

## ORIGINAL PAPER

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**Deficit states in schizophrenia and their association with the length of illness and gender**

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**Abstract** The present study investigated the association between the frequency of deficit states (DS) and the length of illness and gender in schizophrenic patients. The following hypotheses were examined: 1) there is an association between the length of schizophrenic illness and the frequency of DS and 2) the frequency of DS in patients with comparable length of illness is higher in males than in females. Patients, included in the study, were consecutively hospitalized and diagnosed according to ICD-9 criteria (ICD-9: 295–295.9). Psychopathological assessment was performed in a standardized manner. Group differences were evaluated by using the t-test or the chi-square statistics. Variables with a possible impact on the occurrence of DS were entered into a backward multiple logistic regression model. 622 patients (total = 3914) were classified as having a DS. Logistic regression analysis revealed that the risk of having a DS was increased with a longer duration of illness (OR = 1.68) and was reduced for female gender (OR = 0.56). The findings are in line with the hypothesis that apart from a neurodevelopmental origin, the schizophrenic illness may also have a progressive neurodegenerative component, which clinically emerges as DS.

**Key words** schizophrenia · negative symptoms · deficit states · length of illness · gender

**Introduction**

After a certain period of schizophrenic illness, about one third of patients are so severely impaired that they are classified as suffering from a residual or deficit type of

schizophrenia, which is characterized by markedly expressed negative symptoms. Several studies have shown that there are a variety of differences between patients with marked negative symptoms and those without (Andreasen et al. 1982; Buchanan et al. 1990; Eaton et al. 1995; Kulhara et al. 1986). The present study focuses on the association between the frequency of marked negative symptoms in terms of deficit states and the length of illness, and on gender differences between schizophrenic patients with and without markedly expressed negative symptoms. The presented findings will be discussed in light of recent findings which propagate that some of the structural brain anomalies observed in schizophrenia may continue to progress after the onset of clinical illness in a subgroup of schizophrenic patients (Davis et al. 1998; DeLisi et al. 1997; Gut et al. 1998).

Concerning gender and brain abnormalities, many previous studies have shown that patients with markedly expressed negative symptoms were more likely to be of male gender (Angermeyer et al. 1990; Carpenter et al. 1988; Goldstein et al. 1988; Szymanski et al. 1995) and to have brain abnormalities (Davis et al. 1998; Johnstone et al. 1994; Pearlson et al. 1984; Williams et al. 1985). The reason for the better outcome in female patients compared to male patients with schizophrenia was mainly seen in a better premorbid functioning in females than in males (Salokangas et al. 1990). This is seen as a consequence of the later onset of the illness in females, which is explained by protective, antidopaminergic properties of estrogen (for review see Häfner et al. 1998). The observed brain abnormalities were most often regarded to be of a neurodevelopmental origin (Arnold, 1999; Henn et al. 1999; Weinberger, 1995) and to be a static indicator or predictor of a poor clinical outcome in schizophrenia. However, the recent findings that some of the structural brain abnormalities in schizophrenia are related to the length of illness, and that they progress after the onset of clinical illness, may hint at the possibility that, apart from its antecedents in neurodevelopment, there is also a progressive neurodegenerative

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component in schizophrenia, which could represent the organic basis of the observed worsening in clinical outcome in a subgroup of patients.

On this background, one would expect that the frequency of patients with marked negative symptoms in terms of deficit states will increase, the longer the duration of the schizophrenic illness. Although this expectation is supported by several studies (Harris et al. 1991; Hori et al. 1999; Kendler et al. 1985; Murphy et al. 1994) others failed to show this association (Kay et al. 1989; Montague et al. 1989; Ring et al. 1991). Apart from many other methodological differences between the various studies, two major reasons for these contradictory findings may be seen in differences in the length of illness of the assessed patients and in differences in the concept of negative symptoms, whereby most studies deal with a wide concept of negative symptoms and do not differentiate between primary and secondary negative symptoms. In view of these contradictory findings the aim of the present analyses of the data of a large sample of schizophrenic inpatients was to provide further evidence for the hypotheses that 1) there is an association between the length of schizophrenic illness and the frequency of deficit states and that 2) the frequency of deficit states in patients with comparable length of illness is higher in male than in female schizophrenic patients.

## Methods

The patients included in the study were schizophrenic inpatients from the Psychiatric Hospital of the Ludwig Maximilians University, Munich, who had been consecutively hospitalized during the period of 1980 until 1995. All patients were diagnosed according to ICD-9 criteria (ICD-9: 295–295.9).

