Determinants of Clinical Recovery in Schizophrenia

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2.1 Introduction

Schizophrenia is a severe mental disorder with a high heterogeneity in terms of risk factors, comorbidities, clinical presentation, course, response to treatment, and functional outcome [1, 2].

About 75% of people suffering from this disorder show a clinical course characterized by remission and relapse phases, and about one in seven people meet criteria for recovery [3–5].

Recovery, to date, seems to represent the end point of an historical, cultural, and scientific process that, for the care of people with schizophrenia, initially regarded as a target the improvement of symptom severity, then moved to symptomatic remission, and finally to recovery [3, 6–9].

Actually, this reflects the development in the conceptualization of schizophrenia. In the first descriptions it was named "dementia praecox" and regarded as a progressive and irreversible disorder with an unfavorable course [10]. This pessimistic view began to change with the discovery of antipsychotic medications in 1950s, which led to the discharge to the community of the vast majority of people institutionalized due their disorder [6]. Therefore, with the advent of antipsychotics, the main target to achieve was the improvement of severity of schizophrenia symptoms and, consequently, the prognosis was based primarily on the response to treatment. Although a clear agreement on the definition of response to treatment was never reached, "response" is a relative term, which defines an overall improvement of patient's signs and symptoms [11]. Conversely, "remission" is an absolute term,

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defined by a specific threshold of severity of core symptoms (delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, negative symptoms). In particular, according to the Remission in Schizophrenia Working Group, a patient is in remission when schizophrenia core symptoms are scored as mild or less on psychopathological rating scales (e.g., the Positive and Negative Syndrome Scale-PANSS, The Scale for the Assessment of Negative Symptoms and Positive Symptoms, or the Brief Psychiatric Rating Scale) for at least 6 months [12].

However, it became evident that the symptomatic remission concept did not cover all the dimensions of schizophrenia, which include not only core symptoms, but also depressive symptoms, cognitive functions, comorbidities, quality of life, and, more in general, the functional outcome [7].

Therefore, besides the symptomatic remission and the prevention of acute relapses, also the prevention and treatment of comorbidities, as well as the improvement in functional outcome and the subjective well-being, are now considered important targets of the care of people with schizophrenia [3, 6, 8, 13–17]. Within this frame, different stakeholders, such as patients, family members, advocates, and scientists, contributed to the development of the recovery concept. Recovery is a multifaceted and a broad umbrella construct [18]. Different conceptualizations have been described, e.g., internal vs. external recovery; clinical vs. social recovery; subjective or personal recovery vs. objective or clinical/functional recovery [3, 9, 13]. Internal factors refer mainly to hope and health, while external factors to human and patient's rights and opportunities for vocational and social integration [9]. Clinical recovery corresponds to symptoms reduction and improvement in functioning, while social recovery corresponds to economic and social independence [9, 19]. Subjective recovery, also named as personal recovery, refers to the subjective experience of recovery, defined by the quality of life, hope, reliance on others, and not feeling overwhelmed by symptoms [20, 21]. This concept has been developed based especially on narratives of individuals who have experienced mental illness and, therefore, has also been named patient-based recovery. Within this conceptualization, recovery has been defined as "a deeply personal, unique process of changing one's attitudes, values, feelings, goals, skills and roles … living a satisfying, hopeful, and contributing life even with limitations caused by the illness … the development of new meaning and purpose in one's life, as one grows beyond the catastrophic effects of mental illness" [22]. Therefore, recovery means a transformation in which the patient accepts what he or she cannot do or be and discovers who he or she can be and what he or she can do. In this sense, recovery is not a return to a "premorbid state," not an end product or a result, but it is a transformative and developmental process, which changes from person to person and also over time in the same individual [9, 18]. Different authors have tried to define important aspects of personal recovery and described different components and characteristics that are fundamental for reaching recovery: hope, reestablishment of identity, finding meaning in life, connectedness, empowerment, self-direction, individualized and person centered, holistic, nonlinear, strengths based, peer support, respect, and responsibility [6, 18, 22–29]. A systematic review conducted by Leamy et al. (2011) [28] has identified four fundamental components of personal recovery: hope, reestablishment of

identity, finding meaning in life, connectedness and empowerment. Different assessment instruments have been developed to assess these aspects of subjective recovery; some are based entirely on the perspective of mental health service users while others also on the perspective of clinicians, scientists, family members, and legislators [13, 30–33].

