Improving Knowledge on Pathways to Functional Outcome in Schizophrenia: Main Results From the Italian Network for Research on Psychoses

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The identification of factors associated with functional outcome of subjects with schizophrenia is a great challenge in current research oriented to the personalization of care. The Italian Network for Research on Psychoses (NIRP) is a network of 26 university psychiatric clinics and/or mental health departments aimed to carry out multicenter research projects to improve the standards of prevention, diagnosis, and treatments of schizophrenia. The network has promoted 2 main studies, a cross-sectional one and a longitudinal one and seven “add-on” studies. The cross-sectional study of the network included 921 subjects with schizophrenia, 379 unaffected first-degree relatives of these patients, and 780 healthy controls. Results from this study documented that social and non-social cognition, functional capacity, negative symptoms, resilience, and family or social incentives strongly influence a measure of global functioning. The follow-up study included 618 patients from the original sample and has produced evidence of the key role of cognition, functional capacity, the experiential domain of negative symptoms, and everyday life skills in predicting functional outcome. The longitudinal study demonstrated that social cognition and the experiential domain of negative symptoms had an impact on interpersonal functioning, while non-social cognition had an impact on everyday life skills. Both non-social cognition and social cognition predicted work skills. The research question concerning the relationships of cognitive impairment and negative symptoms has been investigated with an innovative approach, using a structural equation model (SEM) and a network analysis. Both analyses demonstrated that only the experiential domain of negative symptoms had a distinct direct effect on functioning. The network analysis showed that expressive deficit was connected to functional capacity, as were social and non-social cognitive variables, and to disorganization. These findings were confirmed by the follow-up study. The add-on studies showed distinct electrophysiological correlates of the two negative symptom domains and the partial overlap between disorganization and neurocognitive impairment. Moreover, they identified and characterized a specific subgroup of patients suffering from...
schizophrenia with autism spectrum symptoms. The NIRP studies have implications for personalized management of patients with schizophrenia and highlight the need for a careful assessment of several domains rarely evaluated in clinical settings.

**Keywords:** schizophrenia, real-life functioning, recovery, neurocognition, social cognition, negative symptoms

**INTRODUCTION**

Schizophrenia is a severe mental disorder that presents a high heterogeneity in terms of risk factors, clinical manifestations, comorbidities, treatment response, and outcomes (1–19).

About 75% of people suffering from this disorder shows a clinical course characterized by relapses and remissions (20–23), and <1 in 7 people meets the criteria for recovery (24, 25). Two aspects are fundamental to achieve clinical recovery in schizophrenia: the remission of symptoms and the improvement in functioning (26–29). However, despite the introduction of innovative pharmacological and psychosocial treatments that facilitate symptomatic remission (3, 6–8, 10), the impairment in different areas of real-life functioning still represents an unmet need in the care of people suffering from schizophrenia, thus causing a huge burden on patients, their families, and health care systems (30–41).

A variety of factors, some related to the illness, some to personal resources, and others to the social context, seem to influence functional outcome, through direct or indirect relationships (18, 41–50). The identification of these factors, as well as their relative impact on the outcome through complex pathways, represents, to date, a main goal of current psychiatric research, in order to develop integrated and individualized treatments aiming at ameliorating functioning and thus at achieving recovery (51, 52).

Within this frame, a national multicenter project, promoted by the Italian Network for Research on Psychoses, has been developed. This is a network of 26 university psychiatric clinics and/or mental health departments, coordinated by the Department of Psychiatry of the University of Campania “Luigi Vanvitelli” (Table 1). By promoting and enhancing the collaboration among the involved centers, this network is intended to carry out research projects in order to improve the standards of prevention, diagnosis, and treatments for people suffering from primary psychotic disorders. So far, the network promoted two main studies, a cross-sectional one and a longitudinal 4-year follow-up one. In addition, seven “add-on” studies have been promoted by the network (Table 2).

The cross-sectional study had been carried out between 2011 and 2013 (32, 33). The primary objective of the study was to identify factors affecting real-life functioning of subjects with schizophrenia and to define their relative contribution. The longitudinal study was conducted after 4 years. This study investigated whether factors identified as predictors and mediators of real-life functioning in the cross-sectional study were confirmed as such as follow-up (34, 37). As compared to previous studies on the topic, both studies analyzed a greater number of variables, some of which have never been examined before. Moreover, these studies used state-of-the-art instruments for the assessment of each variable included and appropriate data analysis methods in order to explore the complex relationships between possible predictors, mediators, and outcome measures.

