Disorganization and real-world functioning in schizophrenia: Results from the multicenter study of the Italian Network for Research on Psychoses

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P. Rocca [a,*], S. Galderisi [b], A. Rossi [c], A. Bertolino [d], P. Rucci [e], D. Gibertoni [e], C. Montemagni [a], S. Bellino [a], E. Aguglia [f], M. Amore [g], A. Bellomo [h], M. Biondi [i], B. Carpiniello [j], A. Cuomo [k], E. D'Ambrosio [d], L. dell'Osso [l], P. Girardi [m], C. Marchesi [n], P. Monteleone [o], C. Montemitro [p], L. Oldani [q], F. Pacitti [c], R. Roncone [r], A. Siracusano [s], E. Tenconi [t], A. Vita [u], P. Zeppegno [v], L. Steardo Jr [b], A. Vignapiano [b], M. Maj [b]

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[1] *University of Turin*

[2] *University of Bari*

[3] *University of Brescia*

[4] *University of Cagliari*

[5] *University of Catania*

[6] *University of Chieti*

[7] *University of Foggia*

[8] *University of Genoa*

[9] *University of L'Aquila*

[10] *Campania University Luigi Vanvitelli*

[11] *University of Naples Federico II*

[12] *University of Eastern Piedmont, Novara*

[13] *University of Milan*

[14] *University of Padua*

[15] *University of Parma*

[16] *University of Pisa*

[17] *Sapienza University of Rome*

[18] *Tor Vergata University of Rome*

[19] *Department of Mental Health, Salerno*

[20] *University of Siena*

[a] *Department of Neuroscience, Section of Psychiatry, University of Turin, Turin, Italy*

[b] *Department of Psychiatry, Campania University Luigi Vanvitelli, Naples, Italy*
[c] *Department of Biotechnological and Applied Clinical Sciences, Section of Psychiatry, University of L'Aquila, L'Aquila, Italy*
[d] *Department of Neurological and Psychiatric Sciences, University of Bari, Bari, Italy*
[e] *Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy*

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* Corresponding author at: Department of Neuroscience, Psychiatric Section, University of Turin, Via Cherasco 11, 10126 Turin, Italy.
E-mail address: paola.rocca@unito.it (P. Rocca).

Abstract

Background: A general consensus has not yet been reached regarding the role of disorganization symptoms in real-world functioning in schizophrenia.

Methods: We used structural equations modeling (SEM) to analyze the direct and indirect associations between disorganization and real-world functioning assessed through the Specific Levels of Functioning Scale (SLOF) in 880 subjects with schizophrenia.

Results: We found that: 1) conceptual disorganization was directly and strongly connected with SLOF daily activities; difficulty in abstract thinking was associated with moderate strength to all SLOF domains, and poor attention was connected with SLOF work skills; 2) grandiosity was only related with poor work skills, and delusions were associated with poor functioning in all SLOF domains; interpersonal relationships were weakly indirectly influenced by hallucinatory behavior, delusions and unusual thought contents through the mediation of social cognition (SC); 3) among the negative symptoms, avolition had only direct links with SLOF work skills and SLOF activities; anhedonia had direct links with SLOF work skills and SLOF interpersonal and indirect link with SLOF work skills through functional capacity (FC); asociality with SLOF interpersonal; blunted affect had direct links with SLOF activities and indirect links with SLOF interpersonal relationships mediated by SC. Lastly, alogia had only indirect links mediated by SC, FC, and neurocognition (NC).

Conclusions: Overall conceptual disorganization is the symptom that contributed more (both

directly and indirectly) to the activities of community living in real-world. Thus, it should be considered as a treatment target in intervention programs for patients with schizophrenia.

1. Introduction

It is now well established that neurocognition (NC) and patients' real-life functioning are associated in schizophrenia (Galderisi et al., 2014; Green, 1996; Green et al., 2000) and compelling evidence indicates that deficits in social cognition (SC) (Brekke et al., 2005; Couture et al., 2006; Galderisi et al., 2014; Horton and Silverstein, 2008; Schmidt et al., 2011; Yager and Ehmann, 2006) and functional capacity (FC) (Galderisi et al., 2014) mediate this relationship. Moreover, in the most recent study of the Italian Network for Research on Psychoses (NIRP) (Galderisi et al., 2014) using network analysis, we found that FC is the node that links NC and SC with real-life functioning nodes, in particular with everyday life skills, such as household activities, handling of personal finances, and use of the telephone or public transportation. SC is highly interconnected with NC, and both nodes show a strong link with FC and, through FC, with real-life functioning. SC may reflect a higher-order cognitive function that is dependent on more basic non-social cognitive processes (Green and Nuechterlein, 1999; Penn et al., 1999). Both NC and FC assess patients' capability of performing tasks and/or behaviors in a standardized setting, however tests of FC do so in more “ecological” way, i.e., simulating everyday life tasks (Bowie et al., 2008a; Patterson and Mausbach, 2010). In the first study of NIRP, we have found that SC and FC also mediate the impact of positive and negative symptoms on real-life-functioning in subjects with schizophrenia (Galderisi et al., 2014). One important factor that has received increasing attention in schizophrenia is disorganization. Disorganization symptoms, which reflect a characteristic, underlying dimension close to the core of the illness, are inversely associated with long-term functioning (Evans et al., 2004; Galderisi et al., 2014; Shenton et al., 1992; Smith et al., 2002) and proved to be a strong predictor of community function (Norman et al., 1999; Ventura et al., 2009). Ventura et al. (2010) hypothesized that the close link between disorganization and functional outcomes may be due to the impact of disorganization symptoms on communication and social interactions, as well as to the lack of compensatory mechanisms. Moreover, it has been suggested that symptoms such as incoherent thinking

