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## Pathways to functional outcome in subjects with schizophrenia living in the community and their unaffected first-degree relatives

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#### ABSTRACT

Rationale: Variables influencing real-life functioning have repeatedly been modeled in schizophrenia subjects but not systematically investigated in their unaffected first-degree relatives (SRs), in whom milder forms of deficits reported in schizophrenia have been observed, but confounders of clinical cohorts are not in play. Demonstrating that pathways to functional outcome are similar between patients and SRs would validate structural models developed in schizophrenia subjects. The present multicenter study aimed to explore whether variables associated with real-life functioning are similar in schizophrenia patients and their unaffected relatives.

Methods: The study sample included 921 schizophrenia patients, 379 SRs and 780 healthy controls. Structural Equation Models (SEMs) were used in patients and SRs to test associations of psychopathological dimensions, neurocognition, social cognition, resilience, perceived stigma and functional capacity with real-life functioning domains, impaired in both patients and SRs.

Results: Interpersonal Relationships and Work Skills were the only functional domains impaired in both patients and SRs. For both domains, functional impairment in patients was found to predict impairment in unaffected relatives, suggesting the involvement of similar illness-related vulnerability factors. In both groups variables significantly associated with Interpersonal Relationships included Social Cognition, Neurocognition, Avolition,

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S. Galderisi et al. / Schizophrenia Research xxx (2016) xxx-xxx

Resilience, Disorganization, Perceived Stigma and Gender, and those significantly associated with Work Skills included Social Cognition, Neurocognition and Disorganization.

*Conclusions*: Pathways to functional outcome for Interpersonal relationships and Work skills are similar between schizophrenia patients and their unaffected first-degree relatives. These findings validate, in the absence of confounders of clinical cohorts, structural models of determinants of functional outcome in people with schizophrenia.

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#### 1. Introduction

Major advances in research on variables influencing real-life functioning in people with schizophrenia have been made in the last decades. It is increasingly acknowledged that psychotic symptoms explain a small amount of the variance of psychosocial functioning, and the key role of negative symptoms, neurocognitive impairment and social cognition deficits has been supported by empirical studies (Bowie et al., 2006; Leifker et al., 2009; Galderisi et al., 2013). More recently, the impact of resilience, internalized stigma, and context-related variables on real-life functioning of people with schizophrenia has also become a focus of attention (Leifker et al., 2009; Harvey and Strassnig, 2012; Park et al., 2013; Galderisi et al., 2014).

The study of real-life functioning and its predictors has received almost no attention in first-degree relatives of people with schizophrenia (SRs), in spite of the fact that they are at 10-fold increased risk to develop the disorder and are significantly more likely than people without a family history of schizophrenia to present milder forms of multidimensional deficits or abnormalities (Snitz et al., 2006; Braff et al., 2007).

In fact, neurocognitive deficits have been reported in SRs and, according to several studies and meta-analyses, these deficits are similar to those found in patients, though less severe (Staal et al., 2000; Michie et al., 2000; Cornblatt and Keilp, 1994; Sponheim et al., 2004; Toulopoulou et al., 2003; Sitskoorn et al., 2004).

Deficits of social cognition, i.e., mental activities underlying social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others (Green and Leitman, 2008), have also been found in SRs. The effect sizes are modest but comparable in magnitude to neurocognitive deficits (de Achaval et al., 2010; Irani et al., 2006; Montag et al., 2012; Bora and Pantelis, 2013). In SRs, as in people with schizophrenia, deficits in social cognition are partially independent of neurocognition deficits (Montag et al., 2012; Eack et al., 2010; Versmissen et al., 2008).

Psychopathological features were also described in SRs. Negative symptoms have been involved more often than positive ones (Tsuang, 1993; Tsuang et al., 1999), and more social isolation and negative schizotypal features, such as poor rapport and aloofness, were observed in SRs than in healthy controls (Kendler et al., 1995).

Problems in real-life functioning or quality of life have been reported in SRs (Kendler et al., 1995; Fanous et al., 2001; Foldemo et al., 2005; Margetic et al., 2011; Margetic et al., 2013), and the presence of negative symptoms in probands with schizophrenia was found to predict schizotypal symptomatology and social dysfunction in unaffected first-degree relatives (Fanous et al., 2001).

In spite of the above evidence, studies on psychosocial functioning of SRs have usually focused on the impact of burden of care (Foldemo et al., 2005; Margetic et al., 2013; Webb et al., 1998), neglecting the contribution of psychopathological traits, cognitive abilities, resilience and stigma. The study of factors influencing the variance of real-life functioning of SRs may be useful to validate predictors and mediators of functioning in people with schizophrenia in the absence of confounders such as full-blown psychosis, medication and disease chronicity.

We previously reported on variables associated with patients' reallife functioning regarded as an overall latent construct (Galderisi et al., 2014). Briefly, we found that variables relevant to the disease, personal resources and social context explained 53.8% of real-life functioning variance in a structural equation model. Neurocognition exhibited the strongest, though indirect, association with real-life functioning. Positive symptoms and disorganization, as well as avolition, proved to have significant direct and indirect relationships, while depression had no significant association, and poor emotional expression was only indirectly and weakly related to real-life functioning. Social cognition, functional capacity, resilience, internalized stigma and engagement with mental health services served as mediators.

The goal of the present study was to evaluate how well data from a large sample of unaffected first-degree relatives of schizophrenia patients fit a model of pathways to functional outcome previously tested in a large sample of patients with schizophrenia living in the community.

#### 2. Materials and methods

#### 2.1. Subjects

The SR sample included first-degree unaffected family members of schizophrenia patients living in the community and recruited for the study of the Italian Network for Research on Psychoses (Galderisi et al., 2014). For each recruited patient who agreed to involve relatives, two SRs 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 to severe mental retardation or of neurological diseases; c) a history of alcohol and/or substance abuse in the last six months; d) inability to provide an informed consent.

The patient sample included subjects consecutively seen at the outpatient units of 26 Italian university psychiatric clinics and/or mental health departments who had 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 the same as listed above for SRs, plus treatment modifications and/or hospitalization due to symptom exacerbation in the last three months.

Healthy subjects matched with patients for gender and geographical area of origin were recruited through flyers from the community at the same sites as the patient sample. Inclusion and exclusion criteria were the same as those listed for SRs.

All subjects signed a written informed consent to participate after receiving a comprehensive explanation of the study procedures and goals.

#### 2.2. Procedures

The study has been conducted in accordance with the principles of the Declaration of Helsinki (59th World Medical Association General Assembly; October 2008). Approval of the study protocol was obtained from the Ethics Committees of the participating centers.

#### 2.3. Assessment tools

Instruments used to assess variables whose association with real-life functioning was hypothesized based on previous literature and

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