The implementation of the longitudinal assessment allowed us to overcome the limitations of the cross-sectional design, which prevented inferences about the direction of causality. In fact, the majority of studies investigating factors associated with functional outcome in schizophrenia have had a cross-sectional design, while only few and inconsistent findings have been reported by investigations with a longitudinal design (44, 53–63). The inconsistency of results might be due to different factors, such as the small sample sizes included in the studies, the use of different measures of functional outcome, and the use of assessment instruments, especially for cognitive impairment and negative symptoms, that were often not in line with their current conceptualization (32, 64–67). Indeed, although negative symptoms and cognitive impairment are stable dimensions of schizophrenia, are often present since the early phases of the illness, persist into clinical remission, and predict outcomes (41, 56, 57), uncertainties still remain about the correct evaluation and management of these dimensions (4, 68–70).

In the present article, we report the main findings of the two studies conducted by the network, which have contributed to the advancement of knowledge on the complex pathways involved in functional outcomes in people with schizophrenia.

**CROSS-SECTIONAL STUDY**

**Participants**

Within the cross-sectional study, 921 patients with a diagnosis of schizophrenia, aged between 18 and 66 years; 379 unaffected first-degree relatives of these patients; and 780 healthy controls were recruited (32, 33). For the patient group, 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 mental retardation or of neurological diseases; a history of alcohol and/or substance abuse in the last 6 months; current pregnancy or lactation; inability to provide an informed consent; and treatment modifications and/or hospitalization due to symptom exacerbation in the last 3 months. For each recruited patient who agreed to involve relatives, two first-degree relatives were recruited, when available. They were preferably the two parents, or one parent and one sibling, or two siblings. These relatives were included in the study if criteria for a current or lifetime psychiatric diagnosis were not met when they were interviewed with the SCID-I–non-patient version and the SCID-II. Exclusion criteria were (a) a history of head trauma with loss of consciousness; (b) a history of moderate
TABLE 1 | Centers involved in the Italian Network for Research on Psychoses and their coordinators.

| Center | Coordinator |
|--------|-------------|
| Department of Psychiatry, University of Campania “Luigi Vanvitelli” | Silvana Galderisi |
| Department of Neuroscience, Section of Psychiatry, University of Turin | Filippo Bogetto/Paola Rocca |
| Department of Translational Medicine, Psychiatric Unit, University of Eastern Piedmont | Patrizia Zeppegno |
| Department of Psychiatry, State University of Milan | Carlo Altamura |
| Psychiatric Unit, School of Medicine, University of Brescia, Brescia | Emilio Sacchetti/Antonio Vita |
| Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health, Section of Psychiatry, University of Genoa | Mario Amore |
| Department of Neurosciences, Psychiatric Clinic, University of Padua | Paolo Santonastaso/Angela Favaro |
| Department of Biomedical and Neuromotor Sciences, University of Bologna | Diana De Ronchi |
| Department of Neuroscience, Psychiatry Unit, University of Parma | Carlo Marchesi |
| Department of Neurosciences, Psychology, Drug Research and Child Health, University of Florence | Stefano Pallanti |
| Department of Health Sciences, Psychiatry Unit, University of Florence | Valdo Ricca |
| Department of Clinical and Experimental Medicine, Section of Psychiatry, University of Pisa | Liliana Dell’Osso |
| Department of Molecular Medicine and Clinical Department of Mental Health, University of Siena | Andrea Fagiolini |
| Department of Life, Health and Environmental Sciences, Unit of Psychiatry, University of L’Aquila | Massimo Casacchia/Rita Roncone |
| Department of Biotechnological and Applied Clinical Sciences, Section of Psychiatry, University of L’Aquila | Alessandro Rossi |
| Department of Neuroscience and Imaging, G. D’Annunzio University of Chieti | Massimo di Giannantonio |
| Department of Neurology and Psychiatry, Sapienza University of Rome | Massimo Biondi |
| Department of Neurosciences, Mental Health and Sensory Organs, S. Andrea Hospital, Sapienza University of Rome | Paolo Girardi/Maurizio Pompili |
| Department of Systems Medicine, Psychiatry and Clinical Psychology Unit, Tor Vergata University of Rome, Rome | Alberto Siracusano |
| Department of Neuroscience, Reproductive Science, and Odontostomatology, Section of Psychiatry, Federico II University of Naples | Andrea De Bartoilemis |
| Department of Medicine, Surgery and Dentistry “Scuola Medica Salernitana,” Section of Neurosciences, University of Salerno | Palmiero Monteleone |

(Continued)

TABLE 1 | Continued

| Center | Coordinator |
|--------|-------------|
| Department of Neurological and Psychiatric Sciences, University of Bari | Alessandro Bertolino |
| Department of Clinical and Molecular Biomedicine, Psychiatry Unit, University of Catania | Eugenio Aguglia |
| Department of Public Health, Clinical and Molecular Medicine, Section of Psychiatry, University of Cagliari | Bernardo Carpiniello |
| Psychiatry Unit, Department of Medical Sciences, University of Foggia | Antonello Bellomo |
| Department of Psychiatry, Neurobiology, Pharmacology and Biotechnologies, UNIPI | Mauro Mauri |

TABLE 2 | Add-on studies of the Italian Network for Research on Psychoses.

