main analysis was done by multigroup latent profile analysis.

Results: Multigroup latent profile analysis resulted in three structurally equivalent neurocognitive profiles ("Best", "Medium", "Worst"), with differences in the severity of neurocognitive deficits measured with successfulness in solving domain specific tasks. The "Best" profile was statistically significantly more prevalent in FEP and "Worst" profile in the SCH. Negative symptom score was the highest in patients with the "Worst" profile and the lowest among those with the "Best" profiles.

Conclusions: Differences in neurocognitive profiles between FEP and SCH appear to be quantitative rather than qualitative nature, possibly reflecting a specific trait of illness that may progress over time. Defining neurocognitive profiles from the first episode of psychosis could help in tailoring individualized treatment options with focus on neurocognitive and negative symptoms and possible influence on patients' overall clinical outcome.

Key words: neurocognitive impairment - neurocognitive profile - psychotic disorders - first-episode psychosis - schizophrenia

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INTRODUCTION

Schizophrenia is a long-term, recurrent disorder characterized by episodes of acute psychosis and their remission (Clementz et al. 2015). While the clinical presentation may be very heterogeneous, generally, the illness usually starts with a prodromal period followed by the first episode of acute psychosis. It is characterized by symptoms that can be divided into five dimensions: positive, negative, neurocognitive, affective and psychomotor. During the following months most patients achieve remission of the first episode usually followed by reoccurring periods of acute psychosis and remission until a stage of residual phase is reached (Wiersma et al. 1998). In contrast to the first episode, every new episode usually requires more time and more medication to achieve remission (Andreasen et al. 2005).

Neurocognitive symptoms are often defined as the core feature of schizophrenia (Barder et al. 2013). Deficits in cognitive functioning are typically 0.5 to 2 standard deviations below healthy control group across a number of cognitive domains (Gold 2004, Keefe 2008). Cognitive impairment seems to be present even in the premorbid and prodromal phases of illness (Bora & Murray 2014, Eisenacher et al. 2016, Fusar-Poli et al. 2012) with a significant decline in all cognitive domains in the first episode and early phase of illness (Mesholam-Gately et al. 2009).

From the clinical point of view, neurocognitive symptoms are relevant as they may be regarded as the most resistant to pharmacological treatment compared to all other symptom dimensions (Ahmed & Bhat 2014, Trampush et al. 2015). Moreover, they seem to be connected with different aspects of functionality as an objective measure and quality of life as a subjective measure of illness outcome (Lepage et al. 2014, Mesholam-Gately et al. 2009, Rodriguez et al. 2015). Neurocognitive decline is directly associated with poor psychosocial functioning, low work productivity and high absenteeism of persons with schizophrenia and consequently present a significant emotional and economic burden to them and the society (Chong et al. 2016, Fett et al. 2011, Kane & Lencz 2008, Rodriguez et al. 2015).

Despite the clinical relevance of neurocognitive decline in schizophrenia, there is a number of uncertainties in the occurrence and progression of these symptoms in schizophrenia. First, it is rather unclear which are the factors influencing neurocognitive decline over time in patients with schizophrenia (SCH). In the current literature, neurocognitive decline over time in SCH was found to be associated with male gender, unemployment, poor premorbid achievement, later age of onset, presence of negative symptoms (Bora 2015, Bora et al. 2009), suicidality (Ventriglio et al. 2016) and lower achievement of stable remission during the first year of illness (On et al. 2016, Rund et al. 2016).

Second, it is unclear whether there are differences in the speed and severity of neurocognitive decline among different neurocognitive functions. Although majority of longitudinal studies report relative stability of neurocognitive decline during the course of illness (Hoff et al. 2005, Rund et al. 2016), some report different changes in specific neurocognitive domains. According to Barder et al. (2013) working memory significantly improved during the first two years of follow-up of patients with first episode of psychosis (FEP), with no further changes in the following three years. However, other authors report decline in some of the domains, e.g. in visuospatial abilities (Stirling et al. 2003) or memory and speed of processing (Øie et al. 2008). Apart from a number of factors that can explain these results, the heterogeneity of assessment methods and applied neurocognitive tests may further contribute to it. Generally, different neurocognitive tests are used for the assessment of specific neurocognitive domains (Mesholam-Gately et al. 2009). In order to avoid multiplication, attempts were made to produce neurocognitive test batteries, for example with The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (Nuechterlein & Green 2006). However, the dimensional structure of these batteries is still not consistently reproduced, at least in the international, European cultural context (Mohn et al. 2017). Thus, the influence of different cultural context on results of psychological tests which are translated from one country to another is not defined.

