Statistical approaches to explore clinical heterogeneity in psychosis

Islam, Atiqul

CHAPTER 4

Long-term course of negative symptom subdomains and relationship with outcome in patients with a psychotic disorder

Annemarie P. M. Stiekema
Md. Atiqul Islam
Edith J. Liemburg
Stynke Castelein
Edwin R. van den Heuvel
Jaap van Weeghel
André Aleman
Lisette van der Meer
GROUP-investigators

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Abstract

Background: Negative symptoms can be divided into social amotivation (SA) and expressive deficits (ED). We investigated *i*) the course of SA and ED over six years, *ii*) whether SA and ED were related to functioning and quality of life six years later, *iii*) whether subgroups based on the course of SA and ED could be identified, and *iv*) the relationship between subgroups and outcomes over six years.

Methods: Measurements at baseline, three and six years from 1067 patients participating in the Genetic Risk and Outcome of Psychosis (GROUP) project were used. We applied mixed models analysis, regression analysis and trajectory analyses.

Results: Results showed that SA and ED decreased over time. Lower symptom levels were related to better functioning (SA, ED) and quality of life (SA) at six years. Within each subdomain, four subgroups were identified: a steady low course (±60%), a course where symptoms increased (±15%), a subgroup where symptoms decreased (±15%), within SA a decreased course but starting at a higher level (±6%) and within ED a course with relatively stable high ED scores (±6%). In general, the low SA and ED groups showed better outcomes than the other subgroups within each domain.

Conclusion: A substantial number of patients do not follow a stable course of negative symptoms. This heterogeneity is related to outcomes later in life. When evaluating treatments, the effects in subgroups with fluctuating symptom levels may be averaged out by the larger groups showing steady low negative symptom levels.

Keywords: negative symptoms; social amotivation; expressive deficits; functional outcome; long-term course

1. Introduction

Psychotic disorders such as schizophrenia are characterized by a variable presentation of positive symptoms, negative symptoms, and cognitive deficits (Mueser and McGurk, 2004; American Psychiatric Association, 2000). Although positive symptoms are usually most dominant in the acute phase of illness, negative symptoms are considered to be most disabling, due to their persistent nature and profound relationship with poor functional outcomes (Bobes et al., 2010; Ventura et al., 2009). Despite the growing body of research, negative symptoms still are difficult to treat; both pharmacological and psychosocial interventions only have a limited effect, if any at all (Savill et al., 2014). The development of treatments for negative symptoms is difficult due to their heterogeneous nature. Current research therefore aims to diminish this heterogeneity by grouping negative symptoms into two subdomains: social amotivation (SA) and expressive deficits (ED) (Messinger et al., 2011; Foussias et al., 2014).

SA encompasses social and emotional withdrawal and reflects diminished interest in or affective commitment to the social environment. SA is thought to be the result of a deficit in anticipating on pleasurable events and activities (Foussias et al., 2014; Buck and Lysaker, 2013). ED involves blunted affect, poverty of speech, and motor retardation. ED reflects a diminished expressive responsiveness that is observed in verbal and non-verbal communication, which is thought to be caused by, or least related to, neurocognitive deficits (Liemburg et al., 2013; Bell et al., 2013; Ergul and UCok, 2015; Hartmann-Riemer et al., 2015). There is ample evidence for a strong relationship between SA and global functioning (Foussias et al., 2011; Fervaha et al., 2014; Rocca et al., 2014). The associations of ED with functioning were found to be less strong (Foussias et al., 2011; Strauss et al., 2013). However, we recently reported that ED, but not SA, predicted residential living status in a chronic population with psychotic disorders (Stiekema et al., 2016), indicating that ED may in fact be related to daily functioning. However, the extent to which scores on subdomains are consistent over time remains unclear. The few studies that have investigated the longitudinal course of SA and ED showed mixed results, varying from long-term stability of both domains (Galderisi et al., 2013), of ED but not of SA (Ergul and UCok, 2015), and vice versa (Norman et al., 2015).

In the current study, we first investigated whether baseline levels of SA and ED were related to functioning (global functioning, social functioning, independent living, and engagement in work or study) and quality of life six years later. Secondly, we examined whether subgroups with different longitudinal courses of SA and ED could be identified. Finally, we tested whether changes in subdomain scores were differentially associated with changes in functioning and quality of life. In accordance with our previous findings, we hypothesized that both subdomains would be related to global functioning and engagement in work or study, that SA would be most strongly related to social functioning and quality of life, while ED would be related to non-independent living status.

2. Methods

2.1. Study design

We used data from the Genetic Risk and Outcome of Psychosis (GROUP) project, in which outpatients and inpatients with a psychotic disorder between 16 and 50 years were recruited from 36 sites in the Netherlands. The procedure of recruitment, informed consent, approval by the accredited Medical Ethics Review Committee (METC), assessment and population characteristics have been described in

detail elsewhere (Korver et al., 2012). Between April 2004 and December 2013, participants were assessed at baseline and three and six years thereafter.

2.2. Participants

The GROUP sample consisted of 1119 patients and 586 healthy controls at baseline (Korver et al., 2012). Fifty-three patients were excluded because their diagnosis was missing (n = 4), unclear (n=21) or other than primary psychotic (n = 27), so that 1067 patients were included in the analysis.

2.3. Assessment

Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS (Kay et al., 1987)). SA score was calculated as the sum of N2 (emotional withdrawal), N4 (passive/apathetic social withdrawal), and G16 (active social avoidance). ED was the sum of N1 (flat affect), N3 (poor rapport), N6 (lack of spontaneity), G5 (mannerisms and posturing), G7 (motor retardation), and G13 (avolition) (Liemburg et al., 2013).

Global functioning was measured with the Global Assessment of Functioning Disability scale (GAF-D (American Psychiatric Association, 2000)), on an anchored scale from 1 (most severe) to 100 (excellent functioning).

Social functioning was measured with the Social Functioning Scale (SFS) (Birchwood et al., 1990), filled out by the participant at three and six years. The SFS score was computed as the mean of the seven subscales scaled scores.

Independent living (single or with partner or own family vs. living with parents or other family members or sheltered living) and engagement in work or study (work/study vs. no work/study) were also used as functional outcome measures.

Quality of life was assessed with the World Health Organization Quality of Life-BREF (WHO-QOL-BREF (Trompenaars et al., 2005)), including four domains of quality of life: physical health, psychological, social relationships, and environment.

Neurocognition was based on a composite score (mean z-scores) of the Continuous Performance Test, Word Learning Task immediate recall and delayed recall and recognition, and WAIS-III Symbol Substitution, Information, Arithmetic and Block Design. Healthy control subjects were used to obtain age and gender specific z-scores for patients.

2.4. Statistical analysis

2.4.1. Longitudinal course and subgroups of SA and ED

Baseline characteristics of completers versus non-completers (patients who did not participate in the three and/or six-year measurement) were compared using the Kruskal-Wallis test for continuous variables and Chi-square tests for categorical variables.

We examined the change in overall SA and ED over time. We checked the average plot on original (non-imputed) data and conducted a linear mixed model was on the imputed scores for SA and ED separately, including only the fixed effect of time as a categorical independent variable.

Group-based trajectory modeling (Jones et al., 2001; Niyonkuru et al., 2013) was conducted using PROC TRAJ procedure in order to identify clusters of patients following similar patterns within each subgroup (i.e. separately on original scores for SA and ED) over time. Since SA and ED are

continuous, a normal distribution model was specified by identifying a minimum and maximum value outside the range of observed SA or ED values. A first order linear and second order quadratic polynomial model was fitted to determine the number of groups over time. A maximum likelihood method was applied to estimate parameters, including group sizes and shapes of trajectories including patients with missing data. The Bayesian Information Criterion (BIC) and logged Bayes factor (2*ΔBIC) were used to select the number of clusters or subgroups that best fit the data (Jones et al., 2001).