and speech can "mask" delusions and hallucinations (including imperative "voices") (Nestsiarovich et al., 2017). However, disorganization remains the least studied of the three psychopathological dimensions of schizophrenia (positive symptoms, negative symptoms and disorganization). As regards their relationship with NC, it has been suggested that disorganization symptoms, which are more strongly related to NC than reality distortion or negative symptoms (Hamm et al., 2012; Ventura et al., 2010, 2013a), are an integral link in cognitive pathways (Minor and Lysaker, 2014). Assessing the links between disorganization and NC presents multiple challenges that must be solved in order to provide robust findings. The methodology employed must control for the effects of other covariates, i.e., positive symptoms, and must be able to estimate the effects of each individual disorganization symptoms on NC. Indeed, research based on this topic is complicated, on one hand, by the fact that many studies combined "reality distortion" and "disorganization" to form the positive cluster (Crow, 1980), not clarifying which symptom has the most relevant impact on NC. On the other hand, the possible overlap of two out of three items of the disorganization factor (defined according the consensus 5-factor solution proposed by Wallwork et al., 2012), i.e., "difficulties in abstract thinking" and "poor attention", with NC impairment should be pointed out. Indeed, in a previous study of the Italian Network for Research on Psychoses (NIRP) (Galderisi et al., 2014), both NC and disorganization showed a similar significant pattern of inverse association with real-world functioning, through FC and SC. Lastly, whereas there is some consensus that cognitive abilities encompassing linking and appraising information, verbal and visual learning and memory, working memory, speed of processing and attention as well as reasoning and problem solving are most relevant to functioning (Kurtz et al., 2015) and are currently considered the most significant predictors of functional status in schizophrenia (Bechi et al., 2017; Best et al., 2014; Bowie et al., 2008b; Green, 1996), no consensus has been reached with regard to disorganization symptoms. What mentioned above suggests the need to discriminate the effect of disorganization in schizophrenia on NC, SC, FC and on the functional outcome from the effects of negative and positive symptoms. To this aim, we designed and empirically tested a structural equations model in which NC, FC and SC mediate the relationship between disorganization and real-world functioning, as assessed using the Specific Levels of Functioning Scale (SLOF) (Mucci et al., 2014; Schneider and Struening, 1983), controlling for positive and negative symptoms. Structural equations models, at odds with network analysis, rely on an a priori model of cause-

effect relationships and address the issue of mediation effects. This study differed from the first NIRP study (Galderisi et al., 2014) on three main points. First, we placed NC (together with FC and SC) as a mediator of the relationship between disorganization and SLOF. Second, we targeted specific positive, negative, and disorganization symptoms, instead of positive, negative, and disorganization dimensions. Third, we focused on specific SLOF domains, whereas in the previous study SLOF was modeled as a latent variable, which is considered as a good strategy, but also might obscure some important findings.

2. Methods

2.1. Study population

The study was conducted in a large representative sample of patients with schizophrenia participating in the multicenter study of the Italian Network for Research on Psychoses (NIRP, Galderisi et al., 2014). Inclusion criteria were a diagnosis of schizophrenia according to DSM-IV, confirmed with the Structured Clinical Interview for DSM-IV - Patient version (SCID-I-P), and an age between 18 and 66 years. Exclusion criteria were: a history of head trauma with loss of consciousness; a history of moderate to severe intellectual disability or neurological diseases; a history of alcohol and/or substance abuse in the last six months; current pregnancy or lactation; inability to provide an informed consent; treatment modifications and/or hospitalization due to symptom exacerbation in the last three months. All patients signed a written informed consent to participate after receiving a comprehensive explanation of the study procedures and goals. Approval of the study protocol was obtained from the Local Ethics Committees of each participating center.

2.2. Assessments

The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to rate symptom severity. Disorganization was assessed using three items of the PANSS scale: P2 (conceptual disorganization), N5 (difficulty in abstract thinking), and G11 (poor attention). Positive symptoms were

assessed using four items of the PANSS: P1 (delusions), P3 (hallucinatory behavior), P5 (grandiosity), G9 (unusual thought content). We used the consensus 5-factor solution proposed by Wallwork et al., 2012 (55). Negative symptoms were assessed using the Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011), which includes 13 items, rated from 0 (normal) to 6 (most impaired), and five negative symptoms domains: anhedonia, asociality, avolition, blunted affect and alogia. A scale total score is calculated by summing the 13 individual items; subscale scores are calculated by summing the individual items within each subscale. The BNSS has possible total scores ranging from 0 to 78.The Italian version of the scale was validated as part of the Italian Network for Research on Psychoses activities (Mucci et al., 2015). NC was measured according to the 7 cognitive domains of the MATRICS Consensus Cognitive Battery (MCCB) (Kern et al., 2008; Nuechterlein et al., 2008), derived from scores on 10 cognitive measures: speed of processing (Trail Making Test Part A; Brief Assessment of Cognition in Schizophrenia: Symbol coding; Category fluency test, animal naming), attention/vigilance (Continuous Performance Test: Identical Pairs), working memory (Wechsler Memory Scale, spatial span subset; Letter Number Span test), verbal learning (refers to immediate verbal memory, Hopkins Verbal Learning Test (HVLT)-Revised, immediate recall), visual learning (refers to immediate visual memory, Brief Visuospatial Memory Test-Revised), reasoning and problem solving (Neuropsychological Assessment Battery (NAB), mazes subtest). The assessment of SC included a test contained in the MCCB: the Mayer Salovey Caruso Emotional Intelligence Test (MSCEIT) (Mayer et al., 2002), managing emotion section, which examines the regulation of emotions in oneself and in one's relationships with others by presenting vignettes of various situations, along with ways to cope with the emotions depicted in these vignettes. It was integrated by the Facial Emotion Identification Test (FEIT) (Kerr and Neale, 1993), which examines emotion perception, and The Awareness of Social Inference Test (TASIT) (McDonald et al., 2006), which is a TOM test consisting of 7 scales (positive emotions, negative emotions, sincere, simple sarcasm, paradoxical sarcasm, sarcasm enriched, lie), organized into three sections: Emotion recognition; Social Inference (minimal); Social Inference (enriched). The manual of the TASIT was translated into Italian by a psychiatrist of the Department of Psychiatry of the University of Campania Luigi Vanvitelli, Naples, who gained experience in the use of the English version of the instrument during his stage at the Department of Psychiatry and Biobehavioral Sciences at University of California, Los Angeles (UCLA), as part of his