To overcome these limitations, we conducted this study aiming to construct comprehensive neurocognitive profiles in schizophrenia, by applying a number of individual neurocognitive tests previously used in the Croatian population. Tests assessed five neurocognitive domains in two large different groups of patients with schizophrenia: the patients with the first episode and patients with multiple episodes. Secondly, we attempted to analyze the correlations of obtained profiles with clinical features of patients and their perceived quality of life.

SUBJECTS AND METHODS

Study protocol

This cross-sectional study was conducted at three Croatian hospitals: Zagreb University Hospital Centre, Neuropsychiatric Hospital Dr. Ivan Barbot, and University Psychiatric Hospital Vrapce. It was nested within the prospective cohort study: "Biomarkers in schizophrenia-integration of complementary methods in longitudinal follow up of FEP patients". The power analysis was done for the main prospective cohort study, and it was not conducted specifically for this analysis. Patients were enrolled between June 2015 and January 2017. The study protocol was approved by the Ethics Committees of the participating institutions, and all participants gave their informed consent before the inclusion. The study was conducted in accordance with World Medical Association Declaration of Helsinki 2013 (World Medical Association 2013).

Participants

Participants were recruited proportionally at the participating hospitals until the sample sizes reached 100 participants from each population. Inclusion criteria for FEP were: no history of antipsychotic use prior to admission to hospital, first episode of psychosis with the fulfillment of the criteria for psychotic episode (codes F23, F29) according to the criteria of International Classification of Disorders, 10th revision (ICD-10) (World Health Organization 1992). Inclusion criteria for SCH were: ≥2 acute psychotic episodes, illness duration >5 years and fulfillment of criteria for schizophrenia spectrum disorders (code F20) according to the ICD-10 criteria (World Health Organization 1992). Exclusion criteria for both groups were: <18 years of age, mental retardation, mental illness in childhood that can present with psychosis, neurological disorders, pregnancy and lactation, organic psychosis, the use of medications that can produce psychotic reactions, comorbid alcoholism or other addictions, use of drugs (included were patients who consummated marijuana no more than 3 times a year), psychiatric confinement and legally incapacitated participants. All patients were assessed during the acute phase of the illness at up to three weeks of treatment. The neurocognitive assessment took approximately 60 minutes and solving other questionnaires additional 20 minutes. None of the participants discontinued the assessments. Sociodemographic and clinical characteristics of FEP and SCH are presented in Table 1.

Assessment of participants and expected outcomes

Our primary outcome was the neurocognitive profile in patients with first episode psychosis and patients with schizophrenia. We used Mini Mental Status Examination

Table 1. Patients sociodemographic and clinical characteristics; only cases with complete data on neurocognitive tests

	FEP (n=87)	SCH (n=90)
Sociodemographic characteristics		
Sex		
male	53 (60.9)	47 (52.2)
female	34 (39.1)	43 (47.8)
Age (years), mean (SD)	28 (9.7)	39 (11.0)
Education		
primary	8 (9.2)	13 (14.4)
secondary	50 (57.5)	63 (70.0)
university or students	29 (33.3)	14 (15.6)
Being in a relationship	18 (20.7)	20 (22.2)
Being employed	25 (28.7)	14 (15.6)
Positive family anamnesis	37 (42.5)	39 (43.3)
Clinical characteristics		
Onset of illness (years), mean (SD)	27 (9.8)	28 (9.7)
Antipsychotics		
monotherapy	45 (51.7)	36 (40.0)
combination therapy	42 (48.3)	54 (60.0)
Antipsychotics type*		
1st generation	31 (36.1)	32 (35.0)
2nd generation	82 (94.4)	65 (72.5)
clozapine	8 (9.7)	38 (42.5)
Antidepressants	4 (4.2)	18 (20.0)
Anxiolytics	59 (68.1)	61 (67.5)
Mood stabilizers	8 (9.7)	38 (42.5)

Abbreviations: FEP = patients with first-episode psychosis; SCH = patients with schizophrenia; SD= standard deviation; * Sum exceeds 100% due to the combination therapies Data are presented as number (percentage) of participants if not stated otherwise.

(MMSE) as a screening test for overall cognitive impairment (Folstein et al. 1975). MMSE result was not used in the definition of latent profiles, but as the additional explanatory variable. Neurocognitive profiles were made of five neurocognitive domains assessed with a battery of neurocognitive tests representing specific domains, as described below.

