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Neurological Soft Signs in First-Episode Schizophrenia

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Key Words: Schizophrenia • First episode • Neurological soft signs

Learning Objectives:

Clinicians will learn about the characteristics of neurological soft signs in first-episode schizophrenia, their associations with the clinical characteristics of the disease—in particular: psychopathological symptoms, genetic liability, and outcome—and their potential importance in clinical practice.

Abstract:

Neurological soft signs (NSS) refer to subtle neurological abnormalities comprising deficits in sensory integration, motor coordination, or sequencing of complex motor acts. It is generally accepted that NSS are more prevalent in schizophrenia patients, including first-episode cases, than in healthy subjects. Moreover, NSS have been consistently demonstrated in neuroleptic naïve first-episode patients; thus, they are thought to be an intrinsic feature of schizophrenia. This notion is underlined by the increased NSS scores in high-risk subjects, such as relatives of schizophrenic patients, and in the unaffected co-twins of monozygotic twin pairs discordant for schizophrenia. However, recent studies clearly demonstrate that NSS are not a static feature of the disease, but rather vary in the clinical course of the disorder. This variation with psychopathological symptoms was first established in the short-term course with the remission of acute symptoms under neuroleptic treatment, but also applied to the long-term course over a follow-up period of up to 5 years. In conclusion, NSS correspond to both genetic liability and the activity of the disease process; future studies in this field may not only enhance our understanding of schizophrenia, but may also establish NSS as one of the clinical predictors of outcome.

Editor's Note

Neurologic soft signs or NSS have been observed and studied in schizophrenia since the 19th century. Although common, the etiology and clinical value of NSS has remained obscure. In this lesson the author reviews the studies to date with an emphasis on the more recent longitudinal studies that have utilized brain imaging technology. This lesson synthesizes the literature with a focus on the clinical relevance of NSS in the treatment of patients with schizophrenia. As such an understanding of NSS holds promise for future clinical applications in the field of schizophrenia. —*P.H.*

Introduction

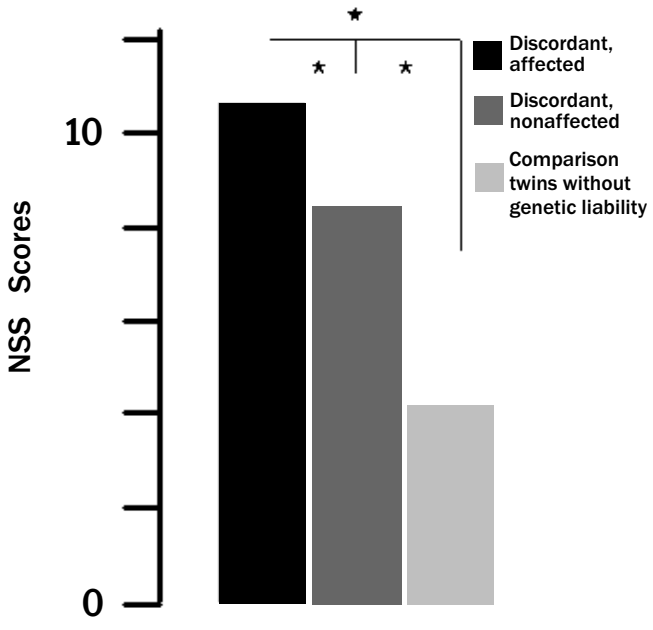
Minor neurological deficits or *neurological soft signs* (NSS) are among the best established biological findings in schizophrenia, and refer to subtle neurological abnormalities comprising deficits in sensory integration, motor coordination, and sequencing of complex motor acts.[1,2] It is generally accepted that NSS are more prevalent in patients with schizophrenia, including first episode cases, than in healthy subjects.[2] Increased NSS scores have also been demonstrated in neuroleptic naïve first-episode patients, indicating that NSS are present prior to medication exposure; thus, they are conceptualized to be inherent to schizophrenia.[3] Moreover, NSS and spontaneous abnormal involuntary movements in schizophrenic patients had already been observed in the preneuroleptic era, and are also typically found in the prodromal phase before the manifestation of psychotic symptoms, or in high-risk subjects such as relatives of schizophrenic patients (Figure 1).[4] **In general, these studies indicate that high-risk subjects take an intermediate position between healthy and schizophrenic subjects. Whereas NSS can be reliably demonstrated in clinical examination, it is generally accepted that the respective signs can hardly be used for topological diagnosis, as emphasized by the suffix 'soft.'**

NSS are closely associated with psychopathological symptoms, in particular negative symptoms and formal thought disorders.[5] This corresponds to earlier findings of our group,[2,6] which demonstrated a significant decrease of NSS paralleling the remission of symptoms under neuroleptic treatment in the short and medium-term course of the disease.

