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The puzzle of quality of life in schizophrenia: putting the pieces together with the FACE-SZ cohort

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Abstract

Background. The determinants of quality of life (QoL) in schizophrenia are largely debated, mainly due to methodological discrepancies and divergence about the concepts concerned. As most studies have investigated bi- or tri-variate models, a multivariate model accounting for simultaneous potential mediations is necessary to have a comprehensive view of the determinants of QOL. We sought to estimate the associations between cognitive reserve, cognition, functioning, insight, depression, schizophrenic symptoms, and QoL in schizophrenia and their potential mediation relationships.

Methods. We used structural equation modeling with mediation analyses to test a model based on existing literature in a sample of 776 patients with schizophrenia from the FondaMental Foundation FACE-SZ cohort.

Results. Our model showed a good fit to the data. We found better functioning to be positively associated with a better QoL, whereas better cognition, better insight, higher levels of depression, and schizophrenic symptoms were associated with a lower QoL in our sample. Cognitive reserve is not directly linked to QoL, but indirectly in a negative manner via cognition. We confirm the negative relationship between cognition and subjective QoL which was previously evidenced by other studies; moreover, this relationship seems to be robust as it survived in our multivariate model. It was not explained by insight as some suggested, thus the mechanism at stake remains to be explained.

Conclusion. The pathways to subjective QoL in schizophrenia are complex and the determinants largely influence each other. Longitudinal studies are warranted to confirm these cross-sectional findings.

Introduction

Quality of life (QoL) is a complex concept, for which the determinants are not well known, although it has become an important treatment target in schizophrenia (Awad &

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Voruganti, 2012). According to the World Health Organization Quality of Life Group (WHOQOL Group, 1995), QoL can be defined as 'an individual's perception about their own position in life within the context of the culture and system of values in which the individual lives, as well as their own aims, expectations, standards and interests'. An increasing number of studies (from 89 studies in 2000 to 260 studies in 2019 registered on PubMed with the keywords 'quality of life' and 'schizophrenia') have investigated this important outcome, which is predictive of relapse in schizophrenia (Boyer et al., 2013) and may increase depression and thereby suicidality (Ehrminger et al., 2019). However, the results concerning the determinants of QoL in schizophrenia are contradictory and depend on the operationalization of the variables, e.g. differences between subjective and objective QoL (Narvaez, Twamley, McKibbin, Heaton, & Patterson, 2008). Here, we focused on subjective health-related QoL, in contrast to objective psychosocial functioning. Approaching an integrated model of the causal factors of QoL requires consideration of various categories of determinants: functional disability, clinical variables, psychological dispositions, such as insight, and cognition.

Several important outcomes may contribute to QoL. Psychosocial functioning was found to be associated with QoL in several studies. For example, a study (Fontanil-Gómez, Alcedo Rodríguez, & Gutiérrez López, 2017) found that the Global Assessment of Functioning (GAF) score correlated with the Quality of Life Scale score ($r = 0.55$), and another one (Chino, Nemoto, Fujii, & Mizuno, 2009) found the GAF score to correlate ($r = 0.53$) with the World Health Organization – QoL score. Concerning clinical variables, schizophrenic symptoms, especially negative symptoms, also appear to be important determinants of QoL (Brissos, Dias, Balanzá-Martinez, Carita, & Figueira, 2011; Eack & Newhill, 2007; Kurtz, Gopal, John, & Thara, 2019; Priebe et al., 2011). According to a study (Brissos et al., 2011), schizophrenic symptoms may even completely cancel the association between functioning and QoL when they are controlled for. Also, depressive symptoms have been shown multiple times to be associated with QoL in schizophrenia (Cotton, Gleeson, Alvarez-Jimenez, & McGorry, 2010; Ehrminger et al., 2019; Narvaez et al., 2008).

