



The role of symptoms and insight in mediating cognition and functioning in first episode psychosis

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ABSTRACT

Introduction: Achieving functional recovery in patients with psychosis is a challenge in clinical practice. Investigating the complex interplay between cognition, symptoms, insight and functional outcome in first episode psychosis will be crucial to understanding the factors leading to better functioning.

Methods: In this 12-month prospective follow-up study, we investigated how cognition, clinical symptoms, and insight into illness affected overall functioning in 160 patients with first episode psychosis recruited from the Early Assessment Service for Young People with Psychosis (EASY) in Hong Kong from July 1, 2014 to June 30, 2016. Cognition was assessed at baseline while symptoms, insight, and functioning were assessed at 12-month follow-up. Structural equation modelling was used to examine the direct and indirect relationships between functioning and other latent constructs.

Results: Symptoms (negative symptoms and general psychopathology) and insight were shown to be significant mediators between cognition and functioning. The significant direct relationship between cognition and functioning ($\beta = 0.387$; $p < 0.001$) became insignificant ($\beta = 0.079$; $p = 0.578$) after including symptoms and insight in the model. Symptoms and insight were significantly associated with cognition (symptoms, $\beta = -0.469$; $p < 0.001$; insight, $\beta = -0.372$; $p < 0.001$) and predicted functioning (symptoms, $\beta = -0.558$; $p < 0.001$; insight, $\beta = -0.264$; $p < 0.01$).

Conclusion: Symptoms and insight mediated the effects of cognition on functioning. Interventions for improving functioning in patients with first episode psychosis should target not only cognition but also symptoms and insight.

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1. Introduction

Psychosis is one of the major causes of disability worldwide (Global Burden of Disease Study 2013 Collaborators, 2015). Although the majority of patients with first episode psychosis show improvement in their symptoms after antipsychotic treatment, many of them continue to have long-term impairments in functioning (Chan et al., 2015; Chang

et al., 2012). Functional impairments can affect various aspects of daily life, including self-care, relationships with family and friends, academic and occupational performance. Given that functional impairments can cause psychological distresses in patients and their families and incur enormous economic burdens on society, a better understanding of the factors leading to these impairments is crucial, particularly during the early stages of illness for timely intervention.

Cognition is one factor that has been strongly linked to functioning in psychosis (Chang et al., 2017; Davies et al., 2016; Lepage et al., 2014). In spite of the significant association found between cognition and functioning, the correlations tended to be moderate as well as the

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measures of cognition could only account for 20%–60% of the variance in functional outcome (Verma et al., 2012). This has prompted the search for other factors such as mediators that may enhance the understanding of the relationships between cognition and functioning. However, most of the studies focused on the direct relationship between cognition and functioning, whereas only a few studies looked at the effects of other mediating factors (Anda et al., 2016; Cuesta et al., 2012; Díaz-Caneja et al., 2015).

One of the most promising mediators is the area of clinical symptoms as it shows a consistent relationship with cognition well as with different functional domains in psychosis (Anda et al., 2016; Cuesta et al., 2012; Díaz-Caneja et al., 2015). In addition, clinical symptoms, particularly the negative symptoms, are linked to functional outcome (Milev et al., 2005; Lin et al., 2013). Negative symptoms and general psychopathology are found to have the strongest relationship with neuro- and social-cognition (Milev et al., 2005; Ventura et al., 2011). Insight into illness is another variable that has a robust association with both cognition and functioning in psychosis. Quee et al. (2011) found that cognition along with clinical symptoms explaining 20% of the variance in the insight of patients with psychosis. Moreover, several studies have illustrated that insight consistently associated with functioning (Díaz-Caneja et al., 2015; Verma et al., 2012). Particularly, general insight into illness was found to explain up to 12% variance in global functioning in FEP patients (Segarra et al., 2012). On the other hand, premorbid functioning is demonstrated to have a solid association with cognition impairment at the early stage of psychosis. For instance, duration of untreated psychosis and education attainment have been found to predict cognition deterioration in first episode psychosis (Amminger et al., 2002).