Verbal memory

Verbal memory was assessed by three tests and their subtests: Rey Auditory Verbal Learning Test (RAVLT) (Schmidt 1996), Wechsler verbal paired associates (Wechsler 1945) and Digit span test (Lichtenberger & Kaufman 2009). RAVLT included three subtests: RAVLT A (immediate verbal memory of 15 random words, 5 repeating), RAVLT B (immediate verbal memory of another set of 15 random words) and RAVLT A30' (delayed verbal memory from RAVLT A list after 30 minutes). We used two subtests of Wechsler verbal paired associates (immediate recall of 6 series of verbal paired associates, Wechsler 6, and delayed recall after 30 minutes, Wechsler 30'). Subtests of Digit span test

were Digit span F for forward repeating of series of numbers and Digit span B for backwards repeating of series of numbers.

Executive functions: problem solving and mental flexibility

Executive functions were assessed by Block design test (Block design) (Hutt 1932), Frontal assessment battery (FAB) (Dubois et al. 2000), Clock drawing test (CDT) (Freedman et al. 1994) and subtests of Stroop test (Golden 1976) (Stroop colours, STROOP 2 and Stroop word-colours, STROOP 3) and Trial Making Test (Tombaugh 2004) (Trial making test B, TMTB).

Attention and speed of processing

Attention and speed of processing was assessed by Digit symbol test (Digit symbol) (Lichtenberger & Kaufman 2009), subtest of Stroop Test (Golden 1976) (Stroop words, STROOP 1) and Trail Making Test (Tombaugh 2004) (Trial making test A, TMTA).

Visuospatial abilities and delayed visual recall

Two subtests of Rey-Osterrieth Complex Figure Test (Fastenau et al. 1999) were used for assessment of visuospatial abilities (ROCF) and delayed visual recall after 30 minutes (ROCF 30').

Language functions

Language functions were assessed by two tests: Semantic (category) and Phonetic fluency test (Semantic, Phonetic) (Lichtenberger & Kaufman 2009). Score was calculated from the number of words generated in each category (categories "animals", "vegetables" and "supermarket" for semantic, and letters "a" and "f" for phonetic fluency).

Secondary outcome were correlations of neurocognitive profile in both patient groups with psychopathology and quality of life. Assessments included: 1) clinical rating of symptoms: Positive and Negative Syndrome Scale, PANSS (Kay et al. 1987) and Calgary Depression Scale for Schizophrenia, CDSS (Addington et al. 1990); 2) self-report questionnaires: Inventory of Depressive Symptomatology-Self Report, IDS-SR (Rush et al. 1996), Barrat Impulsiveness Scale-11, BIS-11 (Patton & Stanford 1995), Aggression questionnaire, AQ (Buss & Perry 1992), The Holmes-Rahe Stress Inventory, STRESS (Holmes & Rahe 1967), Questionnaire on suicide ideation and behavior, SUICIDE (Marušič et al. 2007) and World Health Organization Quality of Life Assessment, WHOQOL-BREF (World Health Organization Group 1998).

Statistical analysis

We enrolled 100 FEP and 100 SCH. Data were missing on at least one neurocognitive test in 13 FEP and 10 SCH. Although Little's MCAR test did indicated that data were missing completely at random (χ^2=146.5; df=157; p=0.716) we did a sensitivity analysis on multiply imputed data after the main analysis done on the cases with complete data only.

Table 2. Fit statistics for different models

	LL	np	BIC_{LL}	$CAIC_{LL}$	BLRT	Entropy R^2
FEP (n=87)						
1 profile	-494	10	1033	1043	-	1.00
2 profiles	-419	21	932	953	<0.001	0.85
3 profiles	-377	32	896	928	<0.001	0.89
4 profiles	-359	43	909	952	0.008	0.89
5 profiles	-346	54	933	987	0.068	0.95
SCH (n=90)						
1 profile	-616	10	1278	1288	-	1.00
2 profiles	-535	21	1165	1186	<0.001	0.85
3 profiles	-504	32	1152	1184	<0.001	0.90
4 profiles	-485	43	1164	1207	0.010	0.83
5 profiles	-475	54	1192	1246	0.196	0.86
Similarity between FEP and SCH						
Complete heterogeneity	-939	39	2077	2126		
Within profiles means equal across FEP and SCH	-948	29	2029	2068		
Complete homogeneity	-946	32	2057	2089		

Abbreviations: LL = log-likelihood; np = number of free parameters; BIC = Bayesian information criterion based on log-likelihood; CAIC = Consistent Akaike's information criterion based on log-likelihood; BLRT = bootstrap likelihood ratio test between the model in row and the model in the first row above the tested one