Concerning psychological disposition, a well-known point in schizophrenia is the 'paradox of insight' (Lysaker, Roe, & Yanos, 2007). Indeed, better insight was found to be negatively associated with QoL in several studies (Ehrminger et al., 2019; Hasson-Ohayon, Kravetz, Meir, & Rozencwaig, 2009; Kurtz & Tolman, 2011; Margariti, Ploumpidis, Economou, Christodoulou, & Papadimitriou, 2015), whereas better insight is generally thought to be associated with a better outcome. In a longitudinal study (Ehrminger et al., 2019), we showed that the level of baseline insight predicts changes in depression, suggesting that insight causally precedes depression; insight also independently predicted changes in QoL. Hence, the negative link between insight and QoL may be at least partially explained by an indirect relationship through depression. Other authors have reported that self-stigma fully mediated the positive association of insight with depression and poor subjective QoL (Lien et al., 2018). Self-stigma is also a moderator of the detrimental effects of insight, which is more pronounced in patients with higher levels of self-stigma than those with lower self-stigma (Cavelti, Kvrgic, Beck, Rüsch, & Vauth, 2012). As a result, it appears possible to theorize and then test the paradox of insight both through a direct negative link between QoL, insight, and depressive symptoms.

Finally, cognition has long been known to be impaired in schizophrenia (Gold & Harvey, 1993; Heinrichs & Zakzanis, 1998). Previous studies have shown that cognition may contribute to QoL. However, the results are contradictory, as several authors found a positive association between cognitive performance and QoL (Alptekin et al., 2005; Herman, 2004; Savilla, Kettler, & Galletly, 2008; Woon, Chia, Chan, & Sim, 2010), whereas others found a negative association (DeRosse, Nitzburg, Blair, & Malhotra, 2018; Kurtz et al., 2019; Meesters et al., 2013; Narvaez et al., 2008), and some, no association (Brissos, Dias, Carita, & Martinez-Arán, 2008; Chino et al., 2009). It appears, however, that cognition has mostly been found to be negatively associated with subjective QoL (Narvaez et al., 2008). Another psychological competence of interest is a cognitive reserve, as it serves as a proxy to study premorbid cognitive performance. To date, it has been little investigated in schizophrenia, although cognitive reserve in patients with bipolar disorder was found to be negatively associated with mental QoL (a dimension of the SF-36 scale, in contrast to physical QoL), whereas it was positively associated with cognitive performance and psychosocial functioning (Anaya et al., 2016).

The negative path between cognition and subjective QoL remains unexplained, but some authors have hypothesized that the relationship may be mediated by insight, as insight was found to be positively associated with cognitive performance (Aleman, Agrawal, Morgan, & David, 2006; Gerretsen et al., 2017; Nair, Palmer, Aleman, & David, 2014) and negatively associated with QoL, as previously noted. This negative path is also yet to be explained.

Aims

Several studies have investigated 'local' relationships in bi- or trivariate systems using multiple regression analyses. However, the complex interplay between the variables and their potential role as mediators of several relationships requires considering them all together to obtain a global view that takes into account all the plausible simultaneous paths and influences, as suggested in a previous study (Lien et al., 2018), in particular through mediation processes. We aimed to assemble the pieces of the puzzle into a coherent model of QoL in schizophrenia using a global approach, allowed by the use of structural equation modeling (SEM), which can handle multiple simultaneous mediation analyses (Fairchild & McDaniel, 2017).

Concerning the set of working hypotheses implemented in the model consisting of direct links, and of mediations, we will verify that: (1) functioning would be positively associated with QoL; (2) cognition would be negatively associated with QoL, but this relationship would at least be partially explained by an indirect relationship *via* insight; (3) insight would be negatively associated with QoL (in line with the 'insight paradox' proposal), but this relationship would be at least partially mediated by depression; and (4) schizophrenic symptoms would be negatively associated with QoL.

Methods

Study design and characteristics of the recruiting network

This multicenter, cross-sectional study included patients recruited into the FACE-SZ (FondaMental Advanced Centers of Expertise for Schizophrenia) cohort within a French national network of 10 centers (Bordeaux, Clermont-Ferrand, Colombes, Créteil, Grenoble, Lyon, Marseille, Montpellier, Strasbourg, and

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Versailles). This network was set up by the Fondation FondaMental (www.fondation-fondamental.org), which created an infrastructure and provided resources to follow clinical cohorts and comparative-effectiveness research on patients with schizophrenia.