Objective recovery, named by some authors as clinical or functional recovery, refers to remission of symptoms and improvement in functioning, in particular in the ability to function in the community, socially and vocationally. In this meaning, recovery is conceptualized as an outcome influenced by several factors [7]. Liberman et al. (2002) [34] defined recovery as the stage at which a patient is socially and professionally well functioning and he or she is relatively free of psychotic symptoms (BPRS<4, moderate) [34]. Other authors have also included living independently, having friends and scores of >65 on the Global Assessment of Functioning (GAF). Therefore, two aspects are crucial in determining clinical recovery, symptomatic remission and satisfactory real-life functioning.

In this chapter we will describe the major determinants of clinical recovery, i.e., symptomatic remission and improvement in real-life functioning. In particular, we will focus on those factors that have an impact on functional outcome, whose identification has a crucial role in the development of integrated and individualized targeted treatments aimed at achieving recovery. Factors most consistently reported in association with functional outcome are deficit of neurocognition, functional capacity and social cognition, as well as the severity of negative symptoms; however, several other psychopathological, personal and environmental variables have shown a potential role in determining functional outcome [14–17, 35].

The literature on the topic has shown that: (1) determinants of functional outcome in subjects with schizophrenia are multifactorial; (2) their relationship with functional outcome is not always direct; therefore, it is extremely important to clarify multiple direct and indirect pathways between potential predictors and functioning, as well as identify the role of mediating variables; and (3) variables explored as potential predictors of functional outcome and variables chosen as indices of functioning represent complex domains, whose assessment modality plays a fundamental role in the reliability of study findings.

In the following paragraphs, main findings on determinants of functional outcome in subjects with schizophrenia and their direct and indirect relationship with indices of functioning will be described.

2.2 Cross-Sectional Assessment of Determinants of Clinical Recovery

2.2.1 Neurocognitive Deficits

The impairment of cognitive functions has been regarded since the early description of the syndrome [10, 36] as a basic characteristic of schizophrenia. Cognitive deficits have been reported in 75–80% of subjects with schizophrenia who showed a

performance on the majority of cognitive tests from 1.5 to 2 standard deviations below normative values [37–41]. Deficits involve different cognitive domains, such as general cognitive abilities (as assessed by IQ), attention, executive functions, speed of processing, secondary memory, working memory, and semantic memory [40, 42–46]. Several findings bring to the assumption that cognitive deficits in schizophrenia are primary and therefore not due to known factors, such as symptoms severity and pharmacological treatments [39, 47, 48]. In fact, an impairment of cognitive functions is observable before the onset of the disorder [49, 50] and often persists after symptom remission [37]. Moreover, cognitive deficits similar to those found in patients with schizophrenia, though less severe, have been found in their unaffected first-degree relatives [41, 51–53], suggesting that they may represent a vulnerability factor for the disorder.

According to the findings of a large body of literature, cognitive deficits are strong predictors of functional outcome in subjects with schizophrenia [14, 35, 42, 54] and have a greater impact on social functioning than positive and negative symptoms [14, 35, 55–57].

Some studies found that deficits of specific cognitive domains influence all or some aspects of functional outcome. According to a meta-analysis [42], specific patterns of associations can be identified: for instance, secondary verbal memory associated with all areas of functioning; immediate verbal memory with psychosocial skill acquisition of basic life skills such as conversation and leisure skills; executive functioning with daily activities; and sustained attention with social problem solving. However, this meta-analysis underlined that effect sizes of the associations tended to be medium, while more robust associations were found when global measures of neurocognition were used. Other domain-specific associations included attention/working memory with work skills; executive functions with interpersonal behavior; and processing speed with all areas of functioning [58]. In other papers, no domain-specific associations were found between neurocognition and functioning [59–63].