Prior to analysis the results of four cognitive tests measuring time (STROOP, 2, 3, TMT-A, and TMT-B) were reversed by multiplying them with -1 and adding the maximum original value, so that higher values in all tests represent better cognitive functioning. To avoid multicollinearity, local dependence, and to increase reliability of measurements we did a categorical, nonlinear principal component analysis of all tests within each neurocognitive domain. In every domain only one categorical principal component was extracted. We determined the number of components within each domain by parallel analysis (Watkins 2006). In comparison of FEP and SCH we did not perform a testing of statistical significance of the differences because the only purpose of this comparison was the detection of potential confounders of our main result. The main analysis was done by multigroup latent profile analysis of these principal components. In the first step, we analyzed configure equivalence, that is: whether the same number of latent profiles had the best fit to the data in samples from both of our targeted populations. We did this by fitted a one-class model to the data separately in both samples, then increasing the number of classes one by one and fitted each model until no further improvement could be achieved. In the second step, we analyzed the structural similarity, that is: whether the particular neurocognitive tests' results were independent of our targeted populations; whether the profiles were characterized by similar neurocognitive tests' results in both samples; whether the nature of neurocognitive profiles was similar in FEP and SCH samples. We did this by fitting model where the neurocognitive tests results' within-profile means were constrained to be equal across two samples. We evaluated different models fit to the data by lowest Bayesian

information criterion based on log-likelihood (BIC), Consistent Akaike's information criterion based on log-likelihood (CAIC), significant bootstrap likelihood ratio test between the model with k and k-1 profiles (BLRT), and entropy R^2 (Finch 2015). In both FEP and SCH sample, the models with three latent profiles had the best fit to the data (Table 2). Therefore, the configured equivalence was confirmed. The model where the within-profile means were constrained to be equal across the two samples fitted the data better than the completely unconstrained or completely homogenous models. We accessed a local independence by the inspection of bivariate residuals. By the protocol, if>5% of participants have missing data on any neurocognitive test, we planned to do a sensitivity analysis on the data set with multiply imputed data. Multiple imputation was done by fully conditional specification of the iterative Markov chain Monte Carlo method (Rubin 2004). Whether the data were missing completely at random was assessed by Little's MCAR test (Little 1988). The level of statistical significance was set at two-tailed p<0.05 and we gave all confidence intervals at 95% level. Correction for multiple testing was done by sequential Holm-Bonferroni correction. Statistical data analysis was performed by Latent GOLD version 5.1. and NCSS 11 Statistical Software (2016) (NCSS, LLC. Kaysville, Utah, USA).

RESULTS

The structural equivalence of three latent profiles across FEP and SCH samples of patients was confirmed. The three profiles were quantitatively and not qualitatively different (Table 3, Figure 1, Figure 2).

**Table 3.** Univariate description of three neurocognitive profiles

	Profile 1 "Best"	Profile 2 "Medium"	Profile 3 "Worst"
Diagnosis, n (%)			
FEP	35 (40.2)	46 (52.9)	6 (6.9)
SCH	9 (10.0)	41 (45.6)	40 (44.4)
Neurocognitive tests, mean (SD)			
Verbal memory			
RAVLT A	47 (8.7)	34 (9.2)	22 (8.8)
RAVLT B	7 (2.0)	5 (1.6)	4 (2.2)
RAVLT A 30	33 (7.9)	20 (7.3)	13 (7.5)
Wechsler 6	43 (6.1)	38 (8.1)	30 (11.4)
Wechsler 30	8 (0.8)	7 (1.4)	5 (2.2)
Digit span F	12 (0.1)	11 (1.8)	9 (2.2)
Digit span B	10 (2.1)	9 (2.4)	5 (2.2)
Executive functions			
Block design	62 (3.6)	47 (14.5)	33 (15.2)
FAB	18 (0.4)	17 (1.4)	14 (3.2)
STROOP 2	364 (23.3)	328 (46.1)	269 (72.1)
STROOP 3	849 (32.3)	791 (67.1)	687 (183.3)
TMTB	403 (41.1)	347 (74.3)	315 (119.8)
CDT	10 (0.5)	9 (1.5)	6 (2.6)
Attention and speed of processing			
STROOP 1	221 (17.7)	194 (34.6)	152 (53.0)
TMTA	296 (10.3)	276 (26.8)	229 (65.9)
Digit symbol	46 (13.2)	37 (12.2)	21 (8.5)
Visuospatial abilities			
ROCF	35 (2.5)	35 (1.7)	26 (9.8)
ROCF 30	20 (7.1)	13 (7.4)	5 (5.0)
Language functions			
Semantic	51 (10.2)	39 (10.1)	30 (8.6)
Phonetic	17 (4.9)	12 (4.3)	9 (4.6)
Mini Mental Status Examination	29 (0.8)	29 (1.5)	27 (3.0)