Participants

All subjects were referred by their psychiatrist. Outpatients with schizophrenia, between 18 and 65 years of age, were eligible for this analysis. The diagnosis of schizophrenia was based on the Structured Clinical Interview for the DSM-IV-TR (SCID) criteria. To avoid potential confounding effects, patients with a history of substance abuse during the month before assessment or with a comorbid neurological disorder were excluded.

The authors assert that all procedures contributing to this study comply with the ethical standards of the relevant national and institutional committees on human experimentation and the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human patients were approved by the local ethics committee (Comité de Protection des Personnes Ile de France IX) on 18 January 2010, under French law for non-interventional studies (observational studies without any risk, constraint, or supplementary or unusual procedure concerning diagnosis, treatment, or monitoring). The board required that all patients be given an informational letter but waived the requirement for written informed consent. However, verbal consent was witnessed and formally recorded.

Measurements

Cognition

A comprehensive battery of cognitive tests was administered by experienced neuropsychologists. Cognition was defined as a latent variable manifested by six indicators, representing consensual cognition dimensions. We used raw scores which were not adjusted for age or education level to avoid overlap with cognitive reserve. The scores were then transformed to percentiles of the sample distribution, such that a higher percentile reflects better performance. We then computed a mean score for each dimension as follows:

- **Memory**: California Verbal Learning Test (Delis, 2000) (long-term free recall), Doors test (Baddeley, Emslie, & Nimmo-Smith, 2006)
- **Working memory**: WAIS (Wechsler, Coalson, & Raiford, 2008) Digit Span and Arithmetic
- **Attention**: Continuous Performance Test (Conners & Staff, 2000) (mean discrimination capacity)
- **Reasoning**: WAIS Matrices and Similarities
- **Executive functions**: Category Verbal Fluency (Lezak, 2004) (animal), Six Elements test (Shallice & Burgess, 1991) (error score), Trail Making Test (Reitan, 1958) (part B)
- **Processing speed**: WAIS Code, Trail Making Test (part A)

Latent cognitive performance was adjusted for age (i.e. age was added as a regressor for cognition).

Cognitive reserve

Cognitive reserve was assessed using a latent variable manifested by the level of education (number of school years since the first mandatory grade), the premorbid IQ, which was estimated with the French version of the National Adult Reading Test (Mackinnon & Mulligan, 2005) (NART), and the score for the Information subtest of the WAIS, as recommended in a previous study (Elkana et al., 2019). Cognitive reserve was adjusted for age at onset, based on a demonstrated association between cognitive reserve and age at onset (Amoretti et al., 2018) (i.e. age at onset was added as a regressor for cognitive reserve).

Insight

This latent variable incorporates both self-reported and clinician-rated measures, as recommended (Jovanovski, Zakzanis, Atia, Campbell, & Young, 2007). Insight was measured as a latent construct manifested by the score for the Birchwood Insight Scale (Birchwood et al., 1994) (BIS) and the mean score for the first three items of the Scale to Assess Unawareness of Mental Disorder (Michel et al., 2013; Raffard et al., 2010) (SUMD; the three items are: consciousness of the disease, of its consequences, and of the necessity to seek treatment). Higher BIS scores and lower SUMD scores indicate better insight. In order to be exhaustive and avoid arbitrary variable selection, we have also included the item 12 of the general psychopathology section of the PANSS.

Functioning

Functioning was assessed using the Global Assessment of Functioning scale (Jones, Thornicroft, Coffey, & Dunn, 1995) (GAF).

Quality of life

QoL was estimated using a latent variable manifested by the eight S-QoL (Boyer et al., 2010) sub-scores: psychological well-being, self-esteem, family relationships, relationships with friends, resilience, physical well-being, autonomy, and sentimental life. Higher scores indicate better QoL. This scale was based on a model which states that QoL is the result of the difference between an individual's potential and achievements (Calman, 1984).

Depression

Depression was assessed using the Calgary depression scale, which has been validated for schizophrenia (Addington, Addington, Maticka-Tyndale, & Joyce, 1992). Higher scores indicate worse depression.