The relationship among premorbid, cognition, symptoms, insight and functioning is complex and an exploration of the effects of the different factors in an integrated model would enhance our understanding of how these factors contribute to the functioning and whether they could be potential targets for intervention. The study prospectively followed up first episode psychosis patients for 12 months and aimed to investigate the complex interplay between cognition, symptoms, insight and functioning using structural equation modelling (SEM). Compared to simple multiple regression and path analyses, SEM aggregates measures to yield the latent constructs of interest. SEM can examine the direct and indirect relationships among a set of measurable variables and latent constructs and can handle measurement errors for more precise parameter estimations (Hoyle, 1995).

We hypothesize premorbid functioning, namely the duration of untreated psychosis and education attainment, is associated with cognition at the early stage of first episode psychosis. Consequently, the relationship between cognition at baseline and functioning at 12 months is mediated by symptoms and insight at 12 months.

2. Methods

2.1. Setting and participants

This 12-month prospective study followed up 160 patients with first episode psychosis between 1 July 2014 and 30 June 2016. Participants were recruited from the Early Assessment Service for Young People with Psychosis (EASY) in Hong Kong, an early intervention service for patients with psychosis (Tang et al., 2010). EASY is a territory-wide, phase-specific, 3-year early intervention service for patients with first episode psychosis. The inclusion criteria for the study were: (1) Cantonese-speaking Chinese, (2) aged 15 to 64 years, (3) a diagnosis of psychotic disorder (schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, or psychosis not otherwise specified) according to DSM-IV (American Psychiatric Association, 1994), and (4) having a first episode and within 1 month of antipsychotic treatment. The exclusion criteria were: (1) a diagnosis of organic brain disorder or drug-induced psychosis and (2) having a

known history of intellectual disability as indicated by an IQ below 70. Trained research assistants approached eligible participants during their first consultation at outpatient psychiatric clinics or after they were admitted to inpatient psychiatric wards. The study was explained to the patients and written informed consent was obtained. Consenting participants were given a face-to-face interview at baseline and at 12 months. The study was approved by the local institutional review board.

2.2. Measures

Basic demographic information including age, gender, years of education, stressful life events occurring in the past 12 months and duration of untreated psychosis (DUP) were recorded at baseline. Premorbid functioning and cognitive functions were assessed at baseline. Symptoms, insight, and functioning were assessed at the 12-month follow-up. Premorbid functioning was assessed using the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982). Cognitive measures were assessed using the information test, logical memory test, digit span test, letter-number span test, digit symbol test, and visual patterns test from WAIS-R (Wechsler, 1981). At follow-up, functioning was measured using the Role Functioning Scale (Goodman et al., 1993). This scale covers four specific aspects: work productivity, independent living and self-care, immediate social network relationships, and extended social network relationships, and is rated on a 7-point scale with higher scores representing better functioning. Positive, negative and general psychopathology symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Insight into the illness was measured using the general items from the Scale to Assess the Unawareness of Mental Disorder (SUMD) (Amador et al., 1993).

2.3. Analysis

Structural equation modelling (SEM) was employed to examine the relationship between cognition, symptoms, insight, and functioning. SEM can evaluate multiple hypothesized relationships among latent variables by combining confirmatory factor analysis with multiple regression analysis. The SEM models of the hypothesized relationship between cognition and functioning mediated by symptoms and insight were estimated in Mplus v.7 using a robust (Huber-White) maximum likelihood algorithm to deal with non-normality and variance heterogeneity. Missing data were handled using the Full Information Maximum Likelihood (FIML) method.

For SEM analysis, a minimum sample of 100 has been recommended by some experts (Hoyle, 1995). Another widely accepted rule of thumb recommended by Nunnally (1967) is that at least 10 participants for each observed variable (10×15 observed variables = 150). Thus, a sample size of 160 participants was considered to be sufficient for SEM analysis.

