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Expressive deficits and amotivation as mediators of the associations between cognitive problems and functional outcomes: Results from two independent cohorts

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ABSTRACT

Many individuals with severe mental disorders have difficulties in vocational and social functioning, which are regarded the most important outcomes, together with clinical symptoms. To understand the underlying mechanisms, research is increasingly focused on factors influencing functional outcomes. One established association has been shown between cognition and community functioning with negative symptoms as a possible mediator. Although it has been shown that negative symptoms consist of two subdomains, thus far negative symptoms have been assessed as one unitary construct. This study considers for the first time subdomains of negative symptoms as putative mediators (expressive deficits, amotivation) of the association between cognition (neuro- and social cognition) and functional outcome (living situation, occupation, social functioning). We expected that specific subdomains of negative symptoms (e.g. amotivation) would mediate the effect of cognition on specific functional outcomes (e.g. social functioning) independently from illness duration. To assess this, we included two independent cohorts, consisting of participants with different illness duration.

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These two independent cohorts consisted of patients with a recent-onset psychotic disorder: PROGR-S (first time treated; $N = 1129$) and GROUP (illness duration preferably <5 years; $N = 1200$). Using linear regression, mediation analyses were performed with two cognition domains (neurocognition and social cognition) as predictors, negative symptoms (Expressive deficits and Amotivation as indexed with items from the Positive and Negative Syndrome Scale) as mediators and three measures of functional outcomes (living situation, occupation and social functioning) as outcome measures. The analyses were repeated with the same outcome measures three years later.

Three main results were obtained. I) Both in the cross-sectional and longitudinal analyses, the associations of neurocognition (both cohorts) and social cognition (GROUP) with social functioning were mediated by amotivation. II) The association between cognition and living situation was mediated by Expressive deficits in one cohort (GROUP) but not in the cohort assessing first-episode psychosis (PROGR-S). III) The association between cognition and occupation was mediated by Amotivation in PROGR-S and by Expressive deficits in GROUP.

Conclusion: The current results show a less robust mediating role for specific negative symptom domains regarding the associations of cognition with occupation and living situation that may depend on the duration of psychotic illness. However, Amotivation, mediates the association between cognition and social functioning, which holds true for patients experiencing a first-onset and patients with a longer illness duration alike. The results may have implications for the development of therapeutic approaches focusing on amotivation to improve social functioning.

General scientific summary: This study stresses the importance of distinguishing subdomains of negative symptoms, cognition and functioning. Our results show that specific negative symptom dimensions mediate the effects of cognition on specific functional outcomes.

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1. Introduction

Besides positive symptoms (delusions and hallucinations), patients with a psychotic disorder often display negative symptoms (such as blunted affect, avolition, anhedonia, and asociality), as well as cognitive deficits, with the latter linked to each other (Addington et al. 1991; Chang et al. 2016b; Strauss et al., 2012a, b). Although initially positive symptoms were regarded as central to functioning, in recent years negative symptoms and cognitive deficits have moved to the center, as both have been associated with poor functional outcome (Chang et al. 2011; Fervaha et al. 2014a; Milev et al. 2005). An outstanding question remains how cognition, negative symptoms and everyday functioning are exactly related (Harvey et al. 2006). As an example, it has been proposed that negative symptoms may mediate the association between cognition and functioning in the community (Lipkovich et al. 2009; Ventura et al. 2014).

Heterogeneity of negative symptoms may contribute to the variability in findings regarding the relationship between cognition, negative symptoms and functional outcome. Indeed, different dimensions of negative symptoms have been established empirically and have been replicated, consisting of two subdomains, namely Expressive deficits and Amotivation (Foussias and Remington 2010; Liemburg et al. 2013; Messinger et al. 2011). Expressive deficits encompass symptoms of blunted affect and avolition, while Amotivation covers deficits in motivation and pleasure, including anhedonia, avolition, and asociality. Importantly, these subdomains may have different links with cognition and with different aspects of outcomes in patients with a psychotic disorder. This would shed more light on their nature and putatively underlying mechanism and could ultimately have implications for the development of therapeutic approaches for recovery.

