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ORIGINAL ARTICLE

From neurological soft signs to functional outcome in young individuals in treatment with secondary services for non-psychotic disorders: a path analysis

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Background. Functional decline among patients with mental illness is not unique to individuals with psychotic disorders. Despite this, research on early predictors of functional outcome mainly focused on individuals thought to have an 'at risk mental state' (ARMS) for psychosis. There is evidence suggesting that certain early vulnerability markers, such as neurological soft signs (NSS), may explain variability in functional outcomes independent of the level of psychosis risk and the traditional diagnostic classification.

Method. Structural equation modeling was applied to baseline data from a prospective longitudinal study of 138 young individuals in treatment with secondary services for non-psychotic disorders. We evaluated theoretically based models of pathways to functional outcome starting from NSS. The intervening variables were established according to previous evidence and drawn from two general categories: cognition (neuro- and social-) and negative symptoms (expressive and experiential).

Results. A final trimmed model was a single path running from NSS to neurocognition to experiential negative symptoms to outcome. It could not be improved by adding or dropping connections that would change the single path to multiple paths. The indirect effect from NSS to outcome was significant. The validity of the model was independent of the ARMS status and the psychiatric diagnosis.

Conclusions. Our results provide evidence for a single pathway model in which the starting and intervening variables represent modifiable trans-diagnostic therapeutic targets to improve functional trajectories in young individuals with a recent-onset psychiatric diagnosis and different levels of psychosis risk.

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Key words: Cognition, functioning, negative symptoms, neurological soft signs, structural equation modeling.

Introduction

Functional disability is common among patients with mental illness (Harvey, 2011; Iosifescu, 2012; Lee *et al.* 2013). Functional impairments are often associated with poor quality of life, low productivity and loss of independence (Carrión *et al.* 2013). Most of the evidence on functional trajectories among psychiatric syndromes pertains to schizophrenia (SCZ) and psychotic spectrum disorders (PSDs) (Bowie & Harvey, 2006; Green *et al.* 2012; Cotter *et al.* 2014). A theoretical based model of functional decline in SCZ has been recently validated in a series of papers by Green and colleagues (Sergi *et al.* 2006; Rassovsky *et al.* 2011; Green *et al.* 2012). The authors suggested that functional outcome in SCZ can be represented as a single pathway running from early vulnerability markers through intervening variables to real-word functional disabilities (Green *et al.* 2012). The intervening variables were drawn from two general categories: ability (i.e. neuro- and social cognition) and beliefs/motivation (i.e. negative symptoms) (Green *et al.* 2012).

Despite PSDs being traditionally associated with greater functional disability than other psychiatric

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syndromes (Lee *et al.* 2015), there is increasing evidence that functional impairments cut across traditional diagnostic boundaries (Kessler *et al.* 2009). Studies of adults with chronic mental disorders have shown that the intervening variables proposed by Green *et al.* (2012) are linked to functional outcome independent of traditional diagnostic classification (Millan *et al.* 2012; Bedwell *et al.* 2015; Lee *et al.* 2015), being expressed not only in SCZ (Harvey, 2011), but also in mood (Baune *et al.* 2010; Baş *et al.* 2015), anxiety (Plaisier *et al.* 2010; Hezel & McNally, 2014) and personality disorders (Ruocco *et al.* 2014). A critical research goal is therefore to identify and intervene to target modifiable risk factors (Wykes *et al.* 2011; Granholm *et al.* 2014; Firth *et al.* 2016) that lead to long-term disability not only in patients with PSDs, but in the broader spectrum of psychiatric syndromes (Millan *et al.* 2012).

However, findings in adult populations are often tempered by chronic illness and prolonged treatment (Allott *et al.* 2011). For these reasons, research efforts targeting functional recovery should be focused on the earlier phases of psychiatric disorders, when individuals are less functional impaired and more amenable to therapeutic intervention (Henry & Coster, 1996; Cannon *et al.* 2008; Fusar-Poli *et al.* 2012). So far, most of the evidence investigating functional decline in early-onset psychiatric syndromes pertains to individuals considered to have an 'at risk mental state' (ARMS) for psychosis (Valmaggia *et al.* 2013; Amminger *et al.* 2015). Given the relevance of the functional outcome in psychiatry (Kessler *et al.* 2009), and the evidence that disability is not a unique characteristic of psychotic disorders (Lee *et al.* 2015), research on early predictors of functional decline should target the full range of recent-onset psychiatric syndromes and not only the ARMS category.