The dysfunctional networks involved in the pathogenesis of NSS are not fully understood to date. Neuroimaging studies have revealed changes in the sensorimotor cortex and the supplementary motor area, the basal ganglia and thalamus, and the cerebellum.[7-9] Although these changes and the interconnections of the respective cerebral sites have not yet been investigated during the clinical course, they conform with the hypothesis that NSS involve deficient

Figure 1

Neurological Soft Sign Scores in Affected and Nonaffected Monozygotic Twins Discordant for Schizophrenia and in Comparison Twins



(*p>0.05; from Niethammer et al., 2000)

frontal thalamic cerebellar pathways as conceptualized in the model of "cognitive dysmetria."[10]

NSS were first described as early as the 19th century. In the 8th edition of his textbook, Kraepelin, for example, quoted Dufour who referred to dysdiadochokinesis, as a signs corresponding to a "cerebellar subtype of dementia praecox."[11] However, systematic research did not begin until the mid 20th century. This delay can be attributed to a variety of factors, most importantly the general assumption that motor symptoms in schizophrenia should either refer to catatonia in a minority or to extrapyramidal side effects of neuroleptic therapy in most cases. In this environment, the American psychologist Meehl played an important role in fostering and stimulating clinical research. To introduce the reader into the field, he quoted his clinical supervisor who advised him during his own clinical education:[12]

> *"As to the "soft neurology" of schizophrenia, I recall vividly a case conference when the psychiatry department head, J. Charnley McKinley, MD, PhD, an old-style "neuropsychiatrist" who always did at least a basic neurologie examination on psychiatric patients, elicited a fairly striking dysdiadocho-kinesia with no other signs of neurologic disease in a patient who was clinically and psychometrically an obvious schizophrene. McKinley warned the medical students that they should be careful not to jump to the conclusion, when somebody had a plus/minus dysdiadochokinesia, or past pointing, or even a positive Romberg sign, that there was neurologie disease in the cerebellum or dorsal columns. He said that for some unknown reason, a sizable minority of schizophrenes showed these kinds of phenomena."* [p. 936]

Along these lines, NSS can complicate the recognition and differential diagnosis of schizophrenia and other neuropsychiatric diseases, in particular when diagnosis is not yet established in first-episode cases. This notion also applies to subjects with an increased susceptibility to the disease. The present lesson will therefore review the more recent studies on NSS in first-episode schizophrenia, and discuss signs with respect to the clinical course and underlying cerebral changes.

Cross Sectional Studies

A selection of representative cross-sectional studies on NSS in first-episode schizophrenia is summarized in Table 1A. The studies have been published in the last eight years and were identified in the databases PubMed and PsycINFO under the key words "neurological soft signs", "NSS," and "schizophrenia" Among the studies, sample size varied between 18 and 242 patients. The majority of the studies focused on schizophrenic disorders—i.e., schizophreniform psychosis, schizoaffective disorder, brief psychosis and psychotic disorder not otherwise specified. Patients with other psychiatric diseases—delusional disorder, bipolar disorder, major depressive disorder and drug induced psychosis—were only included in 4 studies. The majority of studies compared psychotic patients with healthy controls; some authors also included patients with psychiatric diseases other than schizophrenia to evaluate the specificity of their findings. Although the psychometric instruments used varied widely, most authors confirmed the clinical diagnosis by using standardized instruments such as the *Structured Clinical Interview for DSM-IV* (SCID)[13] or the *Schedules for Clinical Assessment*[14] (SCAN), and documented psychopathological symptoms on the *Positive and Negative Syndrome Scale* (PANSS).[15]

NSS were assessed on the *Neurological Evaluation Scale* (NES),[16] the *Condensed Neurological Examination* (CNE),[17] the *Cambridge Neurological Inventory* (CNI)[18] and the *Heidelberg NSS Scale* (Table 2).[2] Potential neuroleptic side effects were rated on the *Simpson Angus Rating Scale,*[19] the *Barnes Rating Scale for Drug Induced Akathisia*