According to the cognitive resource limitation model (Cohen et al. 2012), diminished expression is caused by insufficient cognitive resources needed for the complex coordination of gestures and facial as well as vocal expression. Indeed, Expressive deficits have been linked to poorer performance on neurocognitive measures on the one hand (Chang et al. 2014; Cohen et al. 2013) and to poor (social) functioning on the other hand (Evensen et al. 2012; Galderisi et al. 2013). Thus, it is possible that cognitive impairments lead to aberrant expression of emotions, which in turn leads to poor community functioning. However, we are not aware of previous studies that have directly investigated this pathway.

Motivational deficits (i.e. Amotivation) have furthermore been linked both to cognitive problems and poor community functioning (Chang et al. 2016; Fervaha et al. 2014b; Fervaha et al. 2014c; Fervaha et al. 2015; Konstantakopoulos et al. 2011; Rocca et al. 2014). Studies have suggested that problems with motivation may mediate the relation between cognition and functioning (Chang et al. 2016a; Gard et al. 2009; Nakagami et al. 2008; Ventura et al. 2014). This may specifically concern also social cognition (Gard et al. 2009; Mehta et al. 2015) and social outcome and role functioning (Chang et al. 2016a; Fervaha et al. 2015; Galderisi et al. 2013; Konstantakopoulos et al. 2011; Rocca et al. 2014). According to the cognitive model of Beck (Beck et al. 2009; Rector et al. 2005), negative symptoms, particularly amotivation, could develop from maladaptive attitudinal beliefs caused by repeated unsuccessful goal attainment in real-world circumstances. In other words, cognitive problems may cause patients to lose belief in their own capacities, leading to amotivation and eventually to compromised community functioning (Green et al. 2012).

Other studies have either reported that both negative symptom subdomains are correlated with neurocognitive deficits (Galderisi et al. 2014; Stiekema et al. 2016; Ventura et al. 2014) or that neither is associated with neurocognitive deficits (Chang et al. 2016; Gur and Gur 2015; Kring et al. 2013). These disparaging findings may in part be due to the moderate to strong correlation between Expressive deficits and Amotivation (Liemburg et al., 2014b; Strauss et al., 2012a, b). As a result, studies may find weak associations with negative symptoms as a whole or with both subdomains when analyzed separately, while one dimension actually drives the association. In one of our previous studies, we demonstrated in subgroups with distinct levels of Expressive deficits and Amotivation that these subdomains uniquely predicted functional outcome (Stiekema et al. 2017).

As shown above, findings from studies on negative symptoms up to date are diverse. We assume that one aspect contributing to previous diverse results lies in the disregarding the two subdomains of negative symptoms, and that the underlying mechanisms are more specific. In our analyses, we aim to unravel the relation between cognition and functional outcome via the two subdomains of symptoms more specifically. Finally, the available data provided us with the opportunity to not only explore the associations of interest, but also to evaluate their replicability.

In the current study, we investigated whether Expressive deficits and Amotivation differentially and uniquely mediate associations

between cognitive functioning (neurocognition and social cognition) and domains of functional outcome (living situation, occupation and social functioning (Harvey 2013)). We assessed two different large cohorts, one with recent-onset psychosis ($N = 1129$) and one with a longer duration of illness ($N = 1200$), which enabled us to investigate the robustness of the effects across different stages of the illness. Moreover, follow-up measurements in one cohort allowed us to perform longitudinal analyses to probe influences over time. We hypothesized that Expressive deficits predominantly mediate the association between neurocognition and living situation and occupation, whereas Amotivation predominantly mediates the association between social cognition and social functioning. Moreover, we hypothesized that similar associations would be observed in a longitudinal analysis with outcome measures three years later.

2. Methods

2.1. Study population

Data from two cohort studies were investigated in this study. Most patients in the study samples were outpatients and recently diagnosed with a psychotic disorder (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, psychotic disorder NOS; DSM-IV). Individuals of the first cohort with 1129 cases originated from the province of Groningen, the Netherlands (Psychosis Recent Onset Groningen - Survey, PROGR-S, version 4.1) (Liemburg et al., 2014a, b). These patients followed a diagnostic protocol for first-time treated psychotic complaints at the department of psychotic disorders in the University Center of Psychiatry in Groningen. Study procedures complied with Dutch law requirements as approved by the medical ethical committee of the University Medical Center Groningen. The second cohort ($N = 1200$) consisted of cases of the nationwide, longitudinal study Genetic Risk and Outcome of Psychosis study (GROUP, version 5). This study comprised of three waves of measurements every three years. Subjects were aged 18–50 years, Dutch speaking and on stable treatment (>1 month) (Korver et al. 2012). The study protocol was approved centrally by the Ethical Review Board of the University Medical Center Utrecht and subsequently by local review boards of each participating institute.

