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

This is a pre print version of the following article:

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1902399> since 2023-05-05T22:32:28Z

Published version:

DOI:10.1016/j.schres.2023.04.011

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(Article begins on next page)

1 **Inter-relationships among psychopathology, cognition, and real-life**
2 **functioning in early and late phase schizophrenia: a network analysis**
3 **approach**

4 **Running title:** Network analysis in early and late phase schizophrenia

5

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20 **Keywords:** duration of illness, network comparison test, disorganization, metacognition,

21 neurocognition

22

23

24 **Abstract**

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

31 This study aimed at describing and comparing the inter-relationships between
32 psychopathological, cognitive, and functioning variables in early ($DOI \leq 5$ years) and late (DOI
33 > 5 years) phase SZ with network analyses and at assessing which variables were more strictly
34 and directly associated with the real-life functioning.

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

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

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

48

49 1. Introduction

50 Schizophrenia (SZ) is a severe mental disorder and represents one of the leading causes of
51 disability worldwide (Charlson et al., 2018). Many illness-related factors contribute to this
52 disability in terms of reduction of real-life functioning. These include psychopathological
53 dimensions of the disorder such as positive, negative, disorganization, and depressive
54 symptoms as well as impairment in social and neuro-cognition (Galderisi et al., 2014; Galderisi
55 et al., 2016; Melo Moura et al., 2022, Green et al., 2019). Also, metacognitive deficits, defined
56 as the reduced ability to form an integrated sense of self and others, have been associated with
57 a reduction in patients' functioning (Lysaker et al., 2018; Brune et al., 2011; Lysaker et al.,
58 2020). Moreover, the associations between some of these variables change with the duration
59 of illness (DOI) with a prevalence of positive symptoms in the earlier phases of the disorder
60 and of disorganization and depressive symptoms in later ones (Fountoulakis et al., 2020).

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

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

74 phases of the disorder like FEP (Chang et al., 2019; Griffiths et al, 2021 Isquierdo et al., 2021a,
75 2021b, 2021c), suspected and recent onset psychosis (Jimeno et al., 2020; Heriman et al.,
76 2021), and early and late phase SZ (Duran et al., 2021). Others works explored other aspects
77 of SZ like depressive symptoms (Rooijen et al., 2018; Herniman et al., 2021), autistic
78 symptoms (Isvoranu et al., 2021), metacognition (Hasson-Ohayon et al., 2018), attachment
79 (Pena-Garijo et al., 2021), self-disorders and imagination (Rasmussen et al., 2022), remission
80 (Rooijen et al., 2018), and recovery (Galderisi et al., 2018; Galderisi et al., 2020; Moura et al.,
81 2021). Moreover, some studies exclusively described network characteristics (Chang et al.,
82 2019; Galderisi et al., 2018; Hajduk et al., 2021; Hasson-Ohayon et al., 2018; Herniman et al.,
83 2021; Izquierdo et al., 2021a) while others compared the network structure between two or
84 more sub-samples divided by the DOI (Duran et al., 2021), the duration of untreated psychosis
85 (Izquierdo et al., 2021b), the remission status (Rooijen et al., 2018), the recovery status
86 (Galderisi et al., 2020; Moura et al., 2021), and the neighborhood socio-economic status
87 (Izquierdo et al, 2021c).