Abbreviations: FEP = patients with first-episode psychosis;   SCH = patients with schizophrenia;   SD = standard deviation; RAVLT = Rey Auditory Verbal Learning Test;   Wechsler = Wechsler verbal paired associates;   Digit span F and B = Digit span Forwards and Backwards;   FAB= Frontal assessment battery;   TMTA and TMTB = Trial making test A and B; ROCF = Rey-Osterrieth Complex Figure Test; Semantic = Semantic (category) fluency test;   Phonetic = Phonetic fluency test
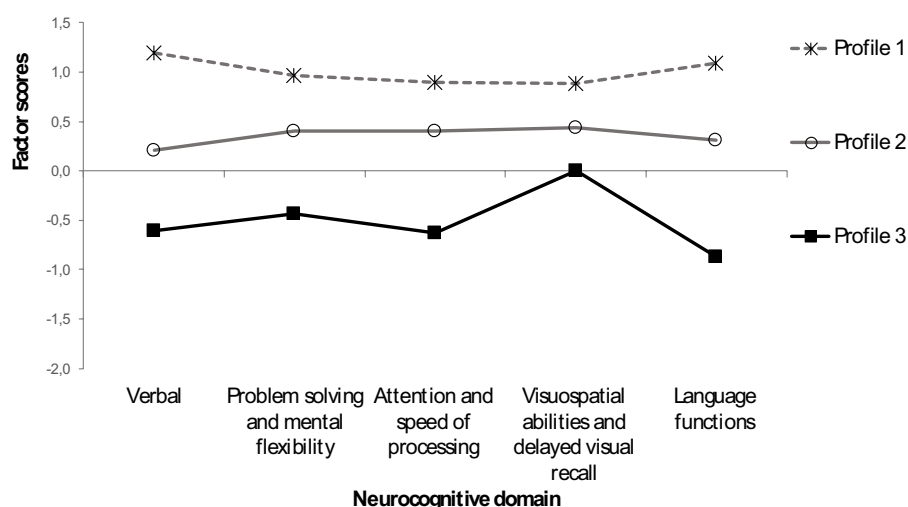
There were no statistically significant differences among the scores of the three neurocognitive profiles in FEP

Figure 1. Neurocognitive profiles in FEP (n=87)
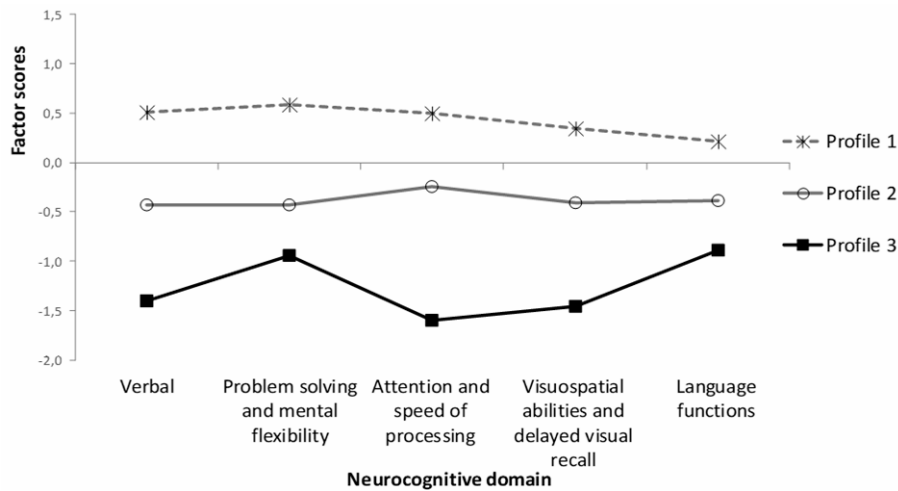
There were no statistically significant differences among the scores of the three neurocognitive profiles in SCH

Figure 2. Neurocognitive profiles in SCH (n=90)

Table 4. Differences in clinical characteristics between three neurocognitive profiles in FEP and SCH adjusted for age and education