In accordance with the causal steps approach by Baron and Kenny (1986), two models were used to estimate the potential mediation effects: (1) a basic model positing a direct relationship between cognition and functioning and (2) a mediation model positing an indirect relationship between cognition and functioning via the association of symptoms and insight. Model fit, which determines the degree of fit of the sample data, was assessed by four commonly used indices, chi-squared test (χ^2), comparative fit index (CFI), Tucker Lewis Index (TLI) and root mean square error of approximation (RMSEA). CFI and TLI values above 0.90 are considered as an acceptable fit while above 0.95 are considered to be desirable (Hu and Bentler, 1995). A RMSEA value of 0.06 or less indicates a close model fit (Hu and Bentler, 1995). Even though the non-significant χ^2 value indicates good model fit, it is not common to get a non-significant χ^2 value in practice because this figure is highly sensitive to the sample size (Bearden et al., 1982). Therefore, multiple fit indices to evaluate model adequacy is essential (Byrne,

2013). In addition, Akaike Information Criterion (AIC) was used to compare the non-nested models.

The mediation effects of symptoms and insight were examined using a bootstrap with 2000 iterations. Bootstrapping has been shown to perform well in terms of power and type I error control. A bootstrap with 2000 iterations should yield a percentile-based confidence interval. If the lower 2.5% and upper 2.5% bounds do not include zero, then one can conclude the indirect effect is significantly different from zero and that mediation is present (Frazier et al., 2004; Preacher and Hayes, 2004).

3. Results

Table 1 shows the baseline demographics and clinical characteristics of the 160 patients with first episode psychosis. The sample (63 males and 97 females) had a mean age of 31 years and a mean education of 11.6 years, and about 38% of them were unemployed. The median duration of untreated psychosis (DUP) was 90 days. The predominant diagnosis was schizophrenia.

Table 2 shows the zero-order correlations of the study measures. The performance of information test and visual patterns test and positive symptom were not significantly correlated with any aspects of functioning, thus violating the requirement for mediation. Therefore, they were excluded as indicators of latent variables in the following statistical procedure. Confirmatory factor analyses revealed all indicator factors were reliable and valid measures of their respective latent variables, as

Table 1
Baseline demographics and clinical characteristics.

Characteristics	N = 160
Male, n (%)	63 (39.4)
Age, mean (SD), years	31.2 (13.1)
Education, mean (SD), years	11.6 (3.9)
Unemployed, n (%)	60 (37.5)
Marital status, n (%)	
Single	111 (69.4)
Married	39 (24.4)
Separated/divorced	9 (5.6)
Widowed	1 (0.6)
Living with others, n (%)	149 (93.1)
Premorbid adjustment scale, mean (SD)	0.2 (0.1)
Presence of family history, n (%)	40 (35.7)
Presence of stressful life event in past 12 months, n (%)	113 (70.6)
Duration of untreated psychosis, median (IQR), days	90 (19–240)
Inpatient, n (%)	100 (62.5)
Chlorpromazine equivalent doses, mean (SD), mg/day	338.8 (223.2)
Diagnosis, n (%)	
Schizophrenia	80 (50)
Delusional disorder	19 (11.9)
Brief psychotic disorder	33 (20.6)
Schizoaffective disorder	1 (0.6)
Psychosis nos	27 (16.9)
History of substance use, n (%)	7 (4.4)
Cognitive function (baseline)	
Logical memory	6.8 (4.8)
Digit symbol	72.6 (20.4)
Letter number span	11.5 (4.8)
Digit span	11.8 (2.3)
Symptoms (12 month follow-up)	
PANSS - Positive	8.7 (3.3)
PANSS - Negative	9.0 (3.1)
PANSS - General	21.2 (5.6)
Insight (12 month follow-up)	
SUMD1 - Awareness of Mental Disorder	1.3 (0.6)
SUMD2 - Awareness of the Consequences of Mental Disorder	1.3 (0.6)
SUMD3 - Awareness of the Effects of Medication	1.3 (0.6)
Role Functioning Scale (12 month follow-up)	
Work productivity	5 (1.3)
Self-care	5.6 (0.8)
Immediate relationship	5.8 (0.8)
Extended relationship	4.8 (1.0)

Abbreviations: n = number; SD = standard deviation; IQR = inter-quartile range.