Differences between the identified subgroups in baseline demographic and clinical characteristics were examined using the Kruskal-Wallis test for continuous variables and Chi-square or Fishers exact tests for categorical variables. Pairwise comparisons were corrected for multiple testing using Bonferroni correction.

2.4.2. Multiple imputation

Multiple imputation was applied to address missing data in outcomes and independent variables. Since the data showed arbitrary missing patterns, a fully conditional specification (FCS) predicted mean matching (PMM) method was used to impute missing values for both continuous and categorical variables (van Buuren, 2007), which generated 10 imputed datasets of 1067 patients. All variables (demographic, clinical and neurocognitive as well as the outcomes) were included in the imputation model at three time points. Subsequently, the analyses as described below were performed on each dataset with our different proposed models and parameter estimates were pooled with Rubin's rule (Rubin, 1987).

2.4.3. Predicting outcome at six years

Multiple linear regression analysis was conducted on six year imputed GAF, SFS and WHO-QOL scores as well as logistic regressions on living situation and work activities to investigate the relationship with baseline SA and ED. Baseline SA and ED were entered into the first block, the confounders gender, duration of illness, positive symptoms (PANSS positive subscale), and neurocognition (composite score) into the second block.

2.4.4. Subgroups predicting functioning

Since repeated measures within patients are correlated, linear mixed models were performed on continuous outcomes and generalized linear mixed models were conducted on categorical outcomes, examining whether changes in subgroups within each subdomain were associated with changes in functioning and quality of life over time. A random intercept (patients) mixed model was chosen. For continuous outcomes, the parameter estimates and their variance components were estimated with restricted maximum likelihood (REML). An adaptive Gaussian quadrature with 10 quadrature points was used to estimate the parameters and their associated standard errors for binary outcomes. The independent variables (including subgroups of subdomains and time as a categorical measure) in the statistical model were all considered as fixed effects. The interaction of the categorical subgroups of subdomains with time was one of our interests. The first block of variables in the model contained the subgroups of subdomains and the second block controlled for gender, duration of illness, positive symptoms, and neurocognition).

Pooled Type-III tests of fixed effects p-values (Rubin, 1987; Li et al., 1991) were used to conclude the marginal effects on different outcomes. Additionally, the mean differences of SA or ED subgroups were compared and corrected for multiple testing using Bonferroni correction. All analyses were done using two-tailed tests at α=0.05. Analyses were performed using Statistical Analysis System (SAS), version 9.4 (SAS Institute, 2013).

3. Results

Baseline characteristics are shown in Table 1. Compared completers, non-completers on average had a significantly shorter duration of illness (3.78 vs 4.53 years), lower education levels (3.75 vs 4.19) and higher SA scores (6.45 vs 6.00) and ED scores (11.34 vs 10.43).

Table 1: Baseline demographic and clinical characteristics of participants (n=1067).

	N	Mean (standard deviation) or percentage
Demographics		
Age, years	1059	27.1 (7.24)
Gender, male	1067	77.1 %
Education[a]	1015	4.0 (2.06)
Caucasian	823	79.2 %
Marital status	1051	
Not married	929	88.4 %
Married/living together	93	8.8 %
Divorced/widowhood	29	2.8 %
Residential status	991	
Single or with partner/family	433	43.7 %
With parent(s) or sheltered living	494	49.8 %
Other	64	6.5 %
Clinical characteristics		
Diagnosis	1067	
Schizophrenia	722	67.7 %
Schizo-affective disorder	120	11.2 %
Psychosis NOS	113	10.6 %
Schizophreniform	62	5.8 %
Other[b]	50	4.7 %
Duration of illness, years	1011	4.2 (3.83)
Recent onset psychosis[c]	1067	32.6 %
Number of hospitalizations	895	1.9
Number of psychotic episodes	1041	1.7
GAF	970	54.4 (16.03)
SFS total[e]	-	-
PANSS total	1014	54.9 (16.77)
PANSS positive	1015	12.7 (5.33)
PANSS negative	1012	14.1 (6.01)
PANSS general	1014	28.1 (8.40)
PANSS social amotivation	1001	6.2 (3.09)
PANSS expressive deficits	996	10,79 (4.76)
WHO-QOL total	946	88.4 (14.82)

GAF: Global Assessment of Functioning; SFS: Social Functioning Scale; PANSS: Positive and Negative Syndrome Scale; WHO-QoL: World Health Organization Quality of Life. [a]Education (Verhage): range 1 (no education), 2 (education but no diploma), 3–5 (school diploma) to 8 (university degree); [b]32 Brief psychotic disorder (2.9 %), 22 delusional disorder (2.1 %), 1 psychotic disorder due to medical condition (0.1%); [c]First psychotic episode <2 years prior to baseline measurement; [d]Dose equivalents of chlorpromazine were evaluated using the methods of (Gardner et al. 2010); [e]The SFS was only administered at the 3 and 6 year measurements.

3.1. Missing data

See Supplementary Table 1 for an overview of missing data. All analyses were conducted on imputed data, except for the trajectory analyses.

3.2. Longitudinal course of SA and ED

SA and ED both significantly reduced over time (overall pooled Type-III fixed effect $F_{2, 2120} = 65.69$, $p < .001$; $F_{2, 2120} = 84.90$, $p < .001$) (See the overall profile in Figure 1).

3.3. Predicting outcome at six years

Lower baseline SA predicted a higher level of global functioning (GAF; β = -0.73, t = -3.46, $p = .001$), social functioning (SFS; β = -0.70, t = -6.30, p <0 .001), better quality of life (β = -0.64, t = -3.62, p <.001) and engagement in work or study (β = -0.08, t = -2.18, $p = 0.03$) six years later.

Lower baseline ED predicted a higher level of global functioning (GAF; β = -0.36, t = -2.09, p = .04) and social functioning (SFS; β = -0.32, t = -3.40, p = 0 .002) six years later.

3.4. Longitudinal course of subgroups of SA and ED

Within each subdomain, four subgroups with a different course of negative symptoms could be identified (Supplementary Table 2). The patterns were similar within each subdomain: low, decreased (-low), (decreased-) high and increased. Figure 1 shows the course of each subgroup and the percentage of patients following each course. Demographic differences between the subgroups can be found in Table 2.

3.5. Relationship between subgroups and the level of functioning

We have examined differences between the subgroups within each subdomain with regard to the level of outcomes at each time point. The low SA group scored higher (better) than the other groups on the GAF, SFS and the WHOQOL-BREF at all time points. The low ED group scored higher (better) than the other groups at all time points on the GAF and SFS, except for the six-year measurement compared to the decreased ED. These differences and other significant differences between specific groups are presented in Supplementary Table 3 and graphically represented in Figure 2 and Supplementary Figure 1.

3.6. Relationship between subgroups and the course of functioning

Significant differences in the course of outcomes were found between the subgroups within SA and within ED. Findings are presented in Supplementary Table 4 and Table 3 and graphically presented in Figure 2 (global functioning, social functioning and quality of life) and Supplementary Figure 1 (living situation and engagement in work/study).