The patients were judged to have a deficit state, if they had at least two of the following symptoms in an at least moderate expression at the time of discharge from their hospital stay: affective rigidity, blunted affect, alogia, lack of drive and social withdrawal. All these symptoms which indicate a deficit state were routinely assessed in a standardized manner. These symptoms are part of a larger psychopathological evaluation of the patients which was performed in a standardized manner by the doctors in charge of the patients, using the AMDP system at the time of admission and at discharge. The AMDP system is a comprehensive rating instrument which is based on traditional descriptive psychopathology and covers all psychopathological manifestations of functional psychoses (Bobon, 1983). Each item of the AMDP can be graduated on a four-point (0–3) scale. Pietzcker et al. (1983) extracted several psychopathological syndromes by using the principal component analysis of AMDP ratings. The analyses presented in this paper refer to the positive and depressive syndromes. The positive syndrome consists of the following items: delusional mood, delusional perception, sudden delusional ideas, delusional ideas, systematized delusions, delusional dynamics (this item means the extent to which the behavior of a person is influenced by delusional thinking), delusions of reference, delusions of persecution, verbal hallucinations, bodily hallucinations, depersonalization, thought withdrawal and other feelings of alien influence. The depressive syndrome consists of the items: depressed mood, hopelessness, inhibition of drive, rumination, feeling of loss of feeling, loss of vitality, feelings of insufficiency, feelings of guilt, worse mood in the morning, interrupted sleep, shortened sleep, early waking and decreased appetite. The summary scores of the corresponding syndrome items were calculated for statistical evaluations. Beside the

psychopathological symptoms, the AMDP also contains a section with somatic symptoms including extrapyramidal symptoms. For calculations in this study, the summary score of the following items was determined: rigor, tremor, acute dyskinesia, hypokinesia and akathisia. Additionally, the Global Assessment of Functioning (GAS) (Endicott et al. 1976) and a set of standardized sociodemographic data were routinely documented.

Statistical analyses were carried out using the SPSS 7.5 Software for Windows. Group differences for GAS ratings and psychopathological syndromes were compared by using the t-test. Group differences in frequencies of deficit states or male gender were evaluated using the chi-square statistics. Variables with a possible impact on the occurrence of deficit states were entered into a backward multiple logistic regression model. The Odds Ratio (OR) and its 95% confidence interval (CI) were calculated for each factor in the presence of the other. A p-value of < 0.05 (2-tailed) was considered statistically significant.

## Results

In total, 3914 hospitalized patients from the years 1980 to 1995 [2314 females (mean age at hospitalization =  $38.30 \pm 12.63$  years; mean age at the onset of illness =  $29.84 \pm 10.62$  years), 1600 males (mean age at hospitalization =  $31.84 \pm 10.15$  years; mean age at the onset of illness =  $25.04 \pm 8.23$  years)] with a diagnosis of schizophrenia according to ICD-9 criteria were entered into the analyses.

### ■ Validity of the performed categorization of patients in those with and without deficit states

Patients were assessed as having a deficit state if they had at least two of the following symptoms in an at least moderate expression at the time of discharge from their hospital stay: affective rigidity, blunted affect, alogia, lack of drive and social withdrawal. According to this categorization, 622 patients from a total of 3914 patients were classified as having a deficit state.

The validity of the performed categorization was proved by evaluating group differences in psychopathological (e.g., depressive symptoms) and extrapyramidal symptoms, both of which can cause secondary negative symptoms. Furthermore, group comparisons were performed concerning the GAS ratings and the negative syndrome, whereby the latter syndrome assesses a wider spectrum of negative symptoms (for item composition, see Material and methods) than the deficit state.

