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ORIGINAL PAPER

Negative symptoms and their association with depressive symptoms in the long-term course of schizophrenia

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Abstract Depressive symptoms abound in schizophrenia and even in subclinical states of the disorder. We studied the frequency of these symptoms and their relationship to negative symptoms from the first psychotic episode on over a long-term course of 134 months on data for 107 patients in our ABC Schizophrenia Study. Prevalence rates of 90 % for presenting at least one negative symptom and of 60 % for presenting at least one depressive symptom in the first psychotic episode illustrate the frequency of these syndromes. After the remission of psychosis the rates fell to 50 % (negative symptoms) and 40 % (depressive symptoms) over a period of 5 years, remaining stable thereafter. After we broke the negative syndrome down into (SANS) subsyndromes, a positive association emerged between anhedonia and depressive symptoms and remained stable over the entire period studied. In contrast, the association between abulia and depression grew increasingly pronounced over the illness course. However, a more detailed look revealed this to be the case in female patients only, whereas male patients showed no such association of these symptom dimensions. We have no explanation at hand for this sex difference yet.

Keywords Schizophrenia · Depressive symptoms · Negative symptoms · Long-term course · Sex differences

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Introduction

Negative and depressive symptoms in the course of schizophrenia

Negative symptoms can occur at any stage in schizophrenia. They feature among the ten most frequent prodromal symptoms [1]. In 73 % of cases they first appear before the onset of positive symptoms and in 20 % of cases within the same month as positive symptoms [2, 3]. Depending on how negative symptoms are defined, 50–90 % of patients at first admission present them [1, 4, 5]. Along with the remission of the first illness episode and following the decrease in positive symptoms the prevalence of negative symptoms, too, falls to values ranging from 35 to 70 % [5, 6]. In the long-term course of schizophrenia, some 20–40 % of patients experience persistent negative symptoms [7–9].

Reports on the prevalence of depression in schizophrenia differ even more because of differences in how these symptoms are defined. In their review Bartels and Drake [10] estimate their prevalence at 20–70 % and Siris and Bench [11] in theirs at 6–75 %. In the ABC Schizophrenia Study the lifetime prevalence of 'depressive mood' at first admission was 84.9 % [1].

Depressive symptoms are among the earliest and most frequent signs of beginning schizophrenia [12–16]. The amount of depressive symptoms increases during the prodromal stage preceding psychosis onset [17–21] and decreases along with the remission of psychotic symptoms. Depressive symptoms have also been assumed to indicate an imminent onset of a psychotic relapse [22–25], but the findings on this are inconsistent. In the long-term course, too, moderate to distinct associations have been reported between depressive and psychotic symptoms [26].

Among the factors discussed as explaining depression in the course of schizophrenia are reactions to both exogenous stressful events and the traumatic experience of psychotic symptoms and immediate psychological and social consequences [27, 28]. Side effects of neuroleptic drugs [29, 30] and alcohol and drug abuse [31–33] are also assumed to cause depression in psychosis.

The association between negative and depressive symptoms

There is a long tradition of studying the association between positive and negative symptoms in schizophrenia [34, 35]. In contrast, the association between negative and depressive symptoms has not been investigated that much, and it has been done mostly on the basis of cross-sectional data [36–38]. Systematic investigations over longer histories of illness are lacking.

In a cross-sectional analysis of patients with schizophrenia spectrum disorder Majadas et al. [39] found a moderate correlation ($r = .54$) between a global measure of depression, based on the Calgary Depression Scale for Schizophrenics (CDSS) [40] and the Scale for the Assessment of Negative Symptoms (SANS) [41] total score. In contrast, Emsley et al. [42], who studied 177 patients of that same diagnosis, found the depression/anxiety score to be associated with the score for positive symptoms and not with the score for negative symptoms of the Positive and Negative Syndrome Scale (PANSS) [43]. Rabany et al. [38] found a low negative correlation between the total SANS score and the CDSS total score ($r = -.18$). In sum, the results are inconsistent [44–49].