Table 2
Zero-order correlations among study measures included in the structural equation models.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Education	-																
2. DUP	-0.271**	-															
3. Information	0.449**	-0.106	-														
4. Logical memory	0.331**	-0.060	0.417**	-													
5. Digit span	0.602**	-0.283**	0.301**	0.486**	-												
6. Letter number span	0.436**	-0.195*	0.487**	0.407**	0.496**	-											
7. Digit symbol	0.343**	-0.139	0.472**	0.426**	0.420**	0.564**	-										
8. Visual patterns	0.342**	-0.118	0.359**	0.413**	0.570**	0.557**	0.381**	-									
9. PANSS_P	0.247**	0.111	-0.139	-0.048	-0.100	-0.100	-0.125	-0.154	-								
10. PANSS_N	-0.141	0.153	-0.233*	-0.301**	-0.233*	-0.296**	-0.161	-0.202	-0.268**	-							
11. PANSS_G	-0.254**	0.161	-0.130	-0.210	-0.334**	-0.293**	-0.278*	-0.255*	-0.612**	0.464**	-						
12. SUMD1	-0.166*	0.211*	-0.342**	-0.321**	-0.272**	-0.272**	-0.198*	-0.195*	0.107	0.339**	0.288**	-					
13. SUMD2	-0.136	0.230**	-0.327**	-0.291**	-0.187*	-0.321**	-0.192*	-0.188	0.048	0.376**	0.285**	0.927**	-				
14. SUMD3	-0.101	0.262**	-0.266**	-0.298**	-0.183*	-0.237**	-0.196*	-0.165	0.036	0.348**	0.210*	0.724**	0.715**	-			
15. Work productivity	0.195*	-0.231*	0.187	0.166	-0.174	0.227*	0.184	0.179	-0.116	-0.268**	-0.194*	-0.266**	-0.239**	-0.290**	-		
16. Self-care	0.140	-0.177	0.137	0.161	-0.204*	0.139	0.109	0.033	-0.134	-0.253**	-0.151	-0.263**	-0.249**	-0.195*	0.580**	-	
17. Immediate relationship	0.249**	0.413**	0.088	0.242*	-0.347**	0.358**	0.272**	0.136	-0.246	-0.376**	-0.267**	-0.300**	-0.337**	-0.286**	0.460**	0.314**	-
18. Extended relationship	-0.013	-0.153	0.085	0.220	0.142	0.235*	0.247*	0.080	-0.243	-0.424*	-0.381**	-0.363**	-0.378**	-0.282**	0.353**	0.363**	0.505**

Abbreviations: DUP, Duration of untreated psychosis; PANSS_N, Positive and Negative Syndrome Scale negative scores; PANSS_P, Positive and Negative Syndrome Scale positive scores; PANSS_G, Positive and Negative Syndrome Scale general scores; SUMD1, Scale to Assess Unawareness of Mental Disorder; awareness of mental disorder; SUMD2, Scale to Assess Unawareness of Mental Disorder; awareness of the consequences of mental disorder; SUMD3, Scale to Assess Unawareness of Mental Disorder, awareness of the effects of medication.

*** $p < 0.001$.
** $p < 0.01$.
* $p < 0.05$.

suggested by their significant moderate to high factor loadings ($\beta = 0.328\text{--}0.969$; $p < 0.001$).

The basic model (Fig. 1) depicted the direct relationship between cognition at baseline and functioning at 1 year. This path was statistically significant (standardized coefficient $\beta = 0.387$, $p < 0.001$). Cognition accounted for only 15.6% of the variance in functioning. Results showed a satisfactory model fit, $\chi^2 = 61.45$ ($df = 34$, $p = 0.0027$), CFI = 0.92, TLI = 0.90 and RMSEA = 0.071 (90% CL = 0.042 to 0.100). In addition, the basic model has an AIC of 5854.83.

