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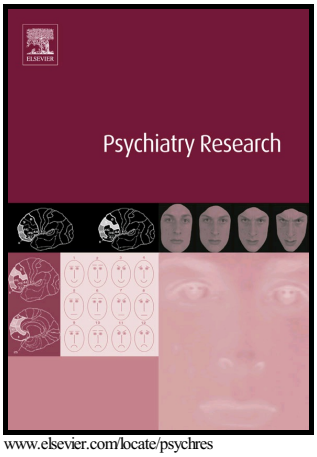

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Psychiatric symptoms mediate the effects of neurological soft signs on functional outcomes in patients with chronic schizophrenia: A longitudinal path-analytic study

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Abstract

Neurological soft signs (NSS) in motor coordination and sequencing occur in schizophrenia patients and are an intrinsic sign of the underlying neural dysfunctions. The present

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longitudinal study explored the relationships among NSS, psychiatric symptoms, and functional outcomes in 151 Chinese patients with chronic schizophrenia across a 6-month period. The participants completed neurological assessments at baseline (Time 1), psychiatric interviews at Time 1 and 3-month follow-up (Time 2), and self-report measures on daily functioning at 6-month follow-up (Time 3). Two possible (combined and cascading) path models were examined on predicting the functional outcomes. Direct and indirect effects of Time 1 NSS on Time 3 functional outcomes via Time 2 psychiatric symptoms were evaluated using path analysis under bootstrapping. Motor coordination and sequencing NSS did not have significant direct effects on functional outcomes. Motor coordination NSS exerted significant and negative indirect effects on functional outcomes via psychiatric symptoms. These results contribute to a better understanding of the determinants of functional outcomes by showing significant indirect pathways from motor coordination NSS to functional outcomes via psychiatric symptoms. That motor sequencing NSS did not affect functional outcomes either directly or indirectly may be explained by their trait marking features.

Keywords

neurological deficits; disorganized symptoms; negative symptoms; daily functioning; mediation; path analysis

1. Introduction

Schizophrenia is an intricate neuropsychiatric disorder associated with deficits in cognitive, affective, and neurological domains (R. W. Heinrichs and Zakzanis, 1998). Neurological soft signs (NSS), defined as subtle neurological abnormalities in sensory integration, motor coordination and sequencing of complex motor acts (D. W. Heinrichs and Buchanan, 1988), occur consistently in patients with schizophrenia (Emsley et al., 2005). A meta-analysis (Bachmann et al., 2014) among schizophrenia patients reveals a declining trend in NSS together with remission of psychopathological symptoms in remitting patients. Other studies (Chen et al., 2000; Prikryl et al., 2012) have found deteriorations in NSS for non-remitting patients with a chronic course. A recent study (Chan et al., 2016) reveals an abnormally flat and elevated lifespan trajectory of NSS in schizophrenia patients. These results suggest that NSS comprise both state- and trait-like features and vary in the clinical course of schizophrenia.

Schizophrenia patients have been found to exhibit significantly more NSS than healthy subjects and patients with other psychiatric disorders (Chan et al., 2010; Wang et al., 2016). Their unaffected first-degree relatives also display higher NSS compared to healthy controls (Xu et al., 2016). Kong et al. (2012) have linked persistent and heightened NSS with progressive cerebral changes in schizophrenia patients. Given the linkage between NSS and genetic variants and neural abnormalities in brain regions (Zhao et al., 2014; Hirjak et al., 2016), NSS have been suggested as a potential endophenotype for schizophrenia. The relative

ease of assessments of NSS implies that NSS could be used to monitor progression of the disorder or to identify subjects at risk to develop chronic schizophrenia.

NSS have been advocated (Sewell et al., 2010; Chan et al., 2015; Chan et al., 2016) as outcome predictors of essential features of the disorder such as psychopathological severity and functional outcomes. Previous studies have established significant and positive associations between NSS and psychiatric symptoms such as positive symptoms (Chan et al., 2010), negative symptoms (Prikryl et al., 2012; Mittal et al., 2014; Chan et al., 2015), and disorganized symptoms (Basso et al., 1998; Bombin et al., 2005) in schizophrenia patients. Both NSS and psychiatric symptoms are associated with poor functional outcomes in schizophrenia. NSS have been correlated with worse functional outcomes (Behere, 2013; Papiol et al., 2016) in the form of social functioning (Jahn et al., 2006), and global functioning (Peralta et al., 2014). Similarly, psychiatric symptoms have been found to contribute to long-term comorbidity and worse functioning (Milev et al., 2005; Chan et al., 2015; Strassnig et al., 2015).