Regarding these group comparisons, one would expect that patients with deficit states would also have more expressed negative syndromes, which could not be mainly understood as a reaction to paranoid-hallucinatory, depressive or extrapyramidal symptoms. Furthermore, it could be hypothesized that patients with deficit states would have lower ratings in the Global Assessment of Functioning scale (GAS) at admission as well as at discharge. Because the GAS rating assesses a dimension which can be regarded as being more stable over time than, for example, acute manifestations of psychopathological symptoms, this finding may be of special rele-

**Table 1** Characteristics of deficit and non-deficit patients with different length of illness

Length (years)	Duration of illness since first manifestation (years)					
	0-4		5-9		10-14	
Deficit-states	Yes	No	Yes	No	Yes	No
Frequency	108 (9%)	1086 (91 %)	269 (17.2 %)	1297 (82.8 %)	104 (20.4 %)	406 (79.6 %)
Male (% of the total)	62.3**	41.9	56.2**	40.8	61.1**	32.8
Age (years)	28.41 ± 9.74*	30.93 ± 10.39	30.32 ± 9.00**	33.17 ± 10.10	39.35 ± 11.53 ns	40.27 ± 9.63
GAS						
at admission (mean ± SD)	30.73 ± 10.65*	34.31 ± 12.97	31.59 ± 9.49**	35.55 ± 12.74	32.37 ± 11.63*	36.52 ± 13.67
at discharge (mean ± SD)	43.87 ± 14.85**	63.03 ± 15.20	42.24 ± 12.62**	60.18 ± 15.04	44.32 ± 12.15**	60.28 ± 16.19
Negative syndrome						
at admission (mean ± SD)	12.98 ± 5.22**	7.41 ± 4.61	13.59 ± 4.73**	7.76 ± 13.58	13.02 ± 5.31**	7.53 ± 4.99
at discharge (mean ± SD)	10.14 ± 3.62**	1.99 ± 2.34	10.37 ± 3.51**	2.54 ± 2.59	10.03 ± 3.54**	2.55 ± 2.57
Paranoid-hallucinatory syndrome						
at admission (mean ± SD)	8.24 ± 7.02 ns	8.71 ± 6.40	7.41 ± 8.05 ns	8.05 ± 6.62	7.24 ± 6.92 ns	6.93 ± 6.58
at discharge (mean ± SD)	3.32 ± 5.34**	0.84 ± 2.33	3.38 ± 4.81**	1.41 ± 3.21	3.11 ± 4.51**	1.21 ± 2.77
Depressive syndrome						
at admission (mean ± SD)	4.46 ± 5.08 na	5.34 ± 4.83	4.23 ± 4.54*	4.83 ± 4.53	3.98 ± 4.22*	5.06 ± 4.55
at discharge (mean ± SD)	2.68 ± 3.62**	0.94 ± 1.80	1.86 ± 2.80**	0.89 ± 1.56	1.75 ± 2.63**	0.84 ± 1.59
Extrapyramidal syndrome						
at admission (mean ± SD)	0.39 ± 1.44 ns	0.176 ± 0.77	0.35 ± 1.29 ns	0.26 ± 0.99	0.41 ± 1.16 ns	0.29 ± 1.01
at discharge (mean ± SD)	0.31 ± 0.95 ns	0.17 ± 0.61	0.25 ± 0.67 ns	0.22 ± 0.67	0.44 ± 1.08*	0.18 ± 0.67

ns not significant; \* =  $p < 0.05$ ; \*\*  $p < 0.001$

**Table 2** Impact of different factors on the occurrence of deficit states

Factor	Coefficient	SE	P	OR	95 % CI
Length of illness	0.52	0.05	< 0.01	1.68	1.51–1.87
Gender (1 = male, 2 = female)	–0.58	0.10	< 0.01	0.56	0.46–0.67
Age	–0.03	0.01	< 0.01	0.97	0.96–0.98
Syndromes					
Depressive	0.19	0.02	< 0.01	1.20	1.16–1.25
Paranoid-hallucinatory	0.13	0.01	< 0.01	1.14	1.11–1.16
Extrapyramidal	0.12	0.06	0.03	1.13	1.01–1.26
Constant	–1.53	0.18	0.01		

SE Standard Error, P Two-tailed P values, OR Odds Ratio, CI Confidence Interval

vance for the evaluation of the validity of the performed categorization.

The results of the analyses mentioned above are shown in Table 1. They indicate that patients with deficit states had significantly lower GAS ratings at admission and at discharge. Furthermore, patients with deficit states had significantly more pronounced negative syndromes at the time of admission and at discharge. The depressive syndrome at admission was less pronounced in patients with deficit states; the paranoid-hallucinatory and extrapyramidal syndrome were equally pronounced in both groups of patients. This was true for all the time intervals which were analyzed. Thus, it seems improbable that the higher pronounced negative syndrome in patients with deficit states can be explained by more frequent secondary factors, influencing the negative syndrome. Although, the patients with a deficit state had more pronounced depressive and paranoid-hallucinatory syndromes at the time of discharge, the mean summary scores were rather low compared to those reached in the negative syndrome at discharge, and therefore do not indicate that these syndromes had a substantial impact on the negative symptom dimension in patients with deficit states at discharge. The extrapyramidal syndrome did not differ significantly between the groups. In summary, the reported results are in line with a sufficient validity of the performed categorization.