Schizophrenic symptomatology

The severity of schizophrenic symptoms was estimated using a latent variable manifested by the three dimensions of the positive and negative syndrome scale (Kay, Fiszbein, & Opfer, 1987) (PANSS), i.e. positive symptoms, negative symptoms, and general psychopathology (excluding the item G12, which was used as a measure of insight).

Statistical analyses

We constructed a global model containing all the variables of interest and the hypothesized paths based on the literature by performing SEM using the *lavaan* package (Rosseel, 2012) in the R environment. We used a maximum likelihood estimator. Missing data were handled using full information maximum likelihood (Enders & Bandalos, 2001). Consensual fit indices (Hu & Bentler, 1999) were inspected: the comparative fit index (CFI) should be >0.9, and the root mean square error of approximation (RMSEA) and the standardized root mean residual should be <0.08 to assume a good fit.

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The required sample size was estimated following the procedure detailed in Supplementary Materials. We computed Bravais–Pearson's correlations between the variables of interest.

Mediation analyses

Within the general model, we estimated the hypothesized mediations using the following procedure: we estimated the **direct effect** between the two variables of interest (c), as well as the **indirect effect** (ab) of the independent variable on the dependent variable through the mediator. The **total effect** equals ab + c and the proportion of the effect mediated by the intermediary variable equals 100×ab/(ab + c). In case of an inconsistent mediation (the direct and indirect effects have opposite signs), Alwin and Hauser (1975) recommend computing this proportion using the absolute values of the direct and indirect effect coefficients, thus estimating the proportion of the absolute total effect mediated by the intermediary variable.

Following this procedure, we simultaneously estimated the hypothesized mediations between cognitive reserve and QoL via cognition and functioning, between cognition and QoL via insight, between insight and QoL via depression, and between cognition and functioning via symptoms. Indeed, when several variables are thought to act as a mediator in a relationship, it is recommended to simultaneously estimate multiple mediations in a multivariate model instead of studying them one at a time in tri-variate models, notably when the potential mediators may influence each other (Lemmens, Müller, Arntz, & Huibers, 2016; VanderWeele & Vansteelandt, 2014). The magnitude of the links, their level of significance as well as the mediation effects, were estimated and tested using a bootstrapping method.

Results

Sample

In total, 1239 patients were included in the cohort. Among them, 289 were excluded because they were diagnosed with a schizophreniform (24) or schizoaffective disorder (265), 10 for a comorbid neurological disorder, 60 because they presented with a characterized substance abuse during the month before assessment, and 20 because they were outside the 18–65 years of age range. Among the remaining 860 patients, 84 were excluded because more than 33.3% of the data were missing for the variables of interest.

A final sample of 776 patients was used for the analyses, in accordance with the estimated required sample size of 148 subjects. Clinical and socio-demographic data are presented in Table 1. Pearson's correlations between the variables of interest are presented in online Supplementary Table S2.

Table 1. Clinical and socio-demographic data of the sample ($n = 776$)

	Mean (s.d.) or % (n)
Age (years)	31.6 (9.3)
Sex (%M)	75.8% (588)
Age at first episode (years)	21.6 (6.6)
Education level (years)	12.4 (2.7)
Estimated pre-morbid IQ (NART)	103.1 (8.6)
PANSS – Total	71.1 (19.1)
PANSS – Positive symptoms	14.9 (5.8)
PANSS – Negative symptoms	20.7 (7.1)
PANSS – General psychopathology	35.6 (10.1)
Calgary Depression Scale	3.8 (4)
Birchwood Insight Scale	8.7 (3)
Scale to Assess Unawareness of Mental Disorder	31.2 (31.6)
PANSS G12	3.2 (1.6)
S-QoL – Total	52 (18.3)
Global Assessment of Functioning	48.9 (13.1)

Latent variables

The latent variables all showed a good fit or were just-identified, making them suitable for their integration into our models. All factor loadings were significant. Details are provided in online Supplementary Table S1.