Nevertheless, few researchers have simultaneously investigated the relationships among NSS, psychiatric symptoms, and functional outcomes in schizophrenia patients. Having a better understanding of these relationships is essential to devise effective interventions that facilitate patients' recovery and enhance their overall functioning. Path-analytic approaches are preferred and suitable to explore these patterns. A meta-analysis by Ventura et al. (2009)

demonstrates that negative symptoms mediate the relationship between neurocognition and functional outcomes. Findings from other studies (Lin et al., 2013; Mehta et al., 2014) support such a mediating role for psychiatric symptoms. Apart from direct effects from NSS to functional outcomes, it is plausible that NSS might have indirect effects on functional outcomes through indirect pathways via psychiatric symptoms. Further research is warranted to elucidate the roles of NSS and psychiatric symptoms in predicting functional outcomes.

To the best of our knowledge, no existing studies have explored the potential mediating role of psychiatric symptoms on the relationship between NSS and functional outcomes. The present longitudinal study adopted a path-analytic approach to evaluate the temporal relationships among NSS, psychiatric symptoms, and functional outcomes in schizophrenia patients across a 6-month period. Figure 1 depicts the conceptual model of the present study, where psychiatric (positive, negative, and disorganized) symptoms are posited as potential mediators of the relationships between NSS (deficits in motor coordination and motor sequencing) and functioning outcomes (IADL and ADL). This study examined two possible path models on predicting functional outcomes in schizophrenia patients – a combined model, comprising both direct and indirect effects of NSS on functional outcomes, and a cascading model, where NSS predicted functional outcomes solely by indirect effects via psychiatric symptoms. We hypothesized that the combined path model would provide a better fit than the cascading path model and that psychiatric symptoms would mediate the associations between

NSS and functional outcomes.

[Insert Figure 1 about here]

2. Methods

2.1. Participants

The present study is a secondary analysis of data from a randomized controlled trial (Ho et al., 2016) on the effectiveness of Tai-chi and physical exercise in schizophrenia patients. The study sample comprised 151 chronic schizophrenia patients recruited from a mental health rehabilitation complex in Hong Kong from September 2013 to January 2014. The patients were receiving long-term residential care in the hostel. Inclusion criteria were fulfillment of the DSM-IV TR criteria for schizophrenia according to a psychiatrist's diagnosis, aged between 18 and 65 years, and ability to understand and speak Cantonese. Exclusion criteria included acute schizophrenia requiring hospitalization, presence of unstable schizophrenic symptoms (such as persistent withdrawal) that limit interaction in an assessment interview, a history of brain trauma or organic mental disorders, and presence of physical disabilities or severe illnesses that could impair cognitive or visuomotor functioning.

At baseline (Time 1), the participants completed neurological assessments on NSS. They underwent structural clinical interviews on psychiatric symptoms at Time 1 and at 3-month follow-up (Time 2) from the same rater. At 6-month follow-up (Time 3), the participants

completed self-report measures on functional outcomes. Written informed consent was sought from the participants and the study protocol was approved by the institutional ethics committee of the University of Hong Kong (HKCTR-1453). Demographic and clinical information such as duration of the disorder and type of antipsychotic medications were obtained via medical record reviews.

2.2. Assessments

2.2.1. Neurological soft signs

Two subscales of the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989) were used to evaluate the participants' NSS in motor coordination and sequencing of complex motor acts. Compared to the Cambridge Neurological Inventory (Chen et al., 1995) and Heidelberg Scale (Schröder et al., 1991), the NES was widely used among longitudinal studies on NSS in schizophrenia (Bachmann et al., 2014). Neurological deficits for motor coordination consist of six items, namely, tandem walk, rapid alternating movements (for dominant and non-dominant hand), finger/thumb opposition (for dominant and non-dominant hand), and finger-to-nose test. Neurological deficits for sequencing in complex motor acts comprise three items, namely, fist-ring test, fist-edge-palm test, and Ozeretski test.

