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Negative symptoms and everyday functioning in schizophrenia: a cross-sectional study in a real world-setting

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Abstract

Negative symptoms have been suggested to have a greater impact on real-world functioning in schizophrenia than other symptoms. We aimed to examine the relationship of specific negative symptoms components ("expressive deficits" - DE - which include alogia and blunted affect, and "avolition" - AA - which includes amotivation, anhedonia, and asociality), with separate domains of real-world outcomes (the Personal and Social Performance Scale - PSP - and selected items of the Heinrichs Quality of Life Scale - QLS - that did not overlap with negative symptoms) and two functional milestones (recent employment and marriage). Regression analyses were performed to identify the determinants of QLS and PSP scores and of the two milestones, in 92 consecutive outpatients with stable schizophrenia. AA was the strongest predictor of QLS interpersonal relations and social network (IRSN), PSP total score and the first three PSP domains. The variance explained ranged from 36% for PSP self care to 54% for the PSP personal and social relationships. Moreover, higher scores in AA were significant predictors of the single status. DE does not appear to have an impact at real-world functional performance. Taken together, our analysis indicates a relatively specific set of relationships between the AA subdomain and aspects of real-world functioning in schizophrenia. These findings, if confirmed, could have important implications for research, diagnostics and treatment: in fact our results would suggest that AA and DE should be analyzed as separate and distinct domains to be rated and treated individually.

Keywords Avolition; Expressive deficits; Real-world functioning; Functional milestones

1. Introduction

Negative symptoms have long been recognized as an integral and clinically important part of schizophrenia, with approximately 28–36% of individuals with schizophrenia showing elevated negative symptoms (Blanchard et al., 2005), that are only minimally responsive to antipsychotic medication. Studies have suggested that their severity has a greater impact on real-world functioning than other symptoms (Rabinowitz et al., 2012), as negative symptoms affect the patient′s ability to live independently, to perform activities of daily living, to be socially active and maintain personal relationships, and to work and study (Novick et al., 2009, Harvey et al., 2012a and Rabinowitz et al., 2012).

However, it has been recently suggested that negative symptoms represent a heterogeneous psychopathological domain as factor analytic studies of the different negative symptom rating scales have found evidence for two distinct negative symptom subdomains, one related to expressive deficits including affective, linguistic and paralinguistic expressions, and the second domain described as social amotivation or avolition (Keefe et al., 1992, Mueser et al., 1994, Peralta and Cuesta, 1995, Kelley et al., 1999, Blanchard and Cohen, 2006, Kimhy et al., 2006, Kirkpatrick and Fischer, 2006, Nakaya and Ohmori, 2008, Horan et al., 2011, Kirkpatrick et al., 2011, Messinger et al., 2011 and Strauss et al., 2012). This includes both a subjective reduction in interests, desires and goals and a behavioral reduction of purposeful acts and self-initiated activities that are available to the patient and encompass more than just social activities (Messinger et al., 2011).

Given the subdomain structure of negative symptoms, an interesting arising question is the impact that these domains have on functioning (Foussias and Remington, 2010). Measurement of everyday functioning can be accomplished through two general approaches: examination of functional achievements (e.g., marriage, competitive employment, and independent living), defined as milestones (Harvey et al., 2012b), and ratings of real-world functioning using structured assessments. The subdomain of AA appears to have the greatest correlation with functional outcomes, rather than the domain of DE (Ventura et al., 2009). Further, although highly specific research is often lacking, there are indications that social outcomes are more strongly affected than vocational or residential ones (Leifker et al., 2009).

The purpose of this article is to expand on our previous finding (Rocca et al., 2009) by examining the relationship of specific negative symptoms components (DE, AA), rather than one global domain, with separate domains of real-world outcomes in a cohort of chronic outpatients with stable schizophrenia attending an university community mental health center. For the specific purpose of the study we chose two measures of real-world outcome: the Heinrichs Quality of Life Scale (QLS) (Heinrichs et al., 1984) and the Personal and Social Performance Scale (PSP) (Morosini et al., 2000). Moreover, we examined two functional milestones, recent employment and marriage, to assess community functioning.