One point arising from studies investigating these relationships is that the deficit in neurocognition, although widely recognized as a factor associated to real-life functioning, is not sufficient by itself to predict functional outcome and other factors contribute with a direct or indirect impact to functional outcome or act as mediators of the relationship between neurocognitive deficits and functional outcome [14–17, 35, 42, 54, 64–66]. Social cognition, functional capacity, and negative symptoms are more frequently reported as predictors of functioning or mediators, but many other variables have been taken into account, although less frequently. The definition of these factors and their role in the pathways between potential predictors and functional outcome are reported in the next paragraphs.

2.2.2 Deficits of Functional Capacity

Functional capacity is the ability to perform everyday life activities measured with tests or role plays in laboratory settings [67]. Its association with functional performance in everyday life is inconsistent since the latter can be influenced by several

aspects such as motivation and environmental factors [54]. An impairment of functional capacity has been reported in patients with schizophrenia, even in early-onset patients, and is considered a key aspect of the disorder [68, 69].

The majority of studies including functional capacity in pathways between potential predictors and functional outcome found that it acts as a mediator between neurocognitive performance and real-life functioning [35]. Bowie et al. [54] reported that neurocognitive performance has a small direct contribution to real-life performance, while it is in large part associated to functional capacity that, in turn, is significantly associated to all domains of real-life functioning. According to the findings of this study, functional capacity represents the stronger predictor of functional outcome with additional variance explained by the direct effect of negative and depressive symptoms.

A network analysis carried out in a large sample of patients within the Italian Network for Research on Psychoses (INRP) showed that functional capacity and everyday life skills were the most central and interconnected nodes in the network and that the former bridged both neurocognition and social cognition with "Everyday life skills" domain, which, in turn, was connected to other areas of real-life functioning, i.e., "Work skills" and "Interpersonal relationships" [15].

A study examining the relationships of specific neurocognitive domains and two different aspects of functional capacity (everyday living skills and social competence) with distinct aspects of real-life functioning reported a complex pattern of associations: both domains of functional capacity mediated the relationship between neurocognition and two domains of functioning, community activities and work skills, while only social competence predicted the interpersonal functioning domain [58]. In addition, social competence seems to act as mediator between social cognition and everyday functioning, suggesting that the impairment of both neurocognition and social cognition predicts the deficit of functional capacity which, in its turn, predicts impairment in different domains of functional outcome [66].

Discrepant findings have also been reported, such as lack of correlation between neurocognitive indices or functional capacity and self-reported functional outcome [70], or an impact of neurocognitive dysfunction on everyday life functioning without influence of functional capacity [71].

2.2.3 Deficits of Social Cognition

Social cognition is the subject's ability to perceive, interpret, and process social stimuli for adaptive social interactions. It is currently considered a domain relatively independent of neurocognition, although related to it [72–74]. It is a complex construct for which four different domains have been identified by a consensus of experts [75]: emotion processing, social perception, theory of mind (ToM), and attributional bias. Deficits of one or more domains of social cognition have been reported in subjects with schizophrenia, even early in the disease process, as well as in subjects at risk to develop the disorder, and have been found to be stable over time [76–78].

Given its impact on social interactions, social cognition has been considered a candidate as mediator in the relationships between functional outcome and its potential predictors. Several studies found that social cognition is associated to functional outcome even more strongly than neurocognition, acting as mediator between the latter and functional outcome [14–17, 65, 66, 72, 74, 79–83].

Patterns of association between specific domains of social cognition, neurocognition, and functional outcome vary among studies depending on the investigated indices. Some examples include social perception as mediator in the relationship between early visual processing and functional outcome, the association of social cognition only with the domain of interpersonal functioning, the role of ToM as mediator between cognition and social competence that, in turn, showed a direct path of association with self-reported functioning [83, 84].

Some studies also found that different domains of social cognition are mediators in the relationship between neurocognition and social aspects of functional capacity (social competence), which then have a direct impact on social functioning [84–86].