Only modest insights have been gained by taking confounding variables into account. Rabany et al. [50] conducted a principal component analysis on CDSS data for 184 inpatients suffering from schizophrenia. The authors found two factors, which explained 57.3 % of the variance: 'depression-hopelessness' and 'guilty idea of reference'. Unlike the 'guilt' factor, the 'depression-hopelessness' factor showed a significantly inverse relationship with negative symptoms (PANSS negative score), but no relationship with positive symptoms. Examining 161 patients with schizophrenia, Maggini and Raballo [51] found, besides the two main factors 'depression/hopelessness' (I) and 'guilt' (II), a third factor consisting of a single feature, 'early wakening' (III). Factor I showed a highly significant positive correlation with the SANS global score for negative symptoms. Lancon et al. [47] found positive correlations between a CDSS-based depression score and both the PANSS positive score in patients who were in an acute phase of illness and the PANSS negative score in patients who were in a residual state.

Only rare studies have focused on sex differences. Müller [52] studied how depressive symptoms (measured by the CDSS) were associated with positive and negative symptoms (e.g. the PANSS), sociodemographic and treatment data in a sample of 77 male and 42 female patients diagnosed with acute schizophrenia according to the DSM-IV. While in female patients depression (CDSS global score) was significantly associated with negative symptoms (PANSS negative score) and younger age, no such association emerged in male patients.

The following analysis of the interrelationship between depressive and negative symptoms in the long-term course of schizophrenia follows up on our earlier analyses which focused primarily on the association between negative and positive symptoms in the long-term course of schizophrenia, but also explored the course of negative symptoms in relation to that of depressive and positive symptoms [1, 53].

Anyone studying these three key symptom dimensions of schizophrenia and their interrelatedness in cross section or longitudinally will be faced with the difficulty of operationalizing them by single symptoms. This circumstance was already reflected in the marked variation, depending on how these symptom dimensions are defined, in the ranges of the point- and the lifetime-prevalence rates of depressive [1, 10, 11] and negative syndromes [1, 4, 5] the systematic analyses and reviews cited report. For this reason, in our earlier analyses we had excluded all those single symptoms showing overlap, for example, between the negative and the depressive syndrome. From among the symptoms classified as belonging to the negative syndrome in the interview tool those analyses were based on, the IRAOS, the following symptoms were excluded: decreased talkativeness, poverty of content of speech, psychomotor inhibition, loss of affective reactivity, loss of drive, apathy, self-neglect, loss of pleasure and reduced sexual interest. As a result, only symptoms showing minimum overlap and sufficiently prevalent were considered as defining the syndromes studied, e.g. depressive mood, loss of self-confidence, excessive feelings of guilt and suicidal thoughts/attempts as the symptoms defining the depression dimension. All these symptoms selected on the basis of their specificity are assessed both in the IRAOS and in the PSE (see below the section "Assessment instruments").

To improve comparability with other studies on the topic our aim in the present study was to include all the symptoms from the CDSS, an internationally accepted instrument for measuring depressive symptoms in schizophrenia, and from the SANS, an instrument for assessing negative symptoms. This was achieved by performing the analyses on those symptoms only that are also contained in these two instruments. So included in the pool of symptoms the present analysis is based on are all the eight depressive symptoms from the IRAOS on the depression dimension and all

the 22 negative symptoms on the negative dimension. This approach naturally entails an increased risk of error. For example, the inclusion of the nine negative symptoms also frequent in depressive disorder among the symptoms of the depression syndrome will change the relative prevalences of these two syndromes. And this is just what happened: there was a slight increase in prevalence on the negative dimension and a slight decrease on the depression dimension.

Anyone exploring the association between negative and depressive symptoms in the long-term course of schizophrenia will also be faced with the following two problems: (1) due to the heterogeneous nature of both syndromes a simple quantitative association cannot be expected to emerge; (2) it is unclear whether the two syndromes are independent components of the illness course.

Given the heterogeneity of the syndromes, it does not seem promising to study their association on the basis of global scores for negative symptoms and depression. Hence, it is reasonable to start with an explorative analysis of their subsyndromes.