2. Methods

2.1. Patient population

The study has been conducted at the Department of Neuroscience, Psychiatric Section, University of Turin, Struttura Semplice di Coordinamento a Valenza Dipartimentale (SSCVD), Department of Mental Health ASL TO1 – Molinette, Italy, during the period between July 2009 and July 2011.

Patients were initially evaluated by a clinician-psychiatrist, and if they met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (APA, 2000) criteria for schizophrenia, they were seen subsequently by our research team (S.Z. and M.S.). Of these, a sample of consecutive subjects routinely treated in a community setting and fulfilling the following criteria were included in the study:

1. Men and women in the 18–65 years age group;
2. diagnosis of schizophrenia according to the DSM-IV-TR, confirmed by two expert clinicians (S.Z. and M.S.) using the Structured Clinical Interview for DSM-IV disorders (SCID) (First et al., 1997). The two psychiatrists were aware of previous diagnosis and they could also review the previous clinical charts, available for all the patients. Subjects were excluded if they had a current disorder other than schizophrenia on Axis I of the DSM-IV-TR, a current or past codiagnosis of autistic disorder or another pervasive developmental disorder, a history of severe head injury (coma ≥48 h) and a diagnosis of organic disorder (especially neurological); and
3. patients with stable schizophrenia. Schizophrenia was considered in stable phase if patients had not had any change in symptomatology during the past year and if they had their antipsychotic regimen unchanged for the last six months (based on chart review). The choice of antipsychotic drug prescribed and dosage were left to the discretion of the treating physicians, which happened well before the initiation of the study. Outpatient status was defined as living outside of any institutional setting, including a nursing home.

Patients were evaluated using a semistructured interview to assess demographic features. Data were collected to determine age, gender, education, age at onset of schizophrenia (report of first contact with a psychiatric service), length of illness, and antipsychotic treatment. All patients were submitted to standard care provided in community mental health centers in Italy (pharmacological treatment, clinical monitoring at least on a monthly basis, home care when required, and psychosocial and rehabilitation interventions tailored to patient′s needs).

Written informed consent was obtained from all subjects after a complete description of the study. The study was carried out in accordance with Declaration of Helsinki 1995 (as revised in Edinburgh 2000) and was approved positively by the Local Research Ethics Commitee (LREC).

2.2. Assessment instruments

2.2.1. Clinical symptom ratings

Overall severity of illness was rated using the Clinical Global Impression-Severity scale, CGI-S (Guy, 1976).

The Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1982) was used to evaluate negative symptoms during the preceding month. This interview-based rating scale contains anchored

items that lead to global ratings of 4 negative symptoms (excluding the Attention scale) (Blanchard and Cohen, 2006): affective flattening, alogia, anhedonia–asociality, and avolition–apathy. We separated negative symptoms into the AA (avolition and anhedonia) and DE (affective flattening and alogia) components. The Scale for Assessment of Positive Symptoms (SAPS) ascertained positive symptom scores (Andreasen and Olsen, 1982), and the Calgary Depression Scale for Schizophrenia (CDSS) were used to measure depressive symptoms (Addington et al., 1990).

2.2.2. Real-world functional outcomes

Real-world functioning was assessed using the QLS (Heinrichs et al., 1984) and the PSP (Morosini et al., 2000).

The QLS is one of the most frequently used objective quality of life (QoL) measures, specially constructed to measure QoL of schizophrenia patients. It is a semi-structured interview used by trained raters to assess functioning based on the patient′s self-report and the rater′s judgment. It includes 21 items rated by the clinician on 7-point scales in 4 domains: interpersonal relations and social network (IRSN), instrumental role functioning (IRF), intrapsychic foundations (IF), and common objects and activities (COA). Following the suggestions of the RAND panel (Leifker et al., 2011), we excluded the Intrapsychic Foundations subscale from the QLS because it measures deficit (i.e.) negative symptoms.