Participants' performance on each item was rated on a 3-point scale based on the number of mistakes they made. Each item score was summed up to produce a subscale score for

motor and sequencing deficits, with higher scores indicating greater levels of NSS. The Chinese version of the NES showed marginal internal consistency for sequencing deficit (Cronbach's $\alpha = 0.59$) and good internal consistency for motor deficit ($\alpha = 0.80$) subscales in a previous study (Fong et al., 2015). In the present study, assessment of NSS was conducted by three professional raters who had a medical-related background and had received relevant trainings from a qualified psychiatrist. Both subscales displayed good inter-rater reliability with intraclass correlation coefficients found to be greater than 0.80.

2.2.2. Psychiatric symptoms

The Positive and Negative Syndrome Scale (Kay et al., 1987) was used to assess the positive, negative, and disorganized symptoms of schizophrenia exhibited by the participants in the past week. Sample items for the subscales include: delusions and hallucinations for positive symptoms (4 items), blunted affect and emotional withdrawal for negative symptoms (6 items), and conceptual disorganization and difficulty in abstraction for disorganized symptoms (3 items). Each subscale was rated on a 7-point scale (1 = absent, 7 = extreme) by three trained research assistants based on a 40-minute semi-structured psychiatric interview with the participants and information from their family members or primary care staff. Higher scores denote higher levels of psychiatric symptoms. The Chinese version of the scale (Jiang et al., 2013; Fong et al., 2015) has shown good psychometric properties in terms of reliability

and convergent validity. In the present study, all three subscales displayed good internal consistency (α = 0.81 - 0.85) at Time 1. Acceptable inter-rater reliability was found for all three subscales with intraclass correlation coefficients found to be greater than 0.70.

2.2.3. Functional outcomes

Functional outcomes were measured using the Activities of Daily Living index (ADL) (Mahoney and Barthel, 1965) and Instrumental Activities of Daily Living scale (IADL) (Lawton and Brody, 1969). ADL inquires 10 basic self-care tasks such as feeding, dressing, toilet use, and climbing stairs and IADL assesses independent living skills in five domains of daily life such as shopping, traveling on public transport, self-medication, and handling finance. Patients' ability to perform these tasks was assessed by their self-report response with reference to information provided by their family members or primary care staff. The total score for ADL and IADL ranges from 0 to 100 and 0 to 5, respectively, with higher scores indicating better functional outcomes in terms of greater independence in daily functioning. The Chinese version of ADL (Leung et al., 2007) and IADL (Tong and Man, 2002) have shown good test-retest reliability and internal consistency and robust convergent validity. In the present study, satisfactory internal consistency was found for ADL (α = 0.71) and IADL (α = 0.67) at Time 3.

2.3. Data analysis

Univariate analyses were employed to obtain descriptive statistics and bivariate correlations between NSS, psychiatric symptoms, and functional outcomes in the sample. Path analysis was performed using Mplus version 7.3 (Muthén and Muthén, 1998-2013). This technique adopts structural equation modeling to examine hypothesized path models and analyze regression paths among multiple observed variables. In the present study, Time 1 NSS in motor coordination and sequencing as were specified as the predictors or independent variables. Psychiatric (positive, negative, and disorganized) symptoms measured at Time 2 were proposed as the mediator variables. Functional outcomes (ADL and IADL) measured at Time 3 were specified as the dependent variables or distal outcomes.

We evaluated the hypothesized cascading and combined path models under the maximum likelihood estimator. In the cascading path model (solid lines in Figure 1), Time 1 motor coordination and sequencing NSS were hypothesized to influence Time 3 ADL and IADL solely indirectly via Time 2 psychiatric symptoms. The combined path model tested the direct effects (additional dashed line) from Time 1 NSS to Time 3 functional outcomes. Potential confounding variables such as gender, age, education level, illness duration, and antipsychotic medication were included in both models as covariates. We also controlled for the autoregressive effects of Time 1 psychiatric symptoms on Time 2 psychiatric symptoms.