All data were handled anonymously and all subjects gave oral and written informed consent. All study procedures were carried out according to the Declaration of Helsinki.

2.2. Cognitive tests

For PROGR-S, psychological assessment included most neurocognitive domains of the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MATRICS) (Nuechterlein et al. 2008), except for social cognition. The assessment protocol included the Stroop Test (Golden 1978; Stroop 1935), Trail Making Test (Spreen and Strauss 1998), California Verbal Learning Test, Dutch edition (Delis et al. 2000; Mulder et al. 1996), Continuous Performance Test (Smid et al. 2006) and the Digit Symbol Substitution, Block Design, Arithmetic and Information subtests of the Wechsler Adult Intelligence Scale (WAIS) III (Blyler et al. 2000; Wechsler 1997).

In GROUP, a similar test battery was administered, which did not contain the Stroop or Trailmaking test, but contained the Verbal Learning tTest (Brand and Jolles 1985), the Response Set-Shifting Task (reasoning and problem solving/working memory) (Bilder et al. 1992), Benton Facial Recognition Test (visuoperception) (Benton et al. 1983), Emotional Mentalizing Task (Shaw et al. 2004) and the Degraded Affect Recognition Task (social cognition) (van 't Wout et al. 2004). In both cohorts, all tests were administered in a fixed order in approximately two hours of testing time. A break was scheduled in case of subject fatigue.

All test scores were converted to Z-scores and inverted if necessary so that a higher Z-score indicated better cognitive performance. Cognitive measures of PROGR-S were combined to one general neurocognitive domain. In GROUP, the Benton Facial Recognition task, Emotional Mentalizing task and the Degraded Affect Recognition Task composed a separate social cognition domain. For the Response Set-Shifting task, only the accuracy cost index score was used, as the reaction time scores had very low correlations with other cognitive measures ($r < 0.1$). For further details and the specific cognitive measures, see Supplementary Table 1.

2.3. Negative symptom measures

Severity of negative symptoms was assessed with the Positive and Negative Syndrome Scale (PANSS), a semi-structured interview with items (response categories 1–7) on symptom severity of psychotic disorders. The PANSS includes three subscales: Positive symptoms, Negative Symptoms and General psychopathology (Kay et al. 1987). Based on previous confirmatory factor analyses two negative symptom subdomains were distinguished (Liemburg et al. 2013; Stiekema et al. 2016), see Supplementary Table 1.

2.4. Measures of functional outcome

Three functional outcomes were assessed: living situation, occupation, and social functioning, however as different variables and different measures. In both cohorts, living situation was defined as a binary variable, comparing independent (single or with partner [and children]) vs. dependent (living at parents or family or sheltered living) and occupation was defined as a binary variable, comparing active work or study vs. no active work/study. In PROGR-S, the Groningen Social Disabilities Schedule (GSDS) was used as a measure of social functioning. The GSDS is a schematic interview on disabilities in social functioning in the domains of self-care, household activities and relations with close family, extended family and partner, societal integration, relationships with friends, work, and daily activities (Wiersma 1990). In GROUP, the Social Functioning Scale (SFS) was used as a measure of social functioning (Birchwood et al. 1990). For both scales, all subscales were combined into one total score.

2.5. Statistical analyses

Mediation analysis was performed using the PROCESS V2.16 toolbox (Hayes 2013). An overview of the used variables can be found in Supplementary Table 1. For longitudinal analyses in GROUP, the second assessment (Wave 2) acted as baseline and the third assessment (Wave 3) as follow-up outcome measure. In all analyses, the neurocognition composite score was used as a predictor variable, PANSS Amotivation and Expressive deficits subscales were used as mediator variables and the functional outcome was used as outcome measure.