Add-on studies

- Investigation of electrophysiological correlates of schizophrenia and their association with psychopathology, social and non-social cognition, and real-life functioning
- Investigation of structural–functional magnetic resonance imaging features associated with diagnosis and real-world functioning in patients with schizophrenia
- Investigation of autistic spectrum symptoms and their impact on real-life functioning in subjects with schizophrenia
- Investigation of sexual functioning in subjects with schizophrenia and its association with psychopathology and social functioning
- Investigation of obsessive symptoms and their impact on real-life functioning in subjects with schizophrenia
- Investigation of resources and global burden of patients’ families and their impact on psychopathology and real-life functioning of subjects with schizophrenia
- Investigation of post-traumatic spectrum symptoms and their impact on real-life functioning in subjects with schizophrenia

(Continued)

to severe mental retardation or of neurological diseases; (c) a history of alcohol and/or substance abuse in the last 6 months; (d) inability to provide an informed consent. Healthy subjects matched with patients for gender and geographical area of origin were recruited from the community at the same sites as the patient sample. Inclusion and exclusion criteria were the same as those listed for first-degree relatives.

Assessment Instruments

The study evaluated the impact on real-life functioning of a larger number of variables compared to previous investigations, some of which had never been investigated before. The assessed variables were grouped into three categories: (a) illness-related variables (positive, negative, disorganized, depressive, and extrapyramidal symptoms; neurocognition; social cognition; and functional capacity); (b) personal resources (resilience and engagement with mental health services); and (c) context-related factors (socio-demographic variables; socioeconomic status; availability of a disability pension; access to family and social incentives; and social network). The variables included
TABLE 3 | Investigated variables in the cross-sectional and follow-up studies of the network.

| Factors                        | Variables                                      | References |
|--------------------------------|------------------------------------------------|------------|
| Illness-related variables      | Neurocognitive deficit (71–73)                 |            |
|                                | Social cognition deficit (74, 75)               |            |
| Negative symptoms              | Depressive symptoms (78, 82, 83)               |            |
| Positive symptoms              | Disorganization (50, 85)                       |            |
| Disorganization                |                                               |            |
| Personal resources             | Resilience (49, 86)                            |            |
| Context-related variables      | Service engagement (87)                        |            |
|                                | Social network (45, 46)                        |            |
|                                | Job or housing opportunities and residential support (45, 46) | |
|                                | Disability compensation (45, 46)               |            |
|                                | Internalized stigma (48, 88)                   |            |

in each category are reported in Table 3. Real-life functioning was chosen as any index of clinical recovery. State-of-the-art instruments were used to assess variables of each category and real-life functioning. The adopted instruments were chosen on the basis of the literature and the researchers’ experience, to overcome limitations of previous studies. When it was necessary, assessment instruments were translated, adapted, and validated for the Italian context.

All the instruments have been used to evaluate subjects with schizophrenia, their first-degree relatives, and healthy controls.

Illness-Related Variables

A clinical form was filled in with data on age of disease onset, course of the disease, and treatments received, using all available sources of information (patient, family, medical records, and mental health workers).

The severity of positive and disorganized symptoms was evaluated using the Positive and Negative Syndrome Scale (PANSS) (89).

Negative symptoms were assessed with the Brief Negative Symptom Scale (BNSS), a second-generation rating scale which is in line with the current conceptualization of negative symptoms (64, 90). As compared to first-generation rating scales, the BNSS shows several advantages. It does not include aspects that are related to cognitive or depressive dimensions; it provides a separate assessment of behavior and inner experience for items referring to experiential deficits such as avolition, thus enabling a better differentiation from social functioning and other subjective experiences such as decreased interest or energy; it provides a separate assessment of consummatory and anticipatory anhedonia; it generates a total score as well as separate scores for the five negative symptom domains (avolition, anhedonia, asociality, blunted affect, and alogia). The two-factor structure, consisting of the experiential domain (avolition, anhedonia, and asociality) and the expressive deficit domain (blunted affect and alogia), is supported by the use of this instrument (64, 66, 90–92). Depressive symptoms were evaluated using the Calgary Depression Scale for Schizophrenia (CDSS) (93); extrapyramidal symptoms, with the St. Hans Rating Scale (SHRS) (94). The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) was adopted to evaluate cognitive impairment (65, 67). This instrument was built up within the MATRICS initiative, aiming to develop a cognitive battery for subjects with schizophrenia designed for use in clinical trials (65, 67). MCCB assesses seven cognitive domains that are reported to be compromised in subjects with schizophrenia: speed of processing, attention and vigilance, working memory, verbal learning and memory, visuospatial learning and memory, reasoning and problem solving, and social cognition (44). The MCCB Mayer-Salovey-Caruso Emotional Intelligent Test (MSCEIT), the Facial Emotion Identification Test (FEIT) (95), and the Awareness of Social Inference Test (TASIT) (96) were used to measure different aspects of social cognition, such as emotional intelligence, emotion recognition, and theory of mind.

