Inter-relationships among psychopathology, cognition, and real-life functioning in early and late phase schizophrenia: A network analysis approach

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Running title: Network analysis in early and late phase schizophrenia

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Abstract

Many illness-related factors contribute to the reduction of the real-life functioning observed in people with schizophrenia (SZ). These include the psychopathological dimensions of the disorder such as positive, negative, disorganization, and depressive symptoms as well as impairment in neurocognition, social cognition, and metacognition. The associations between some of these variables change with the duration of illness (DOI), but this aspect was not explored with a network approach.

This study aimed at describing and comparing the inter-relationships between psychopathological, cognitive, and functioning variables in early (DOI ≤ 5 years) and late (DOI > 5 years) phase SZ with network analyses and at assessing which variables were more strictly and directly associated with the real-life functioning.

A network representation of the relationships between variables and the calculation of centrality indices were performed within each group. The two groups were compared with a network comparison test.

Seventy-five patients with early and ninety-two with late phase SZ were included. No differences in the global network structure and strength were found between the two groups. In both groups, visual learning and disorganization exhibited high centrality indices and disorganization, negative symptoms, and metacognition were directly and strongly associated with real-life functioning.

In conclusion, regardless of the DOI, a rehabilitation aimed at improving visual learning and disorganization (i.e., the most central variables) might reduce the strength of the associations that compose the network and therefore indirectly facilitate functional recovery. Simultaneously, therapeutic interventions targeting disorganization and metacognition might directly improve real-life functioning.

1. Introduction

Schizophrenia (SZ) is a severe mental disorder and represents one of the leading causes of disability worldwide (Charlson et al., 2018). Many illness-related factors contribute to this disability in terms of reduction of real-life functioning. These include psychopathological dimensions of the disorder such as positive, negative, disorganization, and depressive symptoms as well as impairment in social and neuro-cognition (Galderisi et al., 2014; Galderisi et al., 2016; Melo Moura et al., 2022, Green et al., 2019). Also, metacognitive deficits, defined as the reduced ability to form an integrated sense of self and others, have been associated with a reduction in patients' functioning (Lysaker et al., 2018; Brune et al., 2011; Lysaker et al., 2020). Moreover, the associations between some of these variables change with the duration of illness (DOI) with a prevalence of positive symptoms in the earlier phases of the disorder and of disorganization and depressive symptoms in later ones (Fountoulakis et al., 2020).

Functional recovery, i.e., the achievement of good real-life psychosocial functioning, is one of the main goals of the treatment of SZ and is currently reached in about half of cases with higher rates, about 57%, in first-episode of psychosis (FEP) and lower, about 38%, in multiple episodes (Vita and Barlati, 2018; Huxley et al., 2021). This means that many patients treated for SZ maintain impaired psychosocial functioning, especially those with a longer DOI (Altamura et al., 2015). Therefore, understanding the interrelationships between illness-related variables and psychosocial functioning in individuals with long or short DOI might help in identifying targets of a functional recovery-oriented treatment in these two sub-groups of patients.

Network analysis is a quantitative method of studying relationships between variables without any *a priori* model (Borsboom et al., 2013). In recent years this methodological approach has found more space in psychiatry (Borsboom et al., 2017; Fried et al., 2017) and has also been applied to the study of SZ spectrum disorders. Some authors focused on specific

phases of the disorder like FEP (Chang et al., 2019; Griffiths et al, 2021 Isquierdo et al., 2021a, 2021b, 2021c), suspected and recent onset psychosis (Jimeno et al., 2020; Heriman et al., 2021), and early and late phase SZ (Duran et al., 2021). Others works explored other aspects of SZ like depressive symptoms (Rooijen et al., 2018; Herniman et al., 2021), autistic symptoms (Isvoranu et al., 2021), metacognition (Hasson-Ohayon et al., 2018), attachment (Pena-Garijo et al., 2021), self-disorders and imagination (Rasmussen et al., 2022), remission (Roojen et al., 2018), and recovery (Galderisi et al., 2018; Galderisi et al., 2020; Moura et al., 2021). Moreover, some studies exclusively described network characteristics (Chang et al., 2019; Galderisi et al., 2018; Hajduk et al., 2021; Hasson-Ohayon et al., 2018; Herniman et al., 2021; Izquierdo et al., 2021a) while others compared the network structure between two or more sub-samples divided by the DOI (Duran et al., 2021), the duration of untreated psychosis (Izquierdo et al., 2021b), the remission status (Rooijen et al., 2018), the recovery status (Galderisi et al., 2020; Moura et al., 2021), and the neighborhood socio-economic status (Izquierdo et al, 2021c).