Mediation was investigated in two different models: parallel and serial. In the *parallel mediation* analysis two mediators were integrated to independently mediate the associations between the predictor and outcome. However, as we previously showed that both potential mediators are moderately correlated ($r \sim 0.5$) (Liemburg et al. 2013), we accounted for this in a *serial mediation* model that includes an estimate of the effect of the mediators. Here, the direction of the effect has to be implied in the model definition (Hayes 2013). As we had no hypothesis about the direction of the association between Expressive deficits and Amotivation, we conducted serial mediation analyses with both possible effect directions (i.e. Expressive deficits $\rightarrow$ Amotivation and Amotivation $\rightarrow$ Expressive deficits) and assumed that a significant serial effect would indicate a strong effect of one subdomain on the other. The results of these analyses were subsequently compared to the parallel model results to evaluate consistency. To test for multi-collinearity, the Variance Inflation Factor (VIF) was calculated for all models. The following covariates

were added to the model: age, gender, education, and haloperidol equivalents (Gardner et al. 2010). In each model, these covariates were set to influence both the mediator and the outcome. Duration of illness was not included as covariate because it had a moderate correlation with age ($r \sim 0.4$). Significance was set at $\alpha = 0.05$.

For the GROUP database, similar analyses were conducted to evaluate the replicability of the findings found in PROGR-S. Because social cognition was also measured in GROUP, additional analyses were conducted using social cognition as the predictor variable. Crucially, to test whether cognition and subdomains of negative symptoms would predict functional outcome later in life, these analyses were repeated using outcomes measured three years later than the predictor and mediator variables and by adding the baseline outcome measures as covariate. Moreover, changes in predictors, mediators and outcomes (i.e. difference scores in cognition, negative symptoms and outcomes) between two measurements were also investigated. Because social cognition was only available at one time point, longitudinal analyses were restricted to neurocognition.

Table 1
Demographic data of both study samples.

	Total N	PROGR-S		Total N	GROUP	
		Mean/%	SD/N		Mean/%	SD/N
Age	1199	28.4	9.3	811	30.1	7.2
Gender (males)	1200	71%	853	1129	76%	856
Education	1149			1105		
Elementary		17%	195		11%	118
Secondary school/high school		48%	549		52%	572
Vocational education		21%	240		21%	236
Bachelor/master		14%	159		16%	177
IQ	908	99.8	22.4	611	98.7	16.6
Diagnosis	598			738		
Schizophrenia/schizoaffective		56%	336		81%	599
Psychotic/delusional disorder		22%	118		14%	100
Bipolar disorder		5%	31		2%	15
Substance related disorder		5%	32		1%	7
Other		11%	81		2%	17
Duration of illness (months)	793	16.7	36.0	756	92.4	48
Symptom severity						
Haloperidol equivalents (mg)	484	6.2	3.6	510	9.6	16.8
Cognition (Z score vs. healthy subjects)						
Neurocognition	591	−0.40	0.81	764	−0.44	0.86
Social cognition	–	–	–	794	−0.54	0.93
Symptoms						
PANSS Positive Symptoms (range 49–7) ^a	1160	12.9	4.8	785	11.0	4.5
PANSS Negative Symptoms (range 49–7) ^a	1117	13.7	5.7	769	11.7	5.1
PANSS General Psychopathology (range 112–7) ^a	1123	29.8	8.9	775	24.1	7.2
Living situation	1188			741		
With partner		14%	167		16%	121
Alone		43%	512		40%	296
With parents		31%	367		25%	182
Other		12%	142		19%	142
Occupation	1169			1129		
Paid job		28%	335		23%	160
Student		19%	223		22%	158
Unemployed		53%	611		55%	811
Social functioning						
GSDS total score (range 24–0) ^a	957	9.5	5.4	–	–	–
SFS total score (range 41–164) ^a	–	–	–	752	112.5	9.3

^a Ranges from negative - positive outcome.

3. Results

3.1.1. Sample characteristics

The cohorts were similar in terms of demographics, as can be seen from the data in Table 1. As expected based on the inclusion criteria, the GROUP cohort had a longer duration of illness (± 7 years compared to ± 1 year in PROGR-S) and contained more diagnoses of schizophrenia in line with a longer duration of illness.

3.2. Mediation analyses

3.2.1. General observations

Regression results of all mediation analyses are shown in Figs. 1 and 2, and the Supplementary Tables 4, 5 and 6, for every outcome measure. Tests showed absence of multi-collinearity. Some general patterns were observed for most models. As expected, in the univariate regression analyses a strong relation between both negative symptom factors was found for both PROGR-S and GROUP. Significant associations between neurocognition and both Expressive deficits and Amotivation ($X \rightarrow M$) were observed. However, when adding the other negative symptom factor as covariate, i.e. correcting for the other subdomain, only the association of neurocognition with Expressive deficits and the association of social cognition with Amotivation remained significant (noted in this paper as: $X \rightarrow M_1 (M_2)$). There was no direct relation between cognition and outcome measures ($X \rightarrow Y$), except for one analysis.