Of interest, consistent with the research domain criteria (RDoC) initiative from the National Institute of Mental Health (Insel *et al.* 2010), there is evidence suggesting that common early vulnerability markers, such as neurological (Dazzan & Murray, 2002; De la Fuente *et al.* 2006), neurophysiological (Bedwell *et al.* 2015) or brain structural (Hatton *et al.* 2012; Mittal *et al.* 2014) and functional abnormalities (Carrión *et al.* 2013), may predict poor functional outcomes across different recent-onset psychiatric syndromes (Millan *et al.* 2012; Bedwell *et al.* 2015; Lee *et al.* 2015). Among these markers, neurological soft signs (NSS): (i) have shown close ties to specific brain structural and functional connectivity changes, in particular the cerebello–thalamo–prefrontal network (Zhao *et al.* 2014); (ii) precede the onset of cognitive dysfunctions and negative symptoms in young individuals with recent-onset psychiatric disorders (Arango *et al.* 1999; Chan *et al.* 2015); (iii) have not shown specific associations with the ARMS status (De la Fuente *et al.* 2006).

For these reasons, we recruited a large sample of young patients in treatment with secondary mental health services for non-psychotic psychiatric disorders to test the hypothesis that a single common pathway, running from NSS through intervening variables, such as cognitive abilities and negative symptoms, may explain functional outcomes independent of the psychiatric diagnosis and the ARMS status.

We started the outcome model with NSS (as opposed to later stages like neuro- and social-cognition) because NSS have direct and established ties to neural processes and they are relatively less influenced by later processes (Arango *et al.* 1999; Chan *et al.* 2015). The intervening variables and their relation in the model have been chosen according to the work by Green and colleagues in which neuro- and social-cognitive abilities precede and lead to negative symptoms and poor functional outcome (Green *et al.* 2012).

Adequate evaluation of pathways to functional outcome requires statistical modeling approaches such as structural equation modeling (SEM). SEM requires relatively large sample sizes and theoretically based models of outcome to guide the process. We started by evaluating a single-path model because it is consistent with previous empirical (Rassovsky *et al.* 2011; Green *et al.* 2012) and theoretical work (Beck & Rector, 2005; Grant & Beck, 2009), as well as being the most parsimonious starting model.

Method

Participants

Baseline data from a prospective longitudinal study were used for the analysis (Francesconi *et al.* 2016).

The longitudinal study examined the transition rate to psychosis and the functional outcome over time, in a sample of 138 individuals, aged 17–31 years, with a Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) defined diagnosis and mean illness duration of 2.1 years.

Subjects were recruited in three different clinics (Villa Armonia Nuova, Villa Letizia and Policlinico Umberto I; Rome, Italy) that provide secondary general mental health care for adolescents and young adults. For a 17-month period (November 2011 to June 2013), patients were consecutively screened for the following exclusion criteria: (i) current or past diagnosis of SCZ, schizophreniform, schizo-affective, delusional or bipolar disorder; (ii) present or past diagnosis of a brief psychotic disorder with a duration equal to or greater than 1 week; (iii) diagnosis of delirium, dementia, amnestic or other cognitive disorder, mental retardation, psychiatric disorders due to a somatic factor or related to psychotropic substances; (iv) drug

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abuse within the last 3 months; (v) diseases of the central nervous system; and (vi) history or current use of antipsychotic medications. After this first screening patients were referred to a group of three trained interviewers and underwent the Structural Clinical Interview for DSM-IV (SCID) Axis I (SCID-I) and II (SCID-II) (First *et al.* 1997) disorders to certify exclusion criteria and diagnoses.

Inter-rater reliability was established by repeated training sessions involving all raters (A.M, M.F., R.D.C.).

All procedures were approved by the institutional review board of Sapienza, University of Rome. Written informed consent was obtained from participants or their parents/guardians if age was <18 years.

Measures

Clinical

DSM diagnosis was obtained through the SCID-I and SCID-II evaluations. The Comprehensive Assessment of At-Risk Mental (CAARMS) interview was used to define the ARMS status, according to previously operationalized criteria (Yung *et al.* 2004). According to the risk status, patients were divided in ARMS+ and ARMS– (i.e. meeting or not the CAARMS criteria, respectively). The CAARMS inter-rater reliability was assessed in 34 subjects [intra-class correlation coefficient (ICC) = 0.93].

NSS

NSS were evaluated with the Neurological Evaluation Scale (NES) (Buchanan & Heinrichs, 1989). Three subscales of the NES can be considered together to represent 'Integrative neurological dysfunctions', i.e. dysfunctions that are likely to depend on integration within or between the motor and sensory systems (Dazzan & Murray, 2002). The integrative dysfunction domain has been associated with specific brain structural abnormalities both in psychotic (Dazzan & Murray, 2002) and non-psychotic individuals (Dazzan, 2005). Three NES subscales constitute this domain: (i) 'Sensory integration dysfunction', reflecting a dysfunction in the integration of sensory information; (ii) 'Motor coordination dysfunction', reflecting signs of motor incoordination; and (iii) 'Motor sequencing dysfunction', reflecting the ability to perform complex motor sequences.