The tool most frequently used for assessing negative symptoms is the SANS. It is also considered the standard in terms of its psychometric properties. In a recent study Rabany et al. [38] identified four factors by means of principal component analysis (PCA). The factors tallied with the four SANS subscales: affective flattening, avolition-apathy, alogia and anhedonia-asociality. Only one item ('grooming and hygiene') loaded on the 'alogia' factor instead of the original 'abulia-apathy' subscale, and the item 'poor eye contact' loaded on none of the four factors. Although this result is not fully satisfactory and some analyses have failed to find similar agreement [54], it seemed to us reasonable, for a start, to base our analysis on the SANS subscales. The psychometric validation of the recently developed 'Clinical Assessment Interview for Negative Symptoms' (CAINS) [55, 56] has yielded two fairly independent factors: 'expression' and 'motivation/pleasure'. Unlike the SANS, however, this concept of measuring both anticipatory and actually experienced qualities is not applicable to the ABC data (see below).

The instrument best suited for measuring depression in schizophrenia has turned out to be the 'Calgary Depression Scale for Schizophrenics' (CDSS) [40]. In empirical analyses it has permitted depressive symptoms to be discriminated from negative symptoms more reliably than other instruments have [44, 57–59]. Using PCA Maggini and Raballo [51] identified three main factors in the CDSS: 'depression-hopelessness' (Factor I) and 'guilty idea of reference/pathological guilt' (Factor II). The third factor, 'early wakening', was represented only by one item. In a two-factor solution—'depression-hopelessness' and 'guilt'—Rabany et al. [50] found that the same items loaded on Factors I and II.

Materials and methods

Research strategy and objectives

In a first step we assessed the prevalence of global depressive and negative symptoms in schizophrenia over 134 months following first admission in the follow-up sample ($N = 107$) of the A(ge) B(eginning) C(ourse) Schizophrenia Study.

In a further step we compared the course of four negative subsyndromes—'affective flattening', 'alogia-paralogia', 'abulia-apathy' and 'anhedonia-asociality'—with the course of the depression dimension. Finally, we also explored how gender influences the association between affective and negative syndromes.

Study population

In the ABC Study the initial assessments started in 1987 and were completed in 1989. The final follow-up was commenced in 1999 and finished in 2002. The study sample comprised the consecutive first admissions of German-speaking persons with a diagnosis of schizophrenia in age range 12–59 years to one of ten mental hospitals serving a semi-rural, semi-urban population of about 1.5 million. The study population has been described in detail elsewhere [60].

In total, 232 persons or 84 % of the first-admission patients had not previously experienced any psychotic symptoms for more than 14 days (= first-episode sample). In total, 115 first-episode patients were interviewed not only at first admission and at 12-year follow-up, but also 6 months, 1, 2, 3 and 5 years after first admission.

At final follow-up (12.3 years after initial assessment; range 11.2–14.6) 107 patients could be interviewed. Twenty-four persons had died, 11 persons could not be traced, and 90 persons refused interview. A comparison of the follow-up cohort with the original sample revealed no significant differences in demographic and selected illness-related variables. Since the shortest period after which a final follow-up interview was conducted in the sample was 134 months, we right-censored, for the purpose of statistical analyses, the follow-up period accordingly, that is, limited it to 134 months for the entire sample [17].

The retrospectively collected IRAOS data on negative and depressive symptoms were validated on data for a subsample of 63 patients who had participated in all the follow-up assessments. The cross-sectionally established SANS and depression scores were used as reference values for the IRAOS data.

Assessment instruments

Negative and depressive symptoms were measured using the following assessment instruments: the IRAOS—'Interview for the Retrospective Assessment of the Onset of Schizophrenia'—and the SANS 'Scale for the Assessment of Negative Symptoms' [61]. The IRAOS was applied at initial assessment and final follow-up, the SANS at the intermediate assessment waves. The IRAOS was the main instrument used. Originally designed for studying beginning schizophrenia [60], it has been expanded for assessing the course of any type of psychosis [62, 63].

