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, 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.

Keywords

Schizophrenia first-degree relatives; Interpersonal relationships; Work skills; Avolition; Cognition; Structural equation model

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 and 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 and 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 and 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 and 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 and 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 and Versmissen et al., 2008).

Psychopathological features were also described in SRs. Negative symptoms have been involved more often than positive ones (Tsuang, 1993 and 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 and 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 and 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' real-life 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 clinical experience included: the Positive and Negative Syndrome Scale (PANSS) to measure positive and disorganization dimensions (Wallwork et al., 2012); the Brief Negative Symptom Scale (BNSS) to assess avolition and expressive deficit (Kirkpatrick et al., 2011 and Strauss et al., 2012); the Calgary Depression Scale for Schizophrenia (CDSS) to measure depressive symptoms; the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB) to evaluate neurocognitive functions; the Facial Emotion Identification Test (FEIT) and The Awareness of Social Inference Test (TASIT) to integrate the assessment of social cognition partly covered by the MCCB Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT); the Resilience Scale for Adults (RSA) to evaluate resilience; the Perceived Devaluation and Discrimination scale (PDD) to assess perceived stigma; the short version of the University of California San Diego Performance-based Skills Assessment-Brief (UPSA-B) to assess functional capacity, and the Specific Level of Functioning Scale (SLOF) to evaluate real-life functioning.

A detailed description of the study procedures and assessment tools is included in the supplementary materials.

2.4. Statistical analyses

Data were summarized as mean, SD, minimum and maximum. Demographic characteristics were compared among SRs, patients and healthy controls using analysis of variance (ANOVA; DF = 2, 2077) or $\chi 2$ tests (DF = 2), when appropriate. General linear models were used to compare the study groups on psychopathological dimensions, cognitive functioning, resilience and perceived stigma. Age, gender and education were included as covariates to adjust for their effects in these models. Following significant ANOVA F-tests, post-hoc pairwise comparisons were conducted using Tamhane's test, to take into account the heterogeneity of variance among groups. The significance level was adjusted for multiple comparisons according to Bonferroni, to control for type-I error.

For each domain of real-life functioning resulting as impaired in both patients and SRs, the association between impairment in patients and relatives was assessed using a weighted least square regression analysis, weighting for the number of family members of the proband. The dependent variable was the SLOF domain score in family members and the independent variable was the SLOF score for the same domain in probands. Age, gender and relationship with the proband (sibling or parent) were included in the model as covariates.

Structural equation models (SEMs) were used to determine whether predictors and mediators of real-life functioning of patients with schizophrenia were also associated with functioning in SRs. To this aim, we adapted the model previously tested in patients (Galderisi et al., 2014) by focusing on real-life functioning measures that were relevant for SRs and that distinguished them from healthy subjects. A detailed description of SEM analyses is included in the Supplementary materials.

Analyses were carried out using Stata, version 13.1, and Mplus, version 7.3.

3. Results

3.1. Subjects

The 921 schizophrenia patients were 641 males and 280 females, had a mean age of 40.2 years and on average 11.6 years of education (Table 1, supplementary materials).

Three hundred seventy-nine SRs were recruited, with a mean age of 55.1 years and on average 11.3 years of education. They were related to 247 patients and included 109 fathers, 150 mothers and 120 siblings (F = 67; M = 53) (Table 1, supplementary materials). Two hundred forty-seven parents (95.4%) and 37 siblings (30.8%) were living with their affected relative.

The healthy control sample included 780 individuals (402 females and 378 males, with a mean age of 40.6 years and a mean education of 13 years) (Table 1, supplementary materials).

3.2. Group comparisons

Descriptive statistics of the study variables and results of the ANOVA F and $\chi 2$ tests with post-hoc pairwise comparisons are shown in Tables 1 to 3 (supplementary materials).

SRs were less educated and less frequently employed than controls. After adjusting for gender, age and education, significant differences were found on psychopathological variables among the three groups. Post-hoc analyses revealed that SRs had higher scores than controls on avolition and lower scores than patients on all variables (Table 1, supplementary materials).

Group differences were also found in resilience. Post-hoc analyses showed that SRs had lower levels of rsilience than controls on all subscales, with the exception of “perception of the self”, and showed higher scores than patients on all subscales.

The levels of stigma did not differ significantly between SRs and patients (2.5 ± 0.6 versus 2.6 ± 0.5).

For neurocognitive and social cognition indices, significant group effects were observed. Post-hoc analyses revealed that scores of SRs were intermediate between those of controls and patients, and significantly different from both, except for LNS, TMT, TASIT Section 1, FEIT and MSCEIT scores, that were similar between SRs and controls (Table 2, supplementary materials).

Significant differences were also observed for functional capacity and SLOF domains. Post-hoc tests revealed that the functional capacity of SRs was similar to that of controls and significantly better than in patients (Table 3, supplementary materials). SRs had higher functioning in all domains compared with patients and lower SLOF scores than controls in the domains of Interpersonal Relationships and Work Skills (Table 3, supplementary materials). As these two domains were impaired in both patients and SRs, they were used in subsequent analyses.

The SLOF scores of probands with schizophrenia significantly predicted the SLOF score of their family members for both domains ($b = 0.135$, $p < 0.001$, adjusted r-square = 0.05 for Work Skills; $b = 0.229$, $p < 0.001$, adjusted r-square = 0.11 for Interpersonal Relationships).

3.3. SEM analysis

Fig. 1 shows the final SEM model for patients. Goodness of fit was very good, and the variance explained was R2 = 0.243 for SLOF Interpersonal and R2 = 0.234 for SLOF Work.

