During the past few decades, there has been a sustained research effort on the nature and significance of neurological soft signs (NSS) in schizophrenia. Earlier studies revealed there was an increased prevalence of NSS in schizophrenia compared to healthy individuals. This increase also has been found in medication-naive, first-episode patients. Family studies have identified increased NSS among first-degree relatives. Neurological soft signs also are increased in the healthy co-twin of monozygotic twins discordant for schizophrenia. These findings suggest NSS may be considered a target feature or biological marker that mediates the expression of schizophrenia.

Drs. Chen and Chan are from the Department of Psychiatry, University of Hong Kong, China.

Address reprint requests to Dr. Eric YH Chen, Department of Psychiatry, University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong.

The authors have no industry relationships to disclose.
and Ethnic Correlates.

various symptom dimensions. The most robust finding appears to be a relationship with negative symptoms. Neurological soft signs have also been related to disorganization symptoms. Most studies did not find a relationship with positive symptoms.

The specificity of NSS for schizophrenia is, however, unclear as NSS are also increased in mood disorders, though possibly to a lesser extent. In addition, the level of NSS in schizophrenia could be potentially confounded by a number of demographic variables. Importantly, NSS in schizophrenia are correlated with measures of intelligence and education level.

Potential ethnic relationships have not been fully studied. Neurological soft signs have been reported to be increased in African American control subjects and schizophrenic patients, and in control subjects in Nigeria. There are no reports of ethnic effects of NSS in Asian subjects.

The variation of NSS across ethnic

Eric Y.H. Chen, MA Oxon, MBChB Edin, MRCPsych, FHKAM(Psychiatry); and Raymond C.K. Chan, PhD
and demographic groups could play a crucial role in understanding their significance. Research suggests schizophrenia is likely to have a polygenic mode of inheritance in which each gene carries a minor effect. The phenotypic expressions of some contributing genes may be widespread in the normal population. Consistent with this, NSS are also found in the normal population. More detailed knowledge about their association with nonclinical factors, such as intelligence, may help to understand the nature of predisposition.

It is undecided whether NSS and intelligence level contribute independently to the risk for schizophrenia. Likewise, since several clinical and outcome features in schizophrenia exhibit gender effects, it is pertinent to examine whether NSS manifestations also exhibit gender differences.

The variations of NSS expression with age in healthy and pathological circumstances are also important issues. The early development of a feature (trait) such as NSS does not rule out its later involvement in processes associated with aging or degeneration. It is important to follow the longitudinal course of NSS to fully appreciate their value as target features in different stages of the disorder. Understanding the natural history of NSS also may enhance the design of future studies.

In the context of current research in NSS, this article reviews data from a number of our studies with the aim of estimating demographic and ethnic effects by comparing the levels of NSS in Chinese (Hong Kong) and Caucasian (United Kingdom) samples. We also examine the relationship(s) between NSS, age, and illness duration.

**METHODS**

Our data come from studies carried out at two locations (Hong Kong, China, and Cambridge, United Kingdom). Both studies used the Cambridge Neurological Inventory (CNI) for NSS measurement. In order to facilitate comparison of data, the CNI scoring method was standardized across studies. Data analysis was carried out with raw data from the original studies. All studies were approved by the relevant ethics committees, and informed consent was obtained from all participants.

**Samples**

In Hong Kong, patients between ages 18 and 65 who fulfilled DSM-III-R criteria for schizophrenia were recruited from inpatient units. Subjects were excluded if there was a history of neurological or serious medical illness such as epilepsy, head injury, stroke, diabetes, and endocrine disorder or a history of substance abuse. Each participant received clinical and cognitive evaluations in addition to NSS assessment. All patients were taking conventional antipsychotics at the time of the study. Control subjects between the ages of 18 and 65 without a history of psychotic illness, neurological disorder, and substance abuse were unpaid volunteers recruited through public education events. Standardized inclusion/exclusion criteria were adopted in the study sam-