The following domains are included:

- Symptomatology—including unspecific symptoms, prodromal symptoms and deviant behaviour
- Psychological/social disability and functional impairment
- Social indicators
- Help-seeking behaviour (contacts with counselling and health services) and therapies

A key feature of the IRAOS is that it permits a retrospective assessment and description of all the domains listed by characteristics such as time of onset, type of course and duration.

Using the IRAOS and other available sources (medical files, doctor's notes, relatives), we retrospectively documented the occurrence of 126 signs, symptoms and social indicators concerning their onset, type of course and persistence. Data collection was designed so as to permit prevalences to be calculated and described for each relevant item on a monthly basis over the entire 134-month follow-up period starting at first admission.

Operationalizing negative symptoms and depression in the ABC study

Listed in Table 1a are the 22 IRAOS items classified as negative symptoms, as based on the SANS sections 'affective flattening' (AFF), 'alogia-paralogia' (ALO-PAR), 'abulia-apathy' (ABU-APA), 'anhedonia-asociality' (ANH-ASO) and 'attention'(ATT).

Due to the retrospective nature of the IRAOS interview, behavioural items based on observing the patient during the interview had to be left out, e.g. eye contact, increased latency in responding or measuring attention by a test. All the other domains, except one, are represented in the IRAOS with at least five items. The domain pertaining to 'attention' is represented by one item only and will thus be excluded from the analysis.

Table 1b gives the eight IRAOS symptoms classified as part of the depression syndrome and their CDSS item numbers. Most of these IRAOS depression items represent the main factors of the CDSS, 'depression and hopelessness', and one item represents the 'guilt' factor.

Results

Negative and depressive symptoms in the long-term course of schizophrenia

We assessed the prevalence of depressive and negative symptoms over 134 months following first admission in the follow-up sample ($N = 107$).

At first admission 92.5 % of the patients presented at least one negative symptom[1] (Fig. 1). The subsequent decrease was followed by a plateau some 5 years later, and that plateau persisted to the end of the follow-up period with prevalence rates ranging from 40 to 50 %.

The majority of the negative symptoms reported by the probands belong to the SANS subscales 'abulia' and 'anhedonia'. The subsyndromes 'affective flattening' and 'alogia' were far less prevalent, showing rates ranging from 5 to 10 % shortly after first inpatient treatment has been initiated.

The most prevalent depressive symptoms were those belonging to the 'depression and hopelessness' subsyndrome. 'Feelings of guilt' played a minor role with prevalence rates below 5 %. As with negative symptoms, the prevalence of the depressive syndrome, too, resulted in a plateau some 5 years after first admission, without showing any trend.

To simplify matters and due to the low prevalences, the SANS subscales 'affective flattening' and 'alogia' will be excluded from the following analyses.

Validating retrospectively collected data

The validity of the retrospectively collected IRAOS data was ascertained in an analysis based on data for those 63 patients of the ABC cohort for whom there were complete SANS data sets available from all the seven waves of assessment. We calculated two rates for negative symptoms: (1) the proportion of patients presenting at least one item from the SANS abulia, resp. anhedonia sections (attaining a score ≥ 2); (2) the proportion of patients with

[1] Given the approach applied here, i.e. negative items modelled on the SANS and its subscales, the results reported in the present paper in part differ slightly from those reported from our previous analyses of the ABC cohort. Those analyses have been based on the entire spectrum of negative symptoms or the core syndromes with minimum overlap with other syndromes including depression.