The three psychopathological dimensions (Positive, Disorganization and Avolition) were all negatively and significantly associated to functional outcome, as a result of direct and/or indirect effects. BNSS Avolition and PANSS Positive were directly associated with SLOF Interpersonal (the more severe the psychopathology, the more impaired the interpersonal domain of functioning). The strongest association was observed for BNSS Avolition (**Table 1**) and was both direct and indirect, i.e. mediated by Resilience (higher avolition associated with lower resilience and worse interpersonal functioning) and by a complex pathway involving both Perceived stigma (higher avolition associated with higher perceived stigma) and Resilience (higher stigma associated with lower resilience and thus worse interpersonal functioning).

PANSS Positive had both a direct relationship with SLOF Interpersonal (the higher the positive symptoms, the worse the interpersonal functioning) and an indirect effect through Perceived stigma and Resilience (more positive symptoms, more stigma, less resilience and worse interpersonal functioning). PANSS Disorganization had only an indirect pathway to SLOF Interpersonal through Social cognition (the more severe the disorganization, the worse the social cognition, the worse the interpersonal functioning). Neurocognition showed the same indirect pattern of associations observed for Disorganization, i.e. an indirect effect mediated by Social cognition.

Age had a significant and positive association with SLOF Interpersonal, indicating that older age was linked with better interpersonal relationships. Male gender was associated with less perceived stigma, thus with more resilience and better interpersonal functioning, but was also negatively associated with SLOF Interpersonal through Social cognition (being a male was associated with lower social cognition and worse interpersonal functioning).

The three psychopathological dimensions also showed significant negative associations with SLOF Work. BNSS Avolition and PANSS Positive had direct effects only (more severe avolition and positive symptoms were associated with less work skills), while Disorganization had both direct and indirect effects, the latter ones mediated by Functional capacity and Social cognition (the more severe the disorganization the worse the functional capacity and social cognition, the more impaired the work skills). Neurocognition had only indirect effects mediated by Functional capacity or Social cognition (better neurocognitive performance, higher functional capacity or social cognition, better work skills). The association of Neurocognition with both Social cognition and Functional capacity was much stronger when compared to other variables pointing to the same mediators (Fig. 1). Education was positively associated with SLOF Work through the mediation of Functional capacity (the higher the education, the better the functional capacity, the better the Work skills).

Other aspects of the model worth mentioning include the positive correlations among psychopathological dimensions, especially between PANSS Positive and Disorganization, the negative correlations of Age and Disorganization with Neurocognition, and the positive correlation between Education and Neurocognition.

Fig. 2 shows the SEM model for SRs. In this model, Education, PANSS Positive and Functional capacity were removed as they proved to be unrelated with functional domains. Goodness of fit for this model was acceptable. The variance explained was R2 = 0.145 for SLOF Interpersonal Relationships and R2 = 0.152 for SLOF Work Skills.

Compared with the other variables, Social cognition and Neurocognition showed stronger associations with both SLOF Interpersonal Relationships and Work Skills (**Table 2**).

The association of Neurocognition with SLOF Interpersonal Relationships was positive and mediated by Social cognition in a first pathway (better neurocognitive functioning, better social cognition, higher level of interpersonal functioning). A second pathway between Neurocognition and interpersonal functioning involving Stigma and Resilience (the better the neurocognitive functioning, the higher the perceived stigma, the lower the resilience and the interpersonal functioning) had a weak, marginally significant negative effect ($b = -0.008$, $p = 0.078$). BNSS Avolition was associated with SLOF Interpersonal Relationships both directly (the more severe the avolition the worse the interpersonal relationships) and indirectly, through Resilience (more severe avolition, lower resilience and worse interpersonal functioning). Disorganization had an indirect relationship with the same functional domain, mediated by Social cognition (higher disorganization, worse social cognition and worse interpersonal functioning).

Age was also indirectly associated with SLOF Interpersonal Relationships through the same pathway observed for Neurocognition, mediated by Stigma and Resilience (older age, higher perceived stigma, lower resilience and interpersonal functioning). Finally, being male or parent was associated (only directly for the former and mediated by Resilience for the latter) with worse interpersonal functioning.

As to variables associated with SLOF Work Skills, both Neurocognition and Disorganization were indirectly related with it, through the mediation of Social cognition (more severe neurocognitive impairment or disorganization, worse social cognition and work skills).

4. Discussion

To our knowledge, this is the largest study carried out so far on factors associated with specific domains of real-life functioning in people with schizophrenia and their unaffected first-degree relatives.

Assessing multiple domains of real-life functioning, we found that impairment in the domains of Interpersonal relationships and Work skills was similar between patients with schizophrenia living in the community and their unaffected first-degree relatives. The lack of differences in the domains of Personal Care, Social Acceptability and Community Activities is not surprising when considering that SRs care for themselves and in most cases for an affected relative, and therefore are likely to be able to deal with most aspects of everyday life. Discrepant findings on real-life functioning and quality of life in SRs have previously been reported: either a global impairment or no impairment at all has been described (Margetic et al., 2013 and Kurs et al., 2005). Variation in findings among studies may be attributed to kinship (siblings are less likely to have poorer real-life functioning), small sample sizes and heterogeneity in the assessment of real-life functioning (e.g., use of subjective or objective measures, and of instruments in which different aspects of psychosocial functioning are or are not disentangled).