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Chinese Sample (n = 195)</th>
<th>Caucasian Sample (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.1 (12.2)</td>
<td>39.3 (11.0)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>8.1 (3.5)</td>
<td>8.9 (3.0)</td>
</tr>
<tr>
<td>Verbal IQ estimates*</td>
<td>77.9 (14.2)</td>
<td>95.3 (8.6)</td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>120:75</td>
<td>34:18</td>
</tr>
<tr>
<td>Clinical Data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>15.1 (9.8)</td>
<td>17.1 (11.8)</td>
</tr>
<tr>
<td>Chlorpromazine equivalence (mg/d)</td>
<td>955.8 (1020.9)</td>
<td>1728 (6299)</td>
</tr>
<tr>
<td>NSS Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor coordination</td>
<td>20.61 (25.7)</td>
<td>43.97 (29.5)</td>
</tr>
<tr>
<td>Sensory integration</td>
<td>20.90 (30.1)</td>
<td>42.33 (26.3)</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>15.56 (14.1)</td>
<td>18.75 (15.1)</td>
</tr>
<tr>
<td>Total of NSS score</td>
<td>18.33 (18.3)</td>
<td>33.38 (17.6)</td>
</tr>
</tbody>
</table>

*Verbal IQ in Chinese schizophrenia and healthy controls was estimated from the information subscale of the Wechsler Adult Intelligence Scale – Revised; verbal IQ estimates in Caucasian subjects were based on National Adult Reading Test scores; NSS = neurological soft signs.
TABLE 2
Pearson Correlations* Between Neurologic Signs Subscales and Demographic Variables in Healthy Controls

<table>
<thead>
<tr>
<th></th>
<th>Caucasian Healthy Controls (N = 80)</th>
<th>Chinese Healthy Controls (N = 94)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Motor Coordination</td>
<td>Sensory Integration</td>
</tr>
<tr>
<td>Age</td>
<td>0.29*</td>
<td>0.11</td>
</tr>
<tr>
<td>Education</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Intelligence level</td>
<td>-0.30*</td>
<td>-0.32*</td>
</tr>
</tbody>
</table>

*Nonparametric analyses did not in general differ from parametric ones, except for indicating a significant relationship between age and motor coordination (P < 0.05), and education and disinhibition (P < 0.05) among Chinese healthy controls.

P < 0.05

P < 0.01

TABLE 3
Pearson Correlations* Between Subscales and Clinical Variables in Schizophrenic Patients

<table>
<thead>
<tr>
<th></th>
<th>Caucasian Schizophrenia (N = 52)</th>
<th>Chinese Schizophrenia (N = 195)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Motor Coordination</td>
<td>Sensory Integration</td>
</tr>
<tr>
<td>Age</td>
<td>0.17</td>
<td>0.12</td>
</tr>
<tr>
<td>Education</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Intelligence level</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>0.12</td>
<td>0.14</td>
</tr>
<tr>
<td>Medication</td>
<td>-0.1</td>
<td>-0.02</td>
</tr>
</tbody>
</table>

*Nonparametric analyses did not in general differ from parametric ones, except for indicating a significant relationship between medication and sensory integration in Chinese schizophrenic patients (P < 0.05).

P < 0.001

P < 0.05

Subjects also were assessed using the Information subscale in the Weschler Adult Intelligence Scale – Revised (Hong Kong edition) to estimate intelligence.

In Cambridge, patients between ages 18 and 65 who fulfilled DSM-III-R criteria for schizophrenia were recruited from patients at Fulbourn Hospital. All patients underwent only NSS assessments and were taking conventional antipsychotics at the time of the study. Healthy control subjects were paid volunteers from employees of a local company. Subjects also were recruited with the National Adult Reading Test to estimate intelligence.

Assessment

Neurological soft sign assessments were conducted using the CNI, which operationalized the elicitation and scoring of neurological signs in seven domains. Three of the CNI subscales (motor coordination, sensory integration, and disinhibition) were included in the present analysis. Motor coordination signs included finger-thumb opposition, finger-thumb tapping, dysdiadochokinesia, fist-edge-palm test, and Ozeretski test. Sensory integration signs included extinction, finger agnosia, stereognosia, graphesthesia, and left-right disorientation. Disinhibition signs included blinking during saccade, head movement during saccade, winking with one eye, mirror movements, and the go/no-go sign.