Table 1 IRAOS items for assessing, (a) negative symptoms and their SANS item numbers, (b) depressive symptoms and their CDSS item numbers

IRAOS		SANS
(a) Negative symptoms		
	Alogia and paralogia	
25	Decreased talkativeness	9
71	Thought blocking	11
109	Poverty of content of speech	10
	Affective flattening and loss of affective reactivity	
31	Psycho-motor inhibition	2
95	Affective flattening	1
96	Loss of affective reactivity	5
98	Incongruity of affect	6
112	Non-verbal communication	3, 4, 7
	Abulia-apathy	
12	Tiredness, loss of drive	16
102	Apathy	16
113	Self-neglect	14
115	Slowness in daily activities	16
119	Interest in household activities/family life	15
124	Work performance	15
125	Interest in getting a job	15
	Anhedonia-asociality	
11	Loss of pleasure	18
40	Reduced sexual interest	19
114	Leisure activities	18
120	Marital role/emotional relationship	20
121	Martial role/sexual relationship	19
123	heterosexual role behaviour	19
	Attention	
26	Loss of concentration	23
IRAOS		CDSS
(b) Depressive symptoms		
	Depression and hopelessness	
10	Depressive mood	1
13	Loss of self-confidence	3
14	Loss of self-esteem	3
16	Pessimism, hopelessness	2
17	Thoughts of death, suicidal thoughts	8
18	Suicide attempt	8
19	Feeling worst in the morning	6
	Feelings of guilt	
15	Feelings of guilt	4, 5

more severe symptoms (≥3). In Fig. 2 these two rates are compared with the rates based on the retrospectively gathered IRAOS data from the same symptom domain.

In the first months following first admission the SANS-based rates are lower than the IRAOS-based ones. A reason might be that the duration of individual symptoms was overestimated in the retrospective assessments of the early illness stage following first admission. As Fig. 2 shows, there is sufficient agreement between the retrospective and cross-sectional rates.

A comparable analysis of the validity of retrospectively collected data on depressive core symptoms in the ABC study cohort, which yielded satisfactory results, has been published elsewhere [17].

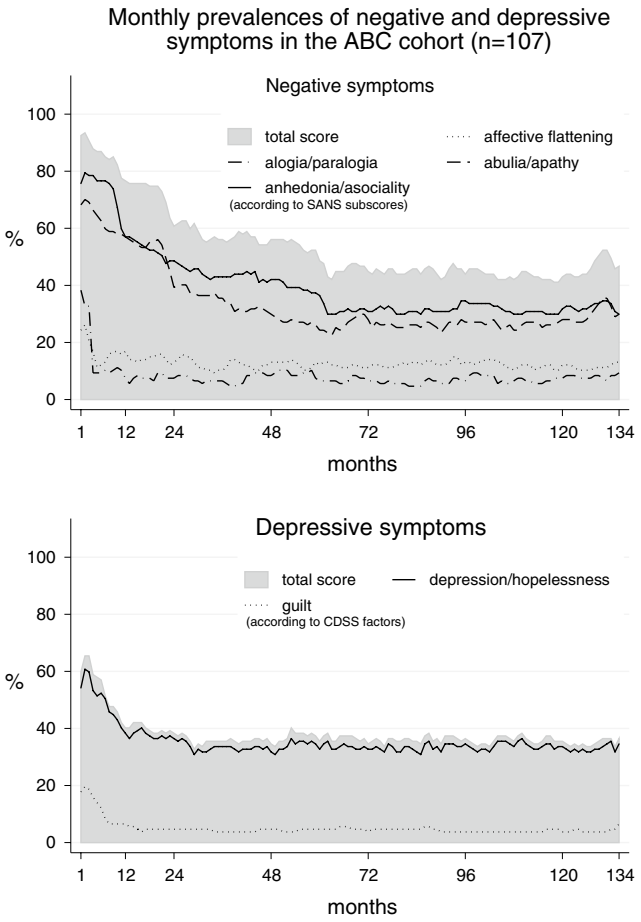

Fig. 1 Monthly prevalence of negative and depressive symptoms in the ABC cohort ($n = 107$)