Table 1A

Recent Cross Sectional Studies of NSS in First-episode Schizophrenia

Study	NSS Scales & Psychometric Instruments	Subjects	Results
Dazzan et al., (2004)[8]	*Neurological Evaluation Scale* (NES), Magnetic resonance imaging (MRI) analyzed by voxel based morphometry	77 patients with psychotic disorders5	NSS associated with reduced gray matter density values in the left putamen, left middle temporal gyrus, right precentral gyrus, right middle temporal gyrus; and, bilaterally, lenticular nucleus, thalamus and pulvinar, and lingual gyrus. In addition, reduced white matter density values in the left internal capsula were also associated with increased NSS scores.
Bottmer et al., (2005)[35]	*Heidelberg NSS Scale*	37 psychotic patients (20 schizophrenia, 14 schizophreniform disorder, 2 schizoaffective disorder, 1 psychotic disorder not otherwise specified (DSM-IV)) 18 healthy controls	Patients with schizophrenia showed lower cerebellar volumes than controls; this finding was associated with higher NSS scores.
Peralta et al., (2006)[33]	*Neurological Evaluation Scale* (NES)	50 neuroleptic-naïve patients with psychosis (22 schizophrenia, 11 schizophreniform disorder, 4 schizoaffective disorder, 7 brief psychotic disorder, 4 delusional disorder, 2 atypical psychotic disorder (DSM-IV)) NSS were only assessed in a subsample of 28 patients.	Obstetric complications were related to admission levels of parkinsonism, dyskinesia, akathisia and NSS; pregnancy complications were associated to parkinsonism, dyskinesia and NSS.
Prikryl et al., (2006)[29]	*Neurological Evaluation Scale* (NES)	92 male patients with schizophrenia	Significant correlations between NSS and negative symptoms as well as poor treatment response
Varambally et al., (2006)[24]	*Modified Neurological Evaluation Scale* (NES)	32 antipsychotic naïve schizophrenia patients (DSM-IV) 32 healthy controls	NSS subscores for cerebellar functioning and sensory integration were significantly higher in patients with schizophrenia than healthy controls.
Zabala et al., (2006)[27]	*Neurological Evaluation Scale* (NES)	9 adolescents with schizophrenia, 15 with non-schizophrenic psychosis 39 healthy controls	Increased NSS scores in adolescents with psychosis when compared to the healthy controls. Adolescence with schizophrenia showed even higher NSS scores than those with non-schizophrenia psychosis.
Poyurovsky et al., (2007)[49]	*Neurological Evaluation Scale* (NES)	59 patients with schizophrenia and obsessive- compulsive disorder (DSM-IV; 20 patients with a first- episode of schizophrenia) 51 patients with schizophrenia (DSM-IV;16 patients with a first-episode of schizophrenia) 20 patients with an obsessive-compulsive disorder (OCD) 51 healthy controls	NSS did not differentiate between schizophrenia patients with and without OCD. Moreover, patients with first-episode schizophrenia in both groups scored similarly to patients with repeated hospitalizations on all NES subscales.
Thomann et al., (2008)[9]	*Heidelberg NSS scale* magnetic resonance imaging (MRI) analyzed by voxel based morphometry	42 patients with first episode schizophrenia (DSM-IV) 22 healthy controls	Significant higher NSS scores in patients than in healthy controls. NSS scores in patients were related to changes in the sensorimotor and premotor cortex, head of the caudate nucleus, thalamus and cerebellum. These associations did not apply for the healthy controls, in whom NSS were associated with frontal cortex changes only.

Table 1B

Follow-up Studies of NSS in First-episode Schizophrenia

Study	NSS Scales	Subjects	Results
Browne et al., (2000)[32]	*Neurological Evaluation Scale* (NES) *Condensed Neurological Examination* (CNE)	56 patients (DSM-IV) with schizophrenia or schizophreniform disorder (35 medication naïve and 21 medicated (‹ 30 days)	97% of the medication naïve patients showed at least 1 NSS. NSS were associated with relative hand preference and clinical symptoms; mixed handedness referred to more severe neurological impairment, poorer scholastic attainment and pre-morbid social adjustment
Lawrie et al., (2001)[28]	*Neurological Evaluation Scale* (NES), *Waldrop Scale*	152 subjects at high risk of developing schizophrenia (at least two first and /or second-degree relatives with schizophrenia) 30 patients with schizophrenia 35 healthy controls	Higher NSS scores were obtained in patients with schizophrenia followed by high risk subjects and healthy controls. NSS subscores for sensory integration deficits and minor physical abnormalities were significantly higher in the high risk group than in the controls.
Shibre et al., (2002)[23]	*Neurological Evaluation Scale* (NES)	200 treatment-naïve patients (DSM-IV) with schizophrenia 78 healthy controls	When compared with the controls, significantly increased NSS scores were found among all patients irrespective of clinical subtypes. In the patients´ group, NSS were not associated with duration of illness, remission status, positive symptoms, negative or disorganized symptoms.
Keshavan et al., (2003)[7]	*Neurological Evaluation Scale* (NES)	90 patients with schizophrenia, (74 with schizophrenia, 3 schizophreniform disorder, 13 schizoaffective disorder (DSM-IV)) 39 non-schizophrenic patients (12 psychotic depression, 11 bipolar disorder with depression, 3 delusional disorder, 13 psychosis not otherwise specified (DSM-IV)) 93 healthy controls	NSS reflecting deficits in repetitive motor tasks were significantly increased among all patients, while cognitively demanding and perceptual tasks were more impaired in patients with schizophrenia than in those with non-schizophrenic psychoses and in the healthy control group.
Mohr et al., (2003)[31]	*Neurological Evaluation Scale* (NES)	41 patients with schizophrenia and 20 patients with schizophreniform disorder 87 healthy controls	Increased NSS scores in the patients´ group were associated with marked neuropsychological deficits in tests sensitive for attention, executive functioning, cognitive flexibility and verbal memory.
Venkatasubramanian et al., (2003)[25]	*Modified Neurological Evaluation Scale* (NES)	21 never treated patients with schizophrenia (DSM-IV) 21 healthy controls	NSS total scores were significantly higher in patients than in controls. No significant correlations between NSS and psychopathological symptoms