Only Duran and colleagues (2021) compared early and late phase SZ patients with a network approach analyzing the differences in the interrelationships of the thirty signs and symptoms assessed by the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987). No significant difference emerged from this comparison (Duran et al., 2021). Considering the lack of studies on this topic, this paper would like to expand the research of Duran et al. (2021) investigating not only the psychopathological dimensions of the disorder but also cognitive and metacognitive alterations and their relationships with real-life functioning.

More specifically, this study aims at describing and comparing the inter-relationships between psychopathological, cognitive, and functioning variables in early and late phase SZ with a network approach. This kind of analysis can provide information about differences and similarities between the two groups of patients in terms of network structure and centrality

indices of the variables included in the analysis. In addition, this approach can show which variables are more strongly associated with real-life functioning in the two groups.

We hypothesize that patients with a longer DOI, as compared to the early-phase SZ group, will show stronger connections between symptoms, cognitive variables, and real-life functioning and that this may result in both a different structure and a stronger global strength of the network.

2. Methods

2.1. Participants

One hundred and sixty-seven people with a diagnosis of SZ according to DSM-5 criteria (American Psychiatric Association, 2013) were included in the study from January 2020 until March 2022. Patients were enrolled at the Struttura Complessa Psichiatria Universitaria, Dipartimento di Neuroscienze e Salute Mentale, Azienda Ospedaliero-Universitaria "Città della Salute e della Scienza di Torino", Turin, Italy.

Inclusion criteria were age between 18 and 65 years and clinical stability as defined below. The diagnosis of SZ was confirmed by two expert clinicians (C.B., C.M.) using the Structured Clinical Interview for DSM-5, Research Version (SCID-5-RV; First et al., 2015). Clinical stability was defined as a period of at least 3 months without hospitalization and/or treatment modifications.

Exclusion criteria were psychiatric comorbidity with any mental disorder (DSM-5) and a history of severe head injury (coma $\geq$ 48 hours). The presence of psychiatric comorbidity was assessed by C.B. and C.M. using the SCID-5-RV.

Patients included in the study were evaluated using a semi-structured interview to assess age, gender, years of education, and age at illness onset. All patients received standard care provided in community mental health centers in Italy.

Written informed consent was obtained from all subjects. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Local Research Ethics Committee (Protocol number: 0057625).

2.2. Psychopathological, cognitive, and functioning assessment

The severity of positive symptoms and disorganization was rated with the Positive and Negative Syndrome Scale (PANSS, Kay 1987) according to the solution proposed by Wallwork et al. (2012) (see supplementary materials for details). Negative symptoms were assessed with the Italian version of the Brief Negative Symptoms Scale (BNSS; Mucci et al., 2015). These symptoms were grouped into the factors "avolition", consisting of anhedonia, asociality, and avolition, and "expressive deficit", including blunted affect and alogia. (Strauss et al. 2012). The Calgary Depression Scale for Schizophrenia (CDSS, Addington et al., 1993) was employed to evaluate depressive symptoms. Compared to the depressed factor proposed by Wallwork et al. (2012) that evaluates depression with the PANSS items anxiety (G2), depression (G3), and motor retardation (G6), the CDSS proposes nine items, namely depression, hopelessness, self-depreciation, guilty ideas of reference, pathological guilt, morning depression, early wakening, suicide, and observed depression, specific for the assessment of depression in patients with SZ. Morover, the choice to switch to the CDSS for the assessments of depressive symptoms is consistent with three previous large studies with a network approach (Galderisi et al., 2018; Galderisi et al., 2020; Moura et al., 2022).

