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

Annemarie P.M. Stiekema [a,b,*], Md Atiqul Islam [c,d,e], Edith J. Liemburg [c,d,f,g], Stynke Castelein [c,g], Edwin R. van den Heuvel [h], Jaap van Weeghel [i,j], André Aleman [f,k], Richard Bruggeman [c,d], Lisette van der Meer [a,c], GROUP-investigators

[a] Department of Rehabilitation, Lentis Psychiatric Institute, Zuidlaren, The Netherlands
[b] School for Mental Health and Neuroscience, Faculty of Health, Medicine and Life Sciences, Maastricht University Medical Centre, Maastricht, The Netherlands
[c] University of Groningen, University Center for Psychiatry, University Medical Center Groningen, Groningen, The Netherlands
[d] University of Groningen, Rob Giel Research Center, University Medical Center Groningen, Groningen, The Netherlands
[e] Department of Statistics, Shahjalal University of Science and Technology, Sylhet 3114, Bangladesh
[f] University of Groningen, Department of Neuroscience, Groningen, University Medical Center Groningen, The Netherlands
[g] Research Department, Lentis Psychiatric Institute, Groningen, The Netherlands
[h] Department of Mathematics and Computer Science, Eindhoven University of Technology, Eindhoven, The Netherlands
[i] Parnassia Group, Dijk en Duin Mental Health Center, Castricum, The Netherlands
[j] Department of TRANZO, Tilburg School of Social and Behavioral Sciences, Tilburg University, The Netherlands
[k] Department of Clinical Psychology and Experimental Psychopathology, University of Groningen, Groningen, The Netherlands

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ABSTRACT

Background: The longitudinal course of the negative symptoms subdomains social amotivation (SA) and expressive deficits (ED) remains largely unknown. We investigated *i*) the longitudinal course of SA and ED subdomain scores, *ii*) whether subgroups based on the course of SA and ED subdomain scores could be identified, *iii*) whether baseline SA and ED subdomain scores were related to functioning and quality of life six years later and *iv*) the longitudinal relationship between subgroups and outcomes.
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: SA and ED subdomain scores decreased over time. Within both subdomains, four subgroups were identified: for both SA and ED a steady low course (±60%), increased (±15%) and decreased course (±15%). Within SA only, a higher level decreased course (±6%) and within ED only, a course with relatively stable high ED scores (±6%) was found. Lower symptom levels at baseline were related to better functioning (SA & ED) and quality of life (SA) at six years. Overall, low SA and low ED subgroups showed better outcomes than the other subgroups.
Conclusion: In many patients the course of negative symptoms is unstable and related to the course of outcome. Patients who do show steady low negative symptom levels (60%) may complicate the interpretation of treatment evaluation studies, as they may average out possible effects in subgroups with fluctuating symptom levels.

1. Introduction

Although positive symptoms are usually most dominant in the acute phase of psychotic disorder, 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, both pharmacological and psychosocial interventions only have a limited effect on reducing negative symptoms (Savill et al., 2014). The heterogeneous nature of negative symptoms makes them difficult to treat. Grouping negative symptoms into two subdomains can diminish this heterogeneity (Foussias et al., 2014b; Messinger et al., 2011). One possibility of grouping symptoms is distinguishing two subdomains on the basis of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987): social amotivation (SA) and expressive deficits (ED) (Liemburg et al., 2013; Stiekema et al., 2016). SA encompasses social and emotional withdrawal and reflects diminished interest in or affective commitment to the social environment. ED involves blunted affect, poverty of speech, and motor retardation. The robustness of such subdomains is illustrated by the finding that similar

* Corresponding author at: Department of Rehabilitation, Lentis Psychiatric Institute, Zuidlaren, The Netherlands.
E-mail address: annemarie.stiekema@maastrichtuniversity.nl (A.P.M. Stiekema).