Table 2

Clinical Rating Scales Used for the Assessment of Neurological Soft Signs

Scale	Reference	Number of Items	Rating	Subscales	Psychometric Properties
Cambridge Neurological Investigation (CNI)	Chen et al., (1995)	80 (11 bilateral)	0, 0.5, 1, 2	hard signs, motor coordination, sensory integration, primitive reflexes,tardive dyskinesia, catatonic signs,extrapyramidal signs,suppression failure	inter-rater reliability Kendall's W = .82 to 1.0 (reported for 14 selected items)
Condensed Neurological Examination (CNE)	Rossi et al., (1990)	19 (7 bilateral)	absent = 0, present = 1 or ordinal scales with maxima between 2 and 6	NA	inter-rater reliability total score: r = .76 Single items: Kappa = .37 to .76 r= .69 to .85
Heidelberg NSS Scale	Schröder et al., (1992)	16 (10 bilateral)	0–3	motor coordination, integrative functions, complex motor tasks,orientation, hard signs	internal consistency Cronbach's α = .83 inter-rater reliability r = .88 (total score) test-retest reliability in healthy controls over a period of 10 months: rtt=80
Neurological Evaluation Scale (NES)	Buchanan & Heinrichs, (1989)	26 (14 bilateral)	0–2	sensory integration, motor coordination, sequencing of complex motor acts, others	inter-rater reliability = .95 (total score) = .0 to 1.0 (items)

and/or the *Abnormal Involuntary Movement Scale* (AIMS).[20,21] While an universally accepted structured instrument is not at hand, most NSS scales in use comprise a set of similar subtests, e.g., tandem gait, Romberg, diadochokinesis, finger-nose tapping, finger-thumb opposition, fist-edge palm test, Ozeretski's test, mirror movements, graphesthesia, stereognosis, right/left orientation. As an example, the *Heidelberg NSS Scale* is summarized in Table 2. That overall data comparability is relatively high is underlined by the higher rates of neurological abnormalities confirmed in virtually all studies.

All studies found increased NSS scores in patients with first episode schizophrenia—including those who were drug-naïve—a finding which was confirmed irrespective of the patient sample or the instrument used.[22,23,24,25] Moreover, increased NSS scores were also described in patients with other psychiatric diseases such as bipolar disorder adolescents with schizophrenia or other psychosis, but also first-degree relatives of patients with schizophrenia.[7,26-28] Some studies explicitly addressed the association between NSS and psychopathological symptoms. One study found NSS scores to be significantly correlated with both negative symptoms and treatment response in 92 male patients with schizophrenia;[29] others reported a moderate although significant correlation between NSS, severity of psychopathological symptoms[26,30] and negative symptoms,[26] respectively. **Moreover, increased NSS scores were related to deficient executive functions,**[7,31] **longer duration of untreated psychosis, and poorer scholastic attainment, premorbid social adjustment,**[32] **and birth complications.**[33,34]

Four studies examined the potential cerebral correlates of NSS by using *magnetic resonance imaging* (MRI).[7-9,35] Bottmer et al. found increased NSS scores to be inversely correlated with right cerebellar volumes, which also proved to be significantly smaller in the 37 patients included with first-episode schizophreniform

disorder in comparison with 18 healthy controls matched for age, gender, education, and handedness.[35] These results were consistent with MRI findings obtained in 12 patients by Keshavan et al.[7] In both studies, cerebellar volumes were measured by using a semiautomatic segmentation algorithm. For practical reasons, a number of important sites such as the sensorimotor cortices or the supplementary motor area could not be addressed. *Voxel based morphometry* (VBM) allows the entire brain to be examined for the structural correlates of clinical signs and symptoms or for group differences. In a first VBM analysis of NSS, Dazzan and colleagues[8] confirmed subcortical structures (e.g., thalamus, putamen and globus pallidus), the precentral, temporal and lingual gyrus as important sites for NSS in a large sample of patients with newly diagnosed schizophrenia. However, these results did not include a healthy comparison group; in addition, potential cerebellar changes were not addressed. The former is of particular importance, since the low NSS scores typically obtained in healthy controls do not necessarily involve the same network of cerebral sites as in patients. Moreover, clarification of this question may also help to better understand the nature of NSS. We therefore examined the potential cerebral correlates of NSS in 42 patients with first-episode schizophrenia and 22 healthy controls by using the VBM of the MRI scans obtained.[9] Within the patient group, NSS were significantly associated with reduced gray or white matter densities in the pre and postcentral gyrus, premotor area, middle and inferior frontal gyri, cerebellum, caudate nucleus and thalamus (Figure 2). These associations did not apply for the control group, in whom only the associations between NSS and reduced frontal gyri white matter densities could be confirmed. Functional neuroimaging studies confirmed the sensorimotor cortices as important sites for NSS and described a reversed lateralization effect with a greater right than left hemispheric sensorimotor cortex under ipsilateral finger movements.[36] This finding did not refer to differences in motor performance between patients and