Personal Resources

The Resilience Scale for Adults (RSA) (97) was used to assess resilience; the Service Engagement Scale (SES) (87), to evaluate the access of subjects with schizophrenia to mental health services.

Context-Related Factors

A socio-demographic questionnaire was developed ad hoc to collect data on gender, age, marital status, schooling, housing, eating habits, substance use, socioeconomic status, availability of a disability pension, and access to family and social incentives (32); The Internalized Stigma of Mental Illness (ISMI) (98) was used to assess stigma in subjects with schizophrenia.

Functional Capacity and Real-Life Functioning

The functional capacity was assessed through the brief version of the University of California, San Diego (UCSD) Performance-Based Skills Assessment—brief version (UPSA-B), a performance-based instrument that assesses “financial skills” and “communication skills” (99).

Real-life functioning was evaluated with the Specific Level of Functioning Scale (SLOF) (100, 101), a hybrid scale endorsed by the panel of experts involved in the Validation of Every-day Real-World Outcomes (VALERO) (100–103), which evaluates different areas of functioning and is based on the key caregiver’s judgment on behavior and functioning of patients. The use of the SLOF allowed us to overcome limitations of previous studies investigating real-life functioning, which examined only a single or fewer domain(s) of functioning and collected only information from patients that could be influenced by many factors (e.g., delusions, hallucinations, lack of insight, disorganized thinking, cognitive deficits, or depression). The SLOF includes 43 items grouped into six domains: physical functioning, personal care skills, interpersonal relationships, social acceptability, everyday life skills, and work skills.

For each category of variables, at least one researcher per site was trained. In order to avoid halo effects, the same researcher could not be trained for more than one category. A
good to excellent agreement among raters was observed for the instruments included in the study (32).

**Translation and Validation of Assessment Instruments**

The BNSS was translated in Italian and validated within the cross-sectional study (92, 104). The validation study showed an excellent inter-rater reliability and a good convergent and discriminant validity, confirming that BNSS is a reliable tool for the assessment of negative symptoms in multicenter studies.

The validation study of the Italian version of the SLOF showed a good construct validity and internal consistency and a well-delineated factor structure of the instrument (100, 105).

The MCCB was translated in Italian (106), and this version was validated in a large sample, composed by subjects with schizophrenia, their unaffected first-degree relatives, and healthy controls (107). Furthermore, in collaboration with the MCCB developers, the standardization of raw scores through the computation of T scores was performed, using the scores of the normative Italian sample (107).

The TASIT manual was translated and the related video clips were dubbed in Italian, at the Fono Roma Studio (www.fonoroma.com) (108). In addition, the Italian version of the FEIT was developed (108).

**Statistical Analysis**

In order to investigate the simultaneous impact on functional outcome of multiple factors interacting with each other, two main statistical approaches were used: the structural equation model (SEM) and the network analysis. The SEM consists in a set of simultaneous multiple regression models for estimating and testing a pathway of relationships among variables (measured variables and latent constructs) (109). This approach allows researchers to infer causal relationship among predictors and outcome and to identify possible mediation and moderation factors, with the estimation of direct, indirect and total effects. It requires a priori assumptions of the possible associations among variables and of possible predictors, mediators, and outcomes, which is not always possible, especially because of the non-unidirectionality of some relationships (e.g., illness-related variables may influence real-life functioning and vice versa). In order to overcome these limits, a second approach, the network analysis, was used (110, 111). This type of analysis is a data-driven approach which does not require an a priori modeling of relationship among variables but generates a spatial ordered network where strongly related variables are at the center of the network and the weakly related ones at the periphery. Furthermore, estimating the number and the strength of variable connections and their closeness, this approach allows us to investigate which variables belong to the same construct and how different constructs are mutually interacting and reinforcing each other (111).