For the domains of Interpersonal Relationships and Work Skills, which were impaired in both patients and unaffected relatives, we found that probands' scores predicted scores observed in family members, indicating a convergence of impairment in both groups and a familial liability for factors that play a role in real-life functioning of both patients and relatives. However, the percentage of explained variance in SR functional impairment was low (11% and 5% for Interpersonal Relationships and Work Skills, respectively), suggesting that factors different from those related to the familial liability for schizophrenia are also in play.

SRs participating in the present study differed from healthy controls on several illness-related variables entered in the SEM model as predictors or mediators, including neurocognition, social cognition and avolition. Impairment of neurocognition and social cognition has been previously found in SRs (Sitskoorn et al., 2004 and Lavoie et al., 2014), and our findings further support the evidence that these deficits might be putative endophenotypes for schizophrenia. Higher scores in SRs than in controls on Avolition also confirm previous findings of the presence of negative symptoms in SRs by using an instrument never used before in this population. According to Kendler et al. (1995), negative schizotypy (a concept partially overlapping with the BNSS construct of Avolition) may reflect familial liability to schizophrenia more than positive schizotypy, and strongly contributes to distinguish SRs from relatives of control probands. In SRs, higher scores on negative symptoms were also found using the PANSS negative factor and regarded as a very sensitive indicator of genetic vulnerability above and beyond cognitive deficits (Delawalla et al., 2006).

We used SEM models to test the hypothesis that pathways to functional outcome in the domains of Interpersonal relationships and Work skills would be similar between patients with schizophrenia living in the community and their unaffected first-degree relatives involving illness-related factors, personal resources and environmental factors.

The SEM model for SRs showed a fit to the data and explained variances of the outcomes that were lower with respect to SEM model for patients. These findings were expected, because the model was developed for schizophrenia patients and then adapted to non-affected subjects in which psychopathology and impairment in neurocognition are present to a minor degree; however the fit parameters resulted in acceptable values, therefore allowing comparisons between the two sets of findings.

The SEM model in SRs confirms the relationships observed in the patient group between Avolition, Neurocognition and Social cognition on the one hand and important domains of everyday life on the other. In fact, Avolition showed a significant association with SLOF Interpersonal Relationships in both models. The use of the BNSS for the assessment of this psychopathological domain strengthens the importance of this finding; in fact, this scale overcomes the limitations of previous instruments for the assessment of negative symptoms, as it does not include items relevant to neurocognition and has a higher focus on internal experience than on behavioral aspects, thus preventing an artefactual inflation of the association with functional outcome measures (Kirkpatrick et al., 2011 and Mucci et al., 2015). In patients with schizophrenia, motivational deficits, rather than reduced emotional expression, appears to have the highest correlation with real-life functioning (Galderisi et al., 2013, Galderisi et al., 2014 and Ventura et al., 2009). Data from the present study confirm this finding in SRs and extend to the latter group previous observations in schizophrenia patients that the impact of motivational deficits is stronger on the social domain than on the vocational one (Leifker et al., 2009).

Our findings indicate that social cognition and neurocognition are the variables with the strongest association with interpersonal relationships and work skills. Moreover, social cognition mediates the impact of neurocognition on both domains, in both patients and relatives. To our knowledge, these findings have not previously been reported; they indicate that cognition has a key role in real-life functioning and validate models developed in patients with schizophrenia in a population in which important confounders, such as the presence of full-blown psychosis, chronicity and antipsychotic medication, do not come into play.

Disorganization has also been previously reported in SRs (Vollema and Postma, 2002 and Remberk et al., 2012). We did not find significantly higher scores in SRs than in controls; however, Disorganization showed a significant indirect association, mediated by Social cognition, with both SLOF domains in both SEM models. The presence in the Disorganization construct of items such as “difficulties in abstract thinking”

and “poor attention” may suggest an overlap with neurocognitive variables; however, its persistence in the final SEM models in both patients and relatives indicates that it provides a unique contribution to real-life functioning, and that even modest levels might contribute to explain the interindividual variability in important domains of everyday life.

Some differences between SEM models in patients and relatives were also observed and involved PANSS Positive, Education and Functional capacity that in relatives proved to be unrelated to functioning domains. SRs had low scores on positive symptoms, comparable to those observed in healthy controls. Education was indirectly associated with SLOF Work through Functional capacity in patients, but not in SRs, in whom Functional Capacity was not impaired and had no relationship with work skills.

Our SEM model in SRs indicates that being a parent contributes to worse interpersonal functioning. Lower functioning in parents compared with siblings has previously been reported (Margetic et al., 2013 and Awadalla et al., 2005). It has been suggested that parents' low functioning/quality of life may reflect, among others, worries about possible relapse, feelings of personal responsibility for the illness, and concern for the future of the ill relative (Jungbauer et al., 2003). Differences in age may also account for impaired real-life functioning (Margetic et al., 2013); according to our data, age, through a pathway mediated by stigma and resilience, adds to (but does not fully account for) the negative impact of being a parent.

As to perceived stigma, PDD scores are in the moderate range (Brohan et al., 2010) in both SRs and schizophrenia patients. In the patient SEM model, perceived stigma exhibited a negative association with resilience and mediated, through the latter, the association of avolition and gender with interpersonal functioning, suggesting a potential benefit of effective anti-stigma programs.

Our findings also underscore in both patients and relatives the key role of resilience as a mediator between several variables and real-life functioning; in fact, resilience mediates the relationship of avolition, age, kinship, stigma and neurocognition with interpersonal functioning.