Neurocognitive functions were assessed with the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (Kern et al., 2008; Nuechterlein et al., 2008) (see supplementary materials for details).

147 Social cognition, in terms of emotion processing, was evaluated using the managing emotion
148 section of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT), also included in
149 the MCCB (Kern et al., 2008; Nuechterlein et al., 2008).
150 The results of the MCCB were expressed as T-scores standardized for age and gender.
151 Higher scores indicate better performance.
152 Metacognitive abilities were assessed with the Metacognition Assessment Scale (MAS;
153 Semerari et al., 2003). This is a clinician-rated scale that evaluates four metacognitive domains,
154 namely self-reflectivity or awareness of oneself, understanding other's minds or awareness of
155 specific others, decentration or awareness of one's larger community, and mastery or the use
156 of metacognitive awareness to make sense of and respond to challenges (Lysaker 2020). For
157 the purposes of this study, we employed the total score of the scale. Higher scores reflect higher
158 metacognitive abilities.
159 Real-life functioning was evaluated with the Italian version of the Specific Level of
160 Functioning Scale (SLOF; Montemagni et al., 2015; Mucci et al., 2014) (see supplementary
161 materials for details). The SLOF was administered to the key caregiver, i.e., the person most
162 frequently and closely in contact with the patient (Galderisi et al., 2020, Rocca et al., 2021).
163 Higher scores indicate better real-life functioning.
164 Experienced psychiatrists (C.B., C.M.) performed psychopathological and metacognitive
165 assessments. To reduce interrater variability, the two raters were trained to administer the
166 PANSS, BNSS, CDSS, and MAS according to common standards. At the beginning of the
167 study, the two psychiatrists performed independent ratings of the interviews that they
168 conducted together with the first 20 patients participating in the study. This procedure was
169 followed by a discussion about each interview to reach consensual ratings. The agreement
170 (within 1 point) between the raters varied from 80% to 95% for all the PANSS items employed
171 to rate positive symptoms and disorganization; from 80% to 90% for all BNSS items; from

85% to 95% for all CDSS items; and was 80% for the MAS total score. To maintain interrater reliability across the entire study period, the two raters participated every three months in an in-depth review of a random sample of interviews with the last author (P.R.).

2.3 Statistical analyses

Following the methodology proposed in a previous network analysis study on SZ (Duran et al., 2021), participants with a DOI ≤ 5 years were included in the early phase SZ group while those with a DOI > 5 years in the late phase one. The normal distribution of the continuous variables was verified with the Kolmogorov-Smirnov test. Between-group comparisons were performed with the χ^2 test, one-way analysis of variance (ANOVA), and the Kruskal-Wallis test according to the type of variable and its distribution. Bonferroni-Holm correction was applied to control for multiple comparisons.

Missing data were imputed using an expectation-maximization algorithm, assuming that the pattern of missing data was random. Sixty-one values were imputed corresponding to 1.9% of the total values in the early phase SZ group and 1.5% in the late phase SZ group. No variable was eliminated because of a high missing rate.

This part of the statistical analysis was conducted using SPSS Statistics (IBM) 28.0, with a critical p-value of 0.05.

A network analysis was performed to compare the pattern of relationships among psychopathological, cognitive, and functioning variables between early and late phase SZ groups. Fourteen continuous variables were included in the network analysis. These variables were chosen in order to assess the principal domains of symptoms and cognition in SZ.

We calculated and depicted two networks, one for the early phase and one for the late phase SZ groups. Since most variables included were not normally distributed, we applied a non-paranormal transformation to relax the normality assumption (Liu et al., 2012). To reduce the

number of false-positive edges we employed the least absolute shrinkage and selection operator (LASSO) (Costantini et al., 2015) that negatively selects small edges by giving them a zero weight. In addition, the number of edges was optimized using a shrinkage parameter. The extended Bayesian information criterion (EBIC) was employed to determine this parameter (Foygel et al., 2010). We followed the Fruchterman-Reingold algorithm to establish the location of the nodes within the networks (Fruchterman et al., 1991).