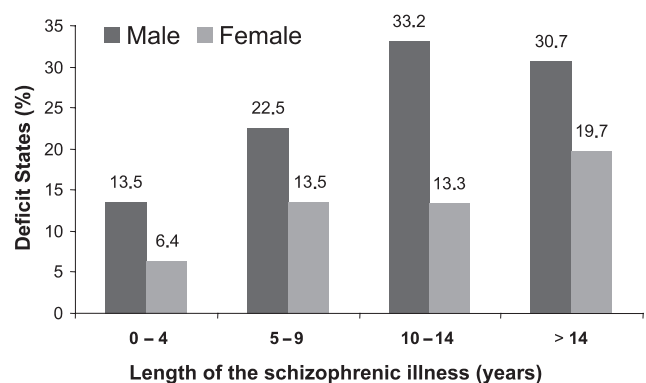
### ■ The impact of the length of schizophrenic illness and gender on the frequency of deficit states

In order to analyze the association between the length of illness (years since the first onset of illness) and the frequency of deficit states, two strategies were followed. As a first step the frequencies of patients with deficit states were determined for four different time intervals concerning the length of illness (see Table 1). These findings indicate that the frequency of deficit states was higher, the greater the length of illness was. To further evaluate the association between the length of illness and the occurrence of deficit states, a logistic regression analysis was performed, in which the following variables were entered simultaneously: length of illness, gender, age,

extrapyramidal, depressive and paranoid-hallucinatory symptoms at discharge. The results are presented in Table 2. The highest impact on the occurrence of deficit states was found for the length of illness and gender, whereby the risk of having a deficit state was significantly increased with a longer duration of illness (OR = 1.68) and was reduced for female gender (OR = 0.56). The variables age, extrapyramidal, depressive and paranoid-hallucinatory symptoms at discharge were also found to have a significant impact on the occurrence of deficit states. However, the odds of these variables were rather low compared to the odds for the length of illness and the gender. For illustration, the differences in frequencies of deficit states for each gender and time interval are presented in Fig. 1. All differences in frequencies between female and male patients were highly significant and indicate significant higher percentages of male patients with deficit states in each time interval.

## Discussion

The present analyses tested the hypothesis that the length of schizophrenic illness is associated with an increase of the frequency of deficit states. On the basis of the analysis of the data of a total sample of 3914 schizophrenic inpatients, this hypothesis was supported. This finding is in line with previous studies. Kendler et al.



**Fig. 1** Frequencies of deficit states in males (N = 1600) and females (N = 2314) with different lengths of schizophrenic illness

(1985;  $N = 139$ ; mean duration of illness = 25 years) reported that the proportion of patients with undifferentiated or residual types of schizophrenia increased with the length of follow-up. Harris et al. (1991;  $N$  (deficit) = 17, mean duration of illness = 19.5 years;  $N$  (nondeficit) = 20, mean duration of illness = 15.0 years) speculated that their finding of a larger proportion of deficit states in older schizophrenic patients (37%) compared to that in younger patients (15%) could be attributed to a longer duration of illness in the older subjects. Murphy et al. (1994;  $N = 169$ ; mean duration of illness = 19.9 years) found that the negative symptom factor was correlated positively with the duration of illness in 169 patients with familial schizophrenia. Because it has been reported that there is an association between negative symptoms and neuropsychological disturbances, the findings concerning an increase in neuropsychological disturbances after a longer duration of the schizophrenic illness also supports our results (Cuesta et al. 1998; Scully et al. 1997).