Although heterogeneous, these findings, together with those reported in the previous paragraphs, strongly suggest the need to focus on specific therapeutic targets, such as deficits of social cognition and deficit of functional capacity, in addition to neurocognitive deficits.

2.2.4 Negative Symptoms

Negative symptoms are a core clinical dimension of schizophrenia. They have been described in prodromal phases of schizophrenia, as well as in unaffected first-degree relatives of subjects with the disorder [57, 87]. Negative symptoms represent an unmet need in the care of the disorder, as they are associated to poor response to available treatments and to poor functional outcome [88–91]. In fact, several data suggest that their presence negatively influences functional outcome of patients with schizophrenia [92–94].

Both direct and indirect relationships between negative symptoms and functional outcome have been reported, as well as evidence of their role as mediators in pathways of functional outcome. In a study exploring the impact of several factors on three different areas of functioning, negative symptoms showed a direct relationship with interpersonal skills, independent of other predictors such as neurocognition and functional capacity, while they did not contribute to the prediction of everyday life skills and work skills [54]. In a further paper of the same authors, the direct relationship between negative symptoms and interpersonal skills was confirmed, but also an indirect effect on all the three areas of functioning (interpersonal skills, community activities, and work skills), mediated by a reduction of social competence, was reported [58]. The finding of a direct relationship of negative symptoms with indices of functional outcome suggests that they may have an impact on functioning that is independent of cognition. Both direct and indirect impact (the latter mediated by social competence) of negative symptoms on outcome were confirmed in a study using self-reported functioning as outcome index [84]. In a paper investigating the

impact of specific PANSS negative symptoms on functioning in the areas of interpersonal functioning and everyday activities, blunted affect and passive-apathetic social withdrawal were found to predict outcome in the former area, while lack of spontaneity in the latter. These specific negative symptoms resulted stronger predictors than the PANSS negative total score and served as mediators between functional capacity and real-world functioning, suggesting that subjects may have the competence for a good functioning but the presence of those specific negative symptoms limits patient's ability to use such competences in real life [55].

The influence of negative symptoms on functioning was confirmed in a meta-analysis showing that they mediate the relationship between neurocognition and functional outcome [95]. In a more recent paper, negative symptoms, together with general psychopathology and insight, were associated to cognition and predicted functioning acting as mediators in the relationship between cognition and functioning [96]. These findings suggest that cognitive deficits have a negative impact on symptoms and insight that, in turn, exert a negative impact on functioning. Some other studies found a prominent role of the negative construct amotivation in influencing functioning in people with schizophrenia [97, 98].

Taken together, these findings confirm that negative symptoms have an impact on functional outcome. However, the heterogeneity of results does not allow conclusions on either the identification of specific negative symptoms associated to functional outcome or on the definition of pathways of associations with other predictors of functioning. Actually, negative symptoms represent a complex and heterogeneous psychopathological dimension, including different constructs that can be grouped, according to studies based on factor analysis, in two main domains: the expressive domain (including blunted affect and alogia) and the experiential domain (including avolition, asociality, and anhedonia) [93, 94, 99]. The two domains seem to be associated with different neurobiological abnormalities and psychosocial outcome [94, 100, 101]. Moreover, within the construct of anhedonia, two different aspects have been described: consummatory anhedonia (reduced experience of pleasure derived from ongoing enjoyable activities) and anticipatory anhedonia (reduced ability to anticipate future pleasure): the former one seems to be relatively intact in schizophrenia, while the latter one seems to be impaired [102, 103]. It has been hypothesized that patients with schizophrenia with persistent cognitive deficits may be unable to retrieve their memories of previous positive experiences, leading to a difficulty in anticipating pleasurable consequences of actions [35]. Therefore, these two aspects of anhedonia may have different patterns of association with functional outcome. Finally, a valid and reliable assessment of negative symptoms is challenging and, as matter of fact, rating scales used in the above-reported studies for the assessment of negative symptoms have been criticized for the inclusion of items assessing neurocognition and the focus on behavioral aspects, as opposed to internal experience, which may lead to artifactual associations with functional outcome measures [104, 105].