The PSP is reliable and appropriate as a measure of personal and social functioning in psychiatric disorders. The ratings are based on the assessment of patient′s functioning in four domains over a 1-week period: (a) socially useful activities, including work and study, (b) personal and social relationships, (c) self-care, and (d) disturbing and aggressive behaviors. Unlike the Global Assessment of Functioning (GAF scale), which conflates patients′ psychopathology with their global functioning, PSP is devoid of this shortcoming. Moreover, PSP helps assess domain-specific disability (Juckel et al., 2008).

2.2.3. Functional milestones achievements

We collected information from patients, informants, and medical records on the achievement of functional milestones. In cases of uncertainty, a consensus was obtained through discussion with the principal investigators and the interviewer. These milestones included social outcomes such as marriage or an equivalent long-term relationship, which we categorized into current relationship or former relationship (divorced or separated), versus never achieved. For employment, we collected current and lifetime history of competitively obtained employment (either part or full time), regardless of duration or reason for termination. We dichotomized these outcome measures.

Clinical ratings were done by research psychiatrists who were well-trained and experienced in the rating scales. Inter-rater reliability was analyzed using the analysis of variance (ANOVA) test. Only raters with an intraclass correlation coefficient of 0.90 or higher during pre-study training were allowed to rate the study patients. In order to maintain high inter-rater reliability and to prevent rater drift, raters met at least once a month for training and reliability retesting.

2.3. Data analysis

Statistical analyses were performed using the software Statistical Package for the Social Sciences, SPSS, version 17 for Windows (SPSS, Chicago, IL, USA).

Data are presented as means±standard deviations (S.D.) or percentages (%), unless stated otherwise.

Analyses were planned in 2 stages.

As for the real-world functional outcomes, in stage 1, the bivariate relationships of the functioning measures (QLS domains and PSP total score and subscales) and AA and DE, and between these variables and potential confounders (age, education, length of illness and SAPS total score) were examined using correlation coefficients. In stage 2, a series of multiple regression analyses using a backward elimination procedure were performed to determine cross-sectional determinants of QLS and PSP scores. QLS domains and PSP (total score and subscales) were used as dependent variables and any significant variables in the initial bivariate analyses ($p<0.05$) as predictors. Backward elimination involves starting with all candidate variables and testing them one by one for statistical significance, deleting any that are not significant.

As for the functional milestones achievements, in stage 1, One-way analysis of variance (ANOVA) was used for group comparisons (according to employment and marital status) on demographic variables, SANS components (AA and DE), and clinical data. In stage 2, all variables significantly different ($p<0.05$) between the groups of subjects (unemployed patients/employed patients; single/engaged patients) were subsequently analyzed, using logistic regression with backward stepwise variable selection (based on the likelihood ratio) separately for each of the two dichotomized outcome measures.

3. Results

Ninety-two consecutive outpatients who met the inclusion criteria were enrolled in the study. Socio-demographic and clinical characteristics of patients′ population are shown in Table 1.

Table 1. Sociodemographic and clinical characteristics of the sample (*n*=92).