The NES was administered by three clinicians (A.M., M.F., R.D.C.); inter-rater reliability was assessed in 34 subjects (ICC = 0.97).

Neurocognition

Neurocognition was assessed with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph *et al.* 1998). The RBANS is composed of 12 subtests that are combined in five index scores (attention, immediate and delayed memory, language and visuospatial indices). Previous evidence has suggested that these neurocognitive indices assess similar constructs as the more widely used Wechsler Adult Intelligence Scale (WAIS-III) and Wechsler Memory Scale (WMS-III) (Holzer *et al.* 2007). The RBANS has been shown to be reliable and sensitive to cognitive deficits in patients with both psychotic and not psychotic disorders (Holzer *et al.* 2007; Baune *et al.* 2010).

Social cognition: theory of mind (ToM)

Social cognition is a multifaceted concept, comprising several subdomains and processes (Nuechterlein *et al.* 2004). We only assessed the ToM subdomain that seems to be the one more closely related to functional outcomes (Martínez-Domínguez *et al.* 2015). ToM abilities were assessed through the Reading the Mind in the Eye Test (RMET) (Vellante *et al.* 2013), the *Faux Pas* (FP) test (Stone *et al.* 1998) and the Theory of Mind Assessment Scale (T.h.o.m.a.s.) (Bosco *et al.* 2009). The RMET consists of 36 black-and-white eye pictures depicting various mental states (Vellante *et al.* 2013). After each stimulus presentation, patients were asked to choose from four choices the most appropriate mental state description for each eye picture. In the FP test, participants were asked to read 20 short stories, 10 of which contained a *faux pas* or social slip and 10 that did not. For FP stories we obtained a score given by the sum of the first ('did anyone say something they shouldn't have said or something awkward?' score: no = 0, yes = 1) and the second questions ('who said they shouldn't have said or something awkward?' score: no = 0, yes = 1) (Stone *et al.* 1998; Wang *et al.* 2008). T.h.o.m.a.s. (Bosco *et al.* 2009) is a semi-structured interview. It consists of 39 open-ended questions, scored from 0, representing poorer ToM abilities, to 4, representing greater ToM abilities. A total score can be computed by the sum of the scores obtained in each question.

Negative symptoms

Negative symptoms were assessed through four items of the CAARMS: avolition, anhedonia, alogia, and observed blunted affect. As previously reported (Green *et al.* 2012), Negative symptoms were divided into experiential (avolition and anhedonia) and expressive (observed blunted affect and alogia) components. Global scores were then averaged for each of the two components (to reduce the number of parameters) and entered into the model (Green *et al.* 2012).

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Functional outcome

Functional outcome was assessed using the Global Assessment of Functioning Scale (Hall, 1995) and The Life Skills Profile 39 items (LSP-39; Rosen *et al.* 1989).

The GAF ranges from 1, representing the hypothetically sickest individual, to 100, representing the hypothetically healthiest. LSP-39 is a 39-item scale with five subscales: self-care, non-turbulence, social contact, communication and responsibility. The items composing the subscales are scored on a four-point ordinal rating. A higher score means greater disability and malfunctioning. For the purpose of the present study, the LSP-39 communication subscale was not taken into account; two different studies (Trauer *et al.* 1995; Parker *et al.* 2007) showed indeed a poor inter-rater reliability and internal consistency for this subscale compared with the others.

Data analysis

SEM uses a combination of indicators (single variables) and latent variables (underlying factors) that can be estimated for constructs with three or more indicators (Doncaster, 2007; Schmidt *et al.* 2011).

Recommendations for the sample size using SEM vary widely between at least 100 and several thousands (Kline & Santor, 1999). The minimum sample size for SEM must be greater than the minimum ratio of at least five participants for each estimated parameter (Lovric, 2011).

In the current dataset, we had a sufficient number of indicators for neurocognition, NSS, ToM and functioning to estimate latent variables for these constructs.

However, when needed, in order to conserve free parameters and increase stability of the parameter estimates for the models, we reduced the latent variables to single factors by using principal component analysis (PCA); a Bartlett test with a p value <0.001 and a Keiser–Meyer–Olkin index (KMO) >0.50 were used to evaluate if data were appropriate for the reduction (Abdi & Williams, 2010).

The ToM domain was thus reduced to a single indicator, prior to starting the SEM analysis, by using PCA, which was deemed appropriate for the data (Bartlett test p value <0.001, KMO = 0.70). The remaining variables (i.e. experiential and expressive negative symptoms) were represented by single indicators.