To overcome these limitations, second-generation rating scales, such as the Brief Negative Symptom Scale (BNSS) [104, 106] and the Clinical Assessment Interview for Negative Symptoms [105], should be preferred. The BNSS is a new-generation

rating scale for the assessment of negative symptoms that has several advantages with respect to the older ones: it does not include symptoms previously considered as part of the negative dimension but now clearly identified as aspects of other dimensions, such as the cognitive or depressive one [93, 104, 106–108]; it provides a separate assessment of the consummatory and anticipatory anhedonia, a total score as well as a separate score for each of the five negative symptom domains, 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. According to several studies, the BNSS five negative symptom domains can be grouped in the two main domains: the Expressive domain, including blunted affect and alogia, and the Experiential domain consisting of anhedonia, asociality, and avolition.

Based on this evidence, in all studies of the Italian Network for Research on Psychoses aimed at identifying factors that affect real-life functioning of subjects with schizophrenia and defining their relative contribution, the BNSS was used to assess the negative psychopathological dimension. In those studies, we found a different impact of the two main domains of negative symptoms on functioning: the Experiential domain showed a direct and indirect effect on real-life functioning and was connected to the areas of real-life functioning "Interpersonal relationships" and "Work skills" in the network analysis, while the Expressive domain was only indirectly and weakly related to real-life functioning and, in the network analysis, resulted connected to "Everyday Life Activities" [14, 15].

2.2.5 Other Potential Predictors or Mediators of Clinical Recovery

Besides the negative ones, other symptoms have been investigated as potential predictors of functioning. Depression has been found to be directly associated to some areas of functioning [54, 58]. However, no impact was found in other studies [14, 109]. Several studies found that disorganization is associated with real-life functioning [14, 15, 57, 63, 95, 110]. The presence of severe disorganization has a negative impact on outcome as it interferes with functioning in the acute phase of the illness and with the achievement of symptomatic remission [111–113]. The role of positive symptoms has been explored in a few studies reporting heterogeneous results, including lack of association with functioning [114], a direct effect on Work skills and Everyday life skills [58], or an association with Community activities only [55]. The presence of autism spectrum disorders symptoms has been found associated to poor functional capacity, real-life interpersonal relationships, and participation in community-living activities [115]. Poor premorbid level of functioning has been also found in association with worse functional outcome [116, 117].

Some studies also investigated the role of personal resources: patients with comparable severity of psychopathology present heterogeneous real-life functioning because of differences in coping strategies, recovery style, and resilience [118, 119]. As to the coping strategies, those defined as "emotion-oriented," together with those "avoidance oriented," are associated with a worse real-life functioning [119, 120]. Resilience has been found in association with patterns of patients' engagement with mental health services, which can affect real-life functioning [121].

Among personal resources, physical health status plays an important role in quality of life and functioning of people with schizophrenia. In these subjects, indeed, high medical comorbidity was reported, and attributed to several factors, including lifestyle and treatment with antipsychotics [122, 123]. Deficit in neurocognition and functional capacity may also impair patients' ability to choose and cook food and contribute to the risk of obesity and other metabolic issues in patients with schizophrenia [66].

Several environmental factors have been found in association to real-world functioning, including poor economic status, lack of disability compensation and of support services, and living in poor neighborhoods [35]. All these factors obviously influence real-life functioning and should be included in studies investigating predictors of functional outcome; however, the identification of the most appropriate indices to capture the complexity of these variables may be difficult [14].

A higher level of internalized stigma (i.e., the incorporation of others' prejudices and stereotypes about people with mental illnesses into beliefs about oneself with consequent anticipation of social rejection) [124] has been found in association with several psychosocial variables such as hope, self-esteem, and empowerment [125]. In addition, an indirect association mediated by resilience has been found between internalized stigma and real-life functioning [14]. Therefore, it is likely to influence real-life functioning and should be included in relevant studies.

Other demographic and clinical factors have been reported as predictors of clinical recovery, including female gender, higher educational level, older age at onset, shorter duration of untreated psychosis, and less cannabis use [3].

