

Significance and Meaning of Neurological Signs in Schizophrenia: Two Decades Later

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Objective: Patients with schizophrenia are characterized by neurological abnormalities, which can be assessed by bedside clinical examination. These abnormalities have been argued to represent core features of the illness. We review studies published since our last review in 1988 that address the validity of neurological signs as a trait feature of schizophrenia. *Methods:* We conducted a literature search in the following computer databases: MEDLINE, PSYCHLIT, EMBASE, and COCHRANE. The search was limited to articles published from January 1988 to May 2005. *Results:* Neurological signs occur in the majority of patients with schizophrenia. Their occurrence is independent of demographic and most medication variables. Neurological signs are strongly associated with negative symptoms and cognitive impairments. There is also evidence to suggest that their occurrence is under genetic control. *Conclusions:* There is compelling evidence to suggest the hypothesis that neurological signs represent a trait feature of schizophrenia.

Key words: schizophrenia/neurological signs/endophenotype/trait marker

Introduction

Over the last several decades, there has been an increasing number of neuroanatomical, neuroimaging, neurophysiological, and neuropsychological studies in pursuit of structural, functional, and cognitive correlates of brain insult(s) that could ultimately lead to unrav-

eling the etiopathophysiology of schizophrenia. These studies have implicated multiple brain regions. Indeed, variations in the localization and severity of brain impairments in patients with schizophrenia have been used to hypothesize that schizophrenia is made up of multiple disease entities.

A direct, easily administered, and inexpensive way of investigating brain dysfunction in schizophrenia is the study of neurological signs. Neurological abnormalities include both “hard” signs and “soft” signs. Hard signs refer to impairments in basic motor, sensory, and reflex behaviors. In contrast, “soft” neurological signs (SNS) are described as nonlocalizing neurological abnormalities that cannot be related to impairment of a specific brain region or are not believed to be part of a well-defined neurological syndrome. This distinction has been argued to be artificial and to reflect the inability to define the brain–behavior relationships that underlie the presence of SNS.¹ Moreover, SNS are frequently clustered in categories attending to their most likely, putative neuroanatomical localization. Although the cluster categories vary among authors, the most common categories are integrative sensory function, motor coordination, sequencing of complex motor acts, and primitive reflexes. Table 1 summarizes the neurological signs most frequently included in each of the cluster categories. The ambiguity over the distinction between soft and hard neurological signs has led to differences in the categorization of neurological signs, but as a whole, SNS have been found to be more strongly related to the presence of schizophrenia than hard neurological signs (see below).

In 1988, Heinrichs and Buchanan reviewed the significance of SNS for our understanding of schizophrenia.¹ The review supports the utility of SNS investigations in schizophrenia and calls for further research on the potential relationships of SNS and sociodemographic, neuroanatomical, and clinical variables, such as negative symptoms, medication status, premorbid functioning, and age at onset.

In the years following this review, the growing interest in SNS has led to the development of multiple, structured instruments to assess neurological impairment: the Woods scale,² the Condensed Neurological Examination (CNE),³ the Modified Quantified Neurological Scale,⁴

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Table 1. Soft and Hard Neurological Signs Most Frequently Assessed Grouped by Their Denomination and Putative Neuroanatomical Localization

Cluster of Neurological Sign Denomination	Putative Localization	Individual Signs Assessed
Integrative sensory function	Parietal lobe	<ul style="list-style-type: none"> ● Bilateral extinction ● Audiovisual integration ● Graphesthesia ● Stereognosis ● Right-left confusion ● Extinction
Motor coordination	Frontal lobe Cerebellar	<ul style="list-style-type: none"> ● Intention tremor ● Balance ● Gait ● Hopping ● Finger-thumb opposition ● Dysdiachokinesis ● Finger-to-nose test
Sequencing of complex motor acts	Prefrontal lobe	<ul style="list-style-type: none"> ● Fist-edge-palm test ● Fist-ring test ● Ozeretski test ● Go/no-go test ● Rhythm tapping (foot or hand)
Primitive reflexes	Frontal	<ul style="list-style-type: none"> ● Glabellar tap ● Jaw jerk ● Palmomentar ● Corneomandibular ● Pout/snout ● Sucking/oral ● Grasp ● Forced groping
Hard neurological signs	Central nervous system including cranial nerves	<ul style="list-style-type: none"> ● Mirror movements ● Synkinesis ● Convergence ● Gaze impersistence ● Extrapyramidal signs ● Pyramidal signs ● Dyskinesia ● Language ● Speech

the Heidelberg Scale,⁵ the Cambridge Neurological Inventory,⁶ and the Neurological Evaluation Scale (NES;⁷ for a further description of these scales and their psychometrics properties, see⁸). Other methodological advances included better-designed studies, with larger sample sizes, longitudinal SNS assessments, and inclusion of drug-naive and first-episode samples and nonaffected relatives.

The present article is an update of our original review, in which we provide new information on the significance of neurological signs and the validity of conceptualizing these abnormalities as a trait feature of schizophrenia.

The literature search was conducted by introducing certain Medical Subject Headings categories—*schizophrenia*, AND *neurological abnormality*, OR *neurological signs*, OR *neurological dysfunction*, OR *soft signs*—in the following computer databases: MEDLINE, PSYCHLIT, EMBASE, and COCHRANE. The search was limited to articles published from January 1988 to May 2005. Only articles that were written in the English language and published in peer-reviewed journals have been included in this review. If there were 2 articles with the same data reported in different journals, only the most comprehensive article was included. Articles included in the original review have occasionally been cited, when they are relevant for the discussion.

Prevalence

Multiple observations have consistently documented a higher prevalence of neurological signs among patients with schizophrenia compared to healthy normal controls.¹ The majority of studies have reported prevalence rates ranging from 50 to 65% in patients with schizophrenia, in contrast to 5% in normal controls.¹ Prevalence rates for other psychiatric disorders have been reported to be in between these 2 groups.¹ The marked variability in reported prevalence rates is due, in large part, to differences in the definition of *neurological impairment*. Studies in which neurological impairment is defined as “at least 1 neurological sign present,” rates range from 88 to 100%,^{9–17} whereas in studies that use a more restrictive definition of neurological impairment (e.g., King et al.¹³ define *neurodysfunction* as having 2 or more neurological signs), prevalence rates are lower and range from 38.6 to 64%.^{18–19} The rate of “neurological impairment” prevalence also depends on the scope of scale coverage. The number of signs assessed ranged from 4 to 108,^{19–20} a fact that in its own right may explain prevalence rate differences. Scales with a small number of signs are likely to have low sensitivity and may omit relevant-to-schizophrenia signs and hence lead to the incorrect conclusion that schizophrenia does not imply neurological impairment (type II error). On the other hand, very comprehensive scales are likely to have low specificity and may include signs that are not directly related to primary neurological impairment (e.g., extrapyramidal symptoms), and therefore they may erroneously classify subjects as “neurologically impaired” when in fact their signs are secondary to other variables (type I error).