| | FEP | | | SCH | | | | | |
	Profile 1 "Best" (n=35)	Profile 2 "Medium" (n=46)	Profile 3 "Worst" (n=6)	Profile 1 "Best" (n=9)	Profile 2 "Medium" (n=41)	Profile 3 "Worst" (n=40)	p_1 diagnosis	p_2 profile	p_3 interaction
PANSS total	100 (23.4)	106 (19.2)	122 (22.2)	85 (20.0)	96 (25.9)	95 (25.1)	*0.002*	0.127	0.401
Positive symptoms	26 (10.3)	28 (6.5)	31 (4.7)	22 (6.6)	23 (10.0)	26 (9.6)	*0.023*	0.504	0.985
Negative symptoms	22 (6.4)	26 (6.8)	33 (7.5)	23 (6.2)	26 (6.8)	26 (7.0)	0.202	*0.010*	0.102
General symptoms	51 (11.0)	52 (9.3)	59 (12.2)	40 (9.1)	46 (12.2)	43 (11.3)	*<0.001*	0.290	0.184
Quality of life									
WHOQOL-BREF total	102 (12.2)	96 (14.1)	101 (17.7)	98 (15.8)	89 (16.4)	91 (18.3)	0.133	0.107	0.904
Physical health	78 (11.7)	71 (16.2)	76 (18.6)	76 (17.9)	61 (20.0)	62 (22.2)	0.165	0.056	0.549
Psychological health	73 (14.4)	65 (20.0)	67 (25.5)	61 (22.4)	57 (20.1)	62 (22.6)	0.118	0.352	0.689
Social relationship	68 (16.6)	58 (22.0)	64 (33.4)	56 (13.1)	55 (23.6)	52 (27.1)	0.066	0.539	0.624
Environment	75 (12.6)	73 (17.7)	78 (14.8)	76 (16.7)	70 (17.2)	72 (20.4)	0.909	0.493	0.921
Suicide	36 (2.8)	36 (2.8)	37 (0.0)	35 (3.0)	35 (3.8)	35 (3.5)	*0.035*	0.834	0.675
BIS total	67 (11.1)	66 (10.3)	63 (7.7)	63 (10.7)	65 (13.8)	62 (10.4)	0.428	0.558	0.867
Attention	11 (1.9)	11 (2.2)	10 (1.0)	10 (2.8)	11 (3.6)	10 (3.3)	0.472	0.763	0.722
Cognitive instability	5.7 (1.64)	5.6 (1.95)	5.8 (1.33)	5.9 (2.57)	5.8 (1.84)	5.8 (2.08)	0.520	0.953	0.997
Motor	14 (3.9)	13 (2.7)	12 (2.9)	13 (4.0)	13 (4.5)	13 (4.5)	0.857	0.540	0.520
Perseverance	8 (2.0)	8 (2.4)	8 (2.0)	8 (1.6)	8 (2.2)	7 (1.9)	0.264	0.460	0.959
Self-control	15 (3.3)	16 (3.5)	15 (2.8)	13 (3.8)	14 (3.8)	13 (2.8)	*0.001*	0.480	0.771
Cognitive complexity	12 (3.0)	12 (2.6)	12 (2.0)	12 (3.2)	14 (3.2)	13 (3.2)			
2nd order									
Attentional	17 (2.9)	17 (3.2)	16 (1.7)	16 (4.0)	17 (5.0)	16 (4.8)	0.848	0.937	0.865
Motor	22 (5.1)	21 (4.0)	19 (3.9)	21 (4.8)	20 (5.4)	20 (4.5)	0.725	0.397	0.709
Non planning	28 (5.7)	28 (5.4)	28 (3.8)	24 (5.7)	27 (6.0)	26 (4.7)	*0.044*	0.336	0.549
Aggression questionnaire	70 (18.4)	76 (23.0)	64 (12.7)	69 (15.1)	74 (16.3)	76 (23.3)	0.475	0.335	0.339
Physical	23 (5.4)	24 (6.7)	21 (5.2)	22 (3.5)	23 (6.1)	23 (8.3)	0.899	0.456	0.648
Verbal	12 (4.0)	14 (4.7)	14 (3.4)	13 (2.9)	14 (3.6)	14 (5.1)	0.176	0.322	0.724
Anger	19 (5.5)	19 (6.3)	16 (4.5)	17 (4.4)	18 (4.7)	18 (5.8)	0.795	0.341	0.506
Hostility	16 (6.4)	19 (8.1)	14 (4.5)	16 (8.2)	18 (6.5)	19 (7.5)	0.301	0.278	0.191
IDS-SR	17 (11.1)	19 (14.7)	12 (12.9)	15 (9.2)	24 (14.5)	25 (16.8)	0.150	0.155	0.222

Data are presented as mean (standard deviation)

Abbreviations: FEP = patients with first episode psychosis;   SCH = patients with schizophrenia;   p = statistical significance of the difference between FEP and SCH adjusted for age; p_1 = statistical significance of the difference between FEP and SCH adjusted for age and education; p_2 = statistical significance of the difference between neurocognitive profiles adjusted for age and education; p_3 = statistical significance of the interaction of diagnosis and the neurocognitive profile, adjusted for age and education;   PANSS = Positive and Negative Syndrome Scale;   WHOQOL-BREF = World Health Organization Quality of Life Assessment;   Suicide = Suicide ideation and behavior scale;   BIS = Barrat Impulsiveness Scale;   IDS-SR = Inventory of Depressive Symptomatology-Self Report