PhD Course. The videotaped vignettes of the TASIT were dubbed in Italian at the Fono Roma Studios (www. fonoroma.com), a prestigious society in the field of film industry. As to the FEIT, the adaptation of the Italian version required the translations of the six emotions reported on the screen above the stimuli. Functional capacity was assessed using the short version of the University of California San Diego (UCSD) Performance-based Skills Assessment Brief (UPSA-B) (Mausbach et al., 2007), a performance-based instrument that assesses "financial skills" and "communication skills". Participants receive scaled scores for each of the subscales (range = 0–50), which are summed to create an overall score ranging from 0 to 100. Higher scores indicate better functional capacity. Real-life functioning was measured using the Specific Levels of Functioning Scale (SLOF) (Montemagni et al., 2015; Mucci et al., 2014; Schneider and Struening, 1983). The original SLOF is a 43-item selfor informant-rated scale of a person's behavior and functioning which was abbreviated to assess the following domains: Interpersonal Functioning (e.g., initiating, accepting and maintaining social contacts; effectively communicating), Independent participation in Everyday Activities (shopping, using telephone, paying bills, use of leisure time, use of public transportation), and Vocational Functioning (e.g., employable skills, level of supervision required to complete tasks, ability to stay on task, completes tasks, punctuality). The dependent variables for the statistical analyses were the scores on these three different subscales. We did not attempt to generate an overall composite score because our previous studies with this scale suggested that the subscales were differentially correlated with real-world functional milestones (Harvey et al., 2011) and our interest was to identify a predictor model aimed at identifying the predictors of each aspect of functioning. The SLOF consists of 43 items. Each of the questions is rated on a 5-point Likert scale, indicating the level of assistance the participant needs to perform the task, with higher score indicating better functioning. Scores on the instrument range from 43 to 215. Three scales were used (working abilities, interpersonal relationships, and community activities), that are the most informative for patients with schizophrenia. The SLOF was endorsed by the panel of experts involved in the Validation of Everyday Real-Life Outcomes (VALERO) initiative as a suitable measure of reallife functioning (Harvey et al., 2011; Leifker et al., 2011). The SLOF differs from the other outcome measures in emphasizing patient's current functioning and observable behavior, as opposed to inferred mental or emotional states, and focuses on a person's skills, assets, and abilities rather than deficits that once served as the central paradigm guiding assessment and intervention

for persons with disabilities. Moreover, the SLOF does not include items relevant to psychiatric symptomatology or NC dysfunctions.

Table 2
Standardized direct, indirect and total effects on SLOF estimated by the SEM model.

	SLOF interpersonal relationships			SLOF activities			SLOF work		
	Direct effect	Indirect effects	Total effect	Direct effect	Indirect effects	Total effect	Direct effect	Indirect effects	Total effect
Disorganization									
Conceptual disorganization	–	−0.023**	−0.023**	−0.150***	−0.072***	−0.222***	–	−0.056***	−0.056***
Difficulty in abstract thinking	–	−0.044***	−0.044***	–	−0.097***	−0.097***	–	−0.083***	−0.083***
Poor attention	–	−0.016*	−0.016*	–	−0.045**	−0.045**	−0.068*	−0.040**	−0.109***
Negative symptoms									
Avolition	–	–	–	−0.085**	–	−0.085**	−0.122***	–	−0.122***
Anhedonia	−0.121**	–	−0.121**	–	0.020*	0.020*	−0.113**	0.009	−0.104**
Asociality	−0.338***	–	−0.338***	–	–	–	–	–	–
Alogia	–	−0.024**	−0.024**	–	−0.087***	−0.087***	–	0.066***	0.066***
Blunted affect	–	0.020*	0.020*	−0.102**	0.014	−0.089*	–	0.017	0.017
Positive symptoms									
Delusions	−0.077**	−0.019*	−0.096***	−0.082**	−0.013	−0.095***	−0.124***	−0.016*	−0.140***
Hallucinatory behavior	–	−0.016**	−0.016**	–	−0.011	−0.011	–	−0.014*	−0.014*
Grandiosity	–	–	–	–	–	–	−0.068*	–	−0.068*
Unusual thought content	–	0.026**	0.026**	–	0.018*	0.018*	–	0.022*	0.022*
Social cognition	0.165***		0.165***	0.114*		0.114*	0.140**		0.140**
Functional capacity				0.248***		0.248***	0.110**		0.110**
Neurocognition				0.109*		0.109*	0.134*		0.134*

The figures reported in the table are standardized linear regression coefficients. Abbreviations: SLOF – Specific Levels of Functioning.
* Significant for $p < 0.05$.
** Significant for $p < 0.01$.
*** Significant for $p < 0.001$.

Patient characteristics.