In addition, most of the neurological sign scales do not offer a cutoff score that delimits the neurological impairment range. However, reports that include a matched healthy control group are able to establish what is “neurologically normal” and hence allow comparisons with the schizophrenia group. This approach of looking for statistically significant differences among groups is less

ambiguous than the use of a subjective definition of *neurological impairment*. Studies that have compared the prevalence of SNS in a sample of patients with schizophrenia with the incidence in healthy controls consistently find significant differences (see “Specificity” section). Thus, the inclusion of healthy controls could ultimately lead to establishing reliable cutoff scores for the most broadly used scales.

Specificity

Among studies that included a healthy control group, all, except 1,¹⁹ have reported increased neurological impairment in patients with schizophrenia.^{3, 5–7, 11, 15, 21–39} The only study reporting no differences between patients with schizophrenia and healthy subjects included only 4 SNS and was conducted with a population in Nigeria, where there is a high rate of obstetric complications. In combination with the studies included in our original review,¹ these results strongly support the proposition that neurological signs significantly differentiate patients with schizophrenia from healthy control subjects.

There have been few comparative studies between patients with schizophrenia and those with other psychiatric disorders since our original review,¹ with only 9 studies addressing this question. Patients with schizophrenia have shown more SNS than patients with obsessive-compulsive disorder,²² alcohol dependence,¹⁵ substance abuse and bipolar disorder,⁴⁰ nonschizophrenia psychosis,²⁸ mood disorders,^{29, 41} and mixed psychiatric diagnosis in cross-sectional studies³⁵ and after 5 years of follow-up, although not at baseline.³⁰ The only negative finding is a comparison with affective disorders, in which both disorders had very high prevalence rates. This is again the study with the Nigerian population.¹⁹

In our original review, we observed that at least 2 subgroups of neurological signs, “sequencing of complex motor acts” and “sensory integration,” occur more frequently in patients with schizophrenia than in those with other psychiatric diagnoses.¹ These signs are putatively associated with frontal/prefrontal and parietal brain areas. The new studies addressing this issue have reported mixed results. Mohr et al. have found that nonchronic patients with schizophrenia showed significantly higher scores on the “motor coordination” subscale and chronic patients with schizophrenia showed significantly higher scores on all subscales than alcohol-dependent patients.¹⁵ Bolton et al. report significantly higher “hard signs” and “motor coordination” signs for patients with schizophrenia, when compared to OCD patients.²² Kinney et al. have found higher prevalence rates of cerebellar and cortical sensory neurological hard signs in patients with schizophrenia than in healthy controls and substance abuse and bipolar disorder patients.⁴⁰ Krebs et al. have found that the “motor integration” factor is the best discrimina-

tor between schizophrenia and mood disorder patients, with patients with schizophrenia showing significantly higher neurological impairment.²⁹ Keshavan et al. have found that schizophrenia patients had more sensory integration and cognitively demanding signs than patients with nonschizophrenia psychosis, with a lack of significant differences between the 2 groups in motor signs.²⁸

In summary, although recent specificity studies have supported the hypothesis that SNS are relatively specific to schizophrenia, they have failed to confirm the hypothesis that the 2 subgroups of neurological signs, “complex motor coordination acts” and “sensory integration” signs, occur more frequently in patients with schizophrenia than in those with other psychiatric disorders. However, there are several methodological issues that may have led to the failure to support the hypothesis. These include the fact that very few studies (4) address the question and the lack of consensus on which signs constitute the categories. Thus, further studies, which take into account these issues, are required to determine whether there are SNS abnormalities specific to schizophrenia.

Neurological Signs and Sociodemographic Variables

The potential influence of sociodemographic variables upon SNS prevalence is an important issue for the conceptualization of neurological abnormalities as a trait feature. If SNS are a trait feature, then their occurrence should be relatively independent of such variables, whereas if these variables are found to mediate their prevalence, then the influence of these variables should be controlled for in future research on SNS.

Gender has consistently been shown not to introduce variance in the presence and severity of SNS, with a total of 12 studies reaching this conclusion.^{7, 9–10, 14–15, 18, 26–27, 41–46} In contrast, 1 study¹⁴ has found a trend for female patients with a family history of schizophrenia to show more SNS ($p = .06$).

Fifteen of 20 studies have not found an association between SNS and age.^{7, 9, 14–15, 18, 20, 27, 34, 40–42, 45–48} The other 5 studies, which tended to use older cohorts, show a positive correlation between older age and more neurological impairment.^{3, 6, 26, 33, 43} Thus, age seems not to affect the severity of neurological dysfunction, until late in life, when there seems to be a progressive deterioration.²³

The role of educational level, socioeconomic status, and ethnicity has not been adequately assessed. Of these variables, educational level has been the most extensively studied. The results have been mixed: 4 studies have reported an inverse correlation between education and neurological impairment;^{3, 15, 43, 46} another study has reported an inverse correlation for only 1 of the 3 NES factors;³³ and 5 studies failed to find a relationship between educational level and neurological status.^{18, 20, 27, 45, 48} In 4 studies, neurological impairment has been found

not to be related to patient^{18, 27, 46} or parental^{18, 34} socioeconomic status, although Griffiths et al. report an inverse correlation between social class and soft and hard neurological signs.²⁶ Only a few studies have examined the role of ethnicity: Buchanan and Heinrichs have found that both African American controls and patients showed more neurological impairment than white people,⁷ an observation that has been made in 3 other studies.^{24, 34, 49} In another study nonwhite patients (including African American and other races) had more cognitive/perceptual neurological abnormalities.²⁸ Further studies controlling for interactions among different sociodemographic variables are needed to reach more reliable conclusions.

Neurological Signs and Psychopathology

If we assume that some kind of brain insult(s) is(are) responsible for the clinical and functional manifestations of the disease(s), as well as for the neurological manifestations, then it would be reasonable to expect associations between psychopathology and neurological functioning. The potential SNS–psychopathology associations would contribute to the view of SNS as an essential feature of schizophrenia and a potential vulnerability marker. Considering the early onset of SNS, if these associations were confirmed, SNS not only could be used as a prognostic marker but also could be assessed as 1 of the variables used in early detection programs.