Model fit was assessed via the following criteria (Hu and Bentler, 1999): insignificant χ^2

($p > 0.05$); comparative fit index (CFI) and Tucker-Lewis index (TLI) ≥ 0.95; and root mean square error of approximation (RMSEA) and standardized root mean square residual (SRMR) ≤ 0.05. Model comparison was based on the chi-square test and Bayesian information criterion (Raftery, 1995). A total of 5, 5, and 7 participants did not join the assessment at Time 1, Time 2, and Time 3, respectively. Instances of missing data were minimal (less than 5.4% of cases for any variable) and were handled via the full information maximum likelihood method under the missing at random assumption (Little and Rubin, 1987).

Unstandardized regression estimates and R^2 values for the mediator and dependent variables are reported. Our path models tested a total of 12 indirect effects from the two NES subscales to ADL and IADL via the three psychiatric symptoms (such as Time 1 motor coordination NSS → Time 2 positive symptoms → Time 3 IADL or Time 1 motor sequencing NSS → Time 2 disorganized symptoms → Time 3 ADL). These indirect effects were estimated using bootstrapping with 5,000 computations (MacKinnon, 2008). The use of bootstrapping allowed for the likely non-normal distribution for the indirect effects as a product of two normally distributed parameters. Statistical significance of the indirect effects was determined by the bias-corrected bootstrap 95% confidence interval excluding zero (MacKinnon et al., 2004).

3. Results

3.1. Sample characteristics

The mean age of the study sample was 54.00 years (SD = 8.40) and 54% (n = 80) were men. The majority of the participants were single (71%, n = 104) with a secondary education level (60%, n = 88). The average illness duration was 29.9 years (SD = 9.8). The majority were receiving atypical antipsychotics (78%, n = 118) such as clozapine, risperidone, or olanzapine and nine patients (6%) were receiving no antipsychotics. Table 1 presents the descriptive statistics of the study variables. At Time 1, the subscale score was 1.63, 2.64, and 2.72 for positive, negative, and disorganized symptoms, respectively, indicating negligible positive symptoms and mild negative and disorganized symptoms at baseline. Participants' levels of psychiatric symptoms remained fairly stable over the 3-month period. At Time 3, the sample demonstrated good basic self-care skills and average independent living skills.

[Insert Table 1 about here]

3.2. Bivariate correlations

Table 2 displays the bivariate correlations among the main study variables. NSS were significantly and positively linked with Time 2 psychiatric symptoms (r = 0.21 to 0.48, p < 0.01). Repeated measures of psychiatric symptoms at Time 1 and 2 showed positive and significant autocorrelations (r = 0.36 to 0.42, p < 0.01). Both NSS and Time 2 psychiatric symptoms were negatively and significantly associated with daily functioning (r = -0.23 to -0.45, p < 0.01), except between Time 2 positive symptoms and IADL (r = -0.15, p > 0.05).

[Insert Table 2 about here]

3.3. Path model estimates

The cascading path model displayed a good model fit to the data: χ^2 (38) = 45.11, p = 0.20, CFI = 0.99, TLI = 0.96, RMSEA = 0.035, SRMR = 0.052, BIC = 7969. Adequate model fit was found for the combined path model: χ^2 (34) = 41.98, p = 0.16, CFI = 0.98, TLI = 0.96, RMSEA = 0.039, SRMR = 0.048, BIC = 7986. The combined model did not provide a significantly better fit ($\triangle\chi^2$ = 3.13, $\triangle df$ = 4, p = 0.54) and had a higher BIC than the cascading model. None of the direct effects from Time 1 NSS to Time 3 functional outcomes were statistically significant (B = -0.010 to -0.271, p = 0.21 – 0.82).