The relationship between the measured variables was estimated using a sample covariance matrix.

The hypothesized latent structures were tested by fitting the measurement model linking the latent variables to their indicators. The latent variable 'neurocognition' was indexed with five indicators: scores of the attention, immediate memory, delayed memory, visuospatial, and language indices of the RBANS.

The NSS (or integrative neurological dysfunctions) domain was indexed with the total scores of the sensory integration, motor coordination and motor sequencing dysfunction subscales of the NES. The latent variable 'functioning' was indexed with five indicators: scores on the GAF, and on the self-care, social contact, responsibility, and non-turbulence subscales of the LSP-39.

The hypothesized SEM models were estimated with the structural equation package IBM® SPSS® AMOS. Of the fit indices available, we provided three commonly reported indices that address different aspects of a well-fitting model to allow for a comprehensive evaluation of model fit. The χ^2 statistic is a measure of absolute fit, it evaluates the difference between the sample covariance matrix and the covariance matrix implied by the fitted model, and it is very sensitive to sample size; the composite fit index (CFI) is a measure of comparative fit and evaluates how much improvement the fitted model offers over a model that assumes all measured variables are uncorrelated; and the root mean square error of approximation (RMSEA) is a measure of absolute fit that is based on the non-centrality parameter of the χ^2 statistic. A non-significant χ^2, a CFI > 0.9 and an RMSEA < 0.08 indicate a good-fitting model (Schermelleh-Engel *et al.* 2003). Prior to evaluating the model, we checked raw data for normality and outliers, and replaced missing values by regression imputation.

Ethical standards

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Sample characteristics as well as means and standard deviations of all indicator variables are listed in Table 1.

Table 2 shows the zero-order correlations of all study measures. As expected, the correlations among variables were generally higher within category (NSS and negative symptoms) than between categories (NSS, neurocognition, ToM, negative symptoms and functioning). The specific associations were then evaluated with SEM in a series of three models.

Measurement model

The first model examined the degree to which the latent variables for neurocognition, NSS and functioning loaded on their respective indicators (Fig. 1). This

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Table 1. *Sample characteristics* (n = *138)*

Characteristic	
Demographics	
Mean age, years (S.D.)	24.3 (3.5)
Mean duration of education, years (S.D.)	11.0 (2.9)
ARMS+, *n* (%)	67 (48)
Male, *n* (%)	7 (53.0)
Clinical	
Mean CAARMS negative symptoms (S.D.)	
Expressive negative symptoms	1.5 (0.8)
Experiential negative symptoms	2.0 (1.9)
DSM-IV diagnosis, *n* (%)	
Mood disorders[a]	53 (38.4)
Anxiety disorder[b]	18 (13.0)
Personality disorder[c]	25 (18.1)
Co-morbidity of mood and anxiety disorders[d]	42 (30.4)
Mean duration of illness, years (S.D.)	2.1 (0.9)
Medication, *n* (%)	
No medication	18 (13.3)
Antipsychotics	0
Antidepressants	88 (65.2)
Anxiolytics	63 (46.7)
Mood stabilizers	35 (25.9)
Functioning	
Mean GAF (S.D.)	63.7 (9.7)
Mean LSP-39 (S.D.)	
Self-care	18.8 (5.2)
Non turbulence	23.4 (5.2)
Social contact	11.1 (2.9)
Responsibility	9.8 (2.1)
Neurocognition	
Mean RBANS (S.D.)	
Immediate memory index	95.1 (9.8)
Language index	89.9 (8.5)
Visuospatial index	92.1 (8.3)
Attention index	84.3 (8.7)
Delayed memory index	91.4 (8.2)
Theory of mind	
Mean *Faux pas* test (S.D.)	
Faux pas questions	17.5 (1.6)
Faux pas controls	38.7 (1.0)
Mean RMET (S.D.)	25.7 (2.9)
Mean Th.o.m.a.s. total (S.D.)	2.9 (0.5)
Neurological soft signs	
Mean NES (S.D.)	
Motor coordination	1.5 (1.3)
Sensory integration	1.3 (1.0)
Sequencing of complex motor acts	1.3 (1.3)

S.D, Standard deviation; ARMS+, positive for the 'at-risk mental state' status; CAARMS, Comprehensive Assessment of At Risk Mental State; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; GAF, Global Assessment of Functioning; LSP-39, Life Skill Profile 39 items; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RMET, Reading the Mind Eyes in the Test; Th.o.m.a.s., Theory Of Mind Assessment Scale; NES, Neurological Evaluation Scale; MDD, major depressive disorder; GAD, generalized anxiety disorder; OCD, obsessive–compulsive disorder.