Except for a few studies that use global measures of psychopathology, such as the Clinical Global Impression or the Brief Psychiatric Rating Scale (BPRS) total score, in which negative³⁴ and positive^{33, 35} associations are reported, the majority of studies have separately assessed negative and positive symptoms. In some of these studies, positive symptoms have been subdivided into hallucinations/delusions and disorganized behavior symptom domains. In the discussion below, the term *positive symptoms* includes both symptom domains.

Positive Symptoms

There is little evidence to support an association between SNS and positive symptoms.^{9–10, 13, 15, 17–20, 30–31, 35, 38–39, 43, 46, 50–53} Moreover, in half of the studies in which associations with positive symptoms have been reported,^{13, 15, 35} there were also significant associations of SNS with negative symptoms^{13, 15, 35} and with global psychopathology,^{13, 35} potentially reflecting a selection bias toward an especially symptomatic subgroup. A major methodological limitation of these studies is the failure to take into account the fact that positive symptoms fluctuate with phase of illness, whereas SNS are conceptualized as a potential trait marker. Since all patients with a diagnosis of schizophrenia have had positive symptoms at some point in their course of illness, the evaluation of the cross-

sectional association between SNS and positive symptoms may not be the best way to assess such a relationship. This hypothesis is supported by the study by Scheffer in which at baseline both positive and negative symptoms correlated with the NES motor coordination score and NES total score, respectively.³⁵ Meanwhile, at 6-week follow-up, only negative symptoms correlated with the NES total and most subscales scores. In addition, a very acute condition with marked positive symptoms may interfere with SNS assessment and produce a higher score, as suggested by the studies by Schroder et al.⁵ and Whitty et al.,⁵⁴ in which a significant reduction of neurological abnormality paralleled the psychopathology remission.

Negative Symptoms

Negative or deficit symptoms⁵⁵ have a more “organic” appearance, sharing clinical manifestations, such as apathy, anergia, social withdrawal, and affective flattening, with other illnesses of demonstrated brain insult. These observations suggest an association between the presence of negative symptoms and SNS, an association that has been repeatedly assessed, with 17 studies reporting positive findings versus 12 negative studies. Buchanan et al. have found that deficit patients were significantly more impaired on the NES sensory integration subscale,⁵⁶ and Tiryaki et al. have found that deficit patients were more severely impaired in all NES subscales.⁵⁷ Moreover, they have found that the sequencing of complex motor acts subscore is a significant predictor of the deficit state. Other authors also report associations between negative symptoms and frontal^{17, 35, 43, 53} and/or prefrontal^{17, 35, 48} signs. The selective relationship between the deficit syndrome and sensory integration has been replicated by the same group⁴⁹ and is in agreement with other studies pointing toward parietal disturbances in deficit patients.⁵⁸ Chen et al. have also found a positive correlation between sensory integration signs and Positive and Negative Syndrome Scale (PANSS) negative symptoms, although significance was lost after controlling for age and duration of illness.⁵⁹ In addition, both sensory (“integrative functions”) and frontal (“complex motor tasks”) signs have been associated with the BPRS negative symptoms³⁵ or BPRS anergia factor,⁵ a symptom complex also associated with overall neurological impairment.⁶⁰ Galderisi et al. have found significant associations between “mental” and “cortico-sensory” neurological signs and apathy and anhedonia.⁶¹ When patients were subdivided into 2 groups on the basis of the presence or absence of neurological dysfunction, the neurologically affected subgroup presented significantly more negative symptoms,^{13, 18} although not always.⁴⁵ Studies using scales that provide continuous values of neurological impairment severity also have found significant positive correlations between overall neurological impairment and

severity of negative symptoms as measured with the PANSS,^{39, 41} the Scale for the Assessment of Negative Symptoms,^{16–17, 50} or the BPRS.^{5, 35}

However, significant relationships between neurological impairment and negative symptoms have not always been found. For instance, 2 studies that compared patients with more negative symptoms and those with less negative symptoms failed to find neurological sign score differences.^{23, 46} Browne et al. have found that a PANSS negative syndrome score does not predict neurological impairment measured by the NES or CNE.¹⁰ Other studies have also reported a lack of significant correlations between negative symptoms and neurological impairment.^{9, 19–20, 30–31, 38, 52, 62–63} However, some methodological issues need to be considered in the interpretation of these results. As seen above, negative symptoms are most frequently associated with frontal (sequencing of complex motor acts) and parietal (sensory integration) neurological signs. Most studies that have failed to find an association between negative symptoms and SNS included either few^{31, 62} or none^{9, 19} of these signs or exclusively assessed hard neurological signs.⁵²

Behavioral Disorganization

There are several studies that have specifically examined the relationship between SNS and symptoms of behavioral disorganization (i.e., inappropriate affect, bizarre behavior, and positive formal thought disorder). Behavioral disorganization symptoms have consistently been associated with neurological dysfunction,^{5, 15, 36, 49, 64} although 1 study failed to find such correlation,³¹ and another study that compared neurologically affected patients with unaffected ones did not find differences in the disorganization cluster.¹⁸ Two studies have examined the association between specific SNS and behavioral disorganization symptoms. Mohr et al. have found that “cognitive disorganization” symptoms (their measure of behavioral disorganization) correlates with the NES total score and all subscale scores.¹⁵ Similarly, our group has found associations⁴⁹ between behavioral disorganization symptoms and the NES sequencing of complex motor acts and sensory integration subscales.

In summary, positive symptoms tend not to be related to SNS; negative symptoms seem to be related to SNS that reflect frontal (motor function) signs and parietal function (sensory integration) signs; and disorganization is related to more broad neurological impairment.

Neurological Signs and Cognitive Functioning

Cognitive impairment is a well-documented phenomenon among patients with schizophrenia and has been associated with impoverished functional outcome and negative or deficit symptoms. In light of the relationship between cognitive impairment and brain insult, we would expect

an association between neurological abnormalities and 1 or more domains of cognitive impairment in schizophrenia. These domains include attention and information processing; processing speed; reasoning and problem solving, also referred to as executive functioning; social cognition; working memory; and verbal and visual learning and memory.⁶⁵ There is also the question of whether specific domains of SNS relate to specific cognitive functions and, if that is the case, to what extent cognitive functioning and SNS are overlapping constructs.