The results for the analyses on social cognition were comparable to those found for neurocognition, even though there was only a minor correlation between them ($r = 0.21$). Moreover, the correlation of both cognitive measures with the mediators was also $r \leq 0.2$. Post hoc analyses on social cognition while correcting for neurocognition by adding it as a covariate showed similar results as the previous analyses, indicating that the similar findings are not caused by shared variance between neurocognition and social cognition.

Longitudinal findings of GROUP are reported in Supplementary Tables 7, 8 and 9. Results were very similar to the cross-sectional findings. Only 14.5% of the cases changed from independent to dependent living and 3.4% vice versa, which may cause the high similarity with the cross-sectional findings. For occupation, 9.8% changed from having an occupation to no occupation and 13.9% vice versa. The correlation between the SFS total score at baseline and follow-up three years later was $r = 0.74$. Because the strong overlap between cross-sectional and longitudinal analyses, they are reported together and not separately specified. See Fig. 2 for an overview of the longitudinal outcome measures. The results on changes in predictor, mediator and outcome are reported in Tables 10, 11 and 12.

3.2.2. Living situation

In GROUP, living situation was related to expressive deficits in the analyses on neurocognition, according to our hypothesis. However, in PROGR-S we did not observe this relation ($M \rightarrow Y$). Parallel mediation analysis of the association between neurocognition and living situation in GROUP showed that the association was mediated by Expressive deficits ($X \rightarrow M \rightarrow Y$). No serial mediation was observed. Additional post-hoc analyses in an older sample (age ≥ 25 years), including individuals that are less likely to live with their parents, showed similar results with regard to living situation. The analyses on change score did not show significant mediation effects.

3.2.3. Occupation

As expected, univariate analyses in GROUP showed that occupation was related to Expressive deficits for neurocognition, but this effect was also found for social cognition. Against our expectations, for PROGR-S the association between neurocognition and occupation was significant via Amotivation. ($M \rightarrow Y$). Parallel mediation analysis showed that for both neurocognition and social cognition occupation

Fig. 1. Cross-sectional significant mediation pathways between predictors (cognition), mediators (Expressive deficits and Amotivation) and functional outcome measures (living situation (A–C), occupation (D–F) and social functioning (G–I)) for PROGR-S (A, D, G), GROUP neurocognition (B, E, H) and GROUP social cognition (C, F, I). Black arrows indicate parallel mediating associations and gray arrows serial associations. Dashed black lines indicate that the parallel mediation pathway was not significant in the serial mediation analysis. Values indicate the regression coefficient for significant pathways.

was significantly mediated by Amotivation ($X \rightarrow M \rightarrow Y$) in PROGR-S, while it was significantly mediated by Expressive Deficits in GROUP ($X \rightarrow M \rightarrow Y$). In the analyses on the changes in measures, only a serial mediation was observed from cognition via Amotivation and then Expressive deficits to Social outcome ($X \rightarrow M_1 \rightarrow M_2 \rightarrow Y$), but no parallel mediation ($X \rightarrow M \rightarrow Y$), which is different from the other findings on occupation.

3.2.4. Social outcome

Parallel mediation analysis showed in both databases that social outcome was significantly mediated by Amotivation ($X \rightarrow M \rightarrow Y$), as was hypothesized. Serial analysis showed a path from cognition via Expressive deficits and then Amotivation to Social outcome for both neurocognition and social cognition ($X \rightarrow M_1 \rightarrow M_2 \rightarrow Y$). However, in serial analysis ($X \rightarrow M_1 \rightarrow M_2 \rightarrow Y$), path via only Amotivation was not significant ($X \rightarrow M \rightarrow Y$) indicating that serial correlation may actually be important to consider. The analyses on change scores showed a similar pattern.

4. Discussion

In this study, we investigated whether the two negative symptom subdomains, Expressive deficits and Amotivation, mediate the association between cognition and functional outcome (living situation, occupation, social functioning). Analyses were based on two large cohorts

of schizophrenia patients, with each more than one thousand participants (PROGR-S and GROUP) and different duration of illness.