[a] DSM-IV diagnoses: MDD, adjustment disorder with depressed mood.

[b] DSM-IV diagnoses: GAD, panic disorder, OCD, adjustment disorder with anxiety.

[c] DSM-IV diagnoses: borderline personality disorder.

[d] DSM-IV diagnoses: MDD and GAD, MDD and OCD, adjustment disorder with depressed mood and anxiety.

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Table 2. *Zero-order correlations*

Intercorrelations among measures included in the models								
	Motor coordination	Sensory integration	Sequencing of complex motor acts	Expressive negative symptoms	Experiential negative symptoms	Theory of mind	Neurocognition	Functioning
Motor coordination								
Sensory integration	0.306**							
Sequencing of complex motor acts	0.383**	0.343**						
Expressive negative symptoms	0.020	0.075	−0.126					
Experiential negative symptoms	0.066	0.065	−0.002	0.558**				
Theory of mind	−0.024	−0.130	0.047	−0.185*	−0.156			
Neurocognition	−0.201*	−0.128	−0.305**	−0.141	−0.270**	0.180*		
Functioning	0.149	0.109	0.135	0.205*	0.305**	−0.199*	−0.208*	

Significant correlation: * $p < 0.05$, * $p < 0.01$ (two-tailed).

analysis showed that all measures of neurocognition (loading range: 0.55–0.79, $p < 0.01$), NSS (loading range: 0.48–0.73, $p < 0.01$) and functioning (loading range: 0.38–0.56; $p < 0.01$) made a significant contribution to their latent variables. Based on this degree of fit, we reduced functioning and neurocognition to single variables for subsequent models as a way to conserve free parameters and increase stability of the parameter estimates for the remaining models. The Bartlett test and a KMO index were deemed appropriated for both neurocognition (Bartlett: $p < 0.001$; KMO = 0.83) and functioning (Bartlett: $p < 0.001$; KMO = 0.66).

Intermediate model

We then added the ToM, the experiential and expressive symptoms domains to create a single path in the model (Fig. 2). Model fit was good ($\chi^2 = 16.46$; $p = 0.28$; CFI = 0.98; RMSEA = 0.03). Next, we made changes to this model based on conceptual and statistical considerations. First, negative expressive symptoms were dropped because they were unrelated to functioning, which was the focus of this model. Next ToM was removed for three reasons: (i) the direct pathway running from ToM to functional outcome was not significant; (ii) the indirect pathways running from ToM to functional outcome thorough expressive or experiential symptoms were not significant; and (iii) the significant connection between neurocognition and ToM reduced the strength of the association between neurocognition and experiential negative symptoms.

Final model

The resulting model reflects a relatively linear sequence leading from NSS to neurocognition to experiential negative symptoms to functioning and had an extremely good fit ($\chi^2 = 8.57$; $p = 0.47$; CFI = 1.00; RMSEA = 0.00; Fig. 3). The strength of the model was supported by the significant standardized indirect effect of NSS through all other variables to functioning ($\beta = 0.033$; 95% confidence interval 0.011–0.090; $p = 0.002$). In other words, we found a significant indirect effect through three intervening variables. This model explains 9.3% of the variance in functioning. The model was not improved by adding a direct link between neurocognition and functioning that would create a pathway separate from negative symptoms and no additional changes were suggested through the modification indices. Compared with the intermediate model, the final model was more parsimonious (requiring fewer constructs and connections) and the fit indices were higher. Because it was more parsimonious, the model was also more stable: there were