Early approaches to this issue have documented a relationship between SNS and overall measures of cognitive functioning, such as IQ (see ¹). More recent investigations of associations between global cognitive impairment and neurological dysfunction have offered mixed results, with fewer negative results^{9, 12, 18, 42, 48} than positive.^{13, 15, 33, 43, 45, 66–70} SNS have most commonly been shown to be associated with attention deficits,^{15, 43, 45, 53, 70–71} though there are negative studies.^{17–18, 66} Frontal neurological signs have been shown to be correlated with visual-spatial memory,^{43, 66, 68, 70} visuo-spatial processing,^{17–18, 20, 43, 53, 66} and visuo-constructive tasks.^{43, 66} Performance on psychomotor tasks has been associated with soft,¹⁸ but not hard,⁵² neurological signs. Two studies have reported negative results with verbal memory.^{18, 48} Finally, reasoning and problem solving, cognitive functions usually associated with the prefrontal cortex, have been repeatedly reported to be associated with neurological frontal signs^{15, 17, 20–21, 43, 53, 66–67, 70} and also with overall neurological functioning.^{15, 17, 20–21, 45, 66} In the 1 study that failed to find a relationship between SNS and executive functioning, frontal/prefrontal soft signs were not included.¹⁸

We have examined⁶⁶ the ability of SNS to predict cognitive performance and have found not only that global neurological impairment predicts impaired global neuropsychological functioning but also that specific neurological sign clusters are selectively correlated with specific domains of cognitive impairment. The NES “sensory integration” subscale is the most frequent predictor of neuropsychological test performance. Mohr et al.¹⁵ and Smith et al.¹⁷ have found that the NES “sequencing of complex motor acts” subscale has the highest correlation with executive functioning. Chen et al. have found that attention deficits correlate with some but not all of the neurological signs subscales,⁷¹ suggesting the need to examine associations between specific cognitive functions and clusters of signs, instead of a single global measure of neurological functioning. These results highlight the importance of neurological sign selection and clustering when predicting cognitive impairments in schizophrenia, since specific signs seem to predict specific cognitive domains.

Several considerations support the conceptualization of SNS and cognitive functioning as partially independent phenomena, though they may be ultimately linked.

First, in contrast to SNS, cognitive functioning seems to be influenced to a greater extent by sociodemographic variables (age, educational level, gender, socioeconomic status). SNS seem to be more independent of these variables. Second, and as a result of the former, cognitive functioning is more heterogeneous than neurological status among patients and healthy subjects. In fact, it is not rare to find studies in which a subgroup of patients with schizophrenia performs “normally” on a neuropsychological test battery,^{72–73} which could lead to the erroneous conclusion that cognitive impairment only occurs in a subgroup of patients, specifically, those with poorer prognoses. However, these studies have gone on to show that these “neuropsychologically normal” patients perform more poorly than would be predicted by measures of premorbid ability and have specific executive function and processing speed impairments. Third, the relationship between SNS and cognitive impairment is not linear, in the sense that intact neurological status does not guarantee good cognitive functioning, and poor cognitive functioning is not solely due to neurological impairment. Moreover, the relationships between neurological and cognitive functioning are also not consistent in non-schizophrenia mentally ill patients.²⁴ We would posit that neurological and neuropsychological functioning refer to epistemologically different levels of analysis. Although cognitive impairments may be more sensitive, SNS seem to be more specific, since there is less variability in SNS than in cognitive function in normals.

Neurological Signs and Neuroimaging

Few studies have examined the relationship between neurological impairment and brain structural measures. Seven^{5, 15, 31, 64, 69, 74–75} out of the 8 studies addressing this issue have found some structural abnormalities associated with the presence of SNS. Ventricular brain ratio and third ventricular enlargement have been associated with overall neurological functioning^{5, 15, 64} and motor coordination signs.⁵ In a magnetic resonance imaging study, reduction of the gray matter volume of subcortical structures (putamen, globus pallidus, and thalamus) was associated with both motor and sensory SNS, whereas sensory SNS were associated with volume reduction in the cerebral cortex.⁶⁹ However, there are negative findings.¹³ Other items that have been associated with SNS include the frontal and hemispheric measures;⁷⁴ the sulci cerebrospinal fluid on slices I and II; the interhemispheric fissure;¹⁵ brain length; and the width of the left Sylvian fissure,³¹ left caudate, cerebellum, and left heteromodal association cortex.²⁸ In these studies, more neurological impairment was associated with more abnormal brain structure. However, these findings are nonspecific and do not inform us of SNS localization, since only associations between neurological impairment and nonspecific structural measures have been reported. These asso-

ciations could be explained solely on the basis that both phenomena occur more frequently in chronic or poor-prognosis patients.

Functional imaging studies may be more useful in SNS localization. However, the potential relationships of neurological status and functional neuroimaging variables have only been assessed in 3 studies and, again, only in the form of comparing nonspecific variables (i.e., overall neurological impairment with overall brain activation). A single photon-emission computerized tomography study failed to find any association of regional cerebral blood flow and neurological signs in either resting or frontal activation paradigms.³¹ A positron-emission tomography study found a relationship among disorganized symptoms, neurological signs, and hyperactivity in the parietal cortex and motor strip, which suggests an association of SNS and sensorimotor cortex dysfunction.⁶⁴ Schroder et al. have compared sensorimotor cortex and supplementary motor area activation during finger-to-thumb opposition using functional magnetic resonance imaging.⁷⁶ Patients with schizophrenia compared to normal controls showed significantly decreased activation of both areas, as well as a reversed lateralization effect, suggesting an association between sensorimotor cortex and supplementary motor area hypoactivity with motor SNS in schizophrenia.

In summary, very few studies have properly assessed the potential relationships between neuroanatomical and neuroimaging findings with SNS. Moreover, in some cases studies have tried to relate unspecific structural abnormalities with SNS without a documented a priori hypothesis. More functional imaging studies with specific relationship hypotheses are needed to further shed some light on this point.

Neurological Signs and Antipsychotic Medication Variables

Antipsychotic treatment often causes the emergence of extrapyramidal symptoms (EPS) and/or tardive dyskinesia (TD). These motor symptoms may be erroneously rated as neurological signs. The demonstration that SNS are independent of antipsychotic treatment or side effects would support the hypothesis that neurological signs are related to disease etiopathophysiology and an overt manifestation of the brain impairment resulting in schizophrenia.

Before reviewing the relationships of SNS with treatment-related effects, some methodological issues need to be considered. First, it is important to remember that neurological impairment is associated with poor prognosis variables, for example, negative and deficit symptoms. Poor-prognosis patients may receive higher antipsychotic doses, which could drive the association between neurological signs and antipsychotic dose. Similarly, it has been found in some studies that more

severe neurological impairment is associated with poorer antipsychotic response,^{16–17} so again there could be a trend for more neurologically impaired patients to be on higher doses. A final methodological issue is the fact that TD and EPS assessments frequently include items common to SNS scales, such as tremor, adventitious overflow, rigidity, and poor balance. This overlapping of assessed signs/symptoms may be a confounding factor that increases the likelihood of finding positive correlations due to the study design. Well-designed longitudinal studies with test-retest measures including SNS assessment, a washout period, or an antipsychotic-naive subgroup are the gold standard, but few such studies have been conducted.