We found evidence for different associations for Expressive deficits and Amotivation. I) There was consistent mediation across cohorts by Amotivation of the association between cognition and social outcome, even though measured with two different instruments in both databases. II) However, regarding living situation, we found no evidence for mediation in patients with a recent-onset (PROGR-S), while Expressive deficits mediated the association only in participants with a longer illness duration (GROUP). III) The association between cognition and occupation was mediated by Amotivation in PROGR-S and by Expressive deficits in GROUP. IV) Mediation analyses with the same predictor variables, but outcomes measured at 3-year follow-up showed similar results as the cross-sectional findings, both with social cognition and neurocognition as predictor.

In the following, we will address the results and discuss their implications with regard to replicability of the results, the effects of the stage of illness and the comparison of cross-sectional and longitudinal effects.

The consistent path of mediation from cognition via Amotivation to social functioning can be expected on bases from previous studies that found motivational problems to mediate the associations of neurocognitive and social cognitive problems with mostly social functional outcome (Chang et al. 2016a; Gard et al. 2009; Nakagami et al. 2008; Ventura et al. 2014). Additionally, studies have shown that motivational attitude is in the path between cognitive problems and

Fig. 2. Longitudinal significant mediation pathways between predictors (cognition), mediators (Expressive deficits and Amotivation) and functional outcome measures (living situation (A, B), occupation (C, D) and social functioning (E, F)) for GROUP neurocognition (A, C, E) and GROUP social cognition (B, D, F). Black arrows indicate parallel mediating associations and gray arrows serial associations. Dashed black lines indicate that the parallel mediation pathway was not significant in the serial mediation analysis. Values indicate the regression coefficient for significant pathways.

amotivation (Chang et al. 2016a; Green et al. 2012). These findings are consistent with the negative symptom model of Beck, in which reduced cognitive abilities are assumed to lead to discouraging life circumstances, which provoke negative attitudes and self-beliefs that, in turn, contribute to decreased motivation and interest. In turn, this may eventually lead to decreased community functioning (Beck et al. 2009; Green et al. 2012; Rector et al. 2005). While we did not hypothesize serial mediation of Expressive deficits and Amotivation, there were serial mediation pathways from cognition via Expressive deficits and then Amotivation to social functioning in participants with a longer duration of a psychotic disorders. Although speculative, neurocognitive problems may lead to Expressive deficits (model of Cohen) (Cohen et al. 2012), which may then lead to dissatisfying interactions in the community.

These may then again lead to loss of belief in the patients' own social capacities, leading to amotivation (Amotivation) and eventually compromised community functioning, as postulated by Beck (Beck et al. 2009; Rector et al. 2005) over the course of time.

Regarding living situation and occupation, we did not observe consistent findings across both cohorts. Differences between both cohorts might be caused on the one hand by differences in the illness duration and the specific type of disorder, on the other hand also by differences of cognitive tests. For instance, the PROGR-S cohort contains more test on executive functioning, such as the Stroop and Trailmaking test, than GROUP. The different durations of illness and higher incidence of schizophrenia in GROUP may also have caused differences in associations between cohorts, as these patients may have poorer and more

instable outcome over time (Harrow et al. 1997). Moreover, participants in PROGR-S were relatively young and may have still lived with their parents. However, selecting persons >25 years did not change the results. A longer duration of illness and higher incidence of schizophrenia may also indicate a poorer prognosis. Most studies discussed in this paper have shown that living situation or occupation as part of a composite outcome measure are predicted by cognitive problems and negative symptoms, but studies showing an association with them as separate outcome measure are relatively scarce (Evensen et al. 2012; Nuechterlein et al. 2011; Rocca et al. 2014; Strauss et al. 2013). Findings on these outcome measures may be limited due to their low rate of occurrence in the population (Harvey 2013). It has also been shown that occupation or living situation versus a global functioning score as outcome measure results in different findings (Harvey et al. 2012). Future studies should select detailed outcome measures on different domains.