General model

The model showed a good fit [CFI = 0.903, RMSEA 90% confidence interval (0.05–0.058), SRMR = 0.054] and explained 40.6% of the variance in QoL. When all the variables of interest were taken together, the significant contributors to QoL were functioning, for which the relationship was positive, and depression, PANSS scores, insight, and cognitive performances, for which the relationship was negative (Fig. 1).

Mediation analyses

According to the results presented in Table 2:

- cognitive reserve is associated with QoL only through its relationship with cognitive performance, and not via functioning (the total effect of the multiple mediation is $\beta = -0.1$, $p = 0.01$);
- cognitive performance is negatively associated with QoL, and this association is not mediated by insight, notably because cognition was not directly linked to insight;
- cognition is only indirectly associated with insight via symptoms;
- insight is directly and negatively associated with QoL, and a moderate part (20%) of the total effect is mediated by depressive symptoms;
- cognition and functioning were only indirectly associated via symptoms.

Discussion

We found that functioning, cognitive performance, insight, depression, and schizophrenic symptoms were significantly associated with subjective QoL. This study is the first to investigate the simultaneous impact of objective cognition, cognitive reserve, functioning, insight, depression, and schizophrenic symptoms as determinants of subjective QoL in schizophrenia on a large sample of patients with stable schizophrenia ($n = 776$). The size of our sample resulted in high statistical power of the analyses. The use of SEM with latent variables makes it possible to estimate complex simultaneous relationships between several latent and manifest

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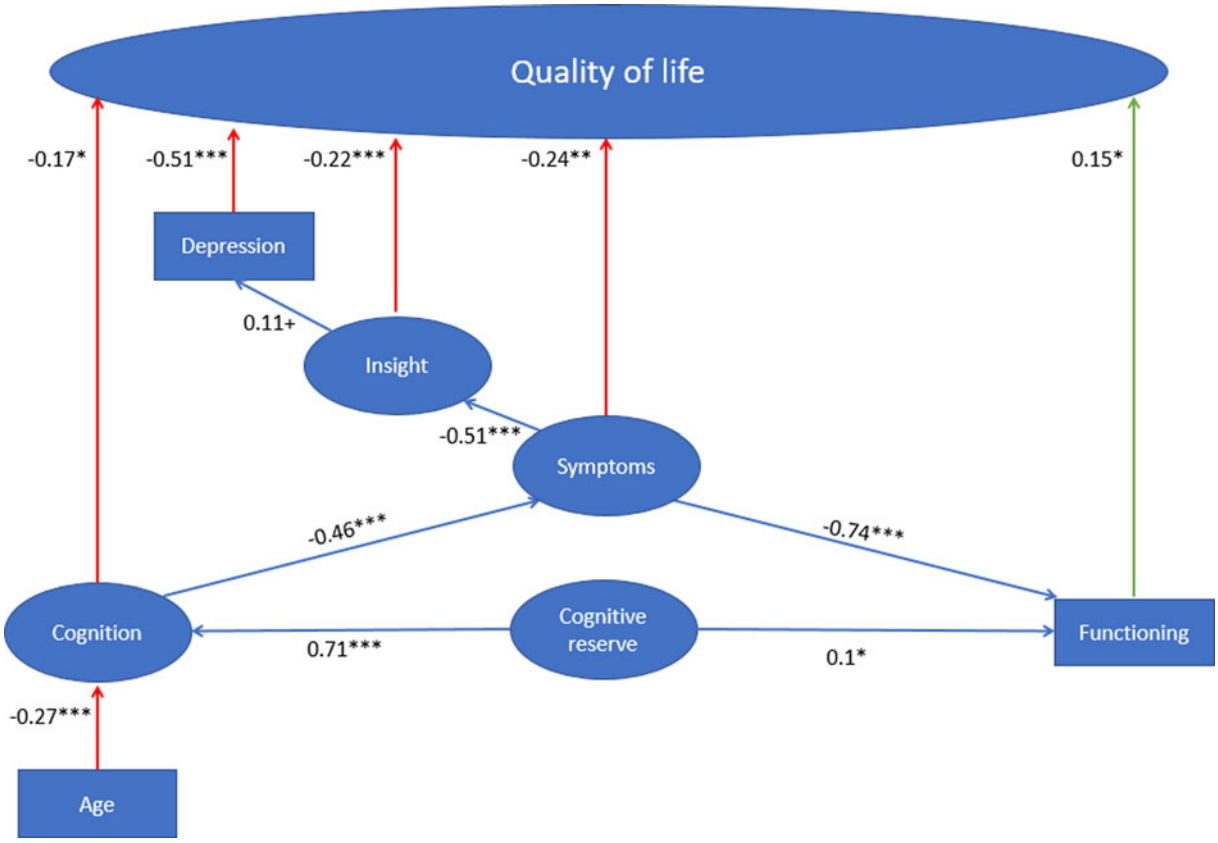