Relationship of SNS to Antipsychotic Medication

The relationship between antipsychotic treatment and SNS has been examined in the form of either current antipsychotic doses,^{3, 6, 9, 13–15, 18–20, 26, 35, 43, 48–49, 52, 59, 62, 77} lifetime antipsychotic exposure,^{13, 18, 20, 27, 52, 77} or longitudinal studies that have assessed symptom response to antipsychotics.^{5, 16, 35, 51, 78} The vast majority of studies have not found associations between antipsychotic dosage and overall severity of neurological impairment^{3, 6, 9, 14–15, 26, 35, 43, 49, 51–52, 59, 77} or severity of impairment in any category of SNS.^{35, 62} Merriam et al. have reported that higher antipsychotic doses are associated with worse performance in prefrontal signs and, surprisingly, with better performance in parietal and nonlocalizing signs.⁴⁸ Gupta et al. have compared a group of antipsychotic-naive versus antipsychotic-treated patients and found a higher rate of SNS in the latter.²⁷ However, when further analyses were carried out within the antipsychotic-treated group, SNS were not predicted by lifetime duration of antipsychotic exposure. Longitudinal studies are better to address this issue. Scheffer and others administered the NES to 26 drug-naive and 3 drug-free patients with schizophreniform psychosis prior to treatment administration and after 6-week antipsychotic treatment and found no significant changes in NES scores.³⁵

Relationship of Neurological Signs to EPS and TD

Five studies have reported a significant association between SNS and EPS,^{18, 27, 39, 51, 79} whereas 5 other studies failed to find an association with EPS.^{5, 15–16, 35, 48} Of these studies, only Buchanan et al. examines the relationship between SNS and EPS within the context of a randomized clinical trial.⁵¹ We found that changes in the NES motor coordination subscale correlate with changes in EPS in patients treated with clozapine or haloperidol. The association between SNS and EPS reported by Emsley et al. is limited to balance.⁷⁹ In a longitudinal study, Scheffer and others found no associations between EPS and changes in NES score after 6 weeks of treatment.³⁵ The presence of TD has been related to SNS in

some^{13, 18, 27} but not all studies.^{15, 33, 35, 42, 51, 80–81} In 1 study, the correlation between TD and neurological impairment was quite high: $r = 0.96, p < .01$.¹³ Gupta et al. have found significant correlations between TD and SNS.²⁷ However, when they examined whether antipsychotic side effects were responsible for SNS differences between antipsychotic-treated and antipsychotic-naive patients, they found that TD and EPS scores were unrelated to group differences. Flashman et al. have also found patients with SNS to have significantly more TD than patients with no signs.¹⁸ Interestingly, Gureje compared patients with and without TD and found a trend for non-TD patients to show more SNS.⁸¹ In addition, in the Emsley et al. study, whose sample was mainly antipsychotic naive, motor coordination at baseline was associated with the emergence of TD at 24 months.⁷⁹

These studies point toward a possible relationship between worse performance on tasks involving motor dexterity and the presence of EPS and/or TD. If this is true, there are 3 possible explanations. First, the presence of EPS/TD could lead to a worsening of SNS. Second, EPS/TD and SNS may have a common etiology, for example, antipsychotics. This latter explanation is unlikely given the apparent lack of association between antipsychotic treatment variables and SNS. Further, SNS are sometimes observed in patients with schizophrenia prior to the onset of antipsychotic treatment. Finally, SNS could be a risk factor for EPS and TD.

Studies with Antipsychotic-Naive Patients

The view that SNS are independent of antipsychotic treatment and not state dependent is further supported by studies of antipsychotic-naive patients. As mentioned above, Gupta et al. have found that SNS and developmental reflexes were present in antipsychotic-naive patients, in a significantly higher proportion than in a normal sample.²⁷ The antipsychotic-naive subgroup showed significantly lower prevalence of SNS than the group on antipsychotics, and the opposite for developmental reflexes, with the antipsychotic-naive subgroup showing a higher prevalence. Scheffer and others have also found that their sample of 26 drug-naive and 3 drug-free schizophreniform patients presented significantly higher scores on all NES subscales than both samples of mixed psychiatric patients and normal controls.³⁵ Similarly, Keshavan et al. have found that their sample of first-episode antipsychotic-naive patients with schizophrenia presented a higher score in the NES sensory integration scale than their first-episode antipsychotic-naive nonschizophrenia psychoses sample.²⁸ Three additional studies^{31, 34, 38} report that SNS prevalence is significantly higher in antipsychotic-naive patients than in healthy volunteers. Another study reports a lack of significant differences in neurological impairment between antipsychotic-naive and treated first-episode patients with

schizophrenia, and it has found that 97% of the former group had at least 1 SNS.¹⁰ Sanders et al. have compared total SNS prevalence and factor structure between antipsychotic-naïve patients and patients off medication and found no significant differences.³³ In another study, antipsychotic-naïve patients presented even more SNS than patients on medication.⁵ Finally, a study of 200 treatment-naïve cases of schizophrenia found that, when an NES score of 2 was used as a cutoff point for neurological abnormality, the prevalence of neurological abnormality was 65% in the patient group and 50% for healthy subjects.⁴⁶ There were also significant differences for the NES total and all subscale scores. The high prevalence of SNS in the healthy controls may have been mediated by the fact that the catchment area was a rural setting in Ethiopia, and the higher rates of neurological impairment among healthy controls may be due to the quality of obstetrical care.¹⁹

In light of the vast majority of studies that report a lack of associations between antipsychotic treatment and SNS prevalence, along with the studies that have demonstrated the presence of SNS in antipsychotic-naïve patients, the hypothesis of SNS being secondary to antipsychotic treatment should be ruled out. The nature of the possible association between SNS and EPS/TD remains unclear. There is a need for better-designed studies that include test-retest measures, incorporate a wash-out period, and are conducted with antipsychotic-naïve patients or patients treated with second-generation antipsychotics, with their educed tendency to produce EPS.