2.3 Longitudinal Assessment of Determinants of Clinical Recovery

As emerged from previous paragraphs, factors most consistently reported in association with functional outcome are deficit of neurocognition, functional capacity and social cognition, as well as the severity of negative symptoms. However, the majority of studies investigating factors affecting functional outcome had a cross-sectional design, which, unfortunately, prevented inferences about the direction of causality. Only few studies had a longitudinal design investigating pathway towards functional outcome. Findings arising from these studies are summarized below.

2.3.1 Neurocognitive Deficits

Several studies with a longitudinal design found that deficits in cognitive domains were associated with later functional outcome at follow-up time points ranging from 6 months to 10 years (20 years in the case of a retrospective study) [16, 17, 43, 126–128]. Lack of such an association has also been found in some studies [43, 129]. More in detail, the review by Green et al. (2004) [43], which included 18 longitudinal studies, reported that the majority of them (N = 14) found associations between baseline impairment of various cognitive indices and later functional outcome with an effect size in the medium to large range. Two studies included in the review did not find any relationships between baseline cognition and outcome, and two more studies reported not clear results (one found associations only for one out of two samples, and the other for one out of two types of community outcome). Among more recent papers not included in the review, one [126] reported that, in a small sample of patients with first-episode schizophrenia, the baseline cognitive domains attention, verbal learning, and verbal working memory were associated with social outcome at follow-up, while attention, verbal working memory, and reasoning/problem solving with role functioning at follow-up. Another paper [127] found that the cognitive domain processing speed predicted self-care, vocational outcome, and social functioning at 6-month follow-up. Baseline global cognition resulted a predictor of 1-year functional outcome, although at a weaker level with respect to avolition in a sample of 114 Chinese patients with first-episode schizophrenia [128]. No associations were found between baseline neurocognition and everyday functioning in a paper conducted in 111 patients with chronic schizophrenia [129].

From the majority of longitudinal studies emerges that cognitive deficits predict later functional outcome; however different patterns of associations have been described in the abovementioned studies, involving different cognitive domains and indices of outcome. This is probably due to methodological problems, including the heterogeneity of instrument used to assess cognitive functions, mainly measured combining tests to evaluate different cognitive domains, and only in one study [126] assessed by means of the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB) that is regarded as the state-of-the-art neuropsychological battery for research purposes in schizophrenia [130, 131]; the heterogeneity of indices of functional outcome; and the small sample size included in the majority of studies.

These points were addressed in a recent study carried out within the Italian Network for Research on Psychosis aimed to verify whether factors identified as predictors and mediators of real-life functioning at the baseline were confirmed as such in a 4-year longitudinal design [16, 17]: state-of-the-art instruments were adopted to assess psychopathology, neurocognitive functions, social cognition, personal resources, and real-life functioning in 618 patients out of the 921 recruited in the cross-sectional study. The study adopted three main strategies of statistical analysis. Two of them—Structural Equation Model (SEM) and Latent Change Score (LCS) modeling—were used to investigate, respectively, whether variables that

showed an impact on real-life functioning in the cross-sectional study confirmed their influence at follow-up and which variables affected changes at follow-up in real-life functioning [17]. Furthermore, also a network analysis with a longitudinal design was conducted to test whether the pattern of relationships among all variables investigated in the cross-sectional study was similar at follow-up and to compare the network structure of patients who were classified as recovered at follow-up versus those who did not recover [16]. The network analysis has the advantage of not requiring the a priori modeling of relationships among variables needed in SEM, but produces spatially ordered networks in which variables are nodes and causal interactions between variables are connections between nodes expressing direction and magnitude of correlations. Strongly related nodes at the center of the graph and weakly related ones at the periphery. Moreover, closeness of nodes, as well as strength and number of their connections, provides estimates of the extent to which variables belong to the same construct and how different constructs are mutually interacting and reinforcing each other [132].