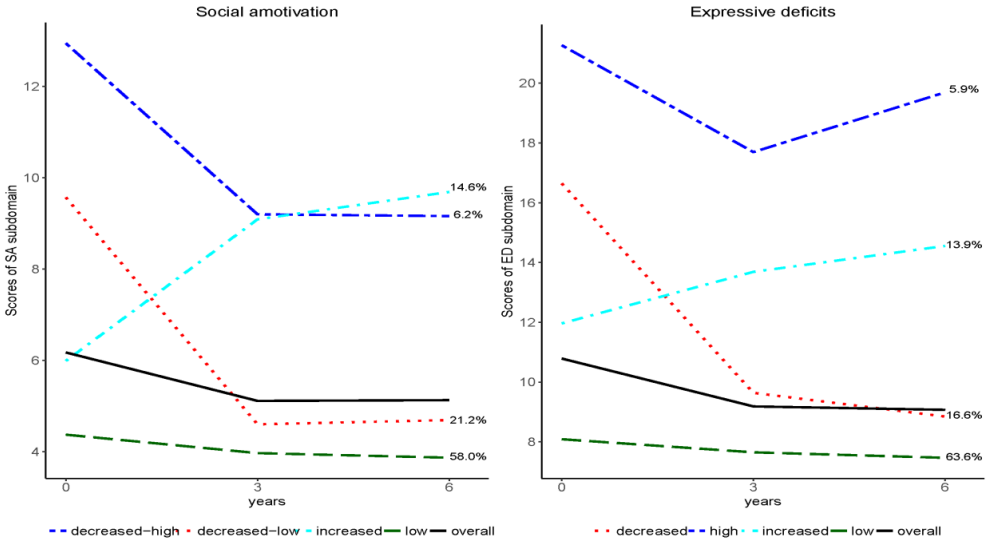

Figure 1: Subgroups with a different course of symptoms over a period of 6 years within SA and within ED.

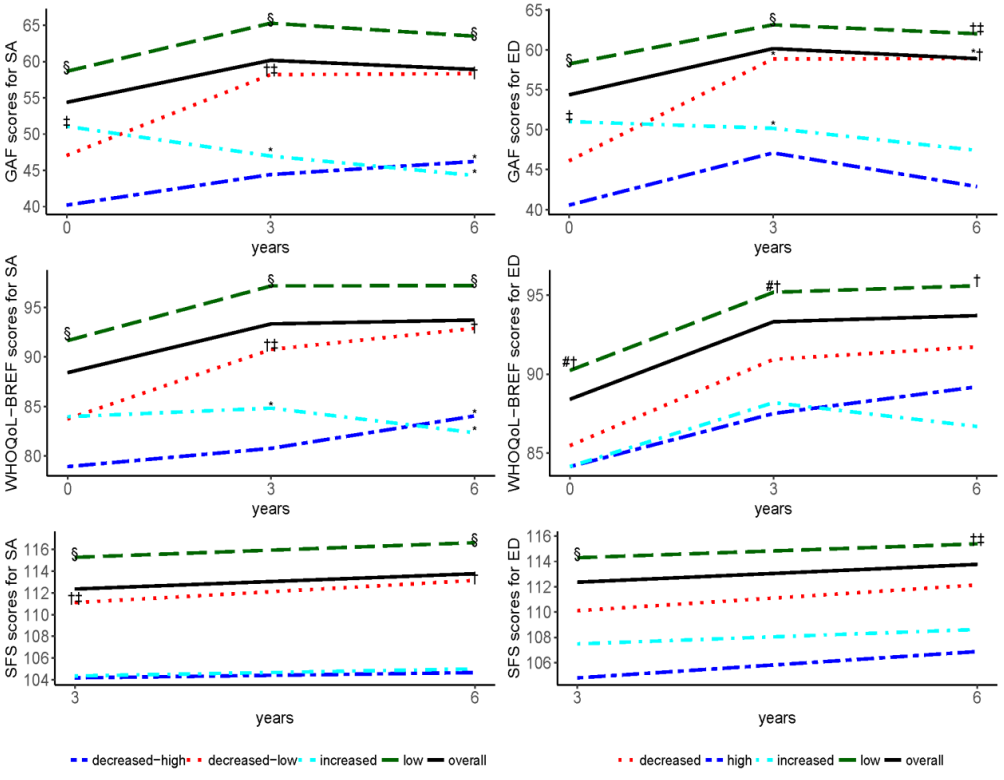

Figure 2: Average values of global and social functioning scores and quality of life (based on imputed data). Analyses were controlled for gender, duration of illness, positive symptoms and cognition. Bonferroni correction (p-value multiplied by 6) was used for the pairwise comparisons. Significant differences between two groups are indicated only at the upper group. Indicated are *significantly different *course* compared to the low group, between study entry and the marked time point (mixed models), significantly different *level* compared to §all other subgroups, #the decreased (-low) group, †the increased group and ‡the (decreased-) high group at the marked time point (pairwise comparisons).

Table 2: Baseline demographic and clinical characteristics per subgroup[a]

	SA				ED			
	Low (n=670)	Decreased-low (n=120)	Increased (n=223)	Decreased-high (n=54)	Low (n=715)	Decreased (n=180)	Increased (n=114)	High (n=58)
Demographic characteristics								
Age, years	26.9 (7.2)#	26.8 (7.2)	28.4 (7.5)	28.4 (7.0)	27.4#	25.4 (6.4)†	28.5 (7.1)‡	26.0 (7.7)
Gender, male	73.3‡	82.1	81.7	94.4	75.0‡	82.2	76.3	89.7
Education	4.2 (2.0)‡	3.8 (2.1)	3.7 (2.0)	3.4 (2.0)	4.2 (2.0)*	3.7 (2.0)	3.7 (2.0)	3.4 (2.1)
Caucasian	82.1†	77.4	70.1	71.7	80.3‡	80.1	77.5	66.1
Marital status								
Not married	86.6	90.0	92.4	94.4	86.6#	82.2	87.6	94.8
Married/living together	10.0	8.1	6.8	1.9	10.0	17.8	10.6	3.4
Divorced/widowhood	3.3	1.8	0.8	3.7	3.4	1.1	1.8	1.7
Residential status								
Single	33.9	32.4	34.5	34.6	36.4	27.5	32.1	24.1
With parent(s)	39.7	39.1	40.9	42.3	37.7	43.9	42.5	48.1
With partner/family	11.7	8.2	7.3	1.9	12.0#	5.3	8.5	3.7
Sheltered living	8.4	13.0	11.8	13.5	8.6	11.7	12.3	16.7
Other	6.3	7.2	5.5	7.7	5.3#	11.7	4.7	7.4
Clinical characteristics								
Diagnosis								
Schizophrenia	61.6*	74.9	80.8	83.3	62.8*	73.9	79.8	84.5
Schizo-affective disorder	12.5	10.3	5.8	11.1	13.0	7.8	7.9	6.9
Psychosis NOS	12.5‡	10.3	5.0	-	11.7	10.6	6.1	5.2
Schizophreniform	7.0#	2.2	5.8	5.6	6.0	5.6	6.1	3.4
Other	6.3	2.3	2.5	-	6.5†	2.1	-	-
Duration of illness, years	4.2 (3.8)	3.9 (3.2)	4.7 (4.6)	5.1 (4.3)	4.3	3.8 (3.4)	4.5 (3.9)	4.1 (3.8)
Recent onset psychosis	32.5	31.8	35.8	29.6	31.9	36.1	33.3	29.3
Number of hospitalizations	1.7 (1.9)	2.1 (2.7)	2.2 (3.0)	2.0 (2.2)	1.8	2.2 (3.2)	1.8 (1.5)	1.9 (2.3)
Number of psychotic episodes	1.8 (1.2)	1.63 (1.1)	1.6 (1.0)	1.8 (1.3)	1.8	1.7 (1.1)	1.6 (.9)	1.7 (1.2)
Chlorpromazine equivalent	322.8 (283.3)	359.9 (342.0)	356.7 (275.9)	342.2 (280.7)	313.3 (291.6)‡	383.2 (326.6)	356.9 (278.2)	420.4 (241.6)