As proposed by Epskamp et al. (2018), we calculated the following three centrality indices of the two networks for all variables: strength or degree centrality, betweenness, and closeness. Strength or degree centrality indicates the sum of the absolute values of the edges reaching a given node, betweenness the number of times a node lies on the shortest path length between any two other nodes, and closeness how easy it is to reach all other nodes from the node of interest. These three centrality indices were standardized to be comparable and graphically represented These three centrality indices were standardized to be comparable and graphically represented (Epskamp et al., 2018).

The robustness of the two networks was evaluated with non-parametric bootstrapping procedures that estimated the accuracy of edge weights and the stability of the centrality indices (Epskamp et al.,2018). These procedures are described in detail in the supplementary materials.

This part of the network analysis was performed using the statistical package JASP 16.2.0. See supplementary materials for a more detailed explanation of this statistical methodology.

To compare the networks of the early and late phase SZ groups we employed the network comparison test (NCT) R-package (van Borkulo et al., 2017) within the R-studio desktop software. Two permutation tests for independent samples were used to compare the structure (M-test) and the global strength (S-test) of the two networks. For the between-group comparison of each edge, we utilized the edge invariance test of the NCT R-package that

applies Holm-Bonferroni correction for multiple comparisons (van Borkulo et al., 2017). Statistical significance was set at $p < 0.05$.

3. Results

Differences between early and late phase SZ groups

Socio-demographic, psychopathological, cognitive, and functioning characteristics of early (n = 75) and late (n = 92) phase SZ groups are shown in table 1. Patients of the early phase group were significantly younger, with lower scores in PANSS-disorganization, better performances in working memory and verbal learning tasks, and better metacognitive abilities. They also exhibited significantly higher real-world functioning.

--- PLEASE INSERT TABLE 1 AROUND HERE ---

Network description

Figure 1 shows the early and late phase SZ groups networks. Visual inspection revealed broad similarities between the two networks. Nodes belonging to the same construct were highly interconnected and spatially contiguous. This is the case of neurocognitive domains, the two domains of negative symptoms, and disorganization and positive symptoms. In both groups, real-life global functioning was highly interconnected with negative symptoms, disorganization, and metacognition.

--- PLEASE INSERT FIGURE 1 AROUND HERE ---

Centrality indices of the network variables of the two groups are shown in Figure 2. In both groups, visual learning and disorganization exhibited high centrality indices as they connected

neurocognitive domains with social cognition, metacognition, symptoms, and global functioning. Verbal learning and working memory had higher centrality indices in the late-phase SZ group, while avolition showed higher strength in patients with a DOI ≤ 5 years.

--- PLEASE INSERT FIGURE 2 AROUND HERE ---

Network comparison

There was no significant difference between the structure of the two networks (M-test = 0.33; p = 0.550). The overall strength of the connections among variables was almost the same in the two groups: 5.38 in the early phase SZ group and 5.44 in the late phase SZ group. This difference was not significant: S-test = 0.07; p = 0.97. The main significant edge difference between the two groups was the strong correlation between disorganization and metacognition present exclusively in the late-phase SZ group.

Network stability

The edge weight estimations were accurate for both groups. In particular, the bootstrap mean of each edge and the original edge value were almost overlapping and the CIs of edge weights estimates were all narrow. Strength centrality means calculated with the bootstrapping procedure of "reduced networks" were correlated with the mean of strength centrally of the original network. Correlations with r > 0.70 were obtained until 43% of nodes (i.e., at least 6 out of 14) were sampled. This indicates that the relationships between variables remained globally stable even after the random elimination of more than half of the network nodes.

4. Discussion

The aims of the study were to evaluate the differences in the structure of the networks generated by the relationships between psychopathology, cognition, metacognition, and real-

world functioning, in early and late phase SZ and to identify which variables included in the network analysis were more strongly associated with real-life functioning in the two groups.