**Results From SEM and Network Analyses**

SEM analysis (32) showed that disorganization, the experiential domain of negative symptoms (including avolition, asociality, and anhedonia), positive symptoms, deficits in neurocognition, social cognition and functional capacity, internalized stigma, low resilience, and poor access to familial and social incentives had a significant direct and/or indirect impact on real-life functioning, explaining 53.8% of the variance. Neurocognition showed the strongest association with real-life functioning. The impact of neurocognition on the outcome turned out to be mainly indirect, mediated by functional capacity, social cognition, engagement with services, and internalized stigma. Social cognition also had a direct influence on real-life functioning, independently from neurocognition and negative symptoms.

Service engagement was directly associated with the functional outcome, while internalized stigma showed an indirect impact on real-life functioning, mediated by resilience. Psychopathology, in particular positive and disorganized symptoms, and the experiential domain of negative symptoms were found to be directly and indirectly correlated with real-life functioning. The impact of positive symptoms was mediated by service engagement; the effect of disorganization, by functional capacity; and the impact of the experiential domain, by services engagement, internalized stigma, and resilience (see Figure 1).

The network analysis (33) confirmed that neurocognition, social cognition, resilience, and real-life functioning are well-defined independent constructs.

With respect to psychopathologic aspects, the experiential and expressive deficit domains of negative symptoms were highly interconnected but showed different associations. In particular, the experiential domain was associated with depression, social competence, “interpersonal relationships,” and “work skills,” while the expressive deficit was associated with disorganization, functional capacity, and “everyday life skills.” Depression did not show any connection with real-life functioning. Positive and disorganized symptoms had few connections to the other nodes and were peripheral nodes in the network.

The most central and interconnected nodes of the obtained network were functional capacity and everyday life skills.

Functional capacity was shown to be the bridge between cognition (neurocognition and social cognition) and real-life functioning, in particular with the “everyday life skills.” The neurocognition and social cognition constructs were adjacent and densely connected and interconnected. Both constructs had a high impact on functional capacity, and through this, on real-life functioning. In the social cognition domain, the TASIT-1, which measures the ability to identify basic emotions, showed the highest connection with functional capacity. This finding might suggest that a good comprehension of social and emotional stimuli may lead to a better acquisition of interpersonal skills required for some of the tasks incorporated in the functional capacity assessment (e.g., communication skills).

Furthermore, also the SLOF domain “everyday life skills” had a central position within the network and connected other real-life functioning domains with psychopathology, internalized stigma, functional capacity, and through this, neurocognition and social cognition.

**Other Results of the Cross-Sectional Study**

In first-degree relatives of subjects with schizophrenia, similar direct or indirect interactions among predictors, mediators, and functional outcome were observed (112). These findings confirm
the results of the main cross-sectional study, in the absence of confounding factors, such as residual psychotic symptoms and pharmacological treatment. In addition, the presence of impairment in the “interpersonal relationships” and “work skills” also in the group of unaffected relatives suggests the possible involvement of schizophrenia vulnerability factors.

The specific impact of personal resources on functional outcome has been investigated in three different network studies (113–115). A greater resilience and a higher degree of education were associated with a better social functioning, while worse problem solving and higher internalized stigma, along with male gender and depression, were associated with more severe symptoms (114). Furthermore, lower resilience, more severe negative symptoms, and female gender were associated with depressive symptoms, while internalized stigma represented a mediator between negative symptoms and resilience, suggesting a complex relationship between personal resources, negative symptoms, and depression in schizophrenia (115). The third study investigated the relationship between self-reported personal recovery and functional recovery, identifying three different clusters of patients: (a) patients with good personal recovery and good functional outcome; (b) patients with poor personal recovery and poor functional outcome; and (c) patients with intermediate personal recovery (between the other two clusters), with good insight and high levels of depression (113). These studies underline the importance and need of an accurate characterization of personal resources in subjects with schizophrenia, in order to implement individualized treatment plans aimed at improving different aspects of these resources, which have a different impact on functioning.

The role of social cognition and its impact on functioning were investigated in a study conducted by Rocca et al. (108). The authors identified three groups of patients: (a) patients without impairment in social cognition; (b) patients with a
moderate impairment in social cognition; and (c) patients with a strong impairment in social cognition. This study revealed a linear relationship between social cognition, neurocognition, disorganization, and real-life functioning across the three groups. Positive symptoms were lower in patients without social cognition impairment, as compared to those with a moderate and a strong impairment in social cognition. Furthermore, negative symptoms were highest in subjects with moderate social cognition deficits, compared to subjects with absent or severe impairment in social cognition (108).

The relationship between disorganization and real-life functioning has emerged in one study that demonstrated that conceptual disorganization, among other disorganized symptoms, was the most relevant one impacting, through direct or indirect associations, “everyday life skills” (116).