Table 2: Baseline demographic and clinical characteristics per subgroup[a]-continued

SA scores	4.4 (1.5)*	9.6 (1.6)*	6.0 (1.8)*	12.9 (2.3)*	5.2 (2.6)*	8.5 (2.7)†	6.7 (2.7)*	10.0 (3.6)
ED scores	9.1 (3.6)*	13.7 (4.8)*	11.6 (4.3)	16.7 (5.9)	8.1 (2.1)*	16.6 (2.4)†	12.0 (2.7)*	21.3 (3.4)
GAF	58.7 (16.4)*	47.1 (12.2)‡	51.1 (13.0)‡	40.4 (9.6)*	58.2 (15.7)*	46.1 (13.2)	51.0 (14.3)‡	40.6 (12.4)
PANSS total	47.8 (13.0)*	67.5 (14.9)*	57.6 (12.7)*	78.6 (16.9)*	48.6 (13.6)*	68.4 (14.1)†	58.5 (12.4)‡	79.1 (16.7)
PANSS positive	11.6 (4.6)*	14.8 (6.1)	13.3 (4.9)	16.3 (6.5)	12.1 (5.2)*	14.0 (5.7)	13.4 (4.7)	15.5 (5.7)
PANSS negative	11.2 (4.1)*	19.2 (5.0)*	14.9 (4.7)*	24.0 (5.8)*	11.1 (3.8)*	20.5 (4.0)†	15.7 (4.1)‡	25.2 (5.7)
PANSS general	25.0 (6.9)*	33.47 (8.1)†	29.4 (6.7)*	38.2 (9.1)	25.4 (7.0)*	33.9 (8.3)†	29.5 (6.6)‡	38.4 (9.1)
WHO-QOL-BREF	91.6 (14.5)*	83.7 (13.9)	84.0 (13.0)	78.9 (14.5)	90.2 (15.2)*	85.5 (13.5)	84.1 (12.6)	84.1 (15.0)
Neurocognition	-.50 (.6)†	-.64 (.6)	-.55 (.7)	-.65 (.7)	-.47 (.6)*	-.74 (.7)	-.67 (.7)	-.73 (.6)

[a] Differences between the subgroups were tested using the Kruskal-Wallis test for continuous variables, the Chi-square test for categorical variables and the Fishers exact test when expected counts were less than five. P-values were multiplied by the number of comparisons (six) to correct for inflated experimentwise error. For the sake of clarity, significant differences between two groups are indicated only in the first column of the groups. * Statistically significant difference compared to all other groups within the subdomain at $\alpha = .05$; [#] Statistically significant difference compared to decreased(-low) group within the subdomain at $\alpha = .05$; † Statistically significant difference compared to increased group within the subdomain at $\alpha = .05$; ‡ Statistically significant difference compared to (decreased-)high group within the subdomain at $\alpha = .05$.

Table 3: Pooled parameter estimates of mixed models analyses adjusted for gender, duration of illness. neurocognition and positive symptoms*.

	Living situation				Work/study				GAF			
	B	SE	95% CI	p-value	B	SE	95% CI	p-value	B	SE	95% CI	p-value
Social amotivation (SA)												
Intercept	0.37	0.32	-0.27; 1.01	0.253	3.25	0.27	2.71; 3.79	<.001	74.28	1.04	72.24; 76.32	<.001
Decreased-high SA	-0.57	0.61	-1.76; 0.62	0.351	-0.92	0.40	-1.71; -0.14	0.021	-11.92	1.97	-15.78; -8.07	<.001
Decreased-low SA	-0.04	0.33	-0.68; .60	0.901	-0.16	0.26	-0.66; 0.35	0.545	-7.24	1.09	-9.38; -5.10	<.001
Increased SA	-0.21	0.42	-1.04; 0.62	0.620	0.06	0.35	-0.63; 0.75	0.864	-5.34	1.38	-8.04; -2.64	<.001
Time: 3 years	0.98	0.20	0.59; 1.37	<.001	0.11	0.23	-0.36; 0.58	0.644	4.03	0.73	2.60;5.48	<.001
Time: 6 years	2.11	0.30	1.50; 2.72	<.001	0.23	0.20	-0.17; 0.62	0.256	2.80	0.72	1.38;4.22	<.001
Decreased-high SA*3 years	-1.04	0.68	-2.37; 0.30	0.128	-0.40	0.56	-1.51; 0.72	0.480	-0.58	2.53	-5.58; 4.43	0.821
Decreased-high SA*6 years	-0.49	0.98	-2.50; 1.51	0.617	-0.21	0.57	-1.34; 0.91	0.708	2.19	2.90	-3.63; 8.02	0.453
Decreased-low SA*3 years	-0.73	0.35	-1.41; -0.04	0.039	-0.37	0.43	-1.23; 0.49	0.388	1.39	1.43	-1.44; 4.21	0.332
Decreased-low SA*6 years	-0.48	0.44	-1.36; 0.40	0.280	-0.24	0.36	-0.95; 0.47	0.509	3.12	1.37	0.41; 5.82	0.024
Increased SA*3 years	-0.09	0.46	-0.98; 0.81	0.851	-1.11	0.44	-1.97; -0.26	0.011	-7.42	1.66	-10.68; -4.17	<.001
Increased SA*6 years	-0.63	0.53	-1.68; 0.41	0.231	-1.33	0.42	-2.16; -0.50	0.002	-5.65	1.79	-9.20; -2.10	0.002
Expressive deficits (ED)	B	SE	95% CI	p-value	B	SE	95% CI	p-value	B	SE	95% CI	p-value
Intercept	0.52	0.32	-0.11; 1.15	0.107	3.40	0.28	2.86; 3.95	<.001	75.34	1.07	73.24; 77.43	<.001
High ED	-1.17	0.59	-2.32; -0.03	0.045	-0.60	0.41	-1.42; 0.21	0.147	-11.66	1.90	-15.38; -7.93	<.001
Decreased ED	-0.94	0.35	-1.64; -0.25	0.008	-0.14	0.28	-0.69; 0.41	0.616	-8.46	1.19	-10.80; -6.11	<.001
Increased ED	-0.54	0.43	-1.38; 0.30	0.204	0.05	0.34	-0.61; 0.71	0.883	-4.85	1.43	-7.64; -2.05	<.001
Time: 3 years	0.85	0.18	0.49; 1.21	<.001	-0.03	0.21	-0.45; 0.39	0.896	2.89	0.68	1.55; 4.22	<.001
Time: 6 years	1.88	0.28	1.29; 2.47	<.001	0.02	0.21	-0.41; 0.45	0.913	1.90	0.78	0.35; 3.45	0.018
High ED*3 years	-0.90	0.67	-2.23; 0.42	0.179	-0.15	0.64	-1.43; 1.14	0.820	1.99	2.58	-3.14; 7.11	0.443
High ED*6 years	-0.53	0.94	-2.48; 1.42	0.579	-0.34	0.53	-1.38; 0.69	0.515	3.14	2.91	-2.73; 9.01	0.287
Decreased ED*3 years	0.14	0.38	-0.60; 0.88	0.708	-0.09	0.39	-0.86; 0.67	0.811	4.52	1.44	1.69; 7.36	0.002
Decreased ED*6 years	0.56	0.42	-0.26; 1.38	0.178	0.05	0.38	-0.70; 0.81	0.895	6.37	1.85	2.62; 10.12	0.002
Increased ED*3 years	-0.50	0.46	-1.41; 0.40	0.276	-0.94	0.42	-1.77; -0.11	0.027	-3.62	1.74	-7.05; -0.19	0.039
Increased ED*6 years	-0.37	0.48	-1.32; 0.57	0.439	-0.42	0.51	-1.426; 0.59	0.413	-2.51	2.02	-6.55; 1.52	0.217