Table 3

The Heidelberg NSS-Scalea
(adapted from Schröder et al., 1992)

Heidelberg NSS Scale; Subscales and Tests

1. Motor coordination
- Ozeretzki's test
- Diadochokinesis
- Pronation/ supination
- Finger/thumb opposition
- Articulation

2. Sensory integration
- Gait
- Tandem gait
- 2-point discrimination

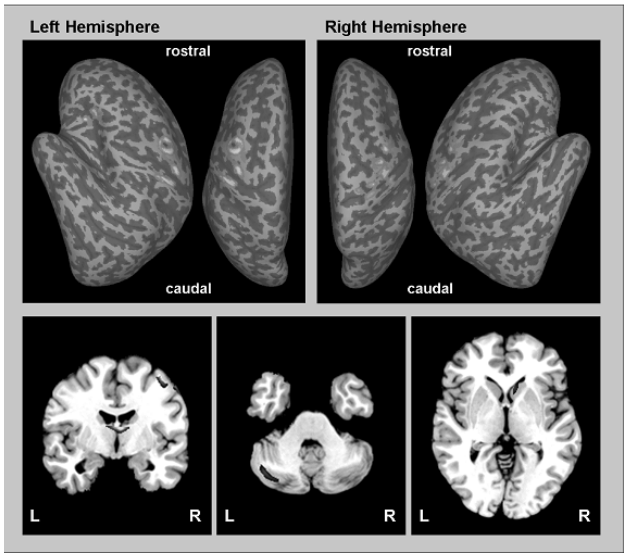
3. Complex motor tasks
- Finger-to-nose test
- Fist-edge-palm test

4. Right/left and spatial orientation
- Right/left orientation
- Graphesthesia
- Face/hand sensory test
- Stereognosis

5. Hard signs
- Arm-holding test
- Mirror movements

Figure 2

Cerebral Correlates of NSS as Revealed by Voxel-based Morphometry



Brain regions showing significant inverse correlation between grey (top, middle) and white (bottom) matter density and neurological soft sign total scores superimposed onto an inflated standard brain surface (top) and onto slices of a T1-weighted standard brain (middle, bottom); height threshold p < 0.001, uncorrected; extent threshold = 200 voxels (from Thomann et al., 2008).

controls and appeared to be rather stable in the short-term course.[37,38]

At this point, an important methodological question has to be raised: NSS refer to a number of trait characteristics of schizophrenia but are not stable over time and vary in the course of the disorder. Statistical associations between NSS and other characteristics of the disease—i.e. psychopathological symptoms, prognostic factors, or cerebral changes—are therefore dependent to the point in time when patients were investigated. This variation affects, in particular, the calculated correlations between NSS scores and trait related parameters such as genetic liability or birth complications but also affects correlations calculated between NSS scores and state variables as the underlying relations are at least not necessarily stable over time. One way to overcome this difficulty is to examine patients in a clinically well defined state of the disease such as after remission of acute symptoms. This design was probably applied in the majority of cross-sectional studies, since most patients find it difficult to comply with scientific examinations as long as they suffer from more acute symptoms. Alternatively, NSS can be investigated longitudinally in the clinical course of the disorder. While this approach is straightforward since it explicitly considers the fluctuations of NSS it necessitates large sample sizes, time, and continuous efforts to guarantee patients' compliance. Hence, it is understandable that the longitudinal studies available focused on the relation of NSS and clinical variables, such as psychopathological symptoms, but did not address neurobiological parameters such as cerebral changes visualized by neuroimaging.