Gender, *n* (%)	
Male	50 (54)
Female	42 (46)
Age, years, mean (S.D.)	42.9 (11.4)
Education, years, mean (S.D.)	11.0 (3.24)
Employment status, *n* (%)	
Employed	20 (22)
Unemployed	72 (78)
Marital status, single, yes/no, *n* (%)	
Single or divorced/separated	73 (80)
Married/stable partnership	19 (20)
DSM-IV-TR diagnosis, schizophrenia subtype, *n* (%)	
Paranoid	53 (57)
Disorganized	22 (24)
Undifferentiated	9 (10)
Residual	8 (9)
Duration of illness, years, mean (S.D.)	16.8 (11.1)
Previous hospitalizations, *n*, mean (S.D.)	4.28 (3.90)
Antipsychotic medication, *n* (%)	
SGAs	72 (79)
FGAs	19 (21)
CGI-S, mean (S.D.)	4.52 (0.95)
SAPS total score, mean (S.D.)	18.5 (17.8)
DE, mean (S.D.)	15.0 (12.9)
AA, mean (S.D.)	19.8 (9.19)
CDSS, mean (S.D.)	4.53 (4.81)
QLS IRSN, mean (S.D.)	22.9 (10.2)
QLS IRF, mean (S.D.)	9.45 (6.39)
QLS COA, mean (S.D.)	8.14 (4.97)
PSP total score, mean (S.D.)	55.5 (20.4)
PSP socially useful activity, mean (S.D.)	3.67 (1.28)
PSP personal and social relationships, mean (S.D.)	3.43 (1.08)
PSP self-care, mean (S.D.)	1.98 (1.10)
PSP disturbing and aggressive behaviors, mean (S.D.)	1.32 (0.073)

S.D.: standard deviation; SGAs:Second Generation Antipsychotics; FGAs: First Generation Antipsychotics; SAPS: Scale for Assessment of Positive Symptoms; CGI-S: Clinical Global Impression Scale-Severity; CDSS: Calgary Depression Scale for Schizophrenia; AA: Avolition; DE: expressive deficits; QLS IRSN: Quality of Life Scale, Interpersonal relations and social network; QLS IRF: Quality of Life Scale, Instrumental role functioning; QLS COA: Quality of Life Scale, Common object and activities; PSP: Personal and Social Performance scale.

3.1. Real-world functional outcomes

Results of the correlation analyses (Stage 1) are presented in Table 2. Bivariate analyses of correlations of the two SANS components with the measures of functioning showed significant relationships. Two QLS domains (interpersonal relations and social network and instrumental role functioning), and the PSP total score as well as three PSP domains (the PSP socially useful activities, the PSP personal and social relationships and the PSP self-care subscales) were significantly correlated with AA, with weak to moderate strength of association. The QLS instrumental role functioning and the PSP (total score and three subscales) showed significant correlation with DE. The direction of the association between negative symptoms and functioning was negative (more severe symptoms were associated with poorer functioning). The QLS interpersonal relations and social network and the PSP were significantly correlated with CGI-S and SAPS scores, and duration of illness. The QLS interpersonal relations and social network, the PSP personal and social relationships, and the PSP self-care had significant correlations with age. The PSP disturbing and aggressive behaviors had significant correlations with CGI-S, SAPS and number of hospitalizations. The PSP self-care had significant correlations with number of hospitalizations.

Table 2. Zero-order correlations among variables.

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1	Age	1.00																
2	Duration of illness	0.759[d]	1.00															
3	Years of education	−0.261[a]	−0.198	1.00														
4	Hospitalizations, n	0.243[a]	0.459[d]	−0.205	1.00													
5	CGI-S	0.067	0.191	−0.094	0.068	1.00												
6	SAPS total score	0.127	0.119	−0.109	0.059	0.407[d]	1.00											
7	CDSS	0.054	0.000	0.032	0.013	0.176	0.026	1.00										
8	DE	0.040	0.138	−0.057	0.074	0.164	0.129	0.013	1.00									
9	AA	0.253[a]	0.317[c]	−0.110	0.103	0.295[c]	0.154	0.032	0.631[d]	1.00								
10	QLS IRSN	−0.232[a]	−0.270[b]	0.145	−0.041	−0.423[d]	−0.211[a]	0.010	−0.411[d]	−0.693[d]	1.00							
11	QLS IRF	−0.082	−0.201	0.047	−0.165	−0.330[d]	−0.005	−0.008	−0.053	−0.242[a]	0.388[d]	1.00						
12	QLS COA	0.029	−0.145	0.056	−0.009	−0.171	−0.065	−0.020	−0.169	−0.130	0.151	0.282[b]	1.00					
13	PSP total score	−0.170	−0.248[a]	0.077	−0.156	−0.504[d]	−0.332[d]	−0.104	−0.334[d]	−0.527[d]	0.560[d]	0.440[d]	0.168	1.00				
14	PSP act	0.180	0.223[a]	−0.103	0.044	0.559[d]	0.382[d]	−0.029	0.304[c]	0.573[d]	−0.599[d]	−0.474[d]	−0.162	−0.607[d]	1.00			
15	PSP rel.	0.209[c]	0.312[c]	−0.50	0.099	0.522[d]	0.374[d]	0.135	0.388[d]	0.629[d]	−0.615[d]	−0.208[a]	−0.039	−0.628[d]	0.731[d]	1.00		
16	PSP self	0.334[d]	0.325[c]	−0.186	0.246[a]	0.326[c]	0.068	0.086	0.410[d]	0.547[d]	−0.408[d]	−0.236[a]	0.053	−0.472[d]	0.536[d]	0.578[d]	1.00	
17	PSP beh.	−0.104	0.036	0.048	0.220[a]	0.377[d]	0.247[a]	0.040	0.086	0.003	−0.046	−0.192	−0.059	−0.279[b]	0.209[a]	0.107	0.188	1.00