Table 3: Pooled parameter estimates of mixed models analyses adjusted for gender, duration of illness. neurocognition and positive symptoms*-continued

	SFS				WHOQOL-BREF			
	B	SE	95% CI	p-value	B	SE	95% CI	p-value
Social amotivation (SA)								
Intercept	119.75	0.82	118.12; 121.38	<.001	98.03	1.22	95.61; 100.46	<.001
Decreased-high SA	-8.51	1.33	-11.14; -5.89	<.001	-9.59	2.05	-13.61; -5.57	<.001
Decreased-low SA	-3.69	0.77	-5.22; -2.16	<.001	-6.04	1.12	-8.24; -3.84	<.001
Increased SA	-8.97	0.91	-10.76; -7.19	<.001	-6.54	1.43	-9.34; -3.74	<.001
Time: 3 years	-	-	-		4.09	0.64	2.81; 5.37	<.001
Time: 6 years	1.30	0.33	0.64; 1.96	<.001	3.79	0.66	2.47; 5.11	<.001
Decreased-high SA*3 years	-	-	-	-	-2.33	2.13	-6.53; 1.87	0.276
Decreased-high SA*6 years	1.15	1.47	-1.86; 4.16	0.440	1.79	2.24	-2.64; 6.21	0.426
Decreased-low SA*3 years	-	-	-	-	0.57	1.20	-1.80; 2.94	0.635
Decreased-low SA*6 years	0.42	0.72	-1.02; 1.86	0.563	2.67	1.17	0.37; 4.97	0.023
Increased SA*3 years	-	-	-	-	-3.49	1.47	-6.39; -0.60	0.018
Increased SA*6 years	0.24	0.75	-1.23; 1.71	0.748	-4.12	1.46	-6.99; -1.25	0.005
	B	SE	95% CI	p-value	B	SE	95% CI	p-value
Expressive deficits (ED)								
Intercept	120.06	0.82	118.42; 121.69	<.001	98.38	1.25	95.92; 100.85	<.001
High ED	-7.05	1.40	-9.84; -4.25	<.001	-3.52	2.04	-7.53; 0.48	0.085
Decreased ED	-3.37	0.77	-4.89; -1.84	<.001	-3.35	1.21	-5.73; -0.97	0.006
Increased ED	-4.92	0.96	-6.81; -3.02	<.001	-4.65	1.44	-7.47; -1.83	0.001
Time: 3 years	-	-	-	-	3.72	0.61	2.51; 4.93	<.001
Time: 6 years	1.13	0.33	0.48; 1.77	<.001	3.58	0.63	2.32; 4.85	<.001
High ED*3 years	-	-	-	-	-1.76	2.16	-6.03; 2.52	0.418
High ED*6 years	1.67	1.53	-1.46; 4.84	0.280	1.04	2.61	-4.25; 6.3	0.693
Decreased ED*3 years	-	-	-	-	-0.05	1.34	-2.71; 2.61	0.970
Decreased ED*6 years	1.07	0.77	-0.48; 2.26	0.172	1.73	1.35	-0.94; 4.41	0.202
Increased ED*3 years	-	-	-	-	-0.35	1.49	-3.27;2.58	0.817
Increased ED*6 years	1.05	0.87	-0.68; 2.78	0.230	-0.12	1.65	-3.40; 3.16	0.941

Reference category for SA is the low SA group, reference category for ED is low ED group. Reference category for time is baseline expect for the SFS. where the three-year measurement was the reference category in the absence of a baseline measurement.

4. Discussion

The aim of this study was fourfold. Firstly, we examined the course of SA and ED over six years. Secondly, we investigated whether SA and ED at baseline were related to functioning and quality of life six years later. Thirdly, we examined whether we could disentangle the heterogeneity of negative symptoms by classifying patients into different subgroups based on the course of SA and ED over time. And finally, we investigated to what extent these subgroups differed in their level and course of functioning over six years. We distinguished separate groups within the subdomains SA and ED, following a different course of negative symptoms over time. Furthermore, we demonstrated that the course of negative symptomatology over time was related to the level and courses of functioning and quality of life over a period of six years.

4.1. Longitudinal course and subgroups of SA and ED

In contrast with previous findings that suggest a stable course of negative symptoms in SA and ED across five years (Galderisi et al., 2013), the current findings demonstrate that whilst this is the case for approximately two third of the patients, approximately one third follows a less stable course. This one third is divided into subgroups showing a decreased or increased SA and ED course over time. The identification of a stably high ED group, but not a stably high SA group, may support previous suggestions that ED is more persistent (Liemburg et al., 2013; Ergul and UCok, 2015), although only a small proportion of patients seems to suffer from stably high ED (6%).

According to the literature, improvement of negative symptoms often takes place in the first few years of illness (Evensen et al., 2012; Eaton et al., 1995; Hovington et al., 2012) and an increase in negative symptoms is predominantly found in chronic patients (Chang et al., 2011). By introducing subgroups, we were able to demonstrate a more detailed account of negative symptom development, namely a differential course for subgroups of patients for both SA and ED over time. Both the decrease and increase of negative symptoms took place mainly in the first three years of the study, indicating that the variability in symptom level may diminish with a longer duration of illness and it could reflect fluctuations in patients within their first years of illness (subgroups did not differ with regard to duration of illness).

In sum, these results show that, not only do the subdomains SA and ED provide more information with regard to the heterogeneity in symptom presentation, the course of negative symptom development over time seems to be more variable between subgroups of patients than was previously assumed, when looking within each subdomain.

4.2. Associations with outcome

The subgroups within SA and ED were differentially related to the level and course of functioning and quality of life across six years. The lower symptom groups generally showed the best outcomes, but depending on the course of negative symptom subdomains, differences between the groups with regard to outcome change over time and between the subdomains. Our findings support and expand the existing evidence for the robust relationship of SA with functioning and quality of life (Messinger et al., 2011; Strauss et al., 2013; Fervaha et al., 2014; Foussias et al., 2014), and are also in line with our previous study in which higher ED was associated with global functioning in chronic patients

(Stiekema et al., 2016). In contrast to the relationship between SA and functioning, the relationship between ED and outcomes is less consistent in the literature. Our results indicate that SA is an important treatment target for improving functioning and well-being, but they also point out the importance of ED and suggest that neglecting this subgroup of negative symptoms may be disadvantageous for negative symptom treatment development.

4.3. Implications

The evidence for different relationships between the subgroups and functioning and quality of life suggests that distinguishing between the subgroups is clinically relevant and may have implications for clinical practice and treatment development. Of the included patients in this study, about half could be classified in both the low SA and low ED group. Thus, for these patients this leaves limited room (and need) for improvement in negative symptoms. This poses a problem for treatment development, as it causes an increased risk of false negative findings of treatment trials aimed at improving negative symptoms (and accompanied improvement in functioning); possibly improvement of the other 48% of the patients for whom improvement is possible and necessary is masked as the steady low group may average out effects for the other groups. This is clearly visible in our graphical representation of the overall and subgroup courses in Figures 1 and 2, where the low groups show the same pattern as the overall group but at a slightly lower level of symptoms and better level of outcomes. The finding that some of the courses of outcomes that appear visibly different were not significant (such as the differences in living situation within ED) could indicate that other factors (such as positive symptoms and neurocognition) are important for the level and course of the outcomes as well, but it could also be due to reduced power of subgroup analysis.