As for the first aim, contrary to our hypothesis, we did not find any significant difference in the global structure of the networks (fig. 1). This result agrees with Duran et al. (2021) about which it adds information on the stability of relationships between cognitive, metacognitive and real-life functioning variables, regardless of the phase of the disorder. From a clinical point of view, this might indicate that treatments aimed at improving symptoms, cognitive deficits, and real-life functioning to reduce the strength of the connections between these aspects of the disorder should be tested in all patients with SZ, including those with longer DOI. This is in line with two recent large meta-analyses that did not find the DOI among the significant moderators of the treatment effect of cognitive remediation (Vita et al., 2021) and metacognitive training (Penney et al., 2022).

At the level of single relationships between variables (edges), the main difference between the two groups concerns the relationship between metacognition and disorganization, found exclusively in subjects with longer DOI (fig.1). Disorganization includes thought and cognitive symptoms, namely conceptual disorganization, difficulty in abstraction, and poor attention. These symptoms may worsen in later stages of SZ (Fountoulakis et al., 2020) and, also in our sample, are more severe in the late-stage SZ group. The severity of disorganization is associated with a decrease in metacognitive abilities (Minor et al., 2014; Minor et al., 2015), which were lower in our sample of patients with a longer DOI. As suggested by Minor and Collaborators (2014), this relationship is probably due to the destructive effects of disorganization on one's ability to synthesize discrete information into an organized whole, which is one of the most important aspects of metacognition.

Focusing on the centrality indices (fig. 2), we found that disorganization and visual learning were central in both groups while experiential negative symptoms, i.e., avolition dimension,

295 are more central in the early phase SZ group and verbal learning and working memory in the
296 late phase one. According to our data, disorganization acts like a “bridge” between
297 neurocognition, negative symptoms, and real-life functioning (fig. 1). This psychopathological
298 dimension is a core feature of SZ and is negatively associated with real-life functioning,
299 especially with interpersonal functioning (Rocca et al., 2018). This relationship may be
300 motivated by the fact that disorganization entails difficulties in communication and social
301 interactions, often in the absence of compensatory mechanisms that limit this negative impact
302 (Ventura et al., 2010). Moreover, its link with negative symptoms was confirmed by a study
303 on the random speech structure of patients with SZ (Mota et al., 2017), where the authors
304 demonstrate a strong correlation between poorly connected speech, which is a quantitative
305 measure of conceptual disorganization, and the severity of negative symptoms. This study
306 suggests that thought and speech might be a common ground for both disorganization and
307 expressive dimension of negative symptoms, (Mota et al., 2017). Finally, focusing on the
308 connection between disorganization and neurocognition, our results are consistent with those
309 of Ventura et al. (2010) and Vignapiano et al. (2019). These two studies demonstrated a partial
310 superimposition between many neurocognitive domains and two of the three symptoms
311 combined in the present study to assess disorganization, namely conceptual disorganization
312 and difficulty in abstract thinking (Ventura et al., 2010; Vignapiano et al., 2019).
313 In our sample, visual learning connects neurocognitive domains with disorganization,
314 avolition, and metacognition (fig. 1). The high centrality of this neurocognitive domain is in
315 agreement with the results of Hasson-Ohayon et al. (2018), who supposed that visual learning,
316 i.e. the ability to acquire, store and retrieve information about objects and spatial locations for
317 more than a few minutes (Green et al., 2019), influences how people are able to think about
318 themselves and others and to understand the inter-relationships between events. This
319 explanation motivates and partly unfolds the connection between visual learning, other

neurocognitive domains, and metacognition. Moreover, this neurocognitive ability is strictly related to visual perception (Hasson-Ohayon et al., 2018), and, according to the structural equation model proposed by Green et al. 2012, visual perception and cognition impairments are strongly related to more severe experiential negative symptoms. These inter-relationships might partially explain the connection between visual learning and the avolition dimension of negative symptoms.

Verbal learning, i.e., the ability to acquire, store and retrieve verbal information for more than a few minutes (Green et al., 2019) and working memory, that is the ability to hold and manipulate information in a temporary store, showed higher centrality indices in late phase SZ group (fig.1, fig. 2). This was mainly due to their stronger relationships with others neurocognitive domains in this subsample of patients. In previous studies, verbal learning performance showed a negative association with the DOI (Rannikko et al., 2012, Tuulio-Henriksson et al., 2004) and working memory with multiple psychotic episodes (Forbes et al., 2009). This is consistent with our results as the performances in verbal learning and working memory tests were significantly worse in the late-phase SZ group.