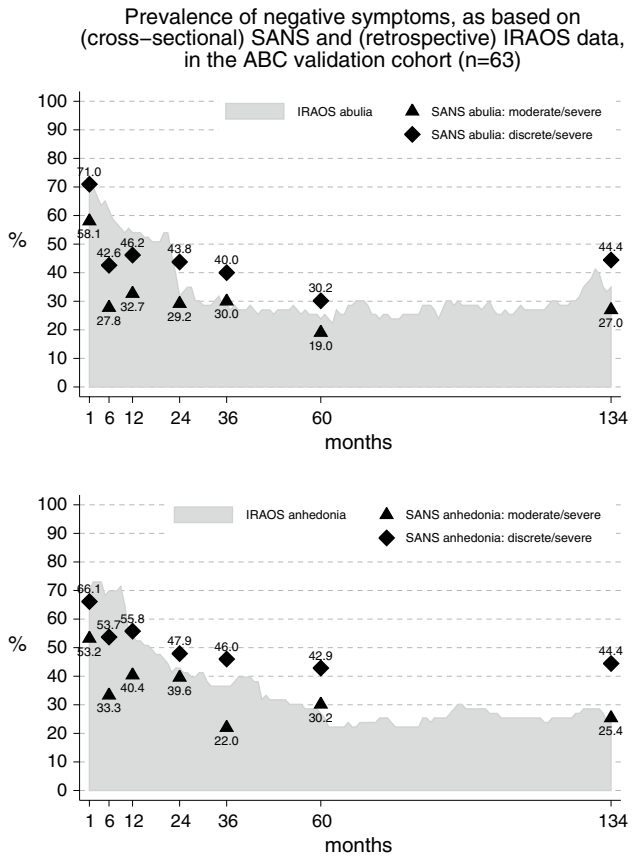

Fig. 2 Prevalence of negative symptoms, as based on (cross-sectional) SANS and (retrospective) IRAOS data, in the ABC validation cohort ($n = 63$)

Independence versus dependence of negative symptoms and depression in the course of schizophrenia

In a next step we tested associations between anhedonia and abulia on the one hand and depression on the other hand over the 134-month illness course. Since information on these symptoms was available for each patient per month as dichotomous data from the IRAOS interview, we chose the odds ratio as a measure of association. The odds ratio denotes the odds of a patient presenting a depressive symptom to also present a negative symptom. To control for multiple testing of dependent data, alpha error (type 1 error) was set at $p < .001$, which comes close to a Bonferroni correction.

As Fig. 3 shows, there is no clear-cut tendency in how closely depressive symptoms are associated with anhedonia over the illness course. The chances that patients presenting a depressive symptom also present an anhedonia item are elevated almost over the entire follow-up period. It exceeds the defined level of significance between months 95 and 120 ($p < .001$).

The relationship between abulia-apathy and depression is different. There is a steady increase, and the correlation becomes highly significant some 7–8 years after first admission. Patients presenting abulia-apathy have a fivefold to eightfold greater odds of also presenting depressive symptoms.

Sex differences in the prevalence of negative symptoms and depression

As we have been able to show in several cross-sectional and longitudinal analyses, there are no clear-cut sex differences in the prevalence and course of positive symptoms. Age at onset not considered, sex differences are to be found in the social course, illness behaviour and the consequences involved [3].

Following up on these findings, we studied how sex influences the frequency, course and mutual relationship of the symptom dimensions in question.

At rates of about 50 % the prevalence of negative symptoms in total did not differ between male and female patients over the long-term course of schizophrenia.