To date, few pharmacological studies have investigated the selective responsiveness of both subdomains, but they do not yet provide enough information for a firm conclusion about a differential response to treatment (Kirkpatrick, 2014; Azorin et al., 2014). Overall, there is only a small number of studies investigating psychosocial interventions with negative symptoms as a primary outcome (Elis et al., 2013), and the differential effects on the subdomains are unclear. SA has been related to the deficits in anticipatory pleasure (Foussias et al., 2014; Buck and Lysaker, 2013) which may make cognitive behavioral therapy a suitable intervention to address defeatists beliefs (Staring et al., 2013). ED has been linked to cognitive deficits (Liemburg et al., 2013; Bell et al., 2013; Ergul and UCok, 2015; Hartmann-Riemer et al., 2015), which may lead treatment development in the direction of restorative and/or compensatory cognitive rehabilitation interventions. However, the significant relation of ED with global functioning while controlling for cognition indicates that cognition cannot fully explain this association. Possibly, interventions targeting expressive skills such as Social Skills Training (Bellack et al., 2004; Turner et al., 2014) could improve ED. As mentioned above, studies evaluating such treatments should only include patients with more profound negative symptoms to prevent treatment effects from being masked by those with low negative symptom levels.

4.4. Strengths, limitations and future directions

Strengths of this study are the large sample size, the longitudinal nature and the used methodology. Furthermore, participants were included from representative inpatient and outpatient services covering 75% of the population in the Netherlands (Korver et al., 2012). Several limitations should also be mentioned. We cannot infer causality from this observational study. Furthermore, we do not know whether changes in negative symptoms are due to relief of secondary negative symptoms, for example by reduced positive symptoms, depressive symptoms or antipsychotic medication (Carpenter and Kirkpatrick, 2015), which may require a different approach than the suggested treatment strategies described above (Carpenter et al., 1985). Also, the current results are most applicable for those with predominant SA or ED (Strauss et al., 2013), because we have compared subgroups within each subdomain. Further, the intervals between the measures are large (3 years). Lastly, due to the relatively demanding protocol of the GROUP study, participants may differ from participants in studies that are less demanding or from patients that refuse to participate (Korver et al., 2012). Notably, in the current study non-completers showed more severe SA and ED, suggesting that patients with high levels of negative symptoms may be less likely to complete and/or participate in the study. Although this is not unique to our study, our findings should be interpreted in light of this possible selection bias.

Thus, future research should investigate possible causal mechanisms for the variability in the subdomain levels over time, e.g. whether improvement in negative symptoms facilitates improvements in outcome or vice versa (Alvarez-Jimenez et al., 2012) and whether the groups differ with regard to the care they (have) receive(d). For those with co-occurring SA and ED, research into the influence of combinations of SA and ED subgroups is needed, but this was beyond the scope of our study. Research on more specific diagnostic groups could be of value as well, since the low SA and low ED group included significantly fewer patients with schizophrenia.

4.5. Conclusion

In summary, our results show that there is a considerable heterogeneity in the course of the subdomains and suggest that negative symptoms are less stable than was previously assumed. The subgroups that we identified within SA and ED, showing a different course of symptoms over time, are clinically relevant as they are differentially related to the level and course of outcomes. Including the whole range of negative symptoms instead of distinguishing subdomains of SA and ED may explain why efforts to develop treatments for negative symptoms have been disappointing, as treatment effects may have been masked. Thus, research on treatments for negative symptoms could benefit from distinguishing subgroups within SA and ED.

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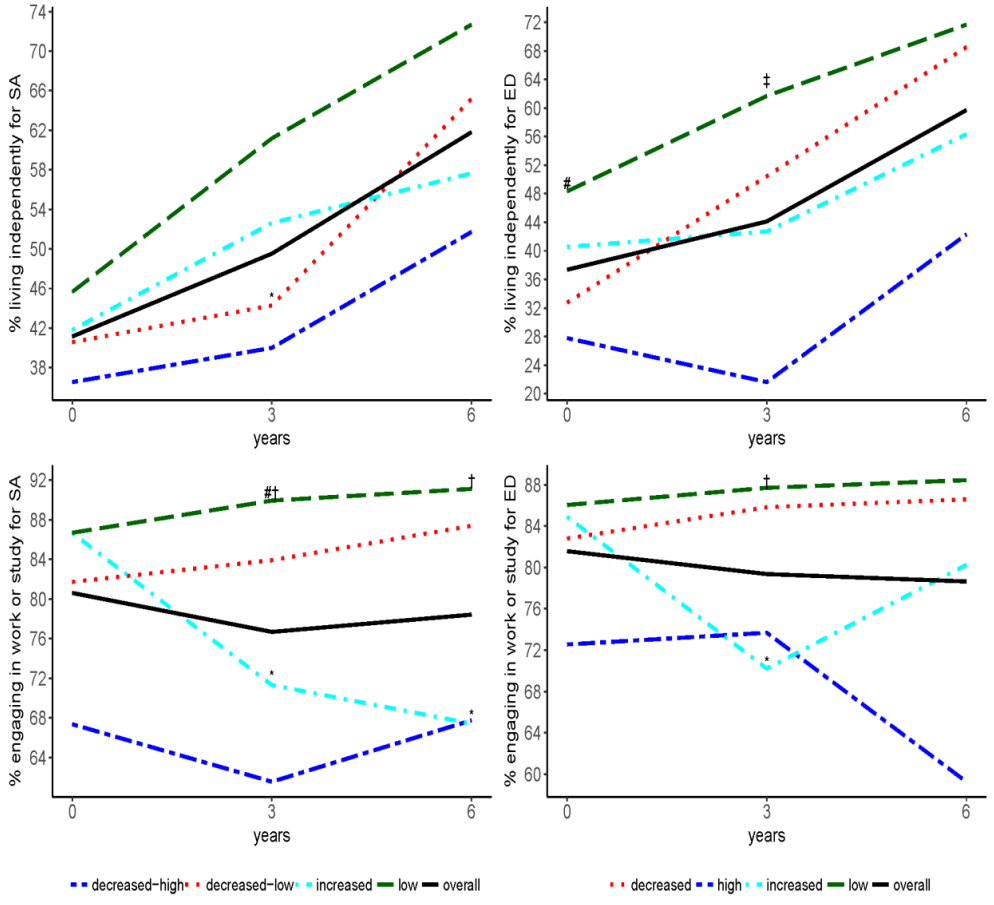
Supplementary Materials

Supplementary table 1: Proportion of missing data for negative symptom subdomain scores and outcome variables.

	SA	ED	GAF	SFS	WHO-QOL	Work/study	Living situation
Study entry	6.2	6.7	9.1	-	11.3	10.8	7.1
3 years	29.2	29.4	32.4	31.6	31.3	27.5	28.0
6 years	43.1	43.5	45.9	45.5	45.8	40.7	44.5

Abbreviations: SA: social amotivation, ED: expressive deficits, GAF: Global Assessment of Functioning; SFS: Social Functioning Scale; WHO-QoL: World Health Organization Quality of Life.



Supplementary Figure 1: Average percentage of patients living independently and engaging in work or study (based on imputed data). Analyses were controlled for gender, duration of illness, positive symptoms and cognition. Bonferroni correction (p-value multiplied by 6) was used for pairwise comparisons. Significant differences between two groups are indicated only at the upper group. Indicated are *significantly different *course* to the low group, between study entry and the marked time point (mixed models), significantly different *level* compared to the #decreased (-low) group, †increased group and the ‡(decreased-) high group at the marked time point (pairwise comparisons).