Longitudinal Studies

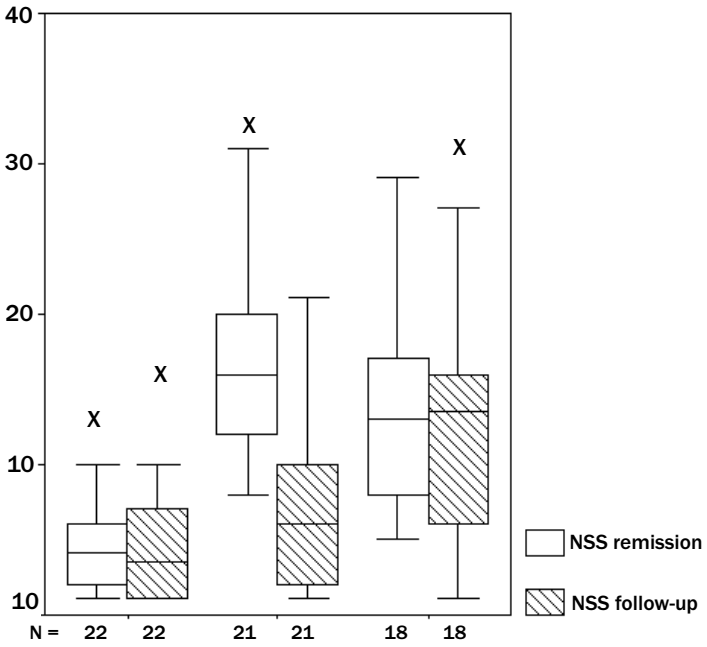
The studies discussed above clearly demonstrated significant associations between NSS and psychopathological symptoms, in particular formal thought disorders and negative symptoms. Symptoms of schizophrenia are transient in nature; hence, one may hypothesize NSS to be a state characteristic of the disease. However, NSS also refer to trait markers such as genetic liability. These questions relate to the clinical course, and can best be discussed with reference to the longitudinal studies of NSS in the course of schizophrenia. The search of the databases identified eight additional longitudinal studies of NSS in first episode patients (Table 1b). The study conducted by our own group[3] may be summarized as an example.

Thirty nine first-episode patients with schizophrenic disorders were examined after remission of acute symptoms and 14 months later using established instruments to assess diagnoses, psychopathological symptoms, predictors of outcome, and handedness.[3] NSS were established on the Heidelberg scale; subjects were also carefully investigated for potential extrapyramidal side effects using the appropriate rating instruments. The group consisted of Caucasians, 21 females and 18 males with a mean of 11.6 years (SD=1.6) of education; mean age intake was 27.0 years (SD=7.7). Patients were discharged on atypical antipsychotics according to their psychiatrists' choice. One year later, patients were invited for follow-up assessment; the exact interval amounted to a mean of 14.2 months (SD=1.6). Twenty two-age and gender-matched controls were also examined twice. NSS scores in patients were significantly elevated compared to controls at both measurement points.

Whereas NSS remained stable in controls (4.8±3.3 at t1; 4.6±3.9 at t2), they significantly ($p<0.001$) decreased in patients (15.7±7.1 at t1; 10.1±7.9 at t2). This effect (Figure 3) was more pronounced in patients with a favorable than with a chronic course and was mainly accounted for by motor signs. **However, even the NSS scores obtained in patients with a favorable course exceeded those obtained in the healthy control group.** Predictors of follow-up NSS scores were NSS at remission and compliance with treatment. Side effects of medication were

Figure 3:

Neurological Soft Sign Levels at Remission and 14-month Follow-Up Evaluation in First-Episode Schizophrenia Patients Classified by Symptom Course and Healthy Comparison Subjects (matched for age and gender).



Decrease of NSS scores was associated with a more favourable course of the disorder; interestingly, NSS scores obtained in patients with a favourable course after remission were in the same range as those measured in otherwise healthy twins of pairs discordant for schizophrenia(see Figure 1; from Bachmann et al., 2005)

low and unchanged on follow up compared to the first assessment, and were not related to NSS. This was the first prospective longitudinal study which directly compared NSS in first episode patients and controls. During the follow-up period, NSS scores clearly decreased in patients but remained almost stable on a low level in control subjects. **In particular, patients with decreasing NSS scores experienced further stabilization of symptoms and functioning, whereas clinical findings of patients with stable scores foreshadowed a rather unfavorable course.**

Similarly, the majority of the longitudinal studies also found NSS to vary in the clinical course (Table 1b). Among these studies, sample size varied considerably from 15 to 242 patients; the duration of the follow-up period also varied, ranging between 4 weeks and 5 years. Similar differences applied for the type of neuroleptic medication described, which included a standardized medication with a high potency butyrophenone in one study,[39] and atypical neuroleptics including clozapine in the majority of studies. Three studies also included healthy subjects for comparison; however, only 2 of them reinvestigated the controls as the patients were. While the authors used all NSS scales available, data on the test retest reliability of the NSS scales employed were only reported by Bachmann and coworkers.[3]

Despite these methodological differences, all but three studies confirmed a decrease of NSS with clinical stabilization. Only Boks et al.,[40] Chen and colleagues[41] and Emsley et al. reported NSS scores to be stable. Boks et al. investigated NSS during a 2-year interval in 29 patients who initially had presented with the first episode of non affective psychosis.[40] NSS scores decreased in patients with reduced antipsychotic medication, while the reverse applied for those with increased dosages. The respective subgroups were rather small; moreover, corresponding changes of the psychopathological state were not considered although the latter may well have led to an adjustment of neuroleptic therapy. Chen et al. recruited a large patient sample (n = 138) and entirely focused on motor signs.[41] However, having lost approximately one-third of the original during follow-up, Chen and colleagues could not entirely exclude the possibility that they did not reexamine the patients with a more favorable course and decreasing NSS. Moreover, their data demonstrated a non significant trend of NSS scores to decline from initial presentation (mean score: 1.87, S.D.