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

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

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

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

105

106 **2. Methods**

107 **2.1. Participants**

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

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

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

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

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

127

128 **2.2. Psychopathological, cognitive, and functioning assessment**

129 The severity of positive symptoms and disorganization was rated with the Positive and
130 Negative Syndrome Scale (PANSS, Kay 1987) according to the solution proposed by
131 Wallwork et al. (2012) (see supplementary materials for details). Negative symptoms were
132 assessed with the Italian version of the Brief Negative Symptoms Scale (BNSS; Mucci et al.,
133 2015). These symptoms were grouped into the factors “avolition”, consisting of anhedonia,
134 asociality, and avolition, and “expressive deficit”, including blunted affect and alogia. (Strauss
135 et al. 2012). The Calgary Depression Scale for Schizophrenia (CDSS, Addington et al., 1993)
136 was employed to evaluate depressive symptoms. Compared to the depressed factor proposed
137 by Wallwork et al. (2012) that evaluates depression with the PANSS items anxiety (G2),
138 depression (G3), and motor retardation (G6), the CDSS proposes nine items, namely
139 depression, hopelessness, self-depreciation, guilty ideas of reference, pathological guilt,
140 morning depression, early wakening, suicide, and observed depression, specific for the
141 assessment of depression in patients with SZ. Moreover, the choice to switch to the CDSS for
142 the assessments of depressive symptoms is consistent with three previous large studies with a
143 network approach (Galderisi et al., 2018; Galderisi et al., 2020; Moura et al., 2022).

144 Neurocognitive functions were assessed with the Measurement and Treatment Research to
145 Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)
146 (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

172 85% to 95% for all CDSS items; and was 80% for the MAS total score. To maintain interrater
173 reliability across the entire study period, the two raters participated every three months in an
174 in-depth review of a random sample of interviews with the last author (P.R.).

175

176 **2.3 Statistical analyses**

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

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

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

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

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

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

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

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

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

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

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

223

224 **3. Results**

225 **Differences between early and late phase SZ groups**

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

231

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

233

234 **Network description**

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

241

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

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

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

248

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

250 **Network comparison**

251 There was no significant difference between the structure of the two networks (M-test =
252 0.33; $p = 0.550$). The overall strength of the connections among variables was almost the same
253 in the two groups: 5.38 in the early phase SZ group and 5.44 in the late phase SZ group. This
254 difference was not significant: S-test = 0.07; $p = 0.97$. The main significant edge difference
255 between the two groups was the strong correlation between disorganization and metacognition
256 present exclusively in the late-phase SZ group.

257

258 **Network stability**

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

266

267 **4. Discussion**

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

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

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

282 At the level of single relationships between variables (edges), the main difference between
283 the two groups concerns the relationship between metacognition and disorganization, found
284 exclusively in subjects with longer DOI (fig.1). Disorganization includes thought and cognitive
285 symptoms, namely conceptual disorganization, difficulty in abstraction, and poor attention.
286 These symptoms may worsen in later stages of SZ (Fountoulakis et al., 2020) and, also in our
287 sample, are more severe in the late-stage SZ group. The severity of disorganization is associated
288 with a decrease in metacognitive abilities (Minor et al., 2014; Minor et al., 2015), which were
289 lower in our sample of patients with a longer DOI. As suggested by Minor and Collaborators
290 (2014), this relationship is probably due to the destructive effects of disorganization on one's
291 ability to synthesize discrete information into an organized whole, which is one of the most
292 important aspects of metacognition.

293 Focusing on the centrality indices (fig. 2), we found that disorganization and visual learning
294 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

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

326 Verbal learning, i.e., the ability to acquire, store and retrieve verbal information for more
327 than a few minutes (Green et al., 2019) and working memory, that is the ability to hold and
328 manipulate information in a temporary store, showed higher centrality indices in late phase SZ
329 group (fig.1, fig. 2). This was mainly due to their stronger relationships with others
330 neurocognitive domains in this subsample of patients. In previous studies, verbal learning
331 performance showed a negative association with the DOI (Rannikko et al., 2012, Tuulio-
332 Henriksson et al., 2004) and working memory with multiple psychotic episodes (Forbes et al.,
333 2009). This is consistent with our results as the performances in verbal learning and working
334 memory tests were significantly worse in the late-phase SZ group.

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

341 Regarding the second aim, no differences were found between early and late phase SZ as in
342 both groups the factors more strongly associated with real-life functioning were negative
343 symptoms, disorganization, and metacognition. These results are in agreement with previous
344 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.

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

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

386

387 **Data Availability**

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

392

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