Socio-demographic variables	n	Mean ± sd	Min; max
Gender (% male)	919	69.6	
Age (years, mean ± sd)	919	40.1 ± 10.7	18;66
Education (years, mean ± sd)	917	11.6 ± 3.4	5; 23
Duration of illness (years, mean ± sd)	915	16.8 ± 10.7	0; 51
Antipsychotic treatment (%)	919		
First generation		14.3	
Second generation		68.5	
Both		14.0	
None		3.2	
Integrated treatment (%)	919	26.9	
Illness-related variables		Mean ± sd	Min; max
PANSS P1 (delusions)	919	3.03 ± 1.64	1;7
PANSS P3 (hallucinatory behavior)	919	2.11 ± 1.48	1;7
PANSS P5 (grandiosity)	919	1.80 ± 1.28	1;7
PANSS G9 (unusual thought content)	919	2.87 ± 1.58	1;7
PANSS P2 (conceptual disorganization)	919	2.67 ± 1.48	1;7
PANSS G11 (poor attention)	919	2.54 ± 1.41	1;7
PANSS N5 (difficulty in abstract thinking)	919	3.35 ± 1.62	1;7
BNSS anhedonia	919	8.63 ± 4.54	0;18
BNSS asociality	919	6.34 ± 3.02	0;12
BNSS avolition (apathy)	919	5.69 ± 3.16	0;15
BNSS blunted affect	919	8.05 ± 5.03	0;18
BNSS alogia	919	4.79 ± 3.52	0;18
TMT (total time)	905	65.76 ± 45.63	15;300
BACS SC (correct responses)	903	31.51 ± 13.24	0;96
Fluency (number of animal names)	906	16.51; 5.71	0;47
CPT-IP (D Prime average)	880	1.67 ± 0.82	−0.39;4.03
WMS-III SS (correct sequences)	906	12.30 ± 4.07	1;26
LNS (correct responses)	906	10.43 ± 4.20	0;21
HVLT-R (correct recalls)	906	19.01 ± 5.56	0;35
BVMT-R (total score)	902	16.34 ± 8.83	0;36
NAB mazes (total score)	902	9.66 ± 6.45	0;26
TASIT Sect. 1 (correct items)	901	19.87 ± 5.14	0;28
TASIT Sect. 2 (correct items)	900	37.19 ± 11.26	0;60
TASIT Sect. 3 (correct items)	899	37.76 ± 11.72	0;64
FEIT (correct responses)	821	36.82 ± 8.47	7;53
MSCEIT	907	78.50 ± 9.02	54.6; 109.2
Functioning		Mean ± sd	Min; max
SLOF activities	907	45.91 ± 8.56	11; 55
SLOF work	913	20.00 ± 6.19	6; 30
SLOF interpersonal relationships	917	22.31 ± 6.06	7;35

PANSS – Positive and Negative Syndrome Scale, BNSS – Brief Negative Symptom Scale, TMT – Trail Making Test - Part A, BACS SC – Brief Assessment of Cognition in Schizophrenia Symbol Coding, Fluency – Category Fluency, Animal Naming, CPT-IP – Continuous Performance Test, Identical Pairs, WMS-III SS – Wechsler Memory Scale Spatial Span, LNS – Letter-Number Span, HVLT-R – Hopkins Verbal Learning Test -Revised, BVMT-R – Brief Visuospatial Memory Test - Revised, NAB – Neuropsychological Assessment Battery, TASIT – The Awareness of Social Inference Test, FEIT – Facial Emotion Identification Test, MSCEIT – Mayer-Salovey-Caruso Emotional Intelligence, SLOF – Specific Levels of Functioning.

2.3. *Statistical analysis*

We used structural equation modeling (SEM) to analyze the fit to the data of a theoretical model positing that the relationship of disorganization, positive and negative symptoms with SLOF is mediated by NC, functional capacity and SC. Social cognition was defined as a latent construct based on the 3 TASIT scales, the FEIT scale and the MSCEIT scale. All measures with the exception of the SLOF scales were standardized: the PANSS scales were internally standardized, while the NC, SC and UPSA-B scales were standardized to the national normative sample obtained by the NIRP project. The strength of the relationships between pairs of variables in a SEM model is quantified by regression coefficients. When two variables are directly connected to each other, the regression coefficient denotes a direct effect. When the relationship between a variable X and the outcome Y involves one or more additional variables acting as mediators (M), then X may influence Y also through the indirect effect of the pathway $X \rightarrow M \rightarrow Y$. The simplest indirect effect includes two direct effects (e.g. $\beta_{XM,}$ from X to the mediator M and β_{MY}, from the mediator M to Y) and is computed as the product of the direct effect coefficients (e.g. $\beta_{XM} * \beta_{MY}$). Indirect effects from one variable to an outcome may be several, when different mediators exist. Therefore, by indirect effects we mean the sum of all specific indirect effects connecting two variables. Finally, the total effect of a variable X on the outcome Y is the sum of the direct effect and of all indirect effects. To allow comparison of effects, we reported them as standardized linear regression coefficients. All clinically plausible direct effects were initially tested, and those resulting non-significant (p N 0.05) were removed one by one to obtain a final parsimonious model. Variables that during the trimming process had no significant outgoing direct effects were removed from the model. Correlations between items associated to the same latent factor, between mediators and between SLOF outcomes that exceeded 0.20 were added in order to improve model fit. SEM rely on several goodness of fit indicators to determine the adequacy of model fit to the data. The Comparative Fit Index (CFI) measures the discrepancy function between the estimated and the theoretical model adjusted for sample size. It ranges from 0 to 1 with a larger value indicating better model fit: a CFI value N0.90 denotes an acceptable model fit. The Root Mean Square Error of Approximation (RMSEA) is related to the model residuals; its values range from 0 to 1 with a smaller

RMSEA value indicating better model fit. Acceptable model fit is indicated by an RMSEA value of 0.05 or less. In the graphical representation of the model, solid lines denote positive associations between variables and dotted lines denote negative associations. The thickness of lines was proportional to the strength of the association between variables, so that thin lines denoted weak associations and thick lines moderately strong associations. To enhance readability, we split the SEM model into three figures, one for each symptom domain. It should be noted that this is just a graphical expedient, because only one SEM model including simultaneously all domains was fit.