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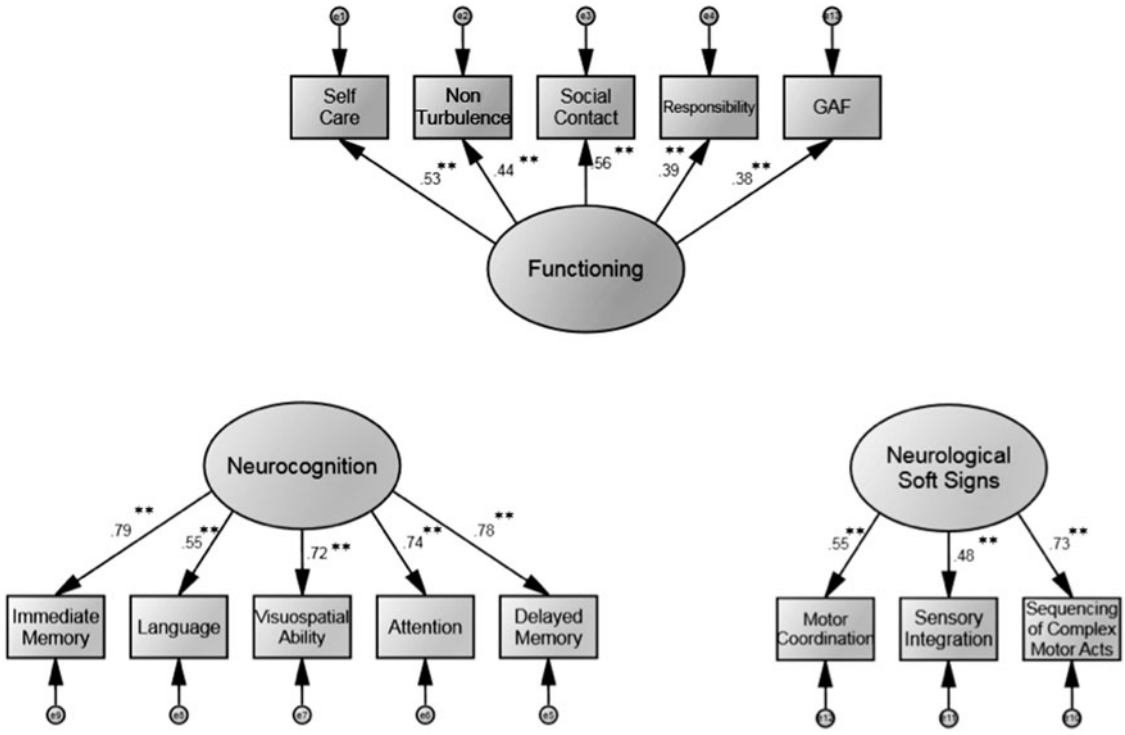

Fig. 1. Measurement model (neurocognition, functioning, neurological soft signs). ** $p < 0.01$. GAF, Global Assessment of Functioning.

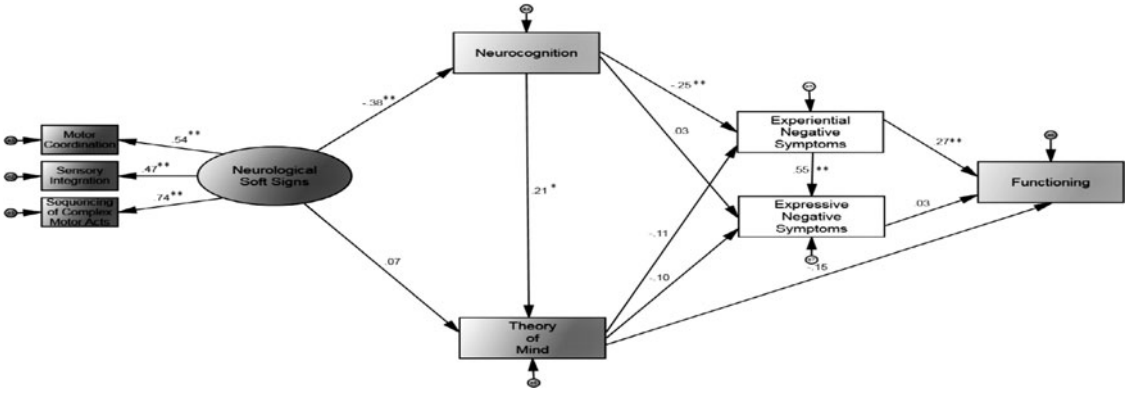

Fig. 2. Initial non-trimmed model. * $p < 0.05$, ** $p < 0.01$.

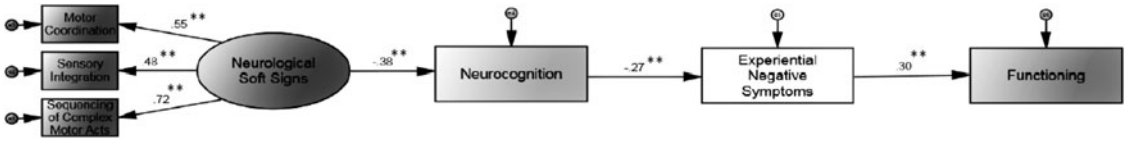

Fig. 3. Final trimmed model: a single path running through neurological soft signs, neurocognition, experiential negative symptoms and functioning. ** $p < 0.01$.

12 free parameters and 138 subjects, which is more than 11 subjects per parameter. Based on these results, it can be concluded that a single pathway running from NSS to neurocognition to experiential negative symptoms to functioning provides good model fit, and additional paths do not improve the model.