In conclusion, our findings support the hypothesis that pathways to functional outcome in the domains of Interpersonal relationships and Work skills are similar between patients with schizophrenia living in the community and their unaffected first-degree relatives. Therefore, our data validate structural models of determinants of functional outcome in people with schizophrenia by demonstrating a key role of neurocognitive and social cognition impairment, as well as avolition, disorganization, resilience and stigma, also in SRs, a group in which many confounders of clinical cohorts are not in play. They add to the evidence that variance in real-life functioning is strongly associated with variables such as cognitive impairment and resilience that are neither implicit in the diagnosis of schizophrenia nor a mere consequence of chronicity or drug treatment. However, the small amount of explained variance of both real-life functioning domains in SRs suggests that other variables, not explored in the present study, may play an important role.

Role of funding source

None.

Contributors

Silvana Galderisi, Armida Mucci, Paola Rucci and Mario Maj drafted the manuscript and contributed to data analysis and interpretation. Paola Rucci and Dino Gibertoni carried out statistical analyses. All Authors

contributed to the study conception and design, critically revised the intellectual content of the manuscript and gave their final approval of the present version of the manuscript.

Conflicts of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

Acknowledgments

The study was funded by the Italian Ministry of Education (grant number: 2010XP2XR4), the Italian Society of Psychopathology (SOPSI), the Italian Society of Biological Psychiatry (SIPB), Roche, Lilly, AstraZeneca, Lundbeck and Bristol-Myers Squibb.

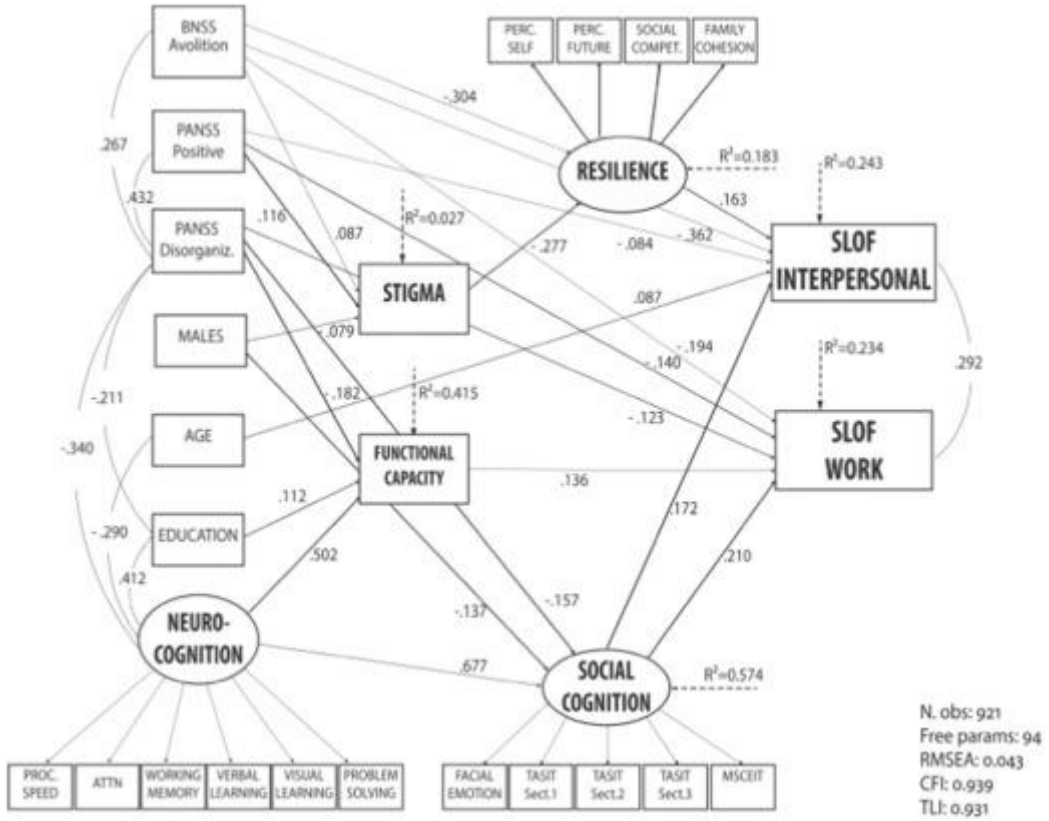

Fig. 1.

Final structural equation model in patients with schizophrenia (N = 921) after trimming of non-significant paths. Neurocognition, Social cognition and Resilience are latent variables. BNSS Avolition, PANSS Positive and PANSS Disorganization, Gender (Males), Age, Education and Neurocognition are independent predictors. Social cognition, Functional capacity, Stigma and Resilience are mediators. SLOF Interpersonal Relationships and SLOF Work Skills are the dependent variables. PANSS = Positive and Negative Syndrome Scale; BNSS = Brief Negative Symptom Scale; PROC SPEED = Processing speed; ATTN = Attention; Facial Emotion = Facial Emotion Identification Test; TASIT = The Awareness of Social Inference Test; MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test; PERC. SELF = Perception of self, PERC. FUTURE = Perception of the future; SOCIAL COMPET. = Social competence; SLOF = Specific Level of Functioning; Interpersonal = Interpersonal Relationships; Work = Work Skills.

Table 1.