Stability Over Time/Course of Illness

The potential validity of SNS as schizophrenia trait features depends not only on them not being secondary to other illness factors but also on their stability across the course of illness. Multiple studies have assessed the presence of SNS in first-episode patients, and in all cases they have documented the early onset of neurological signs.^{5, 10, 27, 30–31, 34–35, 45–46, 52, 54, 79, 82} The 4 studies that have compared first-episode patients with controls found greater SNS in patients than in controls.^{28, 34–35, 38}

In light of the fact that SNS are already present by the time of illness onset, the question then becomes whether neurological impairment follows a progressive deterioration or remains stable across the illness course. Cross-sectional studies have either examined correlations between neurological impairment and illness duration or compared groups of patients who were at different stages of illness, mainly through the inclusion of a first-episode subgroup. The vast majority of studies,^{9, 14–15, 19, 27, 33, 38, 47, 59, 77, 83} although not all,^{39, 43} have failed to find correlations between neurological impairment and illness duration. Comparisons among groups of patients at different stages of illness have also provided evidence for the nonprogression of neurological impairment.⁴⁶

Longitudinal studies are methodologically more appropriate to address the question of neurological impairment evolution over the course of illness. A 5-year follow-up study has shown progressively more neurological impairment.³⁰ The increase in neurological impairment was associated with a family history of psychosis, birth complications, male gender, and a nonremitting course of illness. Chen et al. found a significant increase in SNS in a 3-year period for some neurological signs (i.e., motor coordination, sensory integration, and disinhibition).²³ The sample was made up of long-illness-duration patients, so the authors attribute their finding to a possible deterioration process that occurs late in the course of illness. On the other hand, Smith et al. assessed a sample of chronically hospitalized patients with schizophrenia 2 or more times over a 5-year period and did not find significant changes over time.⁸³ Emsley et al. have found that NES total and subscale scores did not change over 12 months, except for the motor sequencing subscale, which improved at 3 months but not at 6 and 12 months.⁷⁹ This improvement seemed to be associated with symptom reduction. Whitty et al. followed up a sample of 97 first-episode schizophrenia patients and found an improvement of SNS associated with psychopathology amelioration.⁵⁴

Studies of antipsychotic response and SNS have occasionally reported an improvement in neurological status associated with medication response,⁵ although not always.³⁵ The conceptualization of SNS as trait features in schizophrenia is not inconsistent with oscillations in neurological status across the illness course, which may coincide with symptom exacerbations, the appearance of antipsychotic side effects, or exposure to alcohol or street drugs. This would mean that the presence of SNS may be a primary condition, but subtle oscillations may be secondary to other phenomena related to the illness.

In order to find out whether neurological signs are observable in the preschizophrenic child, Walker and others (see⁸⁴) conducted a retrospective study of home movies of children who later developed schizophrenia. They found associations between high rates of abnormal movements in early childhood (first 2 years of life) and subsequent diagnosis of schizophrenia. These abnormalities, which could be viewed as early motor precursors of SNS, appeared during early childhood and subsequently declined to normal levels until the underlying neurobiological structures were called up into action.⁸⁵ Rosso et al. have found that the unaffected siblings of preschizophrenic children show more motor coordination impairments than normal controls.⁸⁶ Hans et al. followed the offspring of (i) parents with schizophrenia, (ii) parents with nonschizophrenic mental disorder, and (iii) parents with no mental illness from infancy, through school age, to adolescence and found that the offspring of parents with schizophrenia were 3 times more likely to show significantly poorer neurobehavioral functioning (measured

by neuropsychological tests and neurological tasks) than the offspring of the other 2 groups and that the neurobehavioral impairment was quite stable over the follow-up period.⁸⁷ Schubert and McNeil have found that the total score for neurological abnormalities (hard and soft signs) at early adulthood (mean age 22.4 years) significantly correlates with neuromotor dysfunction at age 6, among the offspring of mothers with schizophrenia, the offspring of mothers with affective psychosis, and the offspring of healthy mothers.⁸⁸

In summary, the preponderance of data suggests that neurological abnormalities may be the result of early (pre- or perinatal) disturbances in brain function. Their initial expression would be in the form of motor developmental abnormalities during early childhood. They may remain silent for years, reappearing during adolescence in the form of neurological signs, predating the appearance of psychotic symptoms and possibly coinciding with the occurrence of negative symptoms and cognitive impairment. From the onset of the illness on, SNS would remain moderately stable, though they might suffer oscillations depending on state variables.

SNS as Clinical and Functional Outcome Predictors

The association of SNS with selected markers of illness severity, that is, more severe negative and disorganized symptoms and cognitive impairment, together with the fact that they are already present at illness onset, could confer to them the potential role of early-detectable, easily measurable, reliable predictors of functional and clinical outcome. The associations of SNS and antipsychotic treatment response, social and vocational outcome, and number and length of hospitalizations have been examined.

The ability of SNS to predict antipsychotic treatment response has had mixed results. Buchanan *et al.* have failed to find a relationship between baseline NES total or subscale scores and change in positive or negative symptoms in either clozapine- or haloperidol-treated patients.⁵¹ Bartko *et al.* have found that SNS do not correlate or predict treatment response with haloperidol.⁷⁸ Ceskova *et al.* have found that NES total score does not predict acute treatment efficacy.⁸⁹ In contrast, Smith and Kadewari have found that higher NES total and motor sequencing subscale scores (assessed within 3 months of the treatment initiation) predict worse treatment response.¹⁶ Convit *et al.* have found that higher haloperidol plasma levels worsen negative symptoms in high-neurological-impairment patients and improve them in low-neurological-impairment patients.⁶⁷ Das *et al.* have found that a low-SNS subgroup of schizophrenia patients experienced a greater improvement in cognitive and clinical measures than a high-SNS subgroup of patients, when both groups were switched from conventional to second-generation antipsychotics.⁶⁸ The authors explain

these results on the basis of previous studies that show that coarse brain disease patients are more vulnerable to the toxic effects of centrally active drugs. Mohr *et al.* have found that severely disabled treatment-resistant patients are significantly more neurologically impaired than the subgroup of better-functioning and younger patients.¹⁵

In studies of outcome measures, 2 studies have found significant correlations between severity of neurological impairment and poor current social function,^{53, 61} whereas 3 studies failed to find correlations with current³⁴ or premorbid social adjustment.^{56, 90} A prospective study with first-episode patients has found a significant correlation between higher neurological impairment and hospitalization length in a 2-year follow-up period.⁸² In a study of children at risk for schizophrenia,⁸⁷ neurobehavioral functioning at adolescence predicted the global psychiatric adjustment of subjects. Cross-sectional studies have reported both the presence^{18, 82} and the absence^{15, 27} of association between number of previous hospitalizations and neurological impairment.