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subdomains can be grouped based on the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983) even though the composition of both subdomains differs somewhat depending on the instrument that is used to assess symptoms (Foussias et al., 2014a; Liemburg et al., 2013; Stiekema et al., 2016). This difference most importantly concerns the allocation of the apathy item. When the PANSS is used, the factor structure appoints the "apathy item" to the ED subdomain (Liemburg et al., 2013; Stiekema et al., 2016). When the SANS (Andreasen, 1983) is used, the "apathy item" is appointed to SA (Foussias et al., 2014a).

SA is thought to be the result of a deficit in anticipating on pleasurable events and activities (Buck and Lysaker, 2013; Foussias et al., 2014b). ED reflects a diminished expressive responsiveness that is observed in verbal and non-verbal communication, caused by or related to, neurocognitive deficits (Bell et al., 2013; Ergül and Üçok, 2015; Hartmann-Riemer et al., 2015; Liemburg et al., 2013). There is ample evidence for a strong relationship between SA and global functioning (Fervaha et al., 2014b; Foussias et al., 2011; Rocca et al., 2014). The associations of ED with functioning were found to be less strong (Foussias et al., 2011; Galderisi et al., 2014; Strauss et al., 2013). 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 the ED and SA subdomains showed mixed results, varying from long-term stability of both domains (Galderisi et al., 2013), of the expressive but not the amotivation domain (Ergül and Üçok, 2015), and vice versa (Norman et al., 2015).

In the current study, we investigated the longitudinal course of SA and ED subdomain scores. Secondly, we examined whether subgroups with different longitudinal courses of SA and ED could be identified. Thirdly, we 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. Finally, we assessed the longitudinal relationship between subgroups and functioning and quality of life. Following up on 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. Between April 2004 and December 2013, participants were assessed at baseline and three and six years thereafter. Study procedures have been described in detail elsewhere (Korver et al., 2012).

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 ($n = 27$) leading to an inclusion of 1067 patients in the analysis (see Table 1 for demographic characteristics).

2.3. Assessment

Psychopathology in the past week was assessed with the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987). For each patient, SA (sum score of items N2, N4 and G16) and ED (sum score of items N1, N3, N6, G5, G7 and G13) subdomains scores were calculated at baseline (Liemburg et al., 2013). Global functioning in the past month 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). Both the PANSS and the GAF were assessed by a trained interviewer (research assistant, psychologist, psychiatrist, nurse or PhD student).

Social functioning at the moment of assessment 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.

Current living situation, employment and educational activities were assessed at each measurement as part of the demographical information. 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)), a self-report questionnaire based on the past two weeks, 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. Evaluation of missing data

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. Multiple imputation was applied to address missing data (due to absenteeism, attrition, or a failure to complete the questionnaire on time), since ignoring missing data may yield biases as it does not differentiate missing at random mechanism (Little and Rubin, 2002) (see S1 for details). For all analyses two-tailed tests, with $\alpha = 0.05$ were performed using Statistical Analysis System (SAS), version 9.4 (SAS Institute Inc., 2013).

2.4.2. Longitudinal course of SA and ED subdomain scores

The longitudinal course of SA and ED subdomain scores over time was assessed with a linear mixed model applied on imputed data, including only the fixed effect of time as a categorical independent variable. All analyses were conducted for SA subdomain scores and ED subdomain scores separately.

2.4.3. Identification of subgroups based on SA and ED subdomain scores

Subgroups within both SA and ED subdomains were identified with group-based trajectory modeling (GBTM), a semi-parametric statistical method for analyzing developmental trajectories (Jones et al., 2001; Niyonkuru et al., 2013) (See S2 for details). Clusters of patients following similar patterns based on the SA or ED subdomain scores will be referred to as SA or ED subgroups, respectively. Differences between the identified subgroups on 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.

2.4.4. Associations between subdomain scores and outcome at six years

To investigate the relationship between baseline SA and ED subdomain scores and functioning and quality of life six years later, multiple linear regression analysis was conducted on six year imputed GAF, SFS and WHO-QOL scores. Logistic regression was applied on

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