The mediation model (Fig. 2) evaluated the strength of the indirect relationship while controlling for the direct effect of cognition on functioning. After incorporating the mediators into the model, the direct path from cognition to functioning was no longer significant ($\beta = 0.079$, $p = 0.578$). Negative symptoms and general psychopathology ($\beta = -0.469$, $p < 0.001$), and insight ($\beta = -0.372$, $p < 0.001$) were significantly associated with cognition and were predictive of functioning (symptoms, $\beta = -0.558$, $p < 0.001$; insight, $\beta = -0.264$, $p = 0.008$). This model explained 49.6% of the variance in functioning, and the results showed that the mediation model had a good model fit ($\chi^2 = 191.312$, $df = 113$, $p < 0.001$; CFI = 0.92; TLI = 0.91; RMSEA = 0.0066, 90% CL = 0.047 to 0.085) with an AIC of 7982.13. The bootstrapping ($n = 2000$) estimate revealed a significant total indirect effect ($\beta = 0.360$, 95% CI = 0.042 to 0.678) with symptoms and insight. Specific indirect effects were found via the mediation of symptoms ($\beta = 0.262$, 95% CI = 0.017 to 0.506, $p < 0.05$) and insight ($\beta = 0.098$, 95% CI = 0.006 to 0.191, $p < 0.05$). Our data suggests the relationship between cognition and functioning was mediated by symptoms and insight.

4. Discussion

Our mediation analysis suggests that symptoms (negative symptoms and general psychopathology) and insight mediate the path between cognition on functioning. Our findings suggest cognitive impairment has adverse effects on symptoms and insight, and thus exerts a negative impact on functioning.

Our study using SEM found symptoms and insight had mediating roles on functioning in psychosis, compared to previous studies that used regression models (Anda et al., 2016; Cuesta et al., 2012; Díaz-Caneja et al., 2015). This may explain why previous studies found only a moderate association between cognition and functioning when no other factors were taken into account; while SEM is powerful in incorporating a broad span of observed variables and consequently offers more robust results.

Our findings suggest the relationship between cognition and functioning appears to be more complex. We postulate that educational attainment and the duration of untreated psychosis will influence the patient's cognition. Cognitive performance will then affect the clinical presentation (symptoms) as well as the perception of the illness and

adherence to treatments (insight). Subsequently, symptoms and insight combined together will affect the patients' functioning.

Our mediation model explained 49.6% of the variance in functioning, whereas our basic model could only explain 15.6% of the variance. These results fall within the ranges reported by previous studies. For example, Schmidt et al. (2011) found that cognition explained 14% of the variance in functioning, whereas Lin et al. (2013) found that the interaction of cognition, negative symptoms and self-efficacy accounted for 31% of the variance in global functioning. Another model using comprehensive cognitive and symptomatic measurements explained 89% of the variance in global functioning (Lin et al., 2013). The addition of symptoms and insight in our mediation model increased the explained variance, which supports the strong influence of symptoms and insight on functioning. However, the remaining unexplained variance suggests that functioning is also influenced by other factors such as motivation (Schmidt et al., 2011), metacognition (Lysaker et al., 2010), and dysfunctional attitudes (Grant and Beck, 2009; Horan et al., 2010). Future studies should include additional mediators, which may lead to a better fit of the observed data (Rabinowitz et al., 2012; Tomotake, 2011) to explain more of the variability in functioning (Bell et al., 2009; Gard et al., 2009).

Investigating mediator variables that can explain the relationship between cognition and functioning in psychosis is of high clinical and research significance. Identifying elements crucial for improving functioning would help to refine early intervention services in psychosis. It should be noted that combining strategies that target cognition, symptoms and insight may reveal synergistic effects and could be integral to making sustained changes in functioning in patients (Emsley and Dunn, 2010; MacKinnon et al., 2007). Adequate changes to functioning may first require control of symptoms, followed by fostering of insight and cognitive enhancement.