According to mean neurocognitive domains' results we named them: "Best", "Medium", and "Worst". The best neurocognitive profile was significantly more prevalent in FEP, and the worst one in SCH sample. Prevalence of the medium profile was not significantly different between the two targeted populations. After adjustment for all monitored sociodemographic and clinical patients' characteristics by multinomial logistic regression, odds for the medium neurocognitive profile compared to the odds for the best one, were not significantly different between the two samples (FEP OR=0.29; 95% CI 0.07-1.21; p=0.090). However, FEP had significantly lower odds for having the worst neurocognitive profile compared to the odds of having the best one (OR=0.09; 95% CI 0.01-0.59; p=0.013).

We found statistically significant statistical difference in negative PANSS sub-scores between the three neurocognitive profiles adjusted for age and education, with the highest negative symptoms in patients with the "Worst" profile, and the lowest among those with the "Best" profiles, without differences between the FEP and SCH groups. Also, we have not found significant differences in scores of other PANSS sub-scales, quality of life, suicide ideation, impulsiveness, aggression nor depressive symptoms between the three profiles in any of the two samples (Table 4). There was a number of statistically significant differences in the scores of clinical tests between the FEP and SCH sample, as stated in Table 4.

DISCUSSION

When comparing FEP to SCH, we found that three neurocognitive profile models fitted the data the best in both samples. Profile 1 ("Best"), Profile 2 ("Medium") and Profile 3 ("Worst") consisted of five neurocognitive domains (verbal memory, executive functions, attention and speed of processing, visuospatial abilities, language functions) represented with adequate neurocognitive tests. The three profiles were structurally equivalent across FEP and SCH, with differences only in the values of specific neurocognitive tests. All profile scores reflecting results were significantly better in FEP compared to SCH. Profile 3 was more frequent among SCH group and Profile 1 among FEP group. We have not found any statistically significant differences in the level of impairment among specific neurocognitive domains across the sample, but rather an overall decrease of neurocognitive abilities.

Our results may possibly indicate that the difference in neurocognitive profiles between FEP and SCH are quantitative rather than qualitative. In other words, the nature of neurocognitive deficit might not change further after the onset of psychosis, but it may reflect a certain trait of the illness that may be present in an attenuated form from the beginning of the illness. This is in line with neurodevelopmental theory of schizophrenia with the core neurocognitive symptoms as results of aberrations during the development of the brain starting even before the illness onset (Bora 2015, Bora & Murray 2014). According to previous literature, mild neurocognitive deficits are present in the persons at risk for developing psychosis compared to healthy control groups (Fusar-Poli et al. 2012, Lencz et al. 2006), but in lower intensity compared to persons with developed, full-blown psychosis in both first episode or developed illness (Corigliano et al. 2014). Although some authors report less impairment in FEP when compared to SCH, at least on some cognitive tests (Addington & Addington 2002, Braw et al. 2007, Townsend & Norman 2004), the majority of previous studies show that further development of neurocognitive deficits after the illness onset is relatively stable, with similar impairments in FEP and SCH (Corigliano et al. 2014, Mesholam-Gately et al. 2009). McCleery et al. (2014) report subtle differences when comparing these patient groups with healthy controls (e.g. better results in working memory and social cognition in FEP than in SCH), but state that the overall distribution of impairment did not statistically defer between FEP and SCH group. Our results also reflect this stability with structurally identical neurocognitive profiles presented in both patient groups. It seems that after the illness onset, during the acute phase of first episode of psychosis, the full range of neurocognitive deficits is present in the same form as it is later during the course of schizophrenia.

As all neurocognitive domains show deficits in all three profiles and in both patient groups, our results may indicate a diffuse, rather than a specific localized impairment. This is partially in line with previous studies. Although majority of them agree that there is an overall neurocognitive deficit, part of the authors point out some more specific impairments. For example, some studies highlight that speed of processing is more impaired than other domains in both FEP and SCH (McCleery et al. 2014), or suggest that this domain underlies other neurocognitive deficits in schizophrenia as a limiting factor for overall cognitive performance (Dickinson et al. 2007, Ojeda et al. 2012). Besides speed of processing, Mesholam-Gately's et al. meta-analysis (2009) reports impairment in immediate verbal memory as a possible domain specific deficit in FEP, along with diffuse impairment. Henry's et al. meta-analysis suggests higher deficits of semantic store in schizophrenia (Henry & Crawford 2005), while some other studies mention executive functions or working memory (Braw et al. 2007, Gonzalez-Ortega et al. 2013). These specific differences could be the result of heterogeneity of measures used for assessment in previous studies, with some tests possibly being more sensitive than others. Furthermore, patient samples differed across studies regarding e.g. duration of illness or treatment, phase of the illness (acute phase, remission) or recruitment type (outpatients, hospitalized patients etc.).