Analyses were carried out using Stata, version 13.1, and Mplus, version 7.4.

3. Results

The study population consists of 921 patients with schizophrenia participating in the NIRP study, who completed all the assessment procedures. Table 1 provides summary statistics for patient characteristics and item/scale scores. One patient with missing data in all PANSS items and one patient with missing data in all SLOF variables were excluded from the SEM analysis. Missing data of SC and NC items, FC and of single SLOF variables were estimated during SEM analysis with maximum likelihood estimation.

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Poor attention	–	−0.016*	−0.016*	–	−0.045**	−0.045**	−0.068*	−0.040**	−0.109***
Negative symptoms									
Avolition	–	–	–	−0.085**	–	−0.085**	−0.122***	–	−0.122***
Anhedonia	−0.121**	–	−0.121**	–	0.020*	0.020*	−0.113**	0.009	−0.104**
Asociality	−0.338***	–	−0.338***	–	–	–	–	–	–
Alogia	–	−0.024**	−0.024**	–	−0.087***	−0.087***	–	0.066***	0.066***
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** Significant for $p < 0.01$.
*** Significant for $p < 0.001$.

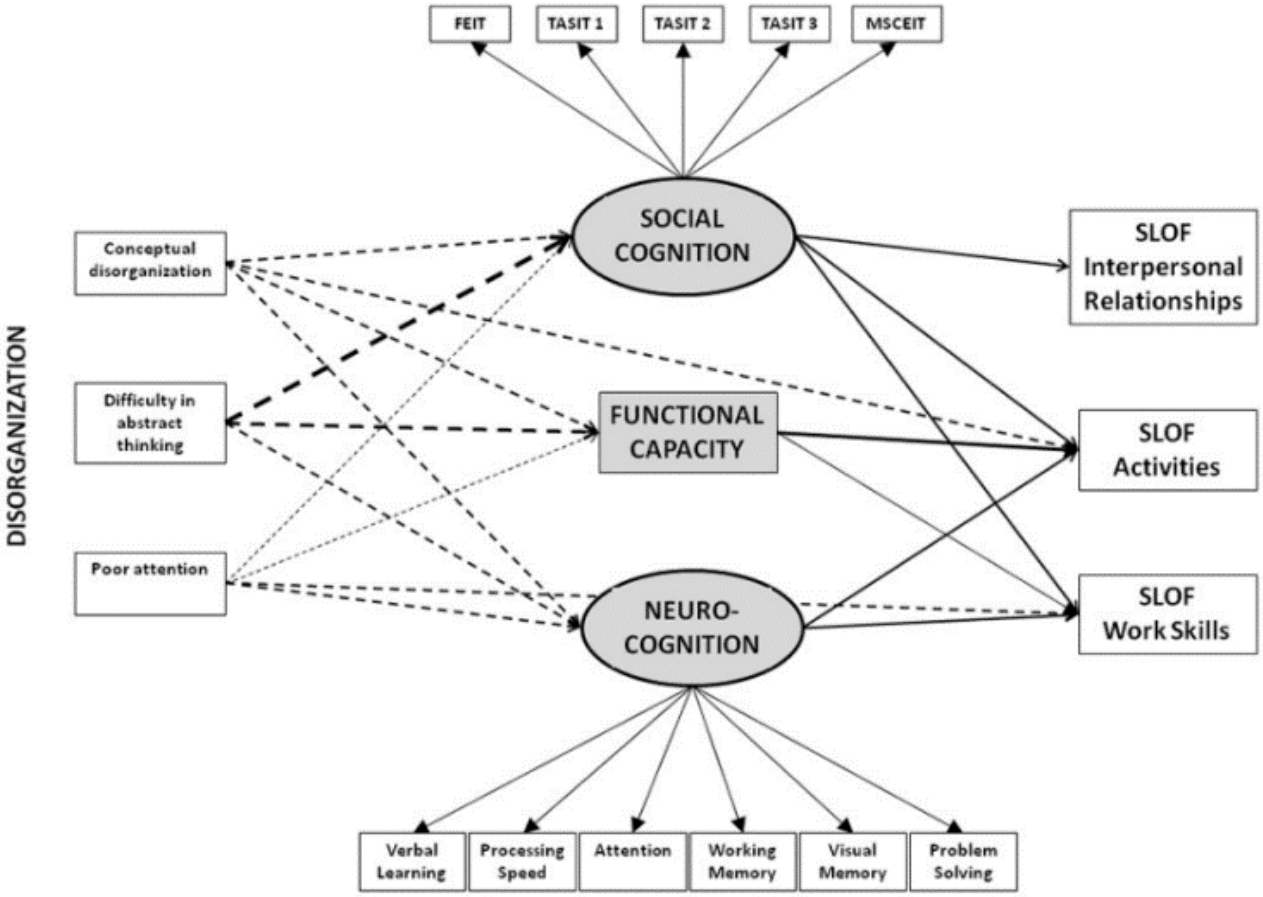
The SEM model showed a very good fit to the data based on information from each indicator: RMSEA 0.029, CFI 0.972, TLI 0.965. All disorganization items had significant direct relationships with all the SLOF domains, or indirect relationships mediated by SC, FC and NC (Table 2; Fig. 1). Positive and negative symptoms were connected only to specific functioning domains, except for delusions, anhedonia and alogia. Specifically, conceptual disorganization was directly and strongly connected with SLOF daily activities, difficulty in abstract thinking was associated with moderate strength to all SLOF domains and poor attention was connected with SLOF work skills. On the contrary, positive symptoms exhibited a limited number of weak direct associations with SLOF domains. In particular, grandiosity was only related with poor work skills, while delusions were associated with poor functioning in all SLOF domains. Interpersonal relationships were (weakly) indirectly influenced by hallucinatory behavior, delusions and unusual thought content through the mediation of SC. Notably, among the five negative symptoms, avolition had only direct links with SLOF work skills and SLOF activities; anhedonia had direct links with SLOF work skills and SLOF interpersonal and an indirect link with SLOF work skills through FC; asociality with SLOF interpersonal; blunted affect had direct links with SLOF activities and indirect links with SLOF interpersonal relationships mediated by SC. Lastly, alogia had only indirect links mediated by SC, FC, and NC. The SLOF community activities scale was the one with the highest percentage of variance explained by the model (37.2%) and was more strongly related with conceptual disorganization ($\beta = -0.150$, p b 0.001) than with BNSS_avolition ($\beta = -0.085$, $p = 0.010$) or BNSS blunted affect ($\beta = -0.102$, $p = 0.003$) and delusions ($\beta = -0.082$, $p = 0.006$). The SLOF interpersonal relationships scale was the one with the lowest explained variance (25.8%) and was strongly related with asociality ($\beta = -0.338$, p b 0.001), anhedonia ($\beta = -0.121$, $p = 0.002$), and delusions ($\beta = -0.077$, $p = 0.009$). The SLOF work skills had 29.4% of variance explained by the model and was strongly related to delusions ($\beta = -0.124$, p b 0.001), avolition ($\beta = -0.122$, $p = 0.001$), anhedonia ($\beta = -0.113$, $p = 0.002$), grandiosity ($\beta = -0.068$, $p = 0.025$), and poor attention ($\beta = -0.068$, $p = 0.028$). Lastly, strong correlations were found between NC and SC ($r = 0.648$), FC and NC ($r = 0.529$), FC and SC ($r = 0.413$), and milder ones between the functioning outcomes (from $r = 0.306$ to $r = 0.386$).