In the standardized analysis for this study, items were categorized as either present or absent. Items that could be scored on both left and right were treated as independent measures. To facilitate comparison between different subscales, a scaled score was defined as the summed score for the subscale items divided by the possible score range and then converted to a percent score. Inter-rater reliabilities were calculated for each of the subscales based on a video-taped examination of 15 subjects. The exercise involved all raters (5 raters from the Hong Kong study and 2 raters from the United Kingdom study). Intra-class correlation coefficients for the NSS subscales ranged from 0.66 to 0.93.

Assessment of Clinical and Demographic Information

Symptom assessment was conducted with the 18-item Brief Psychiatric Rating Scale. Negative symptoms were further assessed with the High Royds Evaluation of Negativity. Antipsychotic drug dosages were converted to chlor-
promazine equivalents. Clinical data were collected blind to NSS findings.

**Data Analysis**

Data were analyzed using the Statistical Package for Social Science (SPSS, version 10.1). Bonferroni corrections were made for multiple comparisons. Covariance analysis or partial correlation coefficients were used to examine potential confounding effects. To explore the effects of age and illness duration, subjects were assigned to different age cohorts and illness duration cohorts for group comparisons. This approach complements simple correlation analysis and should enable non-linear relationships to be identified. In linear trend analyses, $F$ and $P$ values for the weighted linear and nonlinear terms were reported. Descriptive characteristics and NSS scores for each sample are summarized in Table 1.

**RESULTS**

**Relationships Between NSS and Intelligence, Education, and Gender**

In both the healthy Chinese and Caucasian control samples, total NSS were associated with verbal intelligence estimates ($r = -0.3, P = 0.02; r = -0.42, P < 0.001$, respectively) (Table 2). In the Chinese controls, total NSS were correlated with education level ($r = -0.36, P = 0.0005$).

In relation to NSS subscales, the Chinese sample showed verbal intelligence estimates were inversely correlated with motor coordination signs ($r = -0.3, P = 0.01$) and sensory integration signs ($r = -0.31, P = 0.005$). Fewer years of education were also associated with increased motor coordination signs ($r = -0.35, P = 0.0005$). In the healthy Caucasian sample, lower verbal intelligence was associated with increased sensory integration signs ($r = -0.33, P = 0.003$).

For Chinese schizophrenic subjects, total NSS were significantly correlated with age ($r = 0.22, P = 0.004$), education level ($r = -0.37, P = 0.0005$), and verbal intelligence estimates ($r = -0.48, P < 0.001$) (Table 3, page 205).

All three NSS subscales were correlated with education level (motor coordination, $r = -0.33, P < 0.001$, sensory integration, $r = -0.33, P < 0.001$, disinhibition, $r = -0.25, P = 0.001$) and with verbal intelligence estimates (motor coordination, $r = -0.46, P < 0.001$, sensory integration, $r = -0.45, P < 0.001$, disinhibition, $r = -0.36, P < 0.001$). There was no significant gender effect.

**Cross-Ethnic Comparisons**

Analyses of covariance (ANCOVA) were conducted for Chinese and Caucasian healthy control subjects, controlled for age and intelligence. This revealed there was no significant ethnicity effect on total NSS scores. Analyses of subscales scores, however, suggest that after correction for multiple comparisons, there was a trend ($F_{1,165} = 5.80, P = 0.051$) for healthy Caucasian subjects to have higher sensory integration signs than their Chinese counterparts. There was no significant difference in NSS between Chinese and Caucasian schizophrenic patients.

**Clinical Correlates and Gender**

Clinical correlates for NSS were evaluated based on the Chinese patient sample. There was a modest association between antipsychotic dosage and motor coordination subscale score ($r = 0.19, P = 0.007$). There was no correlation between anticholinergic dosage and any of the NSS scores.