Abbreviations: CGI-S: Clinical Global Impression Scale-Severity; SAPS: Scale for Assessment of Positive Symptoms; CDSS: Calgary Depression Scale for Schizophrenia; AA: Avolition; DE: expressive deficits; QLS IRSN: Quality of Life Scale, Interpersonal relations and social network; QLS IRF: Quality of Life Scale, Instrumental role functioning; QLS COA: Quality of Life Scale, Common object and activities; PSP: Personal and Social Performance scale; PSP act.: socially useful activity; PSP rel.: personal and social relationships; PSP self.: PSP self-care; PSP beh.: disturbing and aggressive behaviors.

[a] $P<0.05$.
[b] $P<0.01$.
[c] $P<0.005$.
[d] $P<0.001$.

Multiple regressions (Stage 2) showed that AA was the strongest predictor of QLS interpersonal relations and social network. The standardized regression coefficient (beta) for AA was more than almost three times that of illness severity (−0.622 vs. −0.240) for QLS interpersonal relations and social network. In the model predicting PSP total score and the first three PSP domains, AA was significantly better predictor than all other symptom domains or age (Table 3). As seen by the R-

square, the variance explained range from 36% for PSP self care to 54% for PSP personal and social relationships.

Table 3. Multiple regressions with backward elimination, with QLS IRSN, QLS IRF, PSP total score e PSP subscales as dependent variables and psychopathological indices as predictors.

Dependent variable	Independent variable	Standardized	SE	*t*	*p*	Adjusted R^2
QLS						
IRSN	AA	−0.622	0.085	−8.210	0.000	0.522
	CGI-S	−0.240	0.814	−3.167	0.002	
IRF	CGI-S	−0.330	0.666	−3.320	0.001	0.099
PSP						
Total score	AA	−0.415	0.189	−4.872	0.000	0.398
	CGI-S	−0.382	1.819	−4.488	0.000	
Socially useful activities	AA	0.442	0.011	5.651	0.000	0.500
	SAPS total score	0.168	0.006	2.054	0.043	
	CGI-S	0.357	0.114	4.196	0.000	
Personal and social relationships	AA	0.839	0.026	3.811	0.000	0.540
	CGI-S	0.316	0.091	3.879	0.000	
Self-care	AA	0.454	0.011	4.909	0.000	0.356
	Age	0.222	0.009	2.512	0.014	
Disturbing and aggressive behavior	CGI-S	0.371	0.075	3.806	0.000	0.167
	Number of hospitalizations	0.196	0.018	2.013	0.047	

Abbreviations. CGI-S: Clinical Global Impression Scale-Severity; SAPS: Scale for Assessment of Positive Symptoms; AA: Avolition; DE: expressive deficits; QLS IRSN: Quality of Life Scale, Interpersonal relations and social network; QLS IRF: Quality of Life Scale, Instrumental role functioning; PSP: Personal and Social Performance scale.