The study had several limitations that should be taken into account when interpreting the results. First, although the use of latent variables in the SEM analysis is advantageous for reducing measurement error when estimating study constructs, this might obscure potential differential relationships between specific domains of the variables. Second, it would be interesting to explore differential pathways between cognition and functional domains. However, our sample of 160 patients with first episode psychosis was not sufficient to ensure the SEM analysis had adequate statistical power to include other cognitive dimensions (e.g., social cognition) to derive a more comprehensive prediction model and use other approach relying less heavily on p -values. Third, our sample with majorly female, employed patients, a wide range of admission age range and a heterogeneous sample of different psychotic disorders may limit the generalizability of our study findings. Fourth, only a limited range of cognitive domains was assessed in our study. Future studies (with adequate sample size) could incorporate a wider range of cognitive batteries like BACS or MATRICS to unravel the interplay between the study variables.

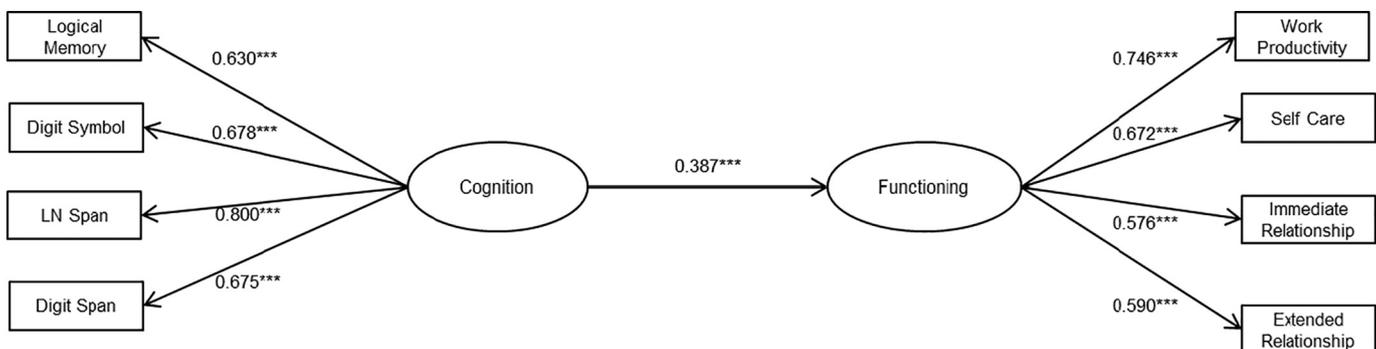


Fig. 1. The basic model reflects the direct relationship between cognition and functioning. This path was statistically significant (standardized coefficient $\beta = 0.387$, $p < 0.001$). Variables under cognition logical memory, digit symbol, letter-number span and digit span. Variables under Role Functioning Scale (RFS) are work productivity, self-care, immediate relationship and extended relationship.

