Subtle minor motor and sensory deficits or neurological soft signs (NSS) are frequently found in patients with schizophrenia. Neurological soft signs encompass a variety of deficits, in particular impairments in sensory integration, motor coordination, or repetitive movements, and are associated with increased genetic liability, poor premorbid adjustment, early onset of the disease, and poor prognosis.

It is generally accepted that NSS antedate the onset of schizophrenia in some cases, but little is known about their course after the illness has manifested itself. Four studies have shown NSS vary during the course of the disorder, with higher scores in the acute active psychotic states than after remission of acute symptoms, both during single episodes and during a 3-year period. This finding corresponds with the significant correlations found between NSS and doses of neuroleptic medication and/or extrapyramidal side effects. However, these findings were not replicated by others. Moreover, increased NSS scores were also found in neuroleptic-naive patients with schizophrenia.

Methodological differences may account for some of these discrepancies. Neurological soft signs are a heterogeneous phenomenon that may be defined in various ways. This is of primary relevance to the potential impact of treatment with conventional neuroleptics because extrapyramidal side effects apparently influence motor NSS more than sensory NSS. Heterogeneity of schizophrenia itself is an additional potential confounding variable. The majority of studies investigated patients with multiple episodes; only some authors focused on first-episode, drug-naive patients. Psychopathological symptoms are highly variable in the acute phase of the disease. Because this phenomenon is likely to interfere with NSS scores in cross-sectional assessments, it should be carefully controlled for. Moreover, extrapyramidal side effects vary considerably among the available neuroleptics.

The following findings are from studies conducted by our Heidelberg group, with respect to the following hypotheses: (1) only minor associations between NSS and measures of neuroleptic motor side effects exist; and (2) NSS, poor treatment response, and motor side effects reflect different dimensions of the pathophysiology of chronic schizophrenia.

**Clinical Studies**

**NSS in the Clinical Course of Acute Psychotic Episodes**

Neurological soft signs were investigated in the clinical course of 50 patients with schizophrenia on admission, on day 7 of treatment, and after remission of the acute illness. The Heidelberg Scale was used to assess NSS; in addition, psychopathological symptoms and extrapyramidal side effects were rated with the Brief Psychiatric Rating Scale and the Simpson-Angus scale, respectively.

Neurological soft signs showed a pronounced decrease as the acute clinical condition improved. The highest scores were obtained after admission, ie, in the most acute psychotic condition. By day 7 of neuroleptic treatment, NSS scores showed a considerable reduction that continued into the remission phase of the acute illness. At all sampled points, NSS scores were higher in the chronically ill than in those patients with a remitting course (Table 1).

Consistent with these findings, NSS scores were significantly correlated with...
psychopathological symptoms, in particular Brief Psychiatric Rating Scale anergia, thought disorders, and activity, but not with extrapyramidal side effects. Moreover, NSS scores showed no difference between patients receiving clozapine and those receiving conventional neuroleptics.26

Similar results were obtained in a second independent study13 involving 50 patients with schizophrenia, of whom 36 underwent follow-up from admission to discharge. Again, NSS significantly decreased with remission of acute symptoms under neuroleptic treatment and were significantly correlated with psychopathological symptoms.

**Motor NSS and Extrapyramidal Side Effects in Subacute Patients**

For this multicenter trial, the Brief Motor Scale was developed for the assessment of motor NSS.15,27 A total of 82 patients with DSM-III-R schizophrenia were recruited in three participating centers. To minimize potential fluctuations of psychopathological symptoms and to ensure stable medication, patients were examined in the subacute state, twice at an interval average of 14 days. Extrapyramidal side effects were rated on an abbreviated version of the Simpson-Angus Scale with the item “salivation” excluded.

Neurological soft signs again correlated significantly with severity of illness, lower social functioning, and negative symptoms. Modest, but significant correlations ($r_s = .38; P = .001$) were found between NSS and extrapyramidal side effects. However, neither neuroleptic dose nor scores for tardive dyskinesia and akathisia correlated significantly with NSS.

Neurological soft sign scores were compared between patients receiving clozapine monotherapy ($n = 33$) and those on conventional neuroleptics ($n = 45$). Neurological soft sign scores obtained in both groups were almost identical, although the clozapine patients displayed significantly less extrapyramidal symptoms. Patients whose psychopathological symptoms remained stable or improved in the clinical course showed a significant reduction of NSS scores. This finding did not apply for those patients whose psychopathological symptoms deteriorated. These observations demonstrate NSS in schizophrenia are relatively independent of neuroleptic side effects, but are associated with severity and persistence of psychopathological symptoms and poor social functioning.