Mucci et al. (107) reported impairment of all MCCB domains in subjects with schizophrenia. First-degree relatives showed a pattern of neurocognitive impairment, with intermediate scores between those of patients and healthy controls. In addition, patients’ MCCB scores were able to predict the first-degree relatives scores on all domains except for visual learning.

One study investigated the role of premorbid academic and social functioning impairment on real-life functioning, cognition, and psychopathology. Subjects with schizophrenia showed an impairment in premorbid academic and social functioning compared to healthy controls, while first-degree relatives had only impairment in academic aspects (117). In patients, impairment of premorbid functioning predicted severity of negative symptoms, working memory deficits, social cognition deficits, and real-life functioning. These data suggest that a poor premorbid functioning might represent a vulnerability marker of schizophrenia and highlight the need to implement early psychosocial and cognitive remediation interventions (118).

One study explored the association between insight and depressive symptoms and reported greater self-depreciation, pathological guilt, morning depression, and suicidal ideation in patients with high levels of insight (119).

Another explored aspect was the prevalence of extrapyramidal symptoms in subjects with schizophrenia and its association with neurocognition, social cognition, and psychopathology. The network analysis showed that parkinsonism was directly connected to both psychopathological and neurocognitive indices, whereas no direct connection emerged between extrapyramidal symptoms and social cognition (120).

Two studies investigated also genetic aspects in this population (121, 122). In particular, one study investigated de novo copy number variations (CNVs) in the whole-genomic DNA obtained from 46 family trios of schizophrenia probands. The authors reported the presence of de novo CNVs in genes involved in brain and neural development, suggesting that these alterations could contribute to the genetic vulnerability to the disorder (122). The study by Gennarelli et al. (121) aimed to explore the genetic basis of social cognition, using a genome-wide study approach. The authors found significant associations between the patients’ ability in social inference and the TMEM7M4 gene.

LONGITUDINAL STUDY

Participants

After 4 years, 618 subjects, out of the 921 subjects with schizophrenia enrolled in the cross-sectional study, agreed to participate in the longitudinal study (34, 37). These subjects did not differ from the rest of the baseline sample with respect to socio-demographic characteristics, illness-related factors, personal resources, context-related factors, and real-life functioning (34, 37). First-degree relatives and healthy controls were not recruited for the longitudinal study.

Assessment Instruments

In order to evaluate illness-related variables, personal resources, context-related factors, and real-life functioning in subjects with schizophrenia after 4 years from the cross-sectional study, the same assessment instruments used at baseline were adopted.

In addition, in the longitudinal study, the patients’ insight on their real-life functioning impairment, as well as the awareness of their own cognitive impairment in several domains, was also investigated. Therefore, the SLOF was administered to both patients and their caregivers, in order to explore their accuracy in self-reporting functioning. Moreover, the Cognitive Assessment Interview (CAI) was introduced in the longitudinal study (123). This is a second-generation co-primary measure and consists of 10 items that investigate six of the seven impaired domains in subjects with schizophrenia (concerning the visuospatial memory domain, no interview question was deemed appropriate). This instrument was administered to the patient and his or her caregiver to measure the perceived severity of the impairment in several cognitive domains. The impact of cognitive impairment on the patients’ daily functioning, the patients’ awareness of their own cognitive deficits, and the possible discrepancy between the patients’ and caregivers’ interviews were evaluated. The CAI was translated and adapted for the Italian context and showed a good to excellent reliability and excellent internal consistency (124).

Statistical Analysis

In order to test whether variables affecting real-life functioning in the cross-sectional study confirmed their influence at follow-up and which variables were related to changes in real-life functioning at follow-up, SEM and latent change score (LCS) modeling were conducted, respectively. Moreover, a network analysis was used to investigate whether the pattern of relationships among variables involved in the cross-sectional study was similar at follow-up and to compare the network structure of recovered and non-recovered patients at follow-up. For the classification of recovered and non-recovered patients at the 4-year follow-up, we used two criteria: (1) the presence or absence of symptomatic remission according to the Andreasen criteria and (2) the presence or absence of functional recovery, defined as a weighted score of at least 76.2 on SLOF “interpersonal relationships,” “work skills,” and “everyday life skills” scales (34).
Results From SEM and Network Analyses in the Longitudinal Study

In the longitudinal study, SEM and LCS analyses (37) showed that baseline measures of neurocognition, social cognition, the experiential domain of negative symptoms, everyday life skills, and to a lesser degree, positive symptoms predicted functional outcome after a 4-year follow-up.