	Direct effects	p	Indirect effects	p	Total effects	p
SLOF Interpersonal Relationships						
BNSS Avolition	− 0.362	< 0.001	− 0.053	< 0.001	− 0.415	< 0.001
Social cognition	0.172	< 0.001	–	–	0.172	< 0.001
Resilience	0.163	< 0.001	–	–	0.163	< 0.001
Neurocognition	–	–	0.116	< 0.001	0.116	< 0.001
PANSS Positive Symptoms	− 0.084	0.007	− 0.005	0.011	− 0.089	0.004
Age	0.087	0.004	–	–	0.087	0.004
Stigma (PDD)	–	–	− 0.045	< 0.001	− 0.045	< 0.001
PANSS Disorganization	–	–	− 0.027	< 0.001	− 0.027	< 0.001
Gender (males)	–	–	− 0.02	0.003	− 0.02	0.003
SLOF Work Skills						
Neurocognition	–	–	0.212	< 0.001	0.212	< 0.001
Social cognition	0.21	< 0.001	–	–	0.21	< 0.001
BNSS Avolition	− 0.194	< 0.001	–	–	− 0.194	< 0.001
PANSS Disorganization	− 0.123	0.001	− 0.058	< 0.001	− 0.18	< 0.001
PANSS Positive Symptoms	− 0.14	< 0.001	–	–	− 0.14	< 0.001
Functional capacity (UPSA-B)	0.136	< 0.001	–	–	0.136	< 0.001
Gender (males)	–	–	− 0.029	< 0.001	− 0.029	< 0.001
Education	–	–	0.015	0.009	0.015	0.009

Direct, indirect and total effects on SLOF in the final model for subjects with schizophrenia.

SLOF = Specific Level of Functioning; BNSS = Brief Negative Symptom Scale; PANSS = Positive and Negative Syndrome Scale; PDD = Perceived Devaluation and Discrimination scale; UPSA-B = University of California San Diego (UCSD) Performance-based Skills Assessment Brief.

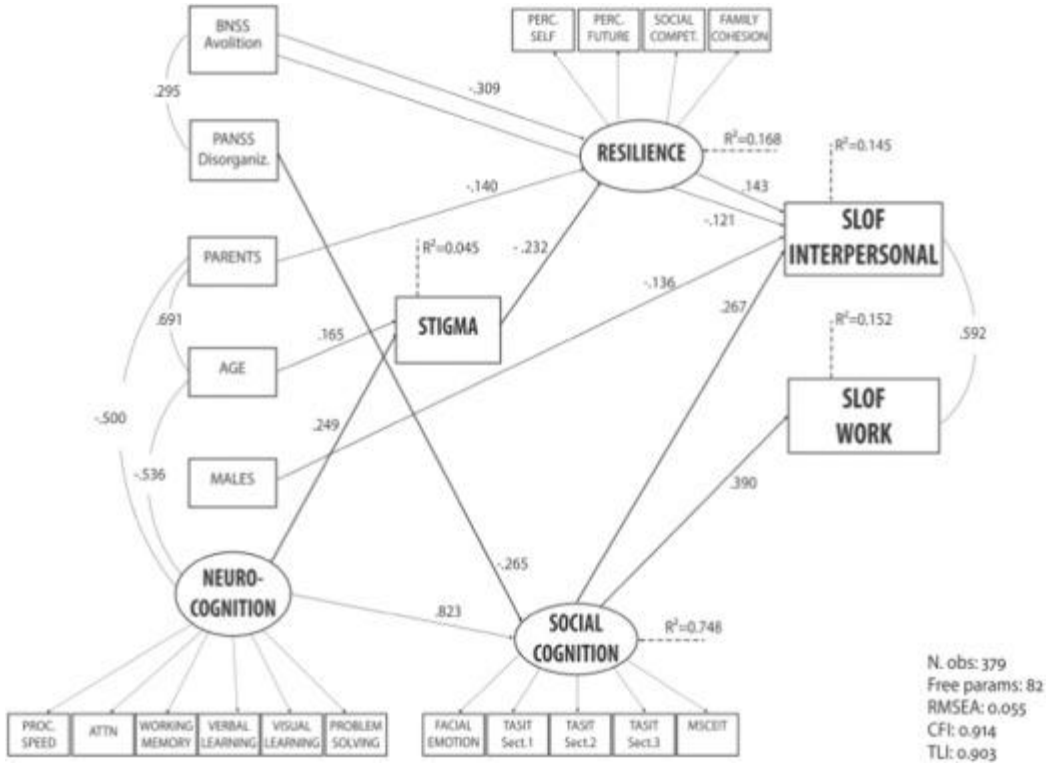

Fig. 2.

Final structural equation model in unaffected relatives (N = 379) of patients with schizophrenia after trimming of non-significant paths. Neurocognition, Social cognition and Resilience are latent variables. BNSS Avolition, PANSS Disorganization, Neurocognition, Kinship (Parents), Age and Gender (Males) are independent predictors. Social cognition, Stigma and Resilience are mediators. SLOF Interpersonal Relationships and SLOF Work Skills are the dependent variables. PANSS = Positive and Negative Syndrome Scale; BNSS = Brief Negative Symptom Scale; PROC SPEED = Processing speed; ATTN = Attention; Facial Emotion = Facial Emotion Identification Test; TASIT = The Awareness of Social Inference Test; MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test; PERC. SELF = Perception of self, PERC. FUTURE = Perception of the future; SOCIAL COMPET. = Social competence; SLOF = Specific Level of Functioning; Interpersonal = Interpersonal Relationships; Work = Work Skills.

Table 2.

Direct, indirect and total effects on SLOF in the final model for unaffected relatives of subjects with schizophrenia.