Finally, patients with higher violence rates have been found to show greater neurological impairment,⁹¹ though history of violence has not always been associated with increased SNS rates.²⁰ Increased rates of neurological impairment have been related to increased persistence of assaultive behavior.⁶⁰ However, SNS do not seem to predict transient violence secondary to positive symptoms.⁹²

In summary, the majority of the studies support the hypothesis of an association between SNS and poorer functional outcome. In short-term clinical trials, in which neurological signs do not predict treatment response, other variables may be important in predicting treatment response in acutely ill patients. Long-term prospective longitudinal studies, including multiple functional outcomes, will provide more reliable data on the issue.

Neurological Signs as Endophenotypes

The identification of valid endophenotypes/intermediate phenotypes is a critical step in the delineation of the genetic etiology of schizophrenia. The feasibility of SNS as a putative endophenotype is supported by their higher prevalence in schizophrenia; conceptualization as a trait feature; early onset; relationship with other illness phenomena, such as negative symptoms and cognitive impairment; and association with outcome variables. In order to test their suitability as phenotypes, several studies have assessed the prevalence of neurological signs among nonschizophrenic relatives of patients with schizophrenia.

Most of the studies assessing neurological signs in healthy relatives of patients with schizophrenia have reported that the level of neurological impairment in relatives is intermediate between patient and healthy control levels (see Table 2). Interestingly, in the study by Ismail

Table 2. Summary of Family Studies Assessing Neurological Impairment Differences Among Patients With Schizophrenia, Their Relatives, and Healthy Controls

Reference	Sample Sizes (<i>n</i>)	Total Score	Sensory Integration	Motor Coordination	Primitive Reflexes	Hard Signs
Kinney, Yurgelun-Todd, & Woods, 1991, ¹⁰⁰ pooled with Kinney, Yurgelun-Todd, & Woods, 1986 ¹⁰¹	R: 52 C: 20	R > C				*
Cantor-Graae, McNeil, Rickler, et al., 1994	S: 22 MT: 22 CT: 14	S > MT > CT	*	*	*	*
Griffiths, Sigmundsson, Takei, Rowe, & Murray, 1998	SS: 28 FS: 32 SSR: 44 FSR: 63 C: 20		FS, FSR > SS, SSR > C	FS, FSR > SS, SSR > C	FS > SS	SS > FS, FSR, SSR, C
Ismail, Cantor-Graae, & McNeil, 1998	S: 60 Si: 21 C: 75		S > C Si > C	S > C	S > C Si > C	S > C Si > C
Kinney, Yurgelun-Todd, & Woods, 1999	S: 54 R: 73 C: 44		S, R > C	S > R, C		S, R > C
Chen, Chen, & Mak, 2000	S: 15 Si: 21 C: 26	S > Si > C	S > Si, C	S > Si > C	S, Si > C	n.s.
Niethammer, Weisbrod, Schiesser, et al., 2000	S: 13 MT: 13 CT: 17	S > MT > CT	n.s.	S > T > C		
Egan, Hyde, Bonomo, et al., 2001	S: 115 Si: 185 C: 88	Woods scale: S > Si > C Neurological Evaluation Scale: S > Si, C	S > Si, C	S > Si, C		Si > C S = Si, C
Lawrie, Byrne, Miller, et al., 2001	S: 30 HR: 152 C: 35	S > HR, C	S > HR > C	n.s.		
Appels, Sitskoorn, de Boo, et al., 2002	P: 32 C: 34	n.s.				n.s.
Yazici, Demir, Yazici, & Gogus, 2002	S: 99 Si: 80 C: 50	S > Si > C	S > Si > C	S > Si > C		
Gourion, Goldberger, Olie, Loo, & Krebs, 2004	S: 61 GLP: 26 NGLP: 50 C: 44	S > GLP > NGLP > C	n.s.	GLP > NGLP	n.s.	

Table 2. Continued

Reference	Sample Sizes (n)	Total Score	Sensory Integration	Motor Coordination	Primitive Reflexes	Hard Signs
Kelly, Cotter, Demihan, et al., 2004	S: 15 MT: 8 DT: 7	n.s.	*	*	*	*
Schubert & McNeil, 2004	OMS: 28 OMAP: 36 OHM: 88	OMS > OMAP, OHM	OMS > OMAP, OHM	OMS > OMAP, OHM	OMS > OMAP, OHM	OMS > OMAP, OHM
Niemi, Suvisaari, Haukka, & Lonnqvist, 2005	HR: 154 C: 97	HR > C	*	*	*	*

Note: C = controls, CT = control twins, DT = dizygotic twins, FS = patients with familial schizophrenia, FSR = relatives of patients with familial schizophrenia, GLP = genetic-loaded parents, HR = high-risk individuals, MT = monozygotic twins, NGLP = Non-genetic-loaded parents, OHM = offspring of healthy mothers, OMS = offspring of mothers with schizophrenia, OMAP = offspring of mothers with affective psychosis, P = parents, R = relatives, S = patients with schizophrenia, Si = siblings, SS = patients with sporadic schizophrenia, SSR = relatives of patients with sporadic schizophrenia, T = twins; * = cluster of signs included in the neurological assessment but whose discriminant power has not been separately assessed, n.s. = cluster of signs that have been included in the neurological assessment but whose discriminant power has been found not to be significant.

et al. comparing patients, siblings, and normal controls, there are significant positive correlations between patients and their own siblings in the scores for total neurological abnormality, soft signs, and motor functions, which suggests that the degree of neurological abnormality may be genetically mediated.¹¹ Ismail et al. also compare the number of obstetric complications (OCs) in these 3 groups and find that both patients and their siblings have more OCs than healthy controls, but no significant differences have been found between patients and their siblings.⁹³ Furthermore, whereas the healthy siblings showed correlations between OCs and neurological signs, no such correlations were found among the patients, a result that has been replicated.^{19, 94} The authors assert that this pattern of results supports a genetic origin of the neurological signs.

Chen et al. have found that whereas sensory integration, motor coordination, and EPS are more prominent in patients than in their siblings, disinhibition and motor coordination signs are significantly higher in siblings than in healthy controls.⁵⁹ Yazici et al. have found a similar pattern for NES total and subscale scores.³⁹ Gourion et al. have compared patients with schizophrenia, their nonpsychotic parents with a second relative with history of schizophrenia, their nonpsychotic parents without a second relative with history of schizophrenia, and healthy controls and found that SNS differ among the 4 groups, including total measures and measures of motor coordination and motor integration.²⁵ There were higher scores in motor coordination and integration subscores in presumed carriers than in presumed noncarriers. Schubert and others (see⁸⁸) have found that the offspring of mothers with schizophrenia present significantly higher scores than both the offspring of mothers with affective psychosis and the offspring of healthy mothers on scales of neurological abnormalities, including hard signs, soft signs, motor functions, and motor coordination.