Supplementary table 2: Bayesian Information Criterion (BIC) and logged Bayes factor (*2*ΔBIC*) for model selection*

Number of groups	BIC	*ΔBIC*	2**ΔBIC*	Evidence against H_0
Social amotivation (N=1039)				
1	-5898.15			
2	-5727.81	170.34	340.68	
3	-5654.44	73.37	146.74	
4	**-5609.96**	**44.48**	**88.96**	**Very Strong**
5	-5626.20	-16.24	-32.48	
Expressive deficits (N=1040)				
1	-6769.99			
2	-6485.22	284.77	569.54	
3	-6416.71	68.51	137.02	
4	**-6351.72**	**64.99**	**129.98**	**Very Strong**
5	-6371.48	-19.76	-39.52	

*Table 2 tabulates the BIC for model fits to the social amotivation (SA) and expressive deficits (ED) data. Based on the results the four-group model is favored for SA as well as for ED because the BIC is the smallest and 2*ΔBIC>10 suggests very strong evidence against the null model.

Supplementary table 3: Pairwise comparison using mixed models analysis adjusted for gender, duration of illness, neurocognition and positive symptoms using Bonferroni correction (p-values were multiplied by 6) and considered significant at an alpha of 0.05.

	Living situation study entry				Living situation 3 years				Living situation 6 years			
	B	SE	95% CI	p-value	B	SE	95% CI	p-value	B	SE	95% CI	p-value
Social amotivation												
decreased-high SA vs decreased-low SA	-0.53	0.64	-1.79; 0.73	1.000	-0.84	0.67	-2.15; 0.47	1.000	-0.54	0.85	-2.26; 1.17	1.000
decreased-high SA vs increased SA	-0.36	0.69	-1.71; 1.00	1.000	-1.31	0.74	-2.76; 0.14	0.464	-0.22	0.91	-2.06; 1.62	1.000
decreased-high SA vs low SA	-0.57	0.61	-1.76; 0.62	1.000	-1.61	0.67	-2.92; -0.29	0.102	-1.06	0.94	-2.99; 0.87	1.000
decreased-low SA vs increased SA	0.17	0.46	-0.74; 1.08	1.000	-0.47	0.46	-1.38; 0.44	1.000	0.33	0.53	-0.72; 1.37	1.000
decreased-low SA vs low SA	-0.04	0.33	-0.68; 0.60	1.000	-0.77	0.34	-1.43; -0.11	0.139	-0.52	0.42	-1.36; 0.32	1.000
increased SA vs low SA	-0.21	0.42	-1.04; 0.62	1.000	-0.30	0.41	-1.11; 0.52	1.000	-0.84	0.48	-1.80; 0.11	0.492
Expressive deficits												
high ED vs decreased ED	-0.23	0.65	-1.51; 1.05	1.000	-1.27	0.69	-2.64; 0.09	0.407	-1.32	0.82	-2.98; 0.34	0.698
high ED vs Increased ED	-0.63	0.68	-1.97; 0.71	1.000	-1.03	0.70	-2.41; 0.35	0.863	-0.79	0.80	-2.37; 0.80	1.000
High ED vs low ED	-1.17	0.59	-2.32; -0.03	0.271	-2.08	0.63	-3.31; -0.84	**0.006**	-1.70	0.84	-3.43; 0.02	0.317
decreased ED vs Increased ED	-0.40	0.50	-1.39; 0.58	1.000	0.24	0.51	-0.76; 1.25	1.000	0.53	0.50	-0.45; 1.52	1.000
decreased ED vs low ED	-0.94	0.35	-1.64; -0.25	**0.046**	-0.80	0.36	-1.51; -0.10	0.157	-0.38	0.42	-1.22; 0.46	1.000
Increased ED vs low ED	-0.54	0.43	-1.38; 0.30	1.000	-1.05	0.42	-1.87; -0.22	0.077	-0.92	0.46	-1.83; 0.00	0.299

	Work activities study entry				Work activities 3 years				Work activities 6 years			
	B	SE	95% CI	p-value	B	SE	95% CI	p-value	B	SE	95% CI	p-value
Social amotivation												
decreased-high SA vs decreased-low SA	-0.77	0.41	-1.58; 0.05	0.388	-0.80	0.45	-1.69; 0.10	0.488	-0.74	0.54	-1.82; 0.34	1.000
decreased-high SA vs increased SA	-0.98	0.49	-1.95; -0.02	0.278	-0.27	0.47	-1.20; 0.66	1.000	0.14	0.55	-0.96; 1.23	1.000
decreased-high SA vs low SA	-0.92	0.40	-1.71; -0.14	0.125	-1.32	0.45	-2.22; -0.42	**0.026**	-1.14	0.50	-2.13; -0.14	0.157
decreased-low SA vs increased SA	-0.22	0.40	-0.99; 0.56	1.000	0.53	0.36	-0.17; 1.23	0.838	0.88	0.34	0.22; 1.54	0.056
decreased-low SA vs low SA	-0.16	0.26	-0.66; 0.35	1.000	-0.53	0.33	-1.18; 0.13	0.677	-0.40	0.28	-0.96; 0.17	0.995
increased SA vs low SA	0.06	0.35	-0.63; 0.75	1.000	-1.05	0.32	-1.69; -0.42	**0.007**	-1.27	0.29	-1.85; -0.70	**<.001**
Expressive deficits												
high ED vs decreased ED	-0.46	0.44	-1.33; 0.40	1.000	-0.52	0.56	-1.64; 0.60	1.000	-0.86	0.51	-1.86; 0.15	0.563
high ED vs Increased ED	-0.65	0.51	-1.66; 0.35	1.000	0.14	0.57	-0.99; 1.27	1.000	-0.58	0.54	-1.66; 0.50	1.000
High ED vs low ED	-0.60	0.41	-1.42; 0.21	0.880	-0.75	0.56	-1.88; 0.38	1.000	-0.95	0.45	-1.84; -0.05	0.228
decreased ED vs Increased ED	-0.19	0.40	-0.97; 0.59	1.000	0.65	0.40	-0.13; 1.44	0.608	0.28	0.47	-0.66; 1.22	1.000
decreased ED vs low ED	-0.14	0.28	-0.69; 0.41	1.000	-0.23	0.33	-0.90; 0.43	1.000	-0.09	0.31	-0.71; 0.53	1.000
Increased ED vs low ED	0.05	0.34	-0.61; 0.71	1.000	-0.89	0.31	-1.49; -0.28	**0.025**	-0.37	0.42	-1.21; 0.48	1.000