It has to be noted that a limitation of reducing latent variables into composite scores is that this does not

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take into account the differential loadings of each measured variable on their latent variables. Thus, in order to further validate the final model, an alternative model, built using latent variables instead of composite scores, can be found in the online Supplementary material. Furthermore, due to the limitation of the GAF (rated based on both functioning and symptoms), we used in this alternative model only the LSP-39 to index functioning; the relationships between variables still reflected a relatively linear sequence leading from NSS to neurocognition to experiential negative symptoms to functioning (more details can be found in the online Supplementary material).

Given the hypothesis that functioning was independent of the ARMS status and DSM-IV diagnosis, we added these two variables to the final model. As expected, neither the ARMS status ($\beta = 0.90$; $p = 0.263$) nor the DSM-IV diagnosis (mood disorders, $\beta = -0.08$; $p = 0.319$; anxiety disorders, $\beta = 0.03$; $p = 0.688$; co-morbid mood and anxiety disorders, $\beta = -0.07$; $p = 0.349$; personality disorders, $\beta = -0.13$, $p = 0.111$) were significantly related to functioning.

Finally, to test whether ARMS status or DSM-IV diagnosis moderates the model, we utilized the multiple-group analysis procedure in AMOS. The results from this analysis suggested that the ARMS status ($\chi^2 = 0.37$, $p = 0.94$) and the DSM diagnosis ($\chi^2 = 2.52$, $p = 0.98$) did not moderate the relationships found in the model.

Discussion

In the current study, using SEM, we evaluated models of functional outcome, running from an early vulnerability marker, such as NSS, to functioning, in non-psychotic young patients treated with secondary mental health services. To the best of our knowledge, this is the first study using a broad trans-diagnostic approach to functional outcome cutting across the ARMS and the DSM-IV categories.

The *a priori* hypothesis that generated this model stemmed from a series of papers published by Green and colleagues (Sergi *et al.* 2006; Rassovsky *et al.* 2011; Green *et al.* 2012), in which the authors validated a single path connection between early vulnerability markers, cognitive abilities, negative symptoms and functioning in an adult chronic cohort of patients with SCZ.

Given the trans-diagnostic nature of functional outcome in psychiatry, we hypothesized that a similar pathway could explain functional impairments in young individuals independent of the level of psychosis risk and the DSM-IV diagnosis. Our results confirm this hypothesis, suggesting that: (1) functional trajectories may be explained by a cascade model running from NSS to neurocognitive impairments to negative symptoms to functioning; and (2) given the trans-diagnostic nature of the starting, intervening and outcome variables (i.e. NSS, neurocognition, negative symptoms and functioning), the validity of the proposed model is not influenced by the ARMS status or the DSM-IV diagnosis.

Furthermore, our findings provide useful information on a young psychiatric sample, in which specific therapeutic interventions have the potential to significantly limit functional disability (Carrión *et al.* 2013).

The association between NSS and neurocognition can be explained in the light of a growing body of evidence suggesting that NSS predict impairment of frontal–subcortical brain network connections (Dazzan, 2005; Zhao *et al.* 2014), which have been proposed as fundamental pathophysiological substrates of cognitive dysfunctions across different psychiatric syndromes (Chan *et al.* 2009). Of interest, a recent work by Mittal *et al.* (2014) suggests that NSS may reflect an abnormal white matter tract development of cerebello–thalamic tracts in ARMS+ individuals; these abnormalities, that the authors suggest to be part of a wider network dysfunction (i.e. the cerebello–thalamo–prefrontal, or cognitive dysmetria network), were associated with severity of negative symptoms and poor functional outcome, but not with positive symptoms or conversion to psychosis. These results provide further evidence on the role of NSS as early vulnerability markers of poor functional outcome cutting across the ARMS status, being not specific for ultimate psychosis conversion.

In line with previous findings (Harvey *et al.* 2006; Tomotake, 2011), our study found that neurocognitive abilities were significantly related to negative symptoms which contributed most to the functional outcome represented by the GAF and LSP-39.

Despite the fact that cognitive dysfunctions and negative symptoms have traditionally been associated with SCZ spectrum disorders (Norman *et al.* 2015), there is a growing body of evidence suggesting that they are expressed in association with specific neurophysiological abnormalities and poor functional outcome across different psychiatric diagnoses (Bedwell *et al.* 2015; Lyne *et al.* 2015). Working and verbal memory, executive functions, processing speed and ToM impairments as well as negative symptoms have been shown to represent poorly controlled and highly relevant dimensions cutting across the diagnostic borders that define SCZ, mood and anxiety disorders (Millan *et al.* 2012).

In light of these findings it is not surprising that the neurocognitive and negative symptoms domain were strongly associated with functional outcome independent of the ARMS status and the DSM-IV diagnosis.

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Although ToM has been reported to be a determinant of outcome in other studies (Schmidt *et al.* 2011; Barbato *et al.* 2014), it was not retained in the final model proposed in the current study.