The SEM model confirmed that neurocognition, social cognition, positive symptoms, the experiential domain, and available incentives had a significant direct or indirect impact on at least one real-life functioning domain at the 4-year follow-up assessment. Higher baseline neurocognitive functioning predicted better everyday life skills and work skills; better social cognition predicted better work skills and interpersonal relationships; more severe positive symptoms predicted lower work skills; more severe experiential domain symptoms predicted worse interpersonal relationships; and more social incentives predicted better everyday life skills. The LCS model showed that the same baseline variables, except incentives, predicted changes in functioning at the 4-year follow-up. In particular, better baseline neurocognition predicted improvement in everyday life skills, work skills, social cognition, and functional capacity after 4 years. Less severe experiential domain symptoms and better social cognition at baseline predicted improvement in interpersonal relationships at follow-up, while less severe positive symptoms at baseline predicted improvement in work skills. Finally, better baseline everyday life skills predicted improvement in work skills and in functional capacity at follow-up.

The network analysis in the longitudinal study (34) confirmed the results of the cross-sectional one (33). The network structure remained substantially unchanged: neurocognition, social cognition, resilience, and real-life functioning were spatially contiguous and highly interconnected; everyday life skills and functional capacity were the most central and interconnected nodes of the network, while psychopathological domains were more peripheral. The number and the strengths of network connections in non-recovered patients were significantly different compared to those of the recovered ones. In fact, the network of non-recovered patients had more connections, whose strengths were higher than those found in recovered patients. The SLOF domain everyday life skills and disorganization had a higher strength among non-recovered patients, as compared to recovered ones.

Other Results of the Longitudinal Study

The network longitudinal study also contributed to the investigation of the accuracy of subjects with schizophrenia in self-evaluation of functioning. The study, conducted by Rocca et al. (125), aimed to investigate the concordance of patients’ reported impairment in real-life functioning with the caregivers’ reported one. Furthermore, it aimed to identify which factors are associated with discrepancies between patients’ and caregivers’ reports. Results indicated that patients systematically reported a higher functional level than their relatives; however, the patient–caregiver discrepancy was significant only in 17.6% of the cases. The strongest predictors of patient–caregiver discrepancies were caregivers’ ratings in each SLOF domain. These findings underline the possibility to use in clinical practice patients’ self-evaluation of functioning in order to design tailored rehabilitative programs.

ELECTROPHYSIOLOGICAL AND OTHER ADD-ON STUDIES

Two investigations were carried out within the electrophysiological add-on study (126, 127). The first study aimed to investigate neurophysiological correlates of negative symptom domains. This study showed that the brain electrical microstate A (microstate associated with the visual network) was related to the experiential domain and not to the expressive one. Within the experiential domain, avolition, asociality, and anticipatory anhedonia, but not consummatory anhedonia, showed a similar pattern of correlation. These data suggest the existence of distinct electrophysiological correlates of the two negative symptom domains and lend support to the hypothesis that only the anticipatory component of anhedonia shares the same pathophysiological underpinnings of the experiential domain (126). The second study aimed to investigate electrophysiological and neurocognitive correlates of the PANSS disorganization dimension, in order to evaluate the heterogeneity of this dimension and its possible overlap with neurocognitive deficits. The authors reported that the slow alpha activity was negatively correlated with disorganization in subjects with schizophrenia. At item level, only the PANSS item “Difficulty in abstract thinking” showed the same correlation. The MCCB neurocognitive composite score was associated with disorganization dimension as well as PANSS items “Conceptual disorganization” and “Difficulty in abstract thinking”. These findings support a partial overlap between disorganization and neurocognitive impairment. In addition, they suggest that some aspects of disorganization could be related to the impairment of basic neurobiological functions that are only partially evaluated using MCCB (127).

Finally, the network longitudinal study contributed also to the characterization of a subgroup of subjects with schizophrenia defined by the presence of autistic spectrum symptoms. Patients with autistic traits represent a specific population of subject with schizophrenia, characterized by specific patterns of functioning, resilience, and coping abilities (128). Moreover, autistic symptoms may have a relevant impact on different aspects of the disease, in particular neurocognitive and social cognition domains, functional capacity, real-world interpersonal relationships, and participation in everyday life activities (129).

The other add-on studies are still ongoing, and their results have yet to be published.