The experiential dimension of negative symptoms including avolition, anhedonia, and asociality, showed higher strength in the early-stage SZ group as it was more connected to metacognition and visual learning. The negative relationship between negative symptoms and metacognitive abilities in FEP was already demonstrated by Trauelsen et al. 2016. The authors suggested that poor metacognitive skills may affect how experiences are perceived and interpreted facilitating the avoidance behaviors such as asociality and avolition.

Regarding the second aim, no differences were found between early and late phase SZ as in both groups the factors more strongly associated with real-life functioning were negative symptoms, disorganization, and metacognition. These results are in agreement with previous network analyses on this topic. In particular, experiential negative symptoms were linked to

345 global psychosocial functioning (Chang et al., 2019) and interpersonal functioning (Galderisi
346 et al., 2018; Hajduk et al., 2021) while disorganization showed an association with everyday
347 life skills (Galderisi et al., 2018) and work skills (Melo Moura et al, 2022).
348 Finally, focusing on metacognitive abilities, no study focused simultaneously on both
349 metacognition and functioning with a network approach. However, the connection between
350 these two variables was already examined with other statistical tools (e.g., structural equation
351 modeling, repeated measures ANOVA, meta-analysis) showing that impaired metacognitive
352 abilities were associated with poorer social and working functioning (Davies et al., 2018;
353 Lysaker et al., 2010; Lysaker et al., 2011).
354 The main limitation of the present work is the cross-sectional nature of the study which does
355 not allow to verify longitudinally the stability of the networks in the two groups. Moreover,
356 with a network analysis approach, we could not verify the direction of the associations between
357 variables. Therefore, the impossibility to assess causal relations limits the clinical significance
358 of the present study. Another limitation of the study is the relatively small sample size of the
359 two groups that prevents increasing the number of variables, otherwise the networks would
360 lose strength and stability. Furthermore, we evaluated only one domain of SC, i.e., emotion
361 management with the MSCEIT managing emotion section. A more complete and broad
362 assessment of SC abilities should be tested in future studies with more complete instruments
363 like those proposed by the Social Cognition Psychometric Evaluation study (Pinkham et al.,
364 2018). In addition, we did not use as input variables the main sociodemographic factors, i.e.
365 age, gender, and education. The inclusion of these variables in the network analysis might have
366 led to partially different findings. Finally, all patients were clinically stable and the vast
367 majority of them was in treatment with an antipsychotic drug. Consequently, these findings
368 cannot be generalized to drug naïve or drug-free subjects with SZ and to acute patients that
369 usually exhibit more severe positive symptoms.

Despite these limitations, this study has some strengths. Firstly, it expanded the results of Duran et al. (2021) comparing not only psychopathological variables but also cognition, metacognition, and real-life functioning between early and late phase SZ patients. Furthermore, to our knowledge, this is the first study that includes metacognition and real-life functioning in the same network analysis thus clarifying the relationship between these two variables in connection with symptoms and cognition.

In conclusion, there are no substantial differences in the relationships between psychopathology, cognition, metacognition, and real-life functioning between subjects with early or late phase SZ. Some neurocognitive domains and disorganization are the variables with higher central rates while metacognition seemed to act as a "bridge" between neurocognition and real-life functioning. Considering these findings, rehabilitative interventions targeting these cognitive deficits might have a positive impact in terms of reduction of the strength of the connections between the network variables both in early and late phase SZ. Moreover, this weakening of the network could indirectly facilitate an improvement in patients' real-life functioning. However, longitudinal pre- versus post-treatment network comparison studies are needed to test this hypothesis.

Data Availability

Due to the anonymity guaranteed in the informed consent paperwork at the time when data were collected, data cannot be publicly shared, and are controlled by the Comitato Etico Interaziendale of the A.O.U. Città della Salute e della Scienza di Torino. Researchers who wish to request access to these data may contact the corresponding author (claudio.brasso@unito.it).

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