Fig. 1. Simplified diagram of the general model. The rectangles are observed variables, and ellipses are latent variables. The arrows and coefficients are standardized regression coefficients. Only significant regression paths are presented. Significance: $^{+}p < 0.1$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Table 2. Mediation analyses, standardized coefficients

	Direct effect	Indirect effect	Total effect	Proportion mediated
CR → QoL via cognition	0 ($p = 0.99$)	−0.12 ($p = 0.01$)	−0.12 ($p < 0.01$)	100%
CR → QoL via functioning	0 ($p = 0.99$)	0.02 ($p = 0.15$)	0.02 ($p = 0.82$)	No mediation
Cognition → QoL via insight	−0.17 ($p = 0.02$)	0.01 ($p = 0.39$)	−0.15 ($p = 0.03$)	No mediation
Cognition → insight via symptoms	−0.06 ($p = 0.36$)	0.23 ($p < 0.01$)	0.17 ($p = 0.02$)	79%[a] of the absolute total effect (= 0.3)
Insight → QoL via depression	−0.22 ($p < 0.01$)	−0.05 ($p = 0.07$)	−0.27 ($p < 0.01$)	20%
Cognition → functioning via symptoms	−0.03 ($p = 0.62$)	0.34 ($p < 0.01$)	0.31 ($p < 0.01$)	92%[a] of the absolute total effect (= 0.37)

[a]In case of an inconsistent mediation, the absolute values of direct and indirect effects were used to compute the absolute total effect and the proportion of the total mediated effect (Alwin & Hauser, 1975). CR, cognitive reserve; QoL, quality of life.

variables, drawing a global picture of the pathways contributing to subjective QoL in schizophrenia and not only local relationships. Our sample benefited from a comprehensive objective neuropsychological assessment. Also, insight was defined as a latent variable manifested by both self-reported and clinician-rated measures, thus integrating both facets of this variable.

Previous studies have reported comparable results with partial models that integrated only some of the variables included in this study. Psychosocial functioning was previously found to be a positive predictor of QoL (Chino et al., 2009; Fontanil-Gómez et al., 2017), but Brissos (Brissos et al., 2011) found that the relationship between functioning and QoL disappeared when symptoms were controlled for, which was not the case in our model, indicating that symptoms and functioning are independent contributors to QoL. Depression (Cotton et al., 2010; Meesters et al., 2013) and symptoms (Eack & Newhill, 2007; Kurtz et al., 2019; Kurtz & Tolman, 2011) were also previously found to be predictors of QoL in schizophrenia. Authors (Anaya et al., 2016) found that cognitive reserve was positively associated with functioning and cognition, and negatively with mental QoL in a sample of patients with bipolar disorder, suggesting the same pattern that we found, with a mediation of the relationship between cognitive reserve and QoL *via* cognitive performance. The authors hypothesized that this negative relationship may be explained by the fact that patients with better cognitive performances, resulting from a higher cognitive reserve, may have an increased awareness of