Furthermore, there was a substantial association between cognition and negative symptom factors, which is consistent with other studies (Addington et al. 1991; Chang et al. 2014; Chang et al. 2016b; Cohen et al. 2013; Fervaha et al. 2014c; Harvey et al. 2006; Strauss et al., 2012a, b). Importantly, in almost all univariate regressions between cognition and outcome measure there was no significant association. This means full mediation occurs via the negative symptoms subdomains. While other studies have observed links between cognition and outcome (Fervaha et al. 2014b; Harvey et al. 2006; Milev et al. 2005; Ventura et al. 2009), there are also studies supporting our findings of an absent of very weak association between cognition and outcome (Fervaha et al. 2015; Gard et al. 2009; Konstantakopoulos et al. 2011; Lipkovich et al. 2009; Nakagami et al. 2008; Simons et al. 2016). Possibly, we did not observe a separate contribution of cognition because the patients sample had a recent-onset psychosis and a majority appeared to have limited cognitive impairment (Meijer et al. 2012; Reichenberg et al. 2009), while associations between cognition and outcome may only be observed in more chronic samples (Milev et al. 2005; Verdoux et al. 2002).

Of note, in GROUP the findings were similar when using neurocognition or using social cognition as a predictor, even when the analyses with social cognition included neurocognition as a covariate. One previous mediation study has shown a path from neurocognition, via social cognition and then from motivation to functional outcome (Gard et al. 2009), showing they may be related. Unfortunately, the social cognition measures in GROUP were limited and there was no readily available independent sample to confirm these findings. One could speculate about other factors causing strong inter-test associations in the test battery, for example, sustained attention is an important determinant of overall test performance in schizophrenia (Hoonakker et al. 2017). Future studies could use more extensive measures of social cognition, e.g. emotion regulation, dynamic emotional video stimuli, or virtual reality paradigms.

Finally, findings of the longitudinal analyses (3 years later) were similar to the cross-sectional findings in GROUP. We observed a high similarity between baseline and follow-up outcome measures, i.e. the status of subjects was often the same at baseline as at follow-up. Although three year follow-up should be a sufficient follow-up period (Swartz et al. 2007), it is difficult to say whether negative symptoms actually predict the association between cognition and outcome, as negative symptoms also remain stable over time in the majority of patients (Galderisi et al. 2013; Stiekema et al. 2017). This has important implications, as it shows it may be difficult to relieve negative symptoms of patients and improve their outcome over time.

Major strengths of our study include the large sample sizes, the adequate neuropsychological tests addressing several domains and the possibility for independent replication. Besides those already discussed, some additional limitations of the study should be mentioned. First, more recent instruments, e.g. the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al. 2013) or Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al. 2011), may be more optimal to study the

structure of negative symptoms. Previous studies have shown that negative symptoms may actually consist of five subdomains (Ahmed et al. 2019; Strauss et al. 2018), and the PANSS may lack construct validity to capture this five-factor structure. The PANSS has a strong focus on expressive signs that can be observed by the interviewer, but lacks items measuring anhedonia or amotivation. It should be noted though, that the measurements for the sample we report on started before the BNSS and CAINS were published, hence those measures could not be included as they were not in use as yet. Concerning cognition, additional tests to measure e.g. verbal fluency and metacognition could have been added to make the measure more comprehensive. Future studies using these newer instruments are therefore warranted. Moreover, although the two samples differed in duration of illness, patients with a long illness duration (>10 years) were not investigated. While PROGR-S is a naturalistic cohort, GROUP includes patients willing to participate in scientific research. Though different recruitment strategies may be a strength, generalizability across cohorts may also be limited. Finally, though outcome measures were also assessed three years after baseline, predictors and mediators were measured at the same time. Indeed, it should be kept in mind that mediation analysis in cross-sectional data should be regarded with caution (Maxwell et al. 2011).

In conclusion, the study reveals specific mechanisms for the association of cognition and functional outcome. Amotivation may be a robust mediator of the association between cognition and social functioning independent on illness duration, whereas evidence for the mediating role of negative symptom domains in the associations of cognition with occupation and living situation is less robust or may depend stronger on the duration of illness. Such different relationships may have clinical implications: assessment of amotivation may aid a personalized therapeutic approach that takes this into account with regard to functional outcome of the patient. Patients with high levels of amotivation may be offered additional social cognitive interventions, as this may contribute towards improving social functioning.

Contributors

PROGR-S investigators and GROUP-investigators designed the databases used in the study. RB and AA contrived the rationale for the study. E.J.L. and K.W. undertook the statistical analysis, and author E.J.L. and SEG wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Declaration of competing interest

AA received speakers fees from Lundbeck. All other authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

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