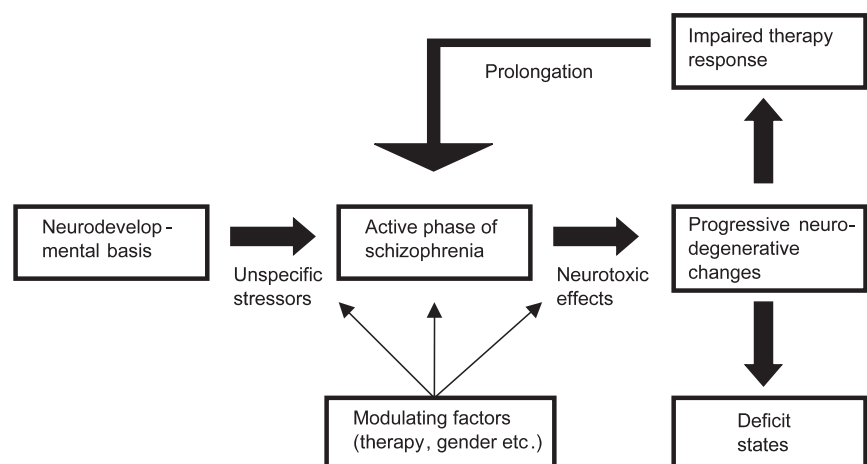
Conflicting results regarding the association between the length of illness and the expression of negative symptoms have been reported for example by Kay et al. (1989), Montague et al. (1989) or Ring et al. (1991).

Apart from differences in conceptualization of negative symptoms (e.g., wide or narrow concepts, distinguishing between primary and secondary negative symptoms) and other methodological differences, which could partially explain the different results of studies, the total duration of illness seems to be of special importance when investigating the association between the length of illness and negative symptoms. It seems quite evident that this association becomes more significant, the longer the duration of the illness. Considering this point, the mean duration of illness (2 years for 79 patients) may have been too short in the study by Montague et al. (1989). The same may be true for the study of Ring et al. (1991) and Kay et al. (1989), where in both studies the percentage of patients with more than 10 years was rather low.

A further question of the present analyses was whether there were gender differences in deficit states.

Gender differences in negative symptoms have been frequently reported (Carpenter et al. 1988; Shtasel et al. 1992). In the present analyses, it was shown that the correlation between the frequency of deficit states and the different length of illness was lower in female than in male schizophrenic patients. Also, the frequency of deficit states was significantly lower in the group of female patients compared to male patients, in each single time interval. A conclusive interpretation of the observation that female patients are less likely to have a deficit state is difficult, because the course and outcome of schizophrenic illness can be influenced by many factors. Most often, the better outcome of female compared to male schizophrenic patients is explained by a better premorbid functioning in females. A possible alternative explanation for this situation comes from the recently propagated hypothesis that apart from its antecedents in neurodevelopment, there are also progressive structural brain abnormalities at least in a subgroup of schizophrenic patients, and that the observed structural brain abnormalities were more pronounced in males than in females (Nasrallah et al. 1986; Lewine et al. 1990). Considering these points, one could hypothesize that the lower frequency of deficit states in female schizophrenic patients may be in part due to a slower progression and a lower severity of the observed structural brain abnormalities. With further regard for the finding that male and female patients with schizophrenia have the same pattern of structural brain abnormalities, which however appear to manifest with greater severity in male than in female patients (Nopoulos et al. 1997), it seems improbable that the postulated neurotoxic effects during the active phase of schizophrenia, leading to progressing structural brain changes (DeLisi et al. 1997; Lieberman, 1993; Lieberman et al. 1996; Loebel et al. 1992) are totally different in male and female patients. On the contrary, it may be more plausible that the same neurotoxic effects are gender specifically modulated by additional, protective or harmful factors (Bottlender et al. 1999), which then leads to different manifestations in terms of the severity of the observed organic and clinical disturbances. A model which illustrates these postu-

**Fig. 2** Association between the neurodevelopmental basis, the active phase of schizophrenia and the development of progressive neurodegenerative changes, therapy response and deficit states in schizophrenia



lated mechanisms is shown in Fig. 2. This model tries to integrate the hypothesis that schizophrenia has its antecedents in neurodevelopmental disturbances and the findings that the observed structural brain abnormalities may be progressive, at least in a subgroup of schizophrenic patients. However, it is not yet known whether this neurodegenerative component reflects just an epiphenomenon or reaction of the brain to a chronic process of the illness, or whether it is an integral part of the illness process itself. In conclusion, the present study provides further evidence that the frequency of marked negative symptoms in terms of deficit states increases over the time. This increase is more prominent in male schizophrenic patients than in female schizophrenic patients, and may go hand-in-hand with an increase of structural brain abnormalities during a longer duration of the illness. The observed differences in gender may hint at the existence of gender specific factors which differently modulate the process of the schizophrenic illness.

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