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their disorder, and thus overestimate its consequences when comparing their current situation to their premorbid situation, i.e. current cognitive performance and insight would explain this relationship. However, our results showed no direct relationship between insight and cognitive reserve or current cognitive performance, whereas previous studies found such a relationship (Aleman et al., 2006; Gerretsen et al., 2017; Nair et al., 2014). We also did not find a relationship between cognition and functioning when symptoms are controlled for, which is coherent with previous results (Ventura, Hellemann, Thames, Koellner, & Nuechterlein, 2009). Thus, the relationship between cognition and functioning should not be investigated without taking into account schizophrenic symptoms. Moreover, our model showed the negative relationship between cognition and subjective QoL that has previously been demonstrated by several researchers (DeRosse et al., 2018; Meesters et al., 2013; Narvaez et al., 2008). Insight has been suggested to be the mediator of this negative relationship. However, we did not find insight to be a mediator between cognition and QoL, as the relationship between cognition and insight was itself mediated by schizophrenic symptoms. Thus, cognition appears to have a direct negative impact on QoL, independently of insight, as neither are directly related [as previously suggested (Kurtz & Tolman, 2011; Zhou et al., 2015)]. The relationship appears to be robust, as it survived in a multivariate context with several potential hypothesized mediators taken into account. The mechanism by which better cognitive performance is associated with worse QoL is not clear and is yet to be elucidated. Authors (Bowie et al., 2007) suggested this relationship could be explained by metacognition, as patients with better cognition tend to overestimate their level of disability and thus to report higher levels of depression leading to a lower QoL. Furthermore, internalized stigma has been shown to be a partial mediator in the relationship between self-perceived cognitive disability and QoL (Shin, Joo, & Kim, 2016). It would thus be informative to operationalize metacognitive performance and internalized stigma as variables in a new model to test whether they can explain the negative relationship between cognition and QoL.

Finally, the significant links found in our model are consistent with the notion of a negative relationship of insight with QoL, which is often referred to as the insight paradox (Lysaker et al., 2007). Here we report that beyond this direct negative link, a partial mediation occurs through depression: insight is associated with depressive symptoms that contribute to poor QoL. For the clinician, these complex relationships indicate the importance of an accurate assessment of depressive symptoms when insight improves due to symptomatic remission or psychoeducation.

Limitations

Despite its strengths, our study had several limitations. Our study had a cross-sectional design, which did not allow us to infer causation. Our results, especially the direction of the arrows, need to be confirmed using longitudinal studies, as cross-sectional mediation analyses are limited to correlational relationships (Fairchild & McDaniel, 2017). Also, our sample was not selected randomly as the participants were patients of the Expert Centers for Schizophrenia of the FondaMental Foundation, and therefore a selection bias is possible. Additionally, we did not take treatment into account in our models. It would also have been informative to include a measure of objective QoL to investigate whether the determinants of objective and subjective QoL would have been the same. Also, our sample is in majority male (76% of males), which may raise questions regarding the generalization of the results and a possible recruiting bias favoring males in our sample. However, the proportion of male participants is in line with other studies, for instance (Galderisi et al., 2016). It would nonetheless be interesting for further analyses to check whether the results presented in this study would remain the same in a sample with a higher proportion of women. Finally, the concept of QoL is complex and can not be reduced to one single scale (here the S-QOL). S-QOL gives a health-related perspective on QoL, which may be different from a more global view on QOL. The latent variable we used to measure QoL may have been enriched with more comprehensive measures of QoL and with measures that are closer to the concept of functioning such as the 36-Item Short-Form Health Survey (SF-36) (Aaronson et al., 1992) and EQ5D (Rabin & de Charro, 2001, p. 2).

Overall, our general model is in accordance with the previous bi- or tri-variate results, but our multivariate approach provides a better picture of the determinants of QoL in schizophrenia by taking into account the complex interplay between the variables and their potential role as mediators of various relationships. The negative relationship between cognition and subjective QoL should be investigated further. When all plausible paths are taken into account, cognition, insight, depression, schizophrenic symptoms, and functioning directly contribute to QoL in schizophrenia. However, the relationships between the variables are intricate. Thus, the results presented here suggest that the difficulty generally encountered by clinicians in achieving an overall improvement in outcome variables (functioning, QoL, and clinical status) is not related to weak causal links or inadequate constructs, but rather to the complexity of the counterbalancing mechanisms. In practice, cognitive remediation should be provided to patients with schizophrenia only with close monitoring of QoL. Insight should also be addressed only with close monitoring of depressive symptoms, as they are related and together contribute negatively to QoL. Functional remediation may also be proposed to increase QoL.

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