Figure 2 presents the unstandardized path coefficients in the cascading path model. Participants who were females or more educated showed significantly fewer negative and disorganized symptoms at Time 1. Females also reported significantly lower levels of motor deficits and more Time 2 positive symptoms. Age, illness duration, and antipsychotic medication were not significantly associated with the study variables. Controlling for the positive autoregressive effects from Time 1 psychiatric symptoms, motor deficits but not sequencing deficits at Time 1 significantly and positively predicted Time 2 positive symptoms (R^2 = 24.1%, p < 0.01), negative symptoms (R^2 = 21.7%, p < 0.01), and disorganized symptoms (R^2 = 30.7%, p < 0.01). Negative and disorganized symptoms at Time

2 significantly predicted Time 3 IADL (R^2 = 19.6%, $p < 0.01$), whereas Time 2 positive and disorganized symptoms significantly predicted Time 3 ADL (R^2 = 27.9%, $p < 0.01$).

[Insert Figure 2 about here]

3.4. Indirect effects of NSS on functional outcomes via psychiatric symptoms

Sequencing deficits did not have a significant total indirect effect on IADL (B = -0.01, bootstrap 95% CI = -0.06 to 0.06) and ADL (B = -0.14, bootstrap 95% CI = -0.73 to 0.19) via psychiatric symptoms. Motor coordination deficits showed a significant total indirect effect on both IADL (B = -0.06, bootstrap 95% CI = -0.10 to -0.02) and ADL (B = -0.42, bootstrap 95% CI = -1.18 to -0.11) via psychiatric symptoms. Table 3 lists the specific indirect effects from NSS to functional outcomes via positive, negative, and disorganized symptoms.

As highlighted in bold and red in Figure 2, motor coordination deficits exerted significant and negative indirect effects on IADL via negative and disorganized symptoms. The two specific indirect effects (T1 motor deficits→T2 negative symptoms→T3 IADL and T1 motor deficits→T2 disorganized symptoms→T3 IADL) were not significantly different (difference = 0.03, BC bootstrap 95% CI = -0.02 to 0.09). Similarly, motor coordination deficits exerted significant and negative indirect effects on ADL via positive and disorganized symptoms. The two specific indirect effects (T1 motor deficits→T2 positive symptoms→T3 ADL and T1 motor deficits→T2 disorganized symptoms→T3 ADL) were not significantly different (difference = 0.02, BC bootstrap 95% CI = -0.43 to 0.35).

[Insert Table 3 about here]

4. Discussion

The present study tested two models of determining functional outcomes using NSS and psychiatric symptoms in patients with chronic schizophrenia via a longitudinal path-analytic approach. The present study is the first to examine the temporal relationships among these variables and explore the mediating role of psychiatric symptoms in the relationships between NSS and functional outcomes. Most of the present sample were on antipsychotic medications and exhibited negligible to mild psychiatric symptoms at both Time 1 and 2. Consistent with previous findings (Arango et al., 2000; Mittal et al., 2007; Bachmann et al., 2014), NSS were positively correlated with psychiatric symptoms over the 3-month period. This study confirms the absence of associations between NSS and demographic characteristics such as antipsychotic medications and illness duration as suggested by existing literature (Bombin et al., 2005; Chan et al., 2010).

4.1. Direct effects from NSS to functional outcomes

Contrary to our hypothesis, the combined model did not provide a superior fit than the parsimonious cascading model. Despite the negative bivariate correlations among NSS and functioning outcomes, neither motor coordination nor sequencing NSS had significant direct

effects on ADL and IADL in the combined model. In a recent study by Bhagyavathi et al. (2015), the combined model provided a better fit than the cascading model in the relationships among cognitive deficits, residual symptoms and functional outcomes in schizophrenia patients. Two remarks could be made regarding our surprising result. On one hand, the study by Bhagyavathi et al. (2015) was based on cross-sectional data while our study adopted a longitudinal design. The temporal relationship between Time 1 NSS and Time 3 functional outcomes could conceivably be weaker across a time lag of 6 months, such that they could be fully mediated by Time 2 psychiatric symptoms. On the other hand, non-significance of the direct effects does not necessarily imply full mediation. It could indicate inadequate power to detect the difference between the total effect and the indirect effect in the present study.