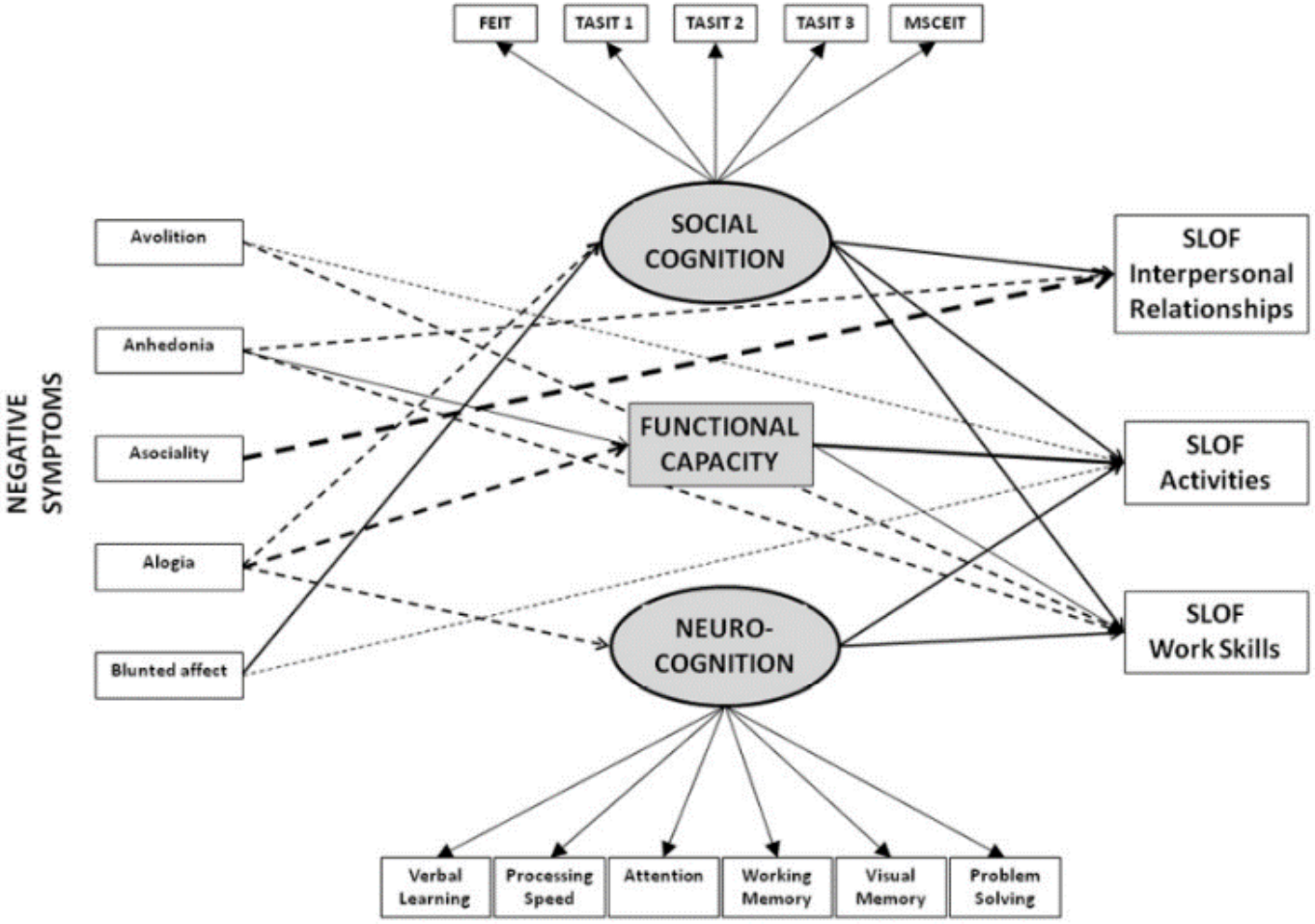
4. Discussion

The objective of the current study was to assess the direct and indirect relationships between specific disorganization symptoms and real- world functioning in subjects with schizophrenia. Four major findings derived from this study. First, only a small amount of SLOF domains' variance was explained. SLOF activities of community living was the real-life functioning domain with the highest explained variance (37.2%), whereas SLOF interpersonal relationships was the domain with the lowest explained variance (25.8%). The SLOF work skills variance was of 29.4%. In previous studies on the same sample, we found that variables relevant to the disease, personal resources and social context explained 53.8% of real-life functioning variance (Galderisi et al., 2014). The small amount of variance we explain in the present paper is not surprising as we focused on individual SLOF domains. Moreover, it suggests that other factors were involved as well, such as disability compensation, job or housing opportunities, residential support, and various elements of attitudes and stigma (Harvey and Strassnig, 2012), the identification of the most appropriate indices to capture the complexity of these variables is not an easy task. Second, the results extend our previous findings that disorganization, positive and negative symptoms were both directly and indirectly related to real-world functioning in schizophrenia (Galderisi et al., 2014). However, disorganization, when considered as a whole and unique dimension, has obviously some conceptual overlap with neuro- psychological constructs as abstraction and attention. Thus, we decided to focus on each individual symptoms of disorganization. Moreover, we considered also each individual positive, and negative symptoms and three SLOF scales. This study supports previous findings (Evans et al., 2004; Shenton et al., 1992; Smith et al., 2002) that showed strong inverse correlation between disorganization and social functions. The more symptomatic the patients are the greater the difficulties in real- world functioning and performance. In addition, this study has shown that the inverse correlation covers all scales of the SLOF (working skills, interpersonal relationships, and community activities). Lastly, significant inverse correlation was also consistently found between SLOF scales and positive and negative symptoms. Third, among the three considered disorganization symptoms, conceptual disorganization, that reflects loose associations, disrupted goal-directed sequencing, and circumstantiality, had direct links with SLOF community activities. Indeed, conceptual disorganization exhibited a twice higher impact than delusions and avolition, and once and a half greater

than blunted affect; while poor attention had a weak direct link with SLOF working abilities. Fourth, schizophrenia symptoms displayed different indirect links with NC, FC, SC, and functioning. Disorganization items and alogia had multiple, moderately strong indirect relationships with the SLOF domains, mediated by the SC, FC and NC domains; blunted affect and three out of four positive symptoms had weak indirect relationships only with interpersonal relationships, mediated by SC. Thus, our results suggest on one hand that disorganization and positive