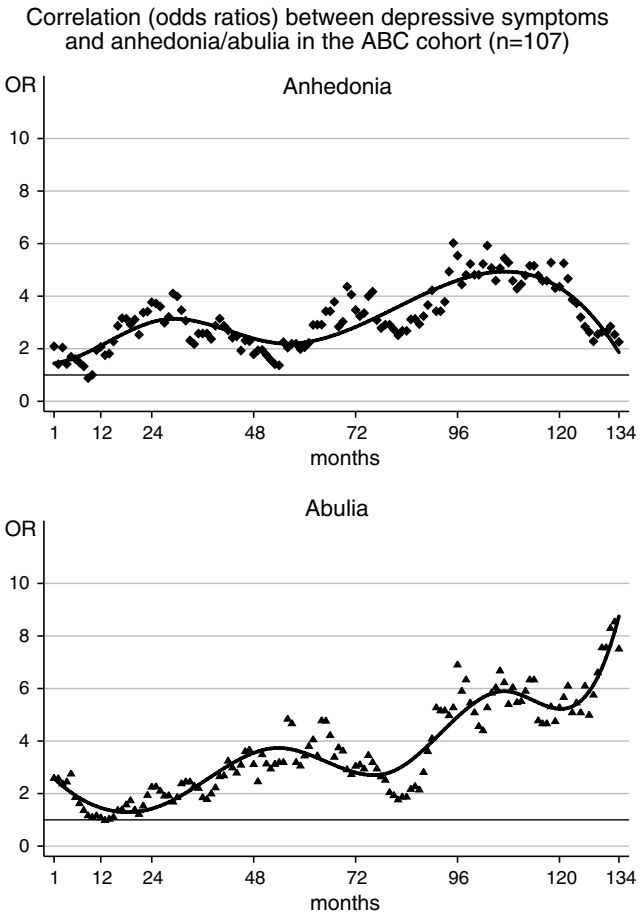

Fig. 3 Correlation between depressive symptoms and anhedonia/abulia in the ABC cohort ($n = 107$)

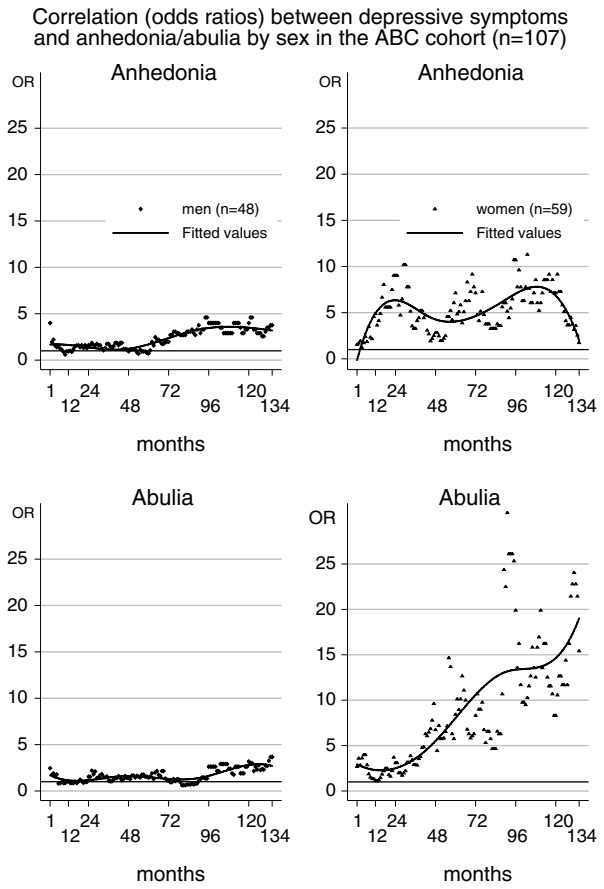

Fig. 4 Correlation between depressive symptoms and anhedonia/abulia by sex in the ABC cohort ($n = 107$)

However, the prevalences showed markedly different gradients of decrease for male and female patients: while the male rates fell over a course of 5 years before reaching a plateau, those for females did so only for about 24 months before exhibiting a plateau. This difference was not attributable to a greater frequency of negative symptoms in male patients, for the difference between the average number of negative episodes experienced by male (11.2) and female (12.1) patients over the observation period was negligible. But there was a highly significant sex difference in the mean duration of negative exacerbations: at 17.4 months it was over eight months shorter for female than for male patients (25.6 months).

Depression showed a different picture. In this category, too, there was a significant sex difference in the mean duration of exacerbations (men 25 months; women 17.2 months), but the mean number of exacerbations differed as well, with women experiencing 4.8 episodes and men 3.8. Due to these two factors the rate of depressive symptoms experienced by female patients over the illness course was some 10 % lower than that experienced by males (30 and 40 %, respectively). Introducing sex as a stratifying variable in the analysis of the association between depression and the subsyndromes 'anhedonia' and 'abulia' yielded a surprising result (Fig. 4):

All the significant associations between the syndromes 'abulia' and 'anhedonia' on the one hand and depression on the other were moderated by sex. Obviously, it was female patients, not male, who accounted for the associations found.