3.2. Functional milestones achievements

Considering employment, age (F=3.969, p=0.049), SAPS total score (F=5.638, p=0.020) and AA (F=5.316, p=0.023) scores were significantly lower in the group of subjects with a competitive employment. The logistic regression analyses showed that competitive employment was predicted by lower scores in SAPS total score (Exp (β)=0.958, 95% C.I. 0.918–0.999, p=0.045) and in AA (Exp (β)=0.945, 95% C.I. 0.890–1.003, p=0.064). For the model considering SAPS and AA as unique predictors, Nagelkerker R2 was 16.6 (16.6% "variability" explained).

Considering single status, the group of single subjects showed significantly lower scores on CDSS (F=12.337, p=0.001) and significantly higher scores on AA (F=3.983, p=0.049). The logistic regression analyses showed that single status was predicted by lower score in CDSS (Exp (β)=0.839, 95% C.I. 0.750–0.939, p=0.002) and higher score in AA (Exp (β)=1.073, 95% C.I. 1.005–1.145, p=0.035). For the model considering CDSS and AA as unique predictors, Nagelkerker R2 was 23.1 (23.1% "variability" explained).

4. Discussion

To our knowledge, our study presents the first data to examine the relationship between the AA and DE subdomains and real-world functioning in a sample of schizophreniaoutpatients, representative of the usual setting and modality of care of community mental health centers in Italy.

Although there were several significant correlations between QLS, PSP and clinical variables in the present study, the beta coefficients of the multiple regression analyses clearly showed that the SANS AA subdomain was the strongest predictor of the level of social activity as assessed by the QLS interpersonal relations and social network, and the personal and social performance measured by the PSP (total score and the subscales socially useful activities, personal and social relationships, and self-care). Moreover, the AA subdomain was a significant predictor of the social outcome milestone marriage. The DE subdomain does not appear to have an impact at real-world functional performance. Lastly, we found that illness severity, as assessed by the CGI-S, and the positive symptom severity also provide significant and independent determinants of QLS and PSP.

There are two points of strength of the present study.

First, we assessed the real-world functioning and two of the three functional milestones in schizophrenia. Theoretically at least, rating of achievements of functional milestones such as independence in residence, financial responsibility, social milestones such as marriage, and employment should be easier to rate with reliability than assessments of the quality of social interactions or level of other functional skills. However, the rating of milestones is affected by their low rates of occurrence (Harvey, 2013). The PSP and the Heinrichs-Carpenter QLS were intended to assess "real-world" functioning. The PSP also takes into account the patients′ various roles and positions and their subsequent performance. The QLS is one of the 6 functional outcome scales selected by the Validation of Everyday Outcomes (Harvey et al., 2011 and Leifker et al., 2011) study. It is a "hybrid scale, examining social, residential, and vocational outcomes. However, to control for the overlap with negative symptoms and to avoid collinearity and over-inflation of observed effects, the QLS was modified by deletion of the IF subscale, as previously reported (Rabinowitz et al., 2012). Other studies did not include negative symptoms (Swartz et al., 2003), or excluded some key negative factor symptoms (Mohamed et al., 2008, Perlick et al., 2008 and Song et al., 2011).