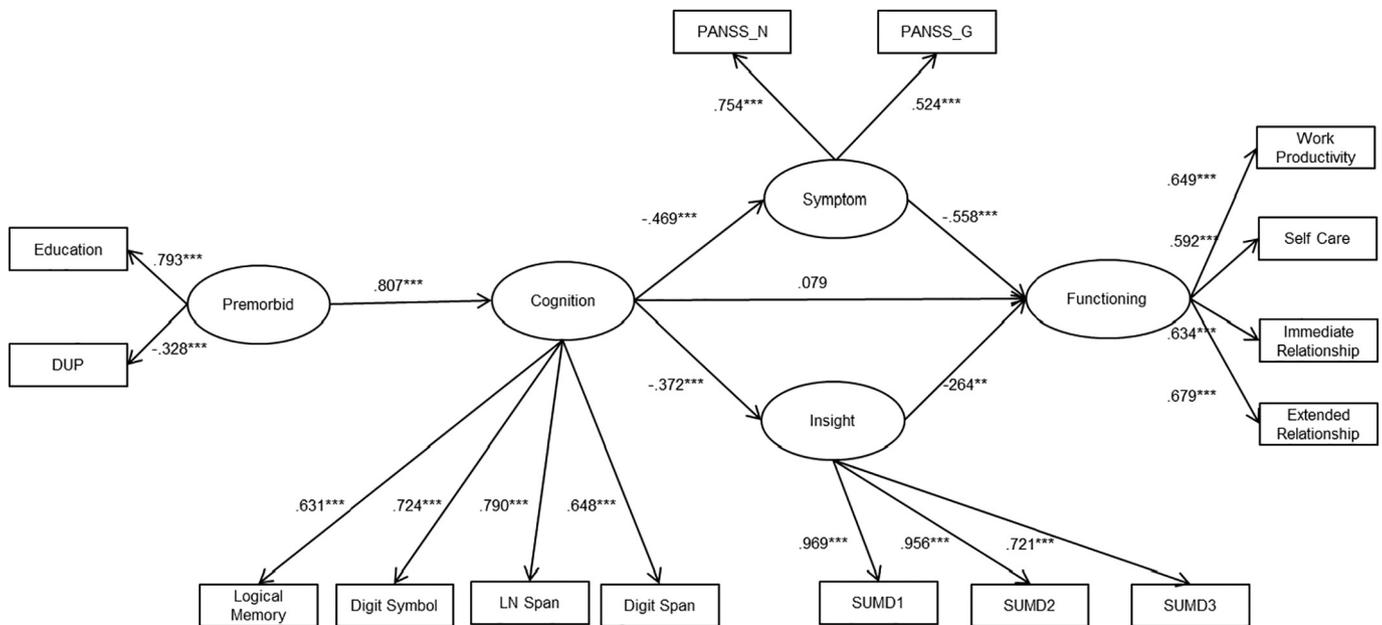


Fig. 2. The mediation model evaluates the strength of the indirect relationship while controlling for the direct effect of cognition on functioning. The direct path from cognition to functioning was no longer significant when the mediators (Symptoms and Insight) were entered into the model ($\beta = 0.079$, $p = 0.578$). Symptoms ($\beta = -0.469$, $p < 0.001$) and Insight ($\beta = -0.372$, $p < 0.001$) were significantly associated with cognition, and were predictive of functioning (Symptoms, $\beta = -0.558$, $p < 0.001$; Insight, $\beta = -0.264$, $p = 0.008$). Variables under Symptom include PANSS_N (Positive and Negative Syndrome Scale - negative symptoms score) and PANSS_G (Positive and Negative Syndrome Scale - general psychopathology score). Variables under Insight include SUMD1 (Scale to Assess Unawareness of Mental Disorder, awareness of mental disorder), SUMD2 (Scale to Assess Unawareness of Mental Disorder, awareness of the consequences of mental disorder) and SUMD3 (Scale to Assess Unawareness of Mental Disorder, awareness of the effects of medication).

5. Conclusion

Despite the limitations, the current study extends the prior research on chronic schizophrenia to first episode psychotic disorders in regards to the central role of symptoms (i.e. negative symptoms and general psychopathology) and insight in determining functioning. Our SEM analysis suggests that symptoms and insight mediate the cognition-functioning relationship in first episode psychosis. Our finding suggests the importance of symptomatic remission and insight enhancement could improve functioning and quality of life of patients. Future longitudinal follow-up studies will be required to clarify the temporal relationship among keys variables in predicting functioning in patients with first episode psychosis. Moreover, further investigation of the interaction of other clinical factors will be needed to increase the predictive power and to target relevant factors to optimize therapeutic strategies.

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Contributors

EHML, CLMH and EYHC participated in the conceptualization, design of methodology, supervision, and funding acquisition. EHML, CLMH, KPCC and PYC participated in data curation, formal analysis, investigation, project administration and writing of the original draft. All authors contributed to review and editing of the final manuscript.

Conflict of interest

E.Y.H.C. has participated on advisory boards for Otsuka; has received research funding from AstraZeneca, Janssen-Cilag, Pfizer, Eli Lilly, Sanofi-Aventis and Otsuka, and an educational grant from Janssen-Cilag. All other authors reported no conflict of interest disclosures.

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