4.2. Indirect effects from NSS to functional outcomes via psychiatric symptoms

Consistent with our hypothesis, Time 2 psychiatric symptoms mediated the effects of Time 1 motor coordination NSS on Time 3 functioning outcomes. This suggests greater neurological deficits in motor coordination are associated with more severe psychiatric symptoms which in turn predict poorer functional outcomes. Our findings resemble previous results in which psychiatric symptoms mediated the effects of neurocognition on functional outcomes (Ventura et al., 2009; Green et al., 2012; Bhagyavathi et al., 2015). However, motor

sequencing NSS did not have any significant (direct or indirect) effects on functional outcomes in our model. This could be attributed to two plausible reasons. First, the motor sequencing subscale of the NES displayed inadequate internal consistency ($\alpha < 0.60$) in this study, which may attenuate its relationships with other variables in the model.

Second, a recent study by Ojagbemi et al. (2015) reveals trait marking features for motor sequencing NSS whereas motor coordination NSS reflect symptomatic states of the disorder. The current results coincide with their results in that the latter but not the former showed temporal influences on psychiatric symptoms and functional outcomes over a 6-month period. The trait-like features for motor sequencing NSS could explain their lack of relationships with the study variables over a relatively short period. Future research should elucidate the predictive effects of motor sequencing NSS over a longer follow-up period.

4.3. Limitations

Several study limitations should be noted. First, the present study included only two subscales (motor coordination and sequencing) of the NES and failed to assess participants' NSS in sensory integration. The lack of relevant data is one of the drawbacks of the study. Future studies should include assessments on sensory integration NSS to allow a complete analysis of the influences of NSS on functional outcomes. Second, our study sample of residential patients with chronic schizophrenia may not represent the general patient

population well. Further research should attempt to cross-validate the present results among first-episode schizophrenia patients. Interestingly, a recent longitudinal study (Chan et al., 2016) finds no significant difference in NSS between first-episode and chronic schizophrenia patients after matching for demographic characteristics.

Third, despite the longitudinal design, cautions should be warranted to interpret the indirect effects as casual since the mediation analysis may not reveal the true casual relation (MacKinnon et al., 2007). The fact that functional outcomes were only assessed at 6-month follow-up in the present study means that functional outcomes are not necessarily the result of NSS and psychiatric symptoms. Randomized intervention studies are more suited to derive causal pathways from NSS to functional outcomes in schizophrenia. Besides, a number of other important predictors of functional outcomes (Galderisi et al., 2014) such as premorbid functioning, memory deficits, coping, and expressed emotions were not included in the present model. These determinants could have accounted for part of the unexplained variance in functional outcomes in the model.

4.4. Clinical implications

Though antipsychotic medications are effective in managing psychotic symptoms, they have limited long-term effects in improving patients' negative and disorganized symptoms (Buchanan et al., 2009; Remington et al., 2010). According to Leifker and colleagues (2009),

functioning outcomes are the product of a complex set of symptoms and neurocognitive deficits. The challenge of facilitating functional recovery is more important among schizophrenia patients with a chronic course. The present study contributes to a better understanding of the determinants of functional outcomes in these schizophrenia patients. Our study elucidates the vital role of psychiatric symptoms in mediating the pathways from motor coordination NSS to functional outcomes, suggesting them to be additional treatment targets in enhancing functional outcomes. Recent studies have suggested that cognitive training alone may not be sufficient to achieve functional recovery (Farreny et al., 2013; Keshavan et al., 2014; Bhagyavathi et al., 2015) and that NSS may be neurodevelopmental markers for schizophrenia disorders (Chan et al., 2016). Integration of NSS assessment into screening programs and neuropsychological rehabilitation into standard treatment programs could be beneficial for the high-risk, non-remitting schizophrenia patients.

5. Conclusion

The present study demonstrates that neurological soft signs influence functional outcomes indirectly through specific pathways of psychiatric symptoms. Strengths of the present study were the longitudinal design with temporal ordering among the predictor, mediator, and outcome variables and inclusion of various demographic and clinical characteristics as model covariates. Holistic interventions that incorporate pharmacotherapy,

psychosocial therapies, and cognitive behavioral interventions should be developed based on the individual neurological deficits and needs of the patients.

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Figure 1. Hypothesized path model on neurological soft signs, psychiatric symptoms and functional outcomes in the present study. Note: Pathways for the cascading model are denoted by solid lines, whereas the dashed line indicates the direct effects from neurological soft signs to functional outcomes.