Although we have not found statistically significant specific domain deficits, we did observe differences in the level of impairment among specific neurocognitive domains in patients with "Worst" profile, especially among SCH, with a higher level of impairment in attention, speed of processing, visuospatial abilities and delayed visual recall. This may possibly reflect specific subgroup of patients who are characterized by more severe symptoms from their first episode. Additionally, we found significant differences in negative symptom scores between the three neurocognitive profiles, with the "Worst" profile having the highest scores on negative PANSS in patients without significant differences between FEP and SCH samples. Consequently, more severe specific neurocognitive deficits along with higher levels of negative symptoms at the beginning of illness may contribute to poorer treatment response or overall outcome of treatment in the later period in these patients. This was previously reported in literature, e. g. Milev et al. (2005) reported significant correlations between poorer neurocognitive performance in different cognitive domains and the severity of negative symptoms and recent meta-analysis by Bora & Murray (2014) reported association of the persistence of negative symptoms with lack of improvement in neurocognitive functions at follow-up. In accordance with this studies, FEP and SCH with "Worst" profile and higher negative symptoms may be especially vulnerable and may require more of differently tailored treatment approaches including specific cognitive training methods (cognitive remediation, metacognitive training, additional pharmacological agents) from the beginning of the treatment compared to FEP or SCH with "Best" neurocognitive profile.

Besides significant differences among profiles regarding negative symptoms, we found no such differences regarding other psychotic symptoms in neither of our two samples of patients. This is concordant with schizophrenia literature. Previous studies generally agree that there are no correlations between neurocognition and positive symptoms (de Gracia Dominguez et al. 2009, Dibben et al. 2009, Ventura et al. 2009), and only minority of them showed connection with other symptoms like disorganization (Nieuwenstein et al. 2001, Ventura et al. 2010). However, our results showed no statistically significant differences between the three profiles with self-measurement scales for quality of life, aggression, depression, suicidality and impulsiveness. This is somewhat inconsistent with some of the previous studies that found that neurocognitive deficits in various domains significantly correlated with perceived quality of life (Rodriguez et al. 2015), suicidality (Ventriglio et al. 2016), impulsivity or aggression (Reinharth et al. 2014). Possible explanation could be the difference in the study method, as we investigated the correlations

of clinical features with the whole neurocognitive profile of single patient and not with specific neurocognitive tests and on a group level. Another explanation is in the use of self-measurement scales in our and other studies that could be biased due to different reasons, e.g. misunderstanding, exaggerating or due to social-desirability bias.

The main limitation of our study is cross-sectional design due to which we could only describe the difference between two samples assessed at the different points during the disease life-span. We have no proves that our current SCH sample will be representative for the neurocognitive profile of our FEP sample in 10 years, nor that our current FEP sample was representative for the neurocognitive profile of our SCH sample 10 years ago. Our sample may not be treated as representative for the entire Croatian population of FEP nor SCH, although there is no ground for the assumption that characteristics of our sample are systematically different in different regions of the country. Due to age differences between our FEP and SCH group, we adjusted the analysis for age, but we cannot exclude the effects of other factors not included in the study analysis, such as illness duration or medication on neurocognitive status of our patients. Another limitation is that a part of our assessments (for quality of life, suicidality, impulsiveness and aggression) are self-measurement questionnaires which results could be potentially biased at some level.

CONCLUSIONS

Presented in a profile manner, neurocognitive differences between FEP and SCH seem to be more of a quantitative than of qualitative nature, suggesting that neurocognitive symptoms are specific trait of illness, present since its beginning and progressing over time. There is a significant association of the three neurocognitive profiles with negative symptoms: patients with the "Best" profiles have the lowest negative symptoms, and those with the "Worst" profile have the highest negative symptom scores, regardless of the number of psychotic episodes (first-episode or multi-episode). There is no association between the three neurocognitive profiles with other psychotic symptoms and clinical features. Putting it into the clinical context, patients who present with the worst neurocognitive profile in the first episode may also have severe negative symptoms and possible be of particular risk for further neurocognitive decline. Thus, definition of neurocognitive profiles can help tailoring individualized treatment options. Special focus and treating with methods specifically designed for neurocognitive and negative symptoms (e.g. cognitive remediation) may possibly influence treatment outcome and warrant further investigation.

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Contribution of individual authors:

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