	Direct effects	p	Indirect effects	p	Total effects	p
SLOF Interpersonal Relationships						
Social cognition	0.267	< 0.001	–	–	0.267	< 0.001
Neurocognition	–	–	0.211	< 0.001	0.211	< 0.001
BNSS Avolition	− 0.121	0.025	− 0.044	0.059	− 0.165	0.001
Resilience	0.143	0.029	–	–	0.143	< 0.021
Gender (males)	− 0.136	< 0.001	–	–	− 0.136	< 0.001
PANSS Disorganization	–	–	− 0.071	< 0.001	− 0.071	< 0.001
Stigma (PDD)	–	–	− 0.033	0.053	− 0.033	0.053
Kinship (parents)	–	–	− 0.02	0.124	− 0.02	0.124
Age	–	–	− 0.005	0.137	− 0.005	0.137
SLOF Work Skills						
Social cognition	0.390	< 0.001	–	–	0.390	< 0.001
Neurocognition	–	–	0.321	< 0.001	0.321	< 0.001
PANSS Disorganization	–	–	− 0.104	< 0.001	− 0.104	< 0.001

SLOF = Specific Level of Functioning; BNSS = Brief Negative Symptom Scale; PANSS = Positive and Negative Syndrome Scale; PDD = Perceived Devaluation and Discrimination scale.

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Supplementary materials

Procedures

Enrolled subjects completed the assessments in three days with the following schedule: collection of socio-demographic information and psychopathological evaluation on day 1, in the morning; assessment of neurocognition, social cognition and functional capacity on day 2, in the morning; assessment of personal resources and perceived stigma either on day 3 (morning or afternoon) or in the afternoon of day 1 or 2, according to the subject's preference.

Assessment tools

Psychopathology and cognition assessment tools

In all recruited subjects, the Positive and Negative Syndrome Scale [PANSS, (1)] was used to rate symptom severity. Scores for the dimensions "disorganization" and "positive symptoms" were calculated based on the consensus 5-factor solution proposed by (2).

Negative symptoms were assessed using the Brief Negative Symptom Scale [BNSS, (3)]. The Italian version of the scale was validated as part of the activities of the Network (4). In line with previous research (3, 5), domains evaluated by the scale loaded on two factors: "avolition", consisting of anhedonia, asociality and avolition, and "expressive deficit", including blunted affect and alogia.

The Calgary Depression Scale for Schizophrenia [CDSS, (6)] was used to rate depressive symptoms.

Neurocognitive functions were evaluated using the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery [MCCB, (7, 8)]. Briefly, the MCCB includes 10 neuropsychological tests (Category Fluency - Animal Naming; Brief Assessment of Cognition in Schizophrenia Symbol Coding; Trail Making Test - Part A; Continuous Performance Test - Identical Pairs; Wechsler Memory Scale Spatial Span; Letter-Number Span; Hopkins Verbal Learning Test - Revised; Brief Visuospatial Memory Test - Revised; Neuropsychological Assessment Battery-Mazes; Mayer-Salovey-Caruso Emotional Intelligence Test) and investigates 7 cognitive domains (Speed of processing; Attention/vigilance; Working memory; Verbal learning; Visual learning; Reasoning and problem solving and Social cognition).

The assessment of social cognition, partly carried out by the MCCB Mayer-Salovey-Caruso Emotional Intelligence Test, was integrated by the Facial Emotion Identification Test [FEIT, (9)] and a theory of mind test, The Awareness of Social Inference Test [TASIT, (10)].

Resilience and perceived stigma

Resilience was evaluated by the Resilience Scale for Adults [RSA, (11)], a self-administered scale examining intra- and inter-personal protective factors thought to facilitate adaptation when facing psychosocial adversity. The RSA has 33 items and 6 subscales (Perception of the Future; Perception of the Self;

Structured Style; Social Competence; Family Cohesion and Social Support) exploring 3 dimensions of resilience, i.e., (i) personal competence, (ii) family support and (iii) social support. Each item is rated on a 5-point scale, with higher ratings indicating higher resilience in the final scoring. The subscales Perception of the Future, Perception of the Self, Social Competence and Family Cohesion were used in this study. The first two subscales explore levels of self-esteem, self-efficacy and hope; Social Competence measures the ability to initiate social activities, communication skills and flexibility in social matters; and Family Cohesion evaluates the amount of family support and stability. The subscales Social Support and Structured Style were not included in the analyses to avoid overlap with other measures.

Perceived stigma was assessed using the Perceived Devaluation and Discrimination scale [PDD, (12)]. This is a 12-item scale measuring the extent to which a person believes that most people will devalue or discriminate someone with a mental illness. Each item is rated on a four-point Likert scale anchored at 1=strongly disagree and 4=strongly agree. A high level of perceived devaluation and discrimination is indicated by agreement with six of the items and by disagreement with the other six. The final score is obtained by reversing the score on the latter six items, so that higher total scores indicate high levels of perceived devaluation and discrimination.

Functional capacity and real-life functioning

Functional capacity, i.e. the ability to perform tasks relevant to everyday life in a structured environment, guided by an examiner, was evaluated using the short version of the University of California San Diego Performance-based Skills Assessment - Brief [UPSA-B, (13)]. The instrument assesses “financial skills” (e.g., counting money and paying bills) and “communication skills” (e.g., dialing a telephone number for emergency and rescheduling an appointment by telephone). The total score was used in statistical analyses. Higher scores indicate better functional capacity.

Real-life functioning was assessed by the Specific Level of Functioning Scale (SLOF), a hybrid instrument that explores skills in self-care, interpersonal relationships, social acceptability, community activities (e.g., shopping, using public transportation), and working abilities. The Italian version of the scale has recently been validated (14). Higher scores indicate better functioning.

Training of researchers

For each category of variables (psychopathology and cognition, personal resources, context-related factors, and real-life functioning), 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.

Details about the assessment of inter-rater agreement for study instruments have been reported elsewhere (15).