symptoms are discrete constructs, with different links with NC, FC, and SC, in line with the meta-analysis conducted by Ventura et al. (2010), that has shown moderate inverse associations between disorganized symptoms and overall NC across six core domains, whereas reality distortion symptoms were only weakly related. On the other hand, even if NC, FC, and SC demonstrated high correlations with one another, in line with prior studies (Hamm et al., 2012; Ventura et al., 2013a), our results support the notion that these three cognitive processes are related but discrete constructs, as each represents trait phenomena that require both lower and higher-order abilities (Allen et al., 2007; Biedermann et al., 2012; Fanning et al., 2012; Hamm et al., 2012; Lysaker et al., 2013; Pinkham et al., 2003; Ventura et al., 2013b). Moreover, our results provide support for the notion that NC symptoms and disorganization represent separate dimensions with differential links to real-world functioning in schizophrenia. This association between disorganization and cognitive processes was first highlighted by Bleuler (1950), who viewed disorganization as the variable that led to dysfunctions in cognitive processes. Due to the NC impairment, the capacity to form the complex thoughts needed to engage in goal- directed behaviors may be affected, given the detrimental effects these symptoms have on one's ability to synthesize discrete information into an organized whole. The notion of “loosening of associations” introduced by Bleuler is similar to the models of disorganized symptoms introduced by Hardy-Bayle´ et al. (2003), that proposes two cognitive processes underlying disorganization in schizophrenia: a deficit in the integration of contextual information, and a theory of mind deficit. The first one can be viewed as patients' difficulty in using contextual information to select an appropriate response among competitive behavioral representations in a way that is appropriate to the situation (Cohen and Servan-Schreiber, 1992; Cohen et al., 1999; Harrow et al., 2000; Widlocher and Hardy-Bayle, 1989). The second one corresponds to the inability to attribute mental states to other, to infer and to take into account the intentions, the desires, and the beliefs of others, as well as

impairments in causal attributions, accuracy of character ascriptions, and integration of social episodes. Moreover, it has been suggested that a difficulty in understanding other people's mental states, i.e., a TOM deficit, could induce signs such as poor, incoherent, or inappropriate speech, i.e. disorganized symptoms (Frith, 1992, 1994; Sarfati et al., 2000). Of all the situations encountered in everyday life, communication with others requires the greatest ability to adapt to the context and to attribute mental states: a conversation, consisting as it does of verbal and nonverbal exchanges with other people, is by definition a shifting and uncertain context, and the data associated with it must be constantly inferred and updated on the basis of peripheral information (Leslie, 1987). Thus, such a deficit would affect patients' social functioning. Indeed, adaptive social behavior and interactions crucially depend on the ability to organize actions in the context of both internal and external goals inferred from other people's behavior.