ToM was significantly associated with the functioning and neurocognitive domains in the zero-order correlation matrix (Table 2), a result in line with previous findings (Schmidt *et al.* 2011). However, when all the variables where taken into account in the intermediate model, ToM did not make a direct significant contribution to functional outcome and reduced the strength of the association between neurocognition and experiential negative symptoms, which were tightly related to functioning (Fig. 2). Furthermore, the final model (Fig. 3) showed better fit indices compared with the intermediate one (Fig. 2), providing further support for the exclusion of ToM from the final model. The fact that ToM does not represent a relevant node in the pathway leading to functional outcome in our prepsychotic sample is not surprising and replicates previous findings on prodromal individuals (Barbato *et al.* 2013). Barbato *et al.* (2013) found that social cognition did not mediate the effect of neurocognition on functional outcome in a large sample of ARMS+ individuals, in contrast to what is observed in patients with full-blown psychotic disorders (Schmidt *et al.* 2011). As the authors suggested, it is possible that during the prodromal phase of psychosis, ToM impairments are expressed in attenuated form compared with later stages of the disorder. Therefore, the relationship between ToM and functioning is weaker than that observed in those with a full-blown psychotic illness who may have more severe deficits.

However, as with all uses of SEM, this analysis is based on an *a priori* theoretical model that guided the initial arrangement of variables. It is possible that other configurations of these variables would work equally well or better. We can only say that the observed data fit the proposed model (NSS to neurocognition to negative symptoms to functioning) rather well, and the final model in Fig. 3 is a highly plausible sequence of steps based on that.

Strengths and limitations

Despite the adoption of SEM, which is more powerful than multiple regression in analysing a set of interactive factors simultaneously (Hoyle, 1995), the current study is limited by several methodological design features. One limitation is its cross-sectional design, which may not necessarily represent the longitudinal relationships among NSS, neurocognition, negative symptoms and functional outcome. However, several longitudinal studies showed separate associations between: (1) NSS and neurocognition (Arango *et al.* 1999); (2) neurocognition and negative symptoms (Meyer *et al.* 2014); and (3) negative symptoms and functional outcomes (Meyer *et al.* 2014). Given this evidence, it is possible to hypothesize that the result of putting these three pieces together in an integrative cross-sectional model could maintain validity even in future studies using a longitudinal design. Also, the strong association between experiential negative symptoms and functional outcome might be partially explained by measurement overlap in these two areas (Green *et al.* 2012). That is one reason for a recent effort to develop new scales that assess experiential negative symptoms as separately as possible from current community functioning. However, in order to reduce the impact of this limitation on the final outcome: (1) we used two different standardized measures to assess functioning; and (2) we built an alternative model dropping the GAF (which is rated based on functioning and symptoms) and using only the LSP-39 (see online Supplementary material). Of note, in this alternative model the relationships between variables still reflected the linear sequence leading from NSS to functioning through the intervening variables neurocognition and experiential negative symptoms.

We found that the indirect effect of NSS on functioning was 0.033. This is considered by statisticians to be not clinically significant (which would require a $\beta > 0.05$). So essentially, the NSS variable has to be considered a significant but not 'meaningful' predictor of functioning, despite its role in predicting the more proximal factors of neurocognition and negative symptoms. Evidence suggests that the NSS domains are each relevant, and may map on to distinct underlying processes. Future studies, with larger sample sizes, should take into consideration the effect on NSS subscales individually.

As previously highlighted, the approach used in the current studies (i.e. examining markers across different categories of recent-onset psychiatric disorders) is consistent with the RDoC initiative. However, it has to be noted that currently there is not a domain or construct representing motor or neurological dysfunction in psychiatric disorders. Our findings, if confirmed by longitudinal data, might represent good evidence for a broader array of motor and neurological signs to be included in RDoC, also given their relevance for staging models.

Finally, while the use of some exclusion criteria (e.g. no drug abuse) helped to provide a clear approach to examining NSS and relationship among the variables included in the model, this may also limit generalizability of our findings.

The single pathway model that is supported in this study helps to provide a rationale for early intervention

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with plasticity-based trainings (Fisher *et al.* 2009, 2015) or non-invasive brain modulation techniques (Bersani *et al.* 2015; Minichino *et al.* 2015) targeting the cerebello–thalamo–prefrontal network. With a single pathway, is possible that an intervention directed to early components (e.g. limitation of brain development abnormalities) may have beneficial effects on the subsequent development of those core cognitive impairments and negative symptoms that are tightly associated with poor functional outcome independent of the levels of risk and the DSM-IV diagnosis.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/S0033291716003056

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Declaration of Interest

None.

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