Figure 2. Unstandardized path coefficients in the cascading path model, with significant mediation paths from Time 1 neurological deficits to Time 3 functional outcomes via Time 2 psychiatric symptoms highlighted in bold and red. Note: Standard errors are shown in parentheses. For baseline covariates, only paths that are statistically significant ($p < 0.05$) are displayed. Residual covariances among Time 1 and Time 2 variables are not shown in the figure. IADL = Instrumental Activity of Daily Living, ADL = Activity of Daily Living.

Table 1 Descriptive statistics of the main study variables (*n* = 151)

Variables	Range	*Mean (SD)*
Neurological soft signs (Time 1)		
Motor coordination	0 – 12	4.88 (3.40)
Sequencing of complex motor acts	0 – 6	4.16 (1.71)
Psychiatric symptoms (Time 1)		
Positive symptoms	1 – 5.5	1.63 (0.85)
Negative symptoms	1 – 5.3	2.64 (1.11)
Disorganized symptoms	1 – 6.7	2.72 (1.32)
Psychiatric symptoms (Time 2)		
Positive symptoms	1 – 5.3	1.82 (0.83)
Negative symptoms	1 – 4.8	2.62 (0.91)
Disorganized symptoms	1 – 6.0	2.76 (0.99)
Daily functioning (Time 3)		
Instrumental activities of daily living	0 – 5	1.90 (1.42)
Activities of daily living	20 – 100	96.35 (8.56)

Table 2 Bivariate correlations among the main study variables

	1	2	3	4	5	6	7	8	9
1. T1 Motor deficit									
2. T1 Sequencing deficit	0.56								
3. T1 Positive symptoms	0.20	0.18							
4. T1 Negative symptoms	0.40	0.33	0.36						
5. T1 Disorganized symptoms	0.49	0.43	0.55	0.56					
6. T2 Positive symptoms	0.25	0.21	0.36	0.10	0.22				

7. T2 Negative symptoms	0.36	0.21	0.01	0.38	0.18	0.26			
8. T2 Disorganized symptoms	0.48	0.34	0.14	0.27	0.42	0.51	0.58		
9. T3 Instrumental ADL	-0.29	-0.25	-0.12	-0.22	-0.35	-0.15	-0.35	-0.40	
10. T3 ADL	-0.27	-0.23	-0.11	-0.10	-0.23	-0.45	-0.26	-0.45	0.29

ADL = Activities of daily living. Correlations with magnitude greater than 0.18 were statistically significant at $p < 0.01$ level.

Table 3 Indirect effects from NSS to functioning outcomes via psychiatric symptoms in the model

Time 1 NSS	Time 2 Psychiatric symptoms	Time 3 Outcome	Indirect effect	BC bootstrap 95% CI
Motor deficit	Positive	IADL	0.01	-0.01 to 0.03
	Negative		-0.02*	-0.05 to -0.01
	Disorganized		-0.05*	-0.10 to -0.02
Sequencing deficit	Positive	IADL	0.00	-0.01 to 0.04
	Negative		0.01	-0.02 to 0.04
	Disorganized		-0.01	-0.07 to 0.04
Motor deficit	Positive	ADL	-0.22*	-0.77 to -0.04
	Negative		0.04	-0.06 to 0.27
	Disorganized		-0.24*	-0.83 to -0.06
Sequencing deficit	Positive	ADL	-0.09	-0.55 to 0.10
	Negative		-0.01	-0.26 to 0.04
	Disorganized		-0.04	-0.44 to 0.14

BC bootstrap 95% CI = Bias-corrected bootstrap 95% confidence interval. ADL = Activities of daily living; IADL = Instrumental activities of daily living. *Significant indirect effects with the bootstrap 95% CI excluding zero.

Highlights

- Path analysis evaluated direct and indirect effects of NSS on functional outcomes via psychiatric symptoms
- Motor coordination and sequencing NSS did not have significant direct effects on functional outcomes
- Motor coordination NSS exerted negative indirect effects on functional outcomes via psychiatric symptoms
- The current results contribute to a better understanding of the determinants of functional outcomes
- That motor sequencing NSS did not affect functional outcomes may be explained by the trait marking features