FEIT
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MSCEIT
SOCIAL COGNITION
FUNCTIONAL CAPACITY
NEURO-COGNITION
NEGATIVE SYMPTOMS
Avolition
Anhedonia
Asociality
Alogia
Blunted affect
SLOF Interpersonal Relationships
SLOF Activities
SLOF Work Skills
Verbal Learning
Processing Speed
Attention
Working Memory
Visual Memory
Problem Solving

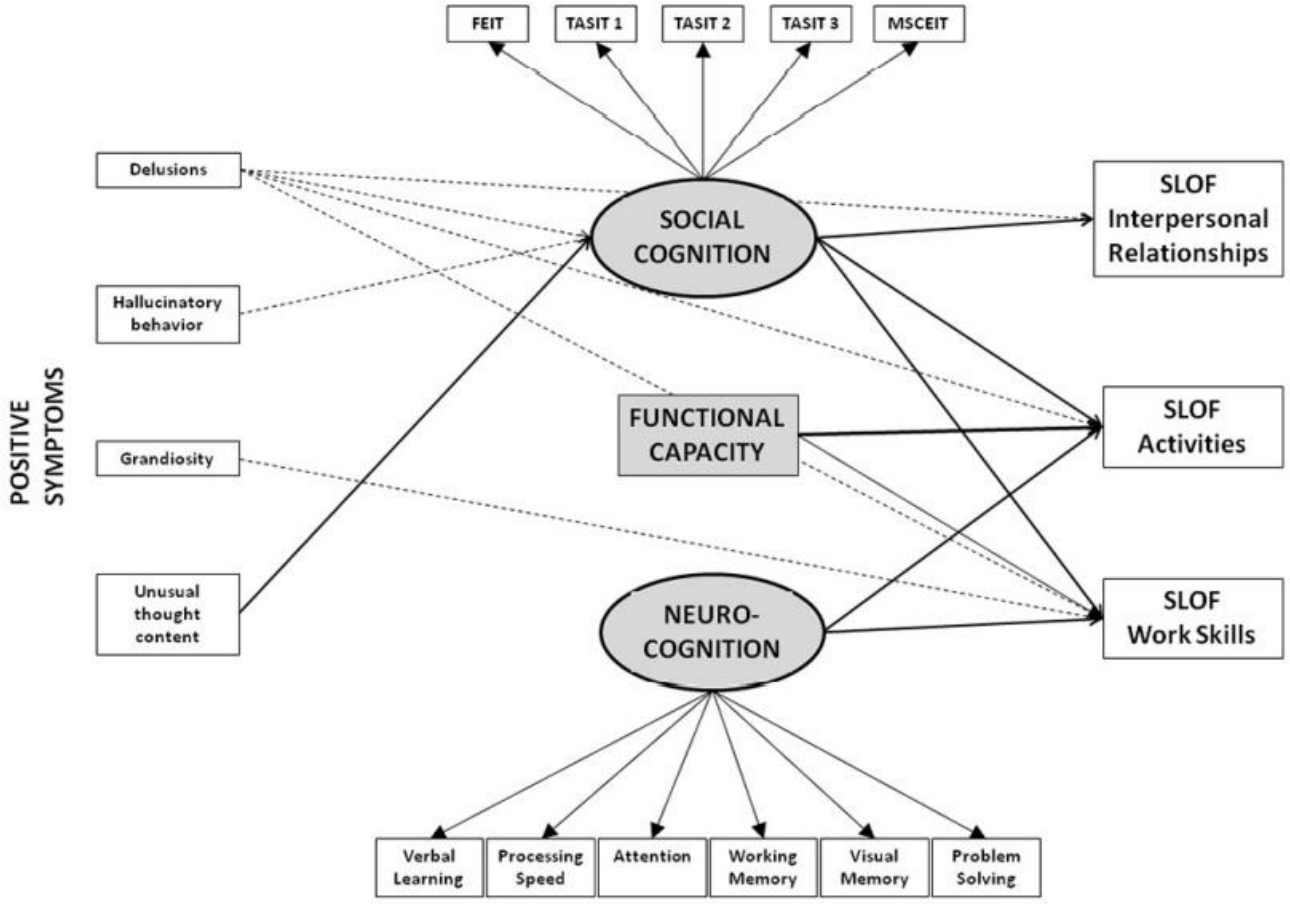

Fig. 1. Graphical representation of the estimated SEM model connecting disorganization, positive and negative symptoms to real-life functioning through the mediation of social cognition, functional capacity and neurocognition. The model is split in three parts to enhance readability. Solid lines indicate positive relationships; dashed lines negative relationships; line thickness is proportional to the strength of relationships. Correlations between mediators, between items of latent variables and between outcomes are not reported.

5. Strengths and limitations

The results of the present study should be considered in light of some limitations. The cross-sectional design of the study cannot rule out the possibility that the interplay between disorganization symptoms and other dimensions of schizophrenia may change over time or may have a phase-dependent effect. Second, study patients were outpatients with stable symptoms, who are not representative of patients in acute phases or in other clinical settings. Despite these limitations, this study has some important strengths: the large sample size, the naturalistic design without selection bias related to randomized

controlled designs, the use of state-of-the-art instruments to assess real-world functioning, NC, psychopathology, and SC variables, and the statistical analysis.

6. Conclusions

This study aimed to contribute to elucidating the role of disorganization symptoms in a well-characterized sample of patients with schizophrenia recruited in the context of a multicenter study of the NIRP. Overall conceptual disorganization is the symptom that contributed more (both directly and through the mediation of NC, SC, and FC) to the activities of community living in real-world. Achieving a deeper understanding of the disorganization symptoms has the potential to inform personalized treatment strategies aimed at improving functioning in patients with schizophrenia, if our results are confirmed in longitudinal studies in which the direction of effects can be tested. Thus, conceptual disorganization should be considered as a treatment target in intervention programs for patients with schizophrenia

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