Both SEM and LCS analyses in the longitudinal study consistently confirmed that neurocognition is among factors predicting functional outcome at 4-year follow-up. In particular, according to the SEM, better baseline neurocognition predicted better everyday life and work skills. The LCS model, used as a control analysis, showed that better baseline neurocognitive functioning predicted improved everyday life skills, work skills, social cognition, and functional capacity at follow-up. As regard to the network analysis [16], the network structure in the longitudinal study did not change significantly with respect to the cross-sectional one. In fact, at both time points, neurocognition, together with social cognition, resilience, and real-life functioning, was spatially contiguous and highly interconnected, confirming the central role of these variables in impacting real-life functioning.

2.3.2 Deficits of Functional Capacity and Social Cognition

Very few longitudinal studies investigated the association between functional capacity and/or social cognition with functional outcome [16, 17, 129, 133, 134]. It has been reported that worsening in measures of functional capacity and of social competence predicts worsening of everyday functioning in the domains everyday life and working skills of the real-life functioning after 18 months [129]. In patients with first-episode schizophrenia, social cognition assessed with three different instruments was found to predict work, independent living, and social functioning at 1-year follow-up [133]. The study of McCleery et al. [134] found a cross-sectional association between social cognition and community functioning, while no association was observed between baseline social cognition and community functioning at 5 years follow-up, suggesting the hypothesis that social cognition may have a short-term rather than long-term implications for outcome. In the longitudinal study of the Italian Network for Research on Psychosis [16, 17] SEM analysis showed that better baseline social cognition predicted better work skills and interpersonal relationships at follow-up, and LCS analysis confirmed the association between the same

baseline variables and interpersonal relationships. As mentioned above, network analysis showed that social cognition is among variables highly interconnected to real-life functioning and that functional capacity and everyday life skills had a high betweenness and closeness in the network.

Overall, although a few studies are available on this topic, findings of longitudinal studies confirm the contribution of social cognition and functional capacity in predicting later functional outcome.

2.3.3 Negative Symptoms

Longitudinal studies exploring the role of negative symptoms in predicting functional outcome showed positive results [16, 17, 90, 97, 128, 135–138]. Different domains and categories of negative symptoms have been explored in the various papers, given the already mentioned complexity and heterogeneity of this psychopathological construct. The presence of persistent negative symptoms in two different cohorts of patients with first-episode schizophrenia was found to be associated to worse psychosocial functioning after 1 year [135] and after 4 weeks [136]. Studies exploring the Experiential and the Expressive domain found that the former has a higher predictive value than the latter on functional outcome [16, 17, 90, 128, 137]. In line with these findings, two more studies reported the role of amotivation in predicting functional outcome [97, 138]. Some discrepancies emerge on the functional domain predicted by negative symptoms, as in one study [138] amotivation was found to predict poor work but not social functioning, while in another paper [16] more severe avolition predicted worse interpersonal relationships. The use of outdated instruments for the evaluation of negative symptoms is among the main limitations of the above-reported studies, as only two of them [16, 17] used a new-generation rating scale (BNSS) for the assessment of this psychopathological domain. In spite of the above limitations, longitudinal studies confirmed that negative symptoms are among strongest predictors of later functional outcome.

2.4 Conclusions

Findings summarized in this chapter confirm that several variables are involved as predictors or mediators of clinical outcome and that their interactions and pathways towards functional outcome are complex.

Social and nonsocial cognition show a key role as predictors of real-life functioning, suggesting that rehabilitation interventions addressing their impairment should be routinely included in integrated treatments aimed at clinical recovery in patients with schizophrenia. Such interventions should be provided as early as possible given the fact that the above-reported impairments have been described since early stage of illness and even before clinical onset.

Negative symptoms have certainly an impact on clinical outcome, although the complexity of this psychopathological domain leads to some heterogeneity in findings regarding the most involved subdomains and their role as direct/indirect predictors or mediators. The search for effective treatments for negative symptoms should represents a priority for research in schizophrenia.

The reported role of many other factors in influencing clinical outcome, either those related to personal resource—such as resilience or physical health status—or those related to the context, underlines the importance of personalized treatments based on a detailed characterization of each individual patient [139].

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