**NSS, Extrapyramidal Side Effects and D2 Receptor Occupancy**

Neuroimaging studies have demonstrated an association between D2 receptor occupancy under treatment with a conventional neuroleptic and extrapyramidal side effects. This association has been replicated and may represent one important mechanism for the development of extrapyramidal side effects. In order to further differentiate NSS from extrapyramidal side effects, we investigated both NSS and extrapyramidal side effects with respect to potential changes of the binding site

<table>
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<tr>
<th>TABLE 1</th>
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<td><strong>Mean (± SD) NSS Scores in the Course of Acute Episodes in Schizophrenia (N = 50)</strong></td>
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<tr>
<td><strong>NSS Score</strong></td>
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<tr>
<td><strong>Clinical Course</strong></td>
</tr>
<tr>
<td>Remitting ($n = 23$)</td>
</tr>
<tr>
<td>Chronic ($n = 27$)</td>
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</table>

$^*$significant difference between remitting and chronic group, $P < .05$.

$^1$significant difference between remitting and chronic group, $P < .001$.


<table>
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<th>TABLE 2</th>
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<tr>
<td><strong>Clinical Characteristics of Schizophrenic Patients</strong></td>
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<tr>
<td><strong>Psychopathology</strong></td>
</tr>
<tr>
<td><strong>Quality of Clinical Response</strong></td>
</tr>
<tr>
<td>Good ($n = 8$)</td>
</tr>
<tr>
<td>Poor ($n = 7$)</td>
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</tbody>
</table>

$^*measured with the Brief Psychiatric Rating Scale.

$^1measured with the Brief Motor Scale.

$^2measured with the Simpson-Angus Scale.

$^3measured during drug-naive state.

$^4measured after neuroleptic treatment.

NSS = neurologic soft signs; EPS = extrapyramidal side effects.

of conventional neuroleptics (ie, the D2 dopamine receptor).14 Fifteen neuroleptic-naive patients with DSM-III-R schizophrenia participated in the study. D2 dopamine receptors were investigated in the drug-dose state and 3 days after completion of a standardized neuroleptic treatment regimen (benperidol 12-16 mg/d combined with the anticholinergic biperiden for 25 days) using single-photon emission computed tomography. Except for a much shorter half life (4 – 6 hours) and a higher neuroleptic potency, benperidol has similar pharmacological properties to haloperidol. Single-photon emission computed tomographic scans were obtained 2 hours after intravenous injection of 185 MBq 123I-IBZM. For analysis, basal ganglia to frontal cortex ratios were calculated and the patient sample was subgrouped into patients with a favorable versus a poor treatment response.

As expected, neuroleptic treatment led to a significant decrease of NSS but a significant increase of scores for extrapyramidal side effects (Table 2). With respect to the D2 dopamine receptor system, basal ganglia to frontal cortex ratios decreased in patients with a favorable response, but increased in the poor responders (Figure). Changes of basal ganglia to frontal cortex ratios were significantly correlated with extrapyramidal side effects but not with NSS.

These findings indicate the decrease of NSS scores under neuroleptic treatment also applies to neuroleptic-naive patients. Extrapyramidal side effects were correlated to D2 dopamine receptor upregulation, which also was associated with a poor treatment response.

**DISCUSSION**

Results from these studies indicate NSS are more closely associated with the core features of schizophrenia rather than with extrapyramidal side effects. In addition, NSS, poor treatment response, and motor side effects may at least partly represent different dimensions in the pathophysiology of chronic schizophrenia.

Clinical studies of acute episodes clearly indicate NSS are closely correlated with psychopathological symptoms in general, and with thought disor-

![Basal Ganglia to Frontal Cortex Ratio](image)

<table>
<thead>
<tr>
<th>Basal Ganglia to Frontal Cortex Ratio</th>
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<tbody>
<tr>
<td>2.4</td>
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<td>2.2</td>
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<td>2.0</td>
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<tr>
<td>1.8</td>
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<td>1.6</td>
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<tr>
<td><strong>Drug-Naive</strong></td>
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<tr>
<td><strong>After Therapy</strong></td>
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<td><strong>Good response</strong></td>
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<td><strong>Poor response</strong></td>
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which only minor psychopathological changes occur.27 Despite these findings, it must be emphasized that in each of the studies described above, even the decreased NSS scores exceeded (on the average) the values measured in healthy controls.