Discussion

Over 90 % of the ABC cohort presented symptoms of the negative syndrome at first admission. The corresponding figure for depression was 60 %.

The most interesting finding concerned the illness course: both syndromes became less prevalent during the first years of illness, reaching plateaus some 2–5 years after first admission, and the plateaus persisted until final follow-up. A further decrease in symptom prevalences could not be confirmed in our first-episode follow-up study. Our

findings indicate that the first 5 years following first admission lay the foundation for long-term course and outcome in schizophrenia. When interpreting the rates depicted in Fig. 1, it should be considered that first-admission patients are always acutely ill, thus presenting maximum symptom scores. This explains the fall in the mean symptom values after therapy has been initiated, and patients have reached a stage where acute episodes alternate with intervals. It should also be born in mind that symptom presentation varies considerably on an individual level over the long-term course of schizophrenia [64]. In the ABC cohort, too, the first 5 years after first admission were characterized by pronounced intra- and interindividual variation in the course of symptoms, whereas after that period considerably less variation occurred and symptom presentation grew intraindividually more stable.

Concerning the association between negative and depressive symptoms, the two negative syndromes in question showed different patterns: anhedonia items showed slightly elevated coincidence with depression items over the follow-up period without exhibiting any particular trend. In contrast, the association between items of abulia and depressive symptoms showed a steady increase over time. When sex was entered as a stratifying variable, that association turned out to be accounted for by female patients.

The results give rise to two essential questions: what explains the steady long-term increase in the association between abulia and depression starting some 5 years after first admission and why does this increase happen in female patients only?

Sex differences were visible in the types of course. Men experienced slightly fewer exacerbations featuring abulia than women did (3.2 and 3.7, respectively), but the mean duration of these exacerbations was significantly longer for men, 29 months, compared with 18.2 months for women from a total of 134 months. Hence, in the ABC cohort a male patient spent more days experiencing symptoms of abulia, a total of 92.8, than a female patient did (67.3 days). In contrast, the corresponding figures for anhedonia were almost identical for both sexes: 2.3 episodes with a mean duration of 35.3 months for males and 33.2 months for women.

We explored whether all symptoms or only some showed this sex difference. A look at the individual symptoms of the negative syndrome showed that not a single of them was significantly correlated with depression in male patients. In contrast, almost all the negative symptoms experienced by women were associated with depression. The trend of increase over time is primarily accounted for by 'tiredness' and 'self-neglect'. Hence, it can be concluded that depression and negative symptoms generally co-occur in women with schizophrenia.

There is only one other study known to us reporting an empirical association between depression, negative symptoms and sex. The authors [52] assume two factors to be responsible for this sex-specific difference: they refer to studies showing that females and males are different in expressing emotions and affective states. In addition to these characteristics, the authors assume negative and depressive symptoms are probably more difficult to tell apart in female patients. The other factor the authors cite is biological: accounting for the association between the two syndromes in women might be sex differences in functional and structural brain anomalies, for example in the morphology and connectivity of the orbitofrontal cortex, because there are signs indicating that these anomalies might be associated with negative symptoms in schizophrenia.

Provided that depressive and negative symptoms are more difficult to distinguish from one another in female patients, one would expect that women show a higher prevalence of depressive symptoms. In our cohort, however, the opposite was true: the monthly prevalence rates were about 10 % higher for men than women at 5-year and later follow-ups. Our study yielded no neurobiological data to explain the findings. We have no indication to offer of what might explain the time trend of the coincidence of abulia symptoms and depression in women. Nevertheless, we decided to publish these results to make them available to interested readers, who might come up with a creative approach to explaining them.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interests in relation to the subject of this study.

Ethical standards All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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