2.00) to 3-year follow-up (mean score: 1.45, S.D. 2.20). Actually, Emsley and colleagues described an initial decrease of NSS reflecting motor sequencing, but not of the total NSS score, during the first 3 months of the study.[42] Furthermore these NSS were also related with two characteristics of the chronicity of the disease, i.e. a longer duration of untreated psychosis and the emergence of persistent dyskinesia at 24 months. An association between improvement in clinical status and neurological performance is also suggested by our group's earlier studies, namely a parallel decrease of NSS and acute symptoms in remitting schizophrenia as well as in first-episode patients under initial treatment with typical neuroleptics.[2,6,39] Hence, from a clinical perspective, stabilization of psychopathological symptoms in particular, and outcome in a more general sense, have to be considered the most important predictors of NSS.

As suggested in previous studies,[2,43] the decrease of NSS scores with clinical stabilization corresponded to disturbed motor and sensory integration signs rather than orientation difficulties or hard signs. Moreover, the cross-sectional studies discussed above reported an association of NSS with increased symptom levels, poor premorbid adjustment, and unfavorable outcome, as well as with neurobiological measures such as neuropsychological deficits, or cerebral changes. These results parallel the difference in NSS between medication responders and nonresponders, as well as the finding that NSS are most prominent in chronic forms of schizophrenia,[1] and underline the necessity of differentiating between patient subgroups according to their symptoms and outcome.

Neuroleptic Medication

Typical or conventional neuroleptic agents may provoke extrapyramidal side effects, such as acute or tardive dyskinesias, Parkinsonian symptoms, or akathisia. For more than a decade up to the introduction of the newer atypical neuroleptics on a large scale, the potential impact of neuroleptic side effects on NSS was something like the "standard critique" of research in this field. **However, in clinical studies, NSS could not be sufficiently explained by extrapyramidal side effects, as the "historical" description of NSS and of related phenomena in the preneuroleptic gave evidence against a causal association between NSS and side effects.** Moreover, D2 dopamine receptor occupancy—the putative cause of extrapyramidal side effects—was not correlated with NSS.[39] The respective clinical findings were even confirmed in a large multi center study which solely included patients with subchronic or chronic schizophrenia (n = 82), i.e. a patient population at an increased risk of developing both NSS and extrapyramidal side effects.[44] Similar to the first episode studies discussed above, NSS again correlated significantly with severity of illness, lower social functioning, and negative symptoms. Modest, but significant correlations (rs = .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. In addition, neurological soft sign scores were comparable between patients receiving clozapine monotherapy (n = 33) and those on conventional neuroleptics (n = 45). A similar finding was communicated in one of the earlier studies. Neurological soft sign scores obtained in both groups were almost identical, although the clozapine patients displayed significantly less extrapyramidal symptoms. Since the trial involved two examinations at a 14-day interval, the stability of NSS could be analysed with respect to clinical stabilization. As expected from the longitudinal studies cited above, 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.

Taken together, these observations demonstrate NSS in schizophrenia are largely independent of neuroleptic side effects, but are associated with severity and persistence of psychopathological symptoms and poor social functioning. The longitudinal studies discussed above shed further light on the complex relation between the chronicity of the disorder, NSS and treatment response. The decrease of NSS with clinical stabilization in patients with favorable outcomes under neuroleptic treatment almost excludes a causal relation between NSS and side effects. Also, compliance with medication or intensification of neuroleptic treatment were identified as predicting decreasing NSS,[3,40] suggesting that NSS may be understood as surrogates of clinical stabilization and outcome.

These findings give rise to the hypothesis that NSS, poor treatment response, and motor side effects represent different aspects of the chronicity of schizophrenia; this is indirectly supported by the observation that extrapyramidal signs can be observed in patients who have never been medicated.[39]

Discussion

Taken together, results from the studies discussed above clearly confirm increased NSS scores as a characteristic feature of schizophrenia. Since NSS are closely related to psychopathological symptoms, important traits such as genetic liability and the clinical course of the disorder, they may even be considered to be inherent to schizophrenia.

That NSS are significantly increased in schizophrenia is in line with the results of a wealth of previously existing studies of schizophrenia and related psychotic disorders. NSS did not seem to be aggravated by neuroleptic drug treatment, supporting the respective results of previous studies. Although NSS in schizophrenia were already noticed in the preneuroleptic area, systematic research into this was not undertaken before 1970. Increased NSS scores were reported in patients with schizophrenia when compared to healthy controls, but also in patients with affective psychosis and subjects with an increased susceptibility to the disease. NSS are associated with psychopathological symptoms; hence, the highest scores were found in the acute psychotic state. In follow-up studies, NSS typically decreased with remission of acute symptoms. While this effect is more pronounced in patients with a favorable rather than a more chronic course of the disease, even the NSS scores of the former remain significantly higher than in healthy control groups. These effects do not correspond to potential confounders, specifically neuroleptic side effects, age, or gender.