DISCUSSION

So far, the network has published more than 20 scientific papers and contributed to the validation of state-of-the-art assessment tools and to the training of many researchers from all the involved centers. Furthermore, in the last decade, the network
contributions have led to an improvement in knowledge about main determinants of functioning and, therefore, of clinical recovery in subjects with schizophrenia. Despite the introduction of innovative pharmacological and psychosocial treatments that facilitate symptomatic remission, the impairment in different areas of real-life functioning still represent an unmet need in the care of people suffering from schizophrenia, thus causing a huge burden on patients, their families, and health care systems (31–35, 37, 39–41). The strengths of the two main network studies, with respect to previous studies, include the analysis of a greater number of variables, some of which had never been examined before; the use of state-of-the-art instruments for the assessment of each variable included; and appropriate data analysis methods, in order to explore the complex relationship between possible predictors, mediators, and functional outcome measures. Finally, the implementation of the longitudinal study allowed us to overcome the limitations of the cross-sectional design that prevented inferences about the direction of causality.

The findings from the network studies (32–34, 37) suggest that different factors—some related to the illness, some to personal resources, and others to the social context—contribute to functional outcome, through direct or indirect associations.

The network findings strongly support the implementation of integrated treatments, combining pharmacological, psychosocial, and rehabilitative interventions. In fact, pharmacotherapy is mainly used in order to achieve the remission of positive symptoms, which had a small impact on real-life functioning of subjects with schizophrenia. Functional capacity and everyday life skills were the most central and interconnected nodes of the schizophrenia network, suggesting that they should be the main target of rehabilitative recovery-oriented programs. Moreover, since impairment in neurocognition and social cognition was the most important predictors of real-life functioning, cognitive remediation interventions should be integrated into routine clinical practice. Negative symptoms, in particular those belonging to the experiential domain, i.e., avolition, asociality, and anhedonia, have a direct impact on interpersonal functioning and predict follow-up levels of functioning in the same domain. These negative symptoms do not show any connections with functional capacity or social and non-social cognitive abilities. Their treatment remains an unmet need of schizophrenia care. Further research is needed in order to disentangle the complexity of this negative symptom domain, looking also at behavioral and neurobiological correlates in order to search for effective treatments (130).

The research question concerning the relationships of cognitive impairment and negative symptoms has been investigated with an innovative approach in the two network studies. In the cross-sectional study, SEM analysis demonstrated that only the experiential domain of negative symptoms had a distinct direct effect on functioning, while the expressive domain was not retained in the model when including cognitive impairment. The network analysis findings added further insight to the issue, showing that expressive deficit had no direct connection to real-life functioning nodes and was connected to functional capacity, as were social and non-social cognitive variables, and to disorganization. The experiential domain was directly connected to the interpersonal relationships and work skills domains of real-life functioning, while having no direct or indirect connections with the cognitive nodes, functional capacity, and disorganization. These findings were confirmed by the network analysis carried out on the follow-up data and have implications for the personalized management of patients with negative symptoms. The implementation of psychosocial interventions focused on motivation and pleasure, which targeted the experiential domain of negative symptoms, is very recent and awaits further testing. Effective treatments such as social skills training and cognitive remediation interventions should be made available to subjects with negative symptoms, in particular to those with expressive deficit, such as alogia and blunted affect. Clinical research on the effectiveness of these interventions for negative symptoms should always include at least as a secondary outcome the differential efficacy on the two domains of the negative symptoms.

The network studies document that many other factors have an impact on functional outcome, such as other aspects of psychopathology, personal resources, or context-related factors. This suggests the importance of personalized treatments based on a detailed characterization of each patient, as recently suggested by a group of experts in the field (51).

Moreover, the electrophysiological add-on studies of the network contributed to improve the knowledge of neurophysiological correlates of psychopathology. In fact, although several papers reported resting-state electrophysiological alterations in subjects with schizophrenia (131–133) and their association with psychopathology and cognitive impairment (134, 135), no study investigated the neurophysiological mechanisms underlying distinct negative symptom domains and the disorganization dimension. The network studies showed the existence of distinct electrophysiological correlates of the two negative symptom domains. Furthermore, they suggested the partial overlap between disorganization and neurocognitive impairment and the relationship of some aspects of disorganization with basic electrophysiological alterations which might represent biomarkers of this dimension.

Finally, moving from the evidence of significant levels of autistic traits in a substantial proportion of patients with schizophrenia (136, 137), the network add-on studies on this topic showed that patients with autistic traits represent a population of subject with schizophrenia, characterized by peculiar patterns of social and non-social cognitive impairment and deficits in real-life functioning, thus suggesting that these patients might benefit from specific and targeted interventions.

The network will continue to promote research in this field in order to improve the functional outcome of people suffering from schizophrenia, thus reducing the burden on patients, their families, and health care systems.

**AUTHOR CONTRIBUTIONS**

The project idea was initiated by SG, involving a collaboration with LG and GG. LG wrote the first draft of the manuscript.
All authors were responsible for the interpretation of the results, contributed to critically revising the content, and approved the final manuscript for submission to Frontiers in Psychiatry.

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