SEM Analyses

Structural equation models (SEMs) were used to determine whether predictors and mediators of real-life functioning of patients with schizophrenia were also associated with functioning in SRs. To this aim, we

adapted the model previously tested in patients (Galderisi et al., 2014) by focusing on real-life functioning measures that were relevant for SRs and that distinguished them from healthy subjects. A detailed description of SEM analyses is included in the Supplementary materials. The initial SEM model included eight independent predictors: seven observed variables (i.e., gender, age, education, kinship, PANSS Disorganization, PANSS Positive and BNSS Avolition), and one latent variable (neurocognition, comprising the six MCCB domains “processing speed”, “attention”, “working memory”, “verbal learning”, “visual learning” and “problem solving”). Four mediators were also included: two observed variables (i.e., stigma and functional capacity) and two latent variables (i.e., social cognition, built on FEIT, TASIT and MSCEIT scores; and resilience, comprising “perception of self”, “perception of the future”, “social competence” and “family cohesion”). The non-independence of data, i.e. the presence of multiple relatives for the same patient, was addressed in the analyses by including the family identifier as a clustering variable to estimate correctly the standard errors.

For the purpose of SEMs, all variables were transformed to z-scores (mean=0 and standard deviation=1). Neurocognition, social cognition and functional capacity measures were standardized with respect to the Italian normative sample. The normative sample was recruited in each geographic macro-area (Northern, Central and Southern Italy) using a quota sampling to approximate the age, gender and education composition provided in the last published census by the Italian National Census Bureau. All non-significant relationships ($p>0.05$) were trimmed from the initial model to get a final parsimonious model. Standardized regression coefficients are provided to allow comparison of relationships pointing to the same dependent variables. Correlations between independent variables or between indicators of a latent construct were added only if their value was >0.20.

The goodness of fit was evaluated using the comparative fit index (CFI), Tucker-Lewis index (TLI) and the root mean square error of approximation (RMSEA). TLI and CFI values >0.90 reflect acceptable fit. RMSEA values <0.05 indicate close model fit; values up to 0.08 suggest a reasonable error of approximation in the population, and values >0.10 indicate poor fit. The fit indices were assessed collectively, such that a single index that fell just outside the acceptable range was not necessarily considered to reflect poor model fit, provided that the other statistics indicated good model fit.

Analyses were carried out using Stata, version 13.1, and Mplus, version 7.3.

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Supplementary Table 1. Demographic, psychopathological characteristics and resilience in unaffected relatives (R), patients (P) and healthy controls (C).

	Unaffected Relatives of Patients (N=379)	**Patients with Schizophrenia (N=921)**	**Healthy Controls (N=780)**	**ANOVA^ F or χ^2 test, p**	**Significant post-hoc Tamhane tests at p<0.016**
Demographic Characteristics					
Gender (% male)	42.7	69.6	48.5	111.1, <0.001	P>R,C
Married (% yes)	71.7	7.8	46.4	573.7, <0.001	R>C>P
Working (% yes)	47.5	29.2	69.0	263.1, <0.001	C>R>P
	mean±SD; min-max	**mean±SD; min-max**	**mean±SD; min-max**		
Age (years)	55.1±13.5; 16-82	40.2±10.7; 18-66	40.6±12.5; 18-65	234.4, <0.001	R>P,C
Education (years)	11.3±4; 5-23	11.6±3.4; 5-23	13±4; 3-23	39.2, <0.001	C>P,R
Psychopathology					
PANSS Positive	4.2±0.7;4-10	9.8±4.7;4-28	4.1±0.3;4-8	749.8, <0.001	P>R,C
PANSS Disorganization	3.6±1.2; 3-13	8.6±3.8; 3-21	3.1±0.5; 3-10	959.9, <0.001	P>R,C
BNSS Avolition	3.6±5.1; 0-27	20.7±9.6; 0-45	1.4±3.1; 0-22	1630.1, <0.001	P>R>C
BNSS Expression deficit	1.8±3.4; 0-20	12.8±8; 0-33	0.7±1.9; 0-18	973.6, <0.001	P>R,C
CDSS	1.2±2.3; 0-16	4.0±4.0; 0-21	0.5±1.4; 0-14	302.8, <0.001	P>R,C
Resilience					
RSA Perception of the self	22.0±4.9; 3-30	18.1±5.5; 0-30	22.6±4.5; 7-30	183.9, <0.001	P<R,C

RSA Perception of the future	12.5±3.7; 1-20	10.8±4.3; 0-20	13.6±3.3; 4-20	107.9, <0.001	P<R<C

Supplementary Table 1. Continued

	Unaffected Relatives of Patients (N=379)	**Patients with Schizophrenia (N=921)**	**Healthy Controls (N=780)**	**ANOVA^ F or χ^2 test, p**	**Significant post-hoc Tamhane tests at p<0.016**
Resilience					
RSA Social competence	22.9±4.6; 10-30	18.9±5.3; 6-30	24.2±4.4; 7-30	251.0, <0.001	P<R,C
RSA Family cohesion	22.7±5.0; 7-30	20.3±5.7; 3-30	24.0±5.0; 6-30	87.1, <0.001	P<R<C

PANSS=Positive and Negative Syndrome Scale; BNSS=Brief Negative Symptom Scale; CDSS=Calgary Depression Scale for Schizophrenia; RSA=Resilience Scale for Adults. ^ANOVAs for psychopathology and resilience variables are adjusted for age, gender and education.

Supplementary Table 2. Neurocognition and social cognition variables in unaffected relatives (R), patients (P) and healthy controls (C).