The studies of NSS in acute psychotic episodes did not reveal significant associations between NSS and extrapyramidal side effects. One possible explanation is that neuroleptic therapy was not standardized in these studies. However, similar results were obtained in neuroleptic-naive patients receiving standardized therapy; moreover, comparison of NSS in patients receiving clozapine with those receiving conventional neuroleptics revealed only minor, nonsignificant differences. Another even more important concern is the heterogeneity of NSS. Because NSS include motor and sensory deficits, analyses of sum scores may blur the potential impact of extrapyramidal side effects on motor signs. From a clinical standpoint, at least some of the signs subsummarized as extrapyramidal side effects tend to develop after a longer duration of treat-

To address these questions, we investigated motor NSS and extrapyramidal side effects in a larger sample of patients in a subacute phase of the disease.27 We found a significant correlation between motor NSS and the degree of parkinsonism (as rated on an abbreviated version of the Simpson-Angus scale) but not akathisia nor tardive dyskinesia. The neuroleptic dose prescribed was not significantly correlated with NSS. Moreover, NSS scores showed only minor,
nonsignificant differences between patients taking clozapine and those taking conventional neuroleptics, although the former showed significantly less extrapyramidal side effects. When psychopathological symptom level was partialled out, the correlation between NSS and parkinsonism decreased to some extent, while adjusting for the level of extrapyramidal side effects when calculating correlations between psychopathology and NSS had far smaller effects. Taken together, these findings point to a closer association between NSS and psychopathology than between these signs and neuroleptic side effects. In contrast, other studies reported substantial correlations between NSS and neuroleptic side effects, such as parkinsonian symptoms, akathisia, or tardive dyskinesia. It is possible methodological differences may account for this discrepancy. Both patients with remitting and chronic schizophrenia were included in these cross-sectional studies. This is of particular importance as neuroleptic side effects and NSS are more pronounced in patients with a chronic than in those with a remitting course of the disorder. Hence, in a cross-sectional study, significant correlations between both parameters may occur.

Long-term follow-up studies of patients may help overcome these methodological limitations. Based on the hypothesis that NSS decrease with remission of psychopathological symptoms, one may expect NSS to vary with outcome of the disease; patients with unfavorable, chronic courses should show higher NSS scores than those with a more favorable, remitting course. Moreover, NSS scores in both groups should exceed scores obtained in the controls at any time of measurement since NSS also refer to genetic liability.

Another strategy to distinguish NSS from extrapyramidal side effects is to investigate both phenomena with respect to their potential underlying pathophysiological mechanisms. Little is known on the pathomechanism of NSS. In contrast, D2 dopamine receptor blockade in the basal ganglia by (conventional) neuroleptics is generally accepted to be among the most important factors in the pathogenesis of extrapyramidal side effects. We therefore investigated both NSS and extrapyramidal side effects, with respect to D2 receptor binding, under a conventional neuroleptic treatment in neuroleptic-naïve patients using single-photon emission computed tomography. Results of this study demonstrated a dissociation in decreasing NSS but increasing scores for extrapyramidal side effects in drug-naïve patients. Moreover, upregulation of striatal dopamine D2 receptors correlated significantly with scores for parkinsonian side effects but not with NSS. That NSS do not relate to basal ganglia changes is further supported by Rubin et al. In contrast, NSS refer to changes in different cerebral sites, such as the sensorimotor cortex and the cerebellum.

Taken together, these findings demonstrate NSS are not attributable to extrapyramidal side effects of conventional neuroleptics. As indicated by the significant correlations with psychopathological symptoms (ie, thought disorders and negative symptoms) and predictors of poor prognosis (ie, premorbid adaptation or early onset), NSS correspond instead with acuity and chronicity of the disease process. The hypothesis that NSS, poor treatment response, and motor side effects represent different aspects of chronicity of schizophrenia is indirectly supported by the observation that extrapyramidal signs can be observed in patients who have never been medicated.

**CONCLUSION**

These studies provide evidence for a significant association between NSS and psychopathological symptoms in schizophrenia and demonstrate NSS scores decrease with clinical improvement. This effect also applies in subacute cases after remission of acute symptoms. Convincing evidence NSS may be related to parkinsonian side effects was found in a study on motor NSS that involved a large sample of subacute patients. Even in this study, NSS decreased in patients with a more favorable course regardless of the form of antipsychotic treatment. Moreover, D2 dopamine receptor occupancy — the putative cause of extrapyramidal side effects — was not correlated with NSS. Neurological soft signs and extrapyramidal side effect vulnerability may represent different dimensions in the pathophysiology of chronic schizophrenia that may co-occur in the individual patient.

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