According to these findings, NSS can be conceptualized as one of the core features of schizophrenia. This interpretation was first suggested in the concept of "schizotaxia" by Meehl where—among others—dysdiadochokinesia constitutes a trait-like marker of a baseline defect ("hypokrisia").[12] Hence, we may hypothesize NSS to be the consequence of the genetic liability towards the disease. On the other hand, the sharp increase of NSS scores in the acute psychotic state and their decrease with remission of acute symptoms clearly refers to an active disease process. Thus, NSS in schizophrenia seem to adopt characteristics of both state-like and trait-like features. While the state characteristics of NSS correspond to the acuity of the illness—the "Prozessaktivität" according to Karl Jaspers[45]—the trait-like features represent the neurobiological background including the genetic liability or obstretic complication of the disease. Hence, NSS may serve as surrogate markers of the schizophrenic disease process with higher scores corresponding to a trait-like liability and fluctuations with increasing or decreasing scores heralding the exacerbation or the remission of acute symptoms, respectively.

This clinical interpretation of NSS as an integral part of schizophrenia corresponds to the neuroimaging studies discussed above. In summary, the latter found increased NSS scores to be associated with changes in the sensorimotor

and premotor cortices, subcortical structures (thalamus and basal ganglia), and the cerebellum. This variety of sites may correspond with the clinical diversity of NSS, which comprise both motor and sensory signs. That the respective associations do not apply for the healthy control group indicates that NSS in patients and controls refer to different pathogenetic factors.

Low levels of NSS can also be demonstrated in healthy individuals where they may relate to peristatic factors, such as age or less developed skills, and their potential cerebral correlates. Since these factors may occur at random in each individual, it appears unlikely that they correspond to the same pattern of cerebral changes as observed in patients with schizophrenia. This hypothesis is supported by the longitudinal studies cited above, which indicate that NSS in schizophrenia do not only refer to premorbid deficits, but also involve changes inherent to the disease.

Further evidence that NSS in healthy subjects and patients with schizophrenia involve different pathogenic factors comes from the North Finland 1966 general population birth cohort study, where ratings for infant motor development at age 1 were related to cerebral changes assessed by MRI at age 33 to 35 years.[46] Delay of infant motor development was associated with cerebral changes in those areas important for NSS in the healthy controls, but not in the patients' group. This dissociation implies that NSS in schizophrenia only partly depend on delays of infant motor development. The corresponding hypothesis that the cerebral changes underlying NSS are not entirely preformatted or static but may also increase as psychosis develops is supported by longitudinal studies indicating progressive changes in areas crucial for motor and sensory functioning such as the sensorimotor cortices and supplementary motor area or the cerebellum.[47,48]

Obviously, these findings are compatible with the hypothesized disruption of the cortico cerebellar thalamic-cortical circuit in schizophrenia as conceptualized in the model of "cognitive dysmetria,"[10] and strongly suggest that the resulting misconnection syndrome is responsible for both psychopathological symptoms and neurological abnormalities. **From a clinical perspective, the fluctuation of NSS in the course of the disorder may serve as a surrogate marker of the underlying disease process and its activity. In this respect, increases of NSS in the clinical course may be used as an early warning sign of acute exacerbations, and may assist in the recognition of these exacerbations earlier, before they lead to severe psychotic symptoms.** These hypotheses warrant further longitudinal examinations of NSS and related clinical and neurobiological variables in first-episode schizophrenia. Results from these studies are not only crucial to establish NSS as a prognostic signs but may also help to further elucidate the interaction between genetic liability and transient state related insults in schizophrenia.

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Questions Based On This Lesson

To earn CME credits, answer the following questions on your quiz response form.

55. Which one of the following is correct? In the clinical course of schizophrenia, increased *neurological soft sign* (NSS) scores:

A. Can be demonstrated in virtually all patients

B. Decrease with remission of acute symptoms

C. Are closely associated with extrapyramidal side-effects

D. Can herald an unfavourable course of the disorder

56. Regarding neurological soft signs (NSS), all of the following statements are correct, *except*:

A. NSS comprise both, motor and sensory signs

B. NSS do not correspond to focal cerebral changes

C. NSS decrease in the clinical course with remission of psychopathological symptoms

D. NSS are also increased in subjects at risk

57. Which one of the following is correct? Increased NSS scores:

A. Are solely found in patients with schizophrenia

B. Do not occur in first episode patients

C. Are stable over time

D. Are associated with genetic liability, poor premorbid adjustment, and unfavourable prognosis