	Unaffected Relatives of Patients (mean±SD; min-max)	**Patients with Schizophrenia (mean±SD; min-max)**	**Healthy Controls (mean±SD; min-max)**	**ANOVA^ F-test, p**	**Significant post-hoc Tamhane tests at p<0.016**
Neurocognitive Domains					
Verbal Learning					
HVLT-R (correct recalls)	23.0±5.6; 8-35	19.0±5.6; 0-35	26.0±4.8; 13-36	356.6, <0.001	P<R<C
Visual Learning					
BVMT_R (total score)	21.6±7.8; 3-36	16.3±8.8; 0-36	26.9±6.4; 0-36	399.4, <0.001	P<R<C
Reasoning and Problem solving					
NAB mazes (total score)	12.0±7.3; 0-26	9.7±6.4; 0-26	16.9±6.8; 0-26	301.4,<0.001	P<R<C
Attention-Vigilance					
CPT-IP (D prime average)	2.0±0.8; -0.0-4.1	1.7±0.8; -0.4-4.0	2.6±0.7; 0.2-4.1	287.9, <0.001	P<R<C
Working memory					
WMS-III SS (correct sequences)	13.7±3.9; 1-25	12.3±4.1; 1-26	16.5±3.7; 7-29	265.3, <0.001	P<R<C
LNS (correct responses)	12.8±4.0; 2-24	10.4±4.2; 0-21	15.0±3.7; 4-24	298.1, <0.001	P<R,C
Processing speed					

FLUENCY (number animal names)	20.1±5.8; 6-39	16.5±5.7; 0-47	23.8±6.0; 3-47	305.8, <0.001	P<R<C
BACS-SC (correct responses)	39.3±14.3; 4-78	31.5±13.2; 0-96	52.0±15.8; 9-110	467.1,<0.001	P<R<C
TMT (total time)	49.9±30.4; 15-300	66.3±46.2; 15-300	34.8±15.8; 11-226	178.3, <0.001	P>R,C

Supplementary Table 2. Continued

	Unaffected Relatives of Patients (mean±SD; min-max)	**Patients with Schizophrenia (mean±SD; min-max)**	**Healthy Controls (mean±SD; min-max)**	**ANOVA^ F-test, p**	**Significant post-hoc Tamhane tests at p<0.016**
Social Cognition Domains					
TASIT Sect. 1 (correct items)	23.0±3.4; 9-28	20.0±4.9; 0-28	25.0±2.6; 14-34	334.4, <0.001	P<R,C
TASIT Sect. 2 (correct items)	45.4±9.6; 4-59	37.4±10.9; 0-60	51.1±7.7; 18-60	412.0, <0.001	P<R<C
TASIT Sect. 3 (correct items)	46.0±10.4; 6-63	38.5±11.4; 0-64	51.9±8.3; 19-84	374.1,<0.001	P<R<C
FEIT (correct responses)	41.8±6.9; 7-54	36.8±8.5; 7-53	44.4±5.3; 21-55	191.1, <0.001	P<R,C
MSCEIT (SS-B4)	84.8±9.3; 62.8-109.8	78.5±9.0;54.6-109.2	86.7±9.5; 47-111.7	180.5,<0.001	P<R,C

HVLT-R=Hopkins Verbal Learning Test - Revised; NAB=Neuropsychological Assessment Battery; BVMT-R=Brief Visuospatial Memory Test - Revised; CPT-IP=Continuous Performance Test - Identical Pairs; WMS-III SS=Wechsler Memory Scale Spatial Span; LNS=Letter-Number Span; Fluency=Category Fluency, Animal Naming; BACS SC=Brief Assessment of Cognition in Schizophrenia Symbol Coding; TMT=Trail Making Test - Part A; TASIT=The Awareness of Social Inference Test; FEIT=Facial Emotion Identification Test; MSCEIT=Mayer-Salovey-Caruso Emotional Intelligence Test; SS-B4=standard score for the managing emotions branch.

^ANOVAs are adjusted for age, gender and education.

Supplementary Table 3. Real life functioning and functional capacity indices in unaffected relatives (R), patients (P) and healthy controls (C).

	Unaffected Relatives of Patients (mean±SD; min-max)	**Patients with Schizophrenia (mean±SD; min-max)**	**Healthy Controls (mean±SD; min-max)**	**ANOVA^ F test, p**	**Significant post-hoc Tamhane tests at p<0.016**
Real Life Functioning					
SLOF Skills in personal care	34.8±1.0; 22-35	31.7±4.0; 10-35	34.9±0.4; 30-35	313.9, <0.001	P<R,C
SLOF Interpersonal relationships	30.6±5.1; 15-35	22.3±6.1; 7-35	33.6±2.4; 21-35	1088.1, <0.001	P<R<C
SLOF Social acceptability	34.4±1.2; 27-35	32.5±3.3; 14-35	34.7±1.2; 9-35	186.6,<0.001	P<R,C
SLOF Community activities	54.2±2.2; 26-55	45.9±8.6; 11-55	54.7±0.8; 46-55	510.9,<0.001	P<R,C
SLOF Working abilities*	27.4±3.8; 12-30	20.0±6.2; 6-30	29.0±2.4; 15-30	766.4, <0.001	P<R<C
Functional Capacity					
UPSA-B	85.1±16.4; 33.8-100	67.8±21.8; 4.6-100	91.9±11.9; 22.7-100	378.9,<0.001	P<R,C

SLOF=Specific Level of Functioning; UPSA-B=UCSD Performance-Based Skills Assessment - Brief.

^ANOVAs are adjusted for age, gender and education