Studies of monozygotic twins discordant for schizophrenia have found similar results, with SNS prevalence rate in the healthy discordant monozygotic twins in between the rate of the affected twins and the rate observed in healthy comparison twins.⁹⁴ Niethammer et al. report higher rates of SNS in patients with schizophrenia than in their unaffected monozygotic twins, as well as a higher prevalence of SNS in both groups than in a sample of 17 pairs of healthy monozygotic twins.⁹⁵ Post hoc analyses have revealed that differences among the 3 groups were limited to motor signs. Kelly et al. do not find significant differences in neurological impairment between monozygotic twins concordant (n = 3) and discordant (n = 5) for schizophrenia and between dizygotic twins concordant (n = 1) and discordant (n = 6) for schizophrenia.⁹⁶

In contrast, 2 studies have failed to find a relationship between neurological impairment and family history of psychosis.^{46, 77} However, neither study used a structured diagnostic interview for family history. Three studies

have failed to find significant differences in neurological impairment between healthy relatives of patients with schizophrenia and normal controls.^{24, 97–98} Egan et al. compared 3 large samples of patients with schizophrenia, their siblings, and normal subjects and found only weak to moderate differences between siblings of patients with schizophrenia and controls on the Woods scale and no significant differences on the NES.²⁴ Appels et al. report higher rates of impairment in all neurological domains except for cranial nerve functions and gait in a sample of parents of schizophrenia patients compared to control subjects.⁹⁷ However, the differences were not significant, and they did not find differences between parents with and without family history of schizophrenia spectrum disorders. Finally, Lawrie et al. have found that subjects at high risk for developing schizophrenia showed rates of neurological impairment between those of patients and normal controls for the NES sensory integration score, whereas patients showed higher NES total and subscales scores than both controls and subjects at high risk.⁹⁸ None of the NES scores was able to distinguish high-risk subjects experiencing psychotic symptoms from those who were not. However, we have previously noted the lack of association between SNS and positive symptoms, which suggests that these results may not argue strongly against a genetic mediation of neurological signs. Furthermore, there were very low rates of negative symptoms and thought disorder among the high-risk subjects, variables more frequently related to neurological signs. The Helsinki high-risk study also detected a greater prevalence of SNS in the offspring of mothers with schizophrenia spectrum disorder than in healthy control children.⁷⁵

In summary, healthy relatives of patients with schizophrenia seem to show higher overall SNS rates than healthy controls and lower overall SNS rates than their affected relatives. Interestingly, the magnitude of these differences is not uniform across different neurological sign clusters, and, although there is not a clear pattern, it seems that there is a trend for soft (versus hard) neurological signs, especially those involving motor tasks, to be more genetically mediated. The study of potential associations between neurological signs and obstetric complications supports the idea of genetic mediation of neurological signs, since correlations between these measures are more common in unaffected relatives than in patients with schizophrenia. Finally, motor signs appear to be less related to OCs, a finding that gives further support to the hypothesis of motor signs being more intimately related to illness genetic vulnerability.

Summary and Conclusions

Research on neurological signs in schizophrenia has provided strong evidence supporting the conceptualization

of neurological signs as a trait feature. However, the full delineation of the significance of SNS in schizophrenia would benefit from continued methodological improvements, including the development of standardized, broadly accepted assessment tools with acceptable sensitivity and specificity. In order to do so, assessment tools should only include SNS that are relevant to the disorder, with “relevancy to schizophrenia” defined by their prevalence, relationship to illness-related phenomena, and conceptual significance. Since not all signs relate homogeneously to different illness phenomena, assessment tools should also provide neurological sign subscales that are related to specific clinical correlates or are of importance because of their putative anatomical localization (i.e., frontal/prefrontal and parietal). Also, comparisons of SNS, a putative trait marker, and other phenomena that are potentially state dependant (i.e., positive symptoms) should be avoided because they increase the likelihood of contradictory results. Consideration of the above-mentioned methodological issues could lead to the clarification of some of the issues concerning SNS in schizophrenia.

Neurological signs seem to be more prominent in patients with schizophrenia than in healthy controls and in patients with other psychiatric disorders. However, the conceptualization of neurological signs as a trait feature of schizophrenia depends not only on their high prevalence among patients with schizophrenia but also on them being directly related to disease etiopathophysiology, rather than being secondary to other phenomena, such as antipsychotics and their side effects. The independence of SNS from antipsychotic treatment has been adequately demonstrated, but the evidence regarding independence from other phenomena, such as EPS and TD, is still limited. In part, this is due to overlapping items among scales assessing neurological signs and those evaluating EPS and TD. Their co-occurrence may also reflect a shared association with the neurological abnormality underlying the illness.⁹⁹

Relationships among neurological signs, symptoms, cognitive impairments, and other schizophrenia phenomena confer to the former the category of an easy-to-assess biological marker. The study of potential relationships with symptomatology has shown negative and disorganized symptoms to potentially be significantly related to neurological impairment, especially prefrontal/frontal and parietal signs, whereas positive symptoms appear to be unrelated to SNS. The lack of a significant SNS–positive symptom relationship is expected, since neurological impairment is hypothesized to be a trait feature, whereas positive symptoms are state dependent. In contrast, negative symptoms tend to be more stable across the course of illness, and their presence may even predate the diagnosis of schizophrenia, although it could be more enlightening to distinguish primary enduring versus secondary negative symptoms.

In light of the fact that SNS appear to be a trait feature of schizophrenia and a possible biological marker of prognosis, their early detection could result in early intervention and, hence, may lead to a better prognosis. In addition, in light of the higher prevalence of SNS in patients with schizophrenia than in patients with other psychiatric illnesses, SNS may be used to identify subjects at high risk for developing schizophrenia (e.g., psychotic first-episode patients, relatives of patients with schizophrenia). As with other risk factors for schizophrenia, the low predictive value of SNS recommends their use in combination with other risk factors.

Finally, neurological signs may represent a valid endophenotype, which could help focus genetic research on the etiopathogenesis of schizophrenia. In order for them to be adopted as a valid biological marker for genetic research, the genetic mediation of neurological signs or specific clusters of neurological signs needs to be demonstrated. Family studies have consistently found a significantly higher presence of neurological signs in the relatives of patients with schizophrenia. However, the possibility that specific neurological signs may be due to pre- or perinatal complications or secondary to the early development of the schizophrenic brain has not been excluded.

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