Second, we focused on two separable dimensions that exist within the broader construct of negative symptoms (AA and DE) as previous studies clearly indicate negative symptoms are important in predicting real-world functioning, although it is not yet clear if there are certain symptoms contained in global symptom subscales that account for the majority of the influence on functioning or if each symptom contributes equally as indexed by the total score (Couture et al., 2011). Some authors have used the term "avolition" as a synonymous with decreased drive, amotivation, or apathy, as reported by Foussias and Remington (2010), whose review concludes that it will be for the purists to tease apart the nuances; the fundamental feature of avolition, regardless of terminology, is a decrease in goal-directed behaviors. It was pointed out that the SANS items used to make the avolition dimension can reflect distinct psychological processes not necessarily linked to motivation (Blanchard et al., 2011). Some Authors have speculated that the "expressive deficits" had a stronger association with neuropsychological function and may reflect directly apparent symptoms that change quickly over time, while "social amotivation" reflects the status of social relationships that may change more slowly (Keefe et al., 1992, Blanchard and Cohen, 2006 and Foussias and Remington, 2010) and had a stronger association with self-reported symptoms and QoL (Foussias and Remington, 2010 and Bell

et al., 2013). Moreover, the first group of symptoms is rated as directly observed behavior, while the social items are based on reports from family members and nursing staff (Messinger et al., 2011).

Our results extend previous studies indicating that AA has several unique associations that are not true of DE. According to a meta-analysis of 73 published English language studies (total n=6519) the negative symptoms that appear to have the greatest correlation with functional outcomes tend to be from the AA domain, rather than the DE domain (Ventura et al., 2009). Liemburg et al. (2013) found that the "expressive deficits" relate stronger to non-social items, and "social amotivation" to social items. Strauss et al. (2013) have found that, in comparison to DE subjects, the AA group demonstrated greater impairment on measures of functional outcome and was less likely to be gainfully employed and to complete high quality work. The pattern of their findings suggests that the AA presentation represents a phenomenologically distinct and more pathological negative symptom profile than DE, which is striking given that DE has more severe total negative symptom scores. Our findings contrast with previous studies, which showed that DE is more strongly associated with worse QoL and functional outcome (Gur et al., 2006 and Gur et al., 2007).

Finally, we found a relationship between positive symptoms with a functional outcome indicator. This is in line with several recent studies (Bowie et al., 2008, Mohamed et al., 2008 and Lipkovich et al., 2009), which have demonstrated a small, albeit statistically significant, association between positive symptom levels and functional domain scores.

However, a number of factors limit the conclusions that may be drawn from this study. First, the data presented are cross-sectional and are unable to address such questions as the evolution of relationships between these domains over time. Second, when we recruited our research participants, there was no attempt to collect a sample that was representative of the population of people with schizophrenia as a whole (Harvey et al., 2012b). Sampling did not consider milestone achievements and the rates of achievement of these milestones may not be representative of the population of people with schizophrenia (Gould et al., 2012). The sample consisted of chronic and clinically stable patients, and it is possible that different results would emerge with patients earlier in the course of illness; thus, our results may not be applicable to schizophrenia patients with different clinical conditions, i.e. inpatient or substance-abusing samples. Future studies should consider these issues in relation to negative symptom heterogeneity. Third, the study group size was not extremely large, and while we were able to explain a significant amount of variance on the outcome variables, some of the non significant predictors might be influenced by the study group size.

Taken together, our analysis indicates a relatively specific set of relationships between the AA subdomain and aspects of functional outcomes in schizophrenia, while DE does not appear to have an impact at real-world functional performance. The AA subdomain was found to be the strongest predictor of real-world functioning, including QoL, interpersonal relations, self care and social performance. Moreover, higher scores in AA were significant predictors of the single status.

These findings, if confirmed, could have important implications for research, diagnostics and treatment (Blanchard and Cohen, 2006 and Messinger et al., 2011). In fact, our results, in line with those of earlier studies, would suggest that AA and DE should be analyzed as separate and distinct domains to be rated individually. By considering DE and AA into the unitary construct of "negative symptoms", crucial information related to the cause and predictive outcome of distinct negative symptoms might be lost (Strauss et al., 2013). Then, when developing and validating a new negative symptoms scale, a suitable sampling should consider AA and DE items (Strauss et al., 2013). Lastly, our findings, along with previous research that showed differences in neural processes thought to underlie these subdomains (Foussias and Remington, 2010), emphasize the potential importance of AA and DE as separate treatment targets.

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