Supplementary table 3-continued

	GAF study entry				GAF 3 years				GAF 6 years			
	B	SE	95% CI	p-value	B	SE	95% CI	p-value	B	SE	95% CI	p-value
Social amotivation												
decreased-high SA vs decreased-low SA	-4.68	2.08	-8.75; -0.61	0.146	-6.64	2.45	-11.52; -1.78	**0.047**	-5.60	2.547	-10.68; -.052	0.187
decreased-high SA vs increased SA	-6.58	2.23	-10.95; -2.21	**0.019**	0.27	2.64	-4.97; 5.50	1.000	1.26	2.667	-4.04; 6.56	1.000
decreased-high SA vs low SA	-11.92	1.97	-15.78; -8.07	**<.001**	-12.50	2.24	-16.93; -8.06	**<.001**	-9.73	2.638	-15.06; -4.40	**0.004**
decreased-low SA vs increased SA	-1.90	1.57	-4.98; 1.18	1.000	6.91	1.72	3.52; 10.29	**<.001**	6.86	1.746	3.41; -1.78	**<.001**
decreased-low SA vs low SA	-7.24	1.09	-9.38; -5.10	**<.001**	-5.85	1.19	-8.19; -3.51	**<.001**	-4.13	1.188	-6.47; -1.78	**0.004**
increased SA vs low SA	-5.34	1.38	-8.04; -2.64	**<.001**	-12.76	1.44	-15.59; -9.94	**<.001**	-10.99	1.547	-14.04; -7.93	**<.001**
Expressive deficits												
high ED vs decreased ED	-3.20	2.11	-7.34; 0.94	0.778	-5.74	2.51	-10.73; -0.74	0.150	-6.43	2.88	-12.26; -0.60	0.778
high ED vs Increased ED	-6.81	2.25	-11.23; -2.39	**0.015**	-1.20	2.49	-6.12; 3.71	1.000	-1.16	2.79	-6.74; 4.43	1.000
High ED vs low ED	-11.66	1.90	-15.38; -7.93	**<.001**	-9.67	2.36	-14.38; -4.96	**0.001**	-8.52	2.75	-14.11; -2.92	**0.024**
decreased ED vs Increased ED	-3.61	1.64	-6.82; -0.40	0.165	4.53	1.80	0.99; 8.07	0.073	5.27	1.83	1.66; 8.88	**0.026**
decreased ED vs low ED	-8.46	1.19	-10.80; -6.11	**<.001**	-3.93	1.23	-6.34; -1.53	**0.008**	-2.09	1.68	-5.52; 1.35	1.000
Increased ED vs low ED	-4.85	1.43	-7.64; -2.05	**0.004**	-8.47	1.47	-11.35; -5.58	**<.001**	-7.36	1.81	-10.98; -3.74	**0.001**

	SFS 3 years				SFS 6 years			
	B	SE	95% CI	p-value	B	SE	95% CI	p-value
Social amotivation								
decreased-high SA vs decreased-low SA	-4.83	1.53	-7.87; -1.78	**0.014**	-4.09	1.61	-7.33; -0.85	0.086
decreased-high SA vs increased SA	0.46	1.50	-2.50; 3.42	1.000	1.37	1.63	-1.88; 4.63	1.000
decreased-high SA vs low SA	-8.51	1.33	-11.14; -5.89	**<.001**	-7.36	1.48	-10.33; -4.39	**<.001**
decreased-low SA vs increased SA	5.29	1.03	3.26; 7.31	**<.001**	5.46	0.98	3.54; 7.38	**<.001**
decreased-low SA vs low SA	-3.69	0.77	-5.22; -2.16	**<.001**	-3.27	0.73	-4.71; -1.83	**<.001**
increased SA vs low SA	-8.97	0.91	-10.76; -7.19	**<.001**	-8.73	0.92	-10.54; -6.93	**<.001**
Expressive deficits								
high ED vs decreased ED	-3.68	1.52	-6.71; -0.65	0.107	-3.07	1.64	-6.36; 0.22	0.403
high ED vs Increased ED	-2.13	1.50	-5.09; 0.83	0.944	-1.50	1.63	-4.74; 1.47	1.000
High ED vs low ED	-7.05	1.40	-9.84; -4.25	**<.001**	-5.36	1.67	-8.76; -1.96	**0.018**
decreased ED vs Increased ED	1.55	1.14	-0.70; 3.80	1.000	1.57	1.28	-0.98; 4.12	1.000
decreased ED vs low ED	-3.37	0.77	-4.89; -1.84	**<.001**	-2.29	0.94	-4.19; -0.40	0.112
Increased ED vs low ED	-4.92	0.96	-6.81; -3.02	**<.001**	-3.86	1.04	-5.93; -1.79	**0.002**

Supplementary table 3-continued

	WHOQOL-BREF study entry				WHOQOL-BREF 3 years				WHOQOL-BREF 6 years			
	B	SE	95% CI	p-value	B	SE	95% CI	p-value	B	SE	95% CI	p-value
Social amotivation												
decreased-high SA vs decreased-low SA	-3.54	2.16	-7.79; 0.70	0.608	-6.44	2.34	-11.07; -1.82	**0.039**	-4.43	2.64	-9.72; 0.86	0.593
decreased-high SA vs increased SA	-3.05	2.34	-7.63; 1.54	1.000	-1.88	2.39	-6.58; 2.81	1.000	2.86	2.59	-2.25; 7.97	1.000
decreased-high SA vs low SA	-9.59	2.05	-13.61; -5.57	**<.001**	-11.92	2.12	-16.09; -7.75	**<.001**	-7.80	2.28	-12.31; -3.29	**0.005**
decreased-low SA vs increased SA	0.50	1.68	-2.80; 3.79	1.000	4.56	1.65	1.32; 7.80	**0.035**	7.29	1.89	3.54; 11.05	**0.001**
decreased-low SA vs low SA	-6.04	1.12	-8.24; -3.84	**<.001**	-5.47	1.13	-7.70; -3.25	**<.001**	-3.37	1.24	-5.82; -0.92	**0.045**
increased SA vs low SA	-6.54	1.43	-9.34; -3.74	**<.001**	-10.03	1.47	-12.92; -7.15	**<.001**	-10.66	1.53	-13.67; -7.65	**<.001**
Expressive deficits												
high ED vs decreased ED	-0.17	2.25	-4.58; 4.24	1.000	-1.88	2.32	-6.43; 2.68	1.000	-0.87	2.62	-6.10; 4.36	1.000
high ED vs Increased ED	1.13	2.33	-3.43; 5.69	1.000	-0.28	2.35	-4.90; 4.33	1.000	2.29	2.90	-3.51; 8.10	1.000
High ED vs low ED	-3.52	2.04	-7.53; 0.48	0.508	-5.28	2.09	-9.38; -1.17	0.071	-2.48	2.59	-7.70; 2.74	1.000
decreased ED vs Increased ED	1.30	1.72	-2.07; 4.67	1.000	1.59	1.82	-1.99; 5.18	1.000	3.16	1.96	-0.72; 7.03	0.655
decreased ED vs low ED	-3.35	1.21	-5.73; -0.97	**0.035**	-3.40	1.26	-5.88; -0.92	**0.044**	-1.62	1.36	-4.30; 1.07	1.000
Increased ED vs low ED	-4.65	1.44	-7.47; -1.83	**0.007**	-4.99	1.51	-7.96; -2.03	**0.006**	-4.77	1.62	-7.96; -1.58	**0.022**

Supplementary table 4: Pooled Type-III tests of fixed effects.

	Social Amotivation					Expressive Deficits				
Effect	Living situation	Work/study	GAF	SFS	WHOQOL-BREF	Living situation	Work/study	GAF	SFS	WHOQOL-BREF
	p-value	p-value	p-value	p-value	p-value	p-value	p-value	p-value	p-value	p-value
Gender	0.002	0.096	0.061	0.001	0.643	0.002	0.044	0.014	0.001	0.395
Duration of illness	<0.001	0.537	0.425	0.265	0.460	<0.001	0.609	0.215	0.113	0.318
Neurocognition	<0.001	0.001	<0.001	<0.001	0.043	<0.001	0.001	<0.001	<0.001	0.058
PANSS positive	0.008	<0.001	<0.001	<0.001	<0.001	0.019	<0.001	<0.001	<0.001	<0.001
Time	<0.001	0.066	0.001	<0.001	<0.001	<0.001	0.123	<0.001	<0.001	<0.001
SA groups	0.040	<0.001	<0.001	<0.001	<0.001	…	…	…	…	…
SA groups*time	0.053	**0.025**	**<0.001**	0.303	**0.001**	…	…	…	…	…
ED groups	…	…	…	…	…	0.001	0.005	<0.001	<0.001	<0.001
ED groups*time	…	…	…	…	…	0.170	0.236	**<0.001**	**0.030**	0.260

Part B: Statistical Analysis for Associations