When the whole sample was considered, only nonsignificant correlations were found for Brief Psychiatric Rating Scale and High Royds Evaluation of Negativity symptom ratings and NSS. Further correlation analyses were conducted separately for male and
female patients. In female patients, the “Thought” domain of the High Royds Evaluation of Negativity negative symptom scale was significantly correlated with motor coordination ($r = .37$, $P = .001$) and with sensory integration ($r = .36$, $P = .003$), as well as total NSS ($r = .42$, $P = .0005$). In contrast, there was no significant correlation between NSS and symptom domains in male schizophrenic patients.

**Relationship Between NSS and Age**

Chinese schizophrenic patients and healthy controls were assigned to four groups according to age (16-25 years, 26-35 years, 36-45 years, > 45 years). For patient subjects, analysis of variance with linear trend analysis revealed a significant linear trend increase in total NSS across the groups ($F = 5.2$, $P = .023$). Nonlinear trend was insignificant. Subscale score analyses showed the increase was only in the motor coordination subscale ($F = 12.5$, $P = .003$) and not in the sensory integration and disinhibition subscales (Figure). However, this difference became nonsignificant when ANCOVA was controlled for education level. There was also no significant age effect in the control group.

**Illness Duration and NSS**

Patients were categorized into six groups according to illness duration (< 5 years, 6-10 years, 11-15 years, 16-20 years, 21-25 years, > 25 years). Analysis of covariance revealed a significant linear increase in total NSS associated with longer illness duration ($F = 13.3$, $P = .0004$); no significant nonlinear trend was identified. Among the subscales, only motor coordination signs were significantly increased ($F_{1, 187} = 18.8$, $P < .001$). Analysis of covariance when controlled for education also confirmed a significant increase in motor coordination signs with longer illness duration ($F_{5, 181} = 3.677$, $P = .003$).

**DISCUSSION**

In this article, we have reviewed various demographic and clinical correlates of NSS in schizophrenia. We have analyzed standardized NSS data from our studies of the CNI in a Caucasian sample as well as a Chinese sample in order to identify relationships between NSS and intelligence, education, gender, ethnicity, age, and illness duration.

**Intelligence and Education**

The relationship between lower intelligence and NSS has been reported in a number of studies. The correlation between NSS and intelligence level was found not only in patients with schizophrenia, but also in patients with personality disorder and mood disorders. Analysis revealed the correlation was found in all three subscales of the CNI studied.

In the light of increasing recognition that schizophrenia has a neurodevelopmental component, intelligence and education level probably should not be viewed as mere “demographic” variables that constitute simple antecedent risks for the disorder. Instead, similar to NSS, intelligence and education level could be construed as downstream consequences.
of earlier developmental events. Thus, it may be more appropriate to consider both NSS and intelligence level as reflections of developmental endophenotypes that indicate a neurointegrative dysfunction.\textsuperscript{31} From this perspective, an important consideration is the extent to which NSS and intelligence are in line with Malla et al.,\textsuperscript{9} who found negative symptoms correlated with different NSS factors in male and female patients. Such gender-related patterns of correlation might underlie inconsistencies in some previous findings. As in most previous NSS studies, significant gender differences in total NSS was not found.\textsuperscript{1,7,9,11,18,34-37}

In order to fully appreciate the significance and meaning of NSS, it is important to examine their relationship to ethnic, demographic, and clinical correlates in healthy and schizophrenic patient populations.

**Gender Effects and Symptoms**

In contrast to previous studies, we did not find any relationships between symptom domains and NSS in the entire sample. However, we found that in female schizophrenic patients, the subdomain of thought, among the negative symptoms, was specifically associated with NSS, while no such association was found for male schizophrenic patients. This finding suggests there may be gender variations in the pattern of symptom correlations among neurological signs. The finding of gender difference in symptom correlates of NSS is independent expressions of underlying risk factors.

**Ethnicity Effects**

Buchanan and Heinrichs\textsuperscript{20} reported healthy African Americans have an increased level of NSS compared with Caucasians. The increase was particularly notable in the sensory integration subscale. In our study, we found no significant difference in the total NSS score between Chinese and Caucasian healthy subjects. However, there was a trend for Chinese subjects to have lower scores in the sensory integration subscale. This suggests that among the subscales in NSS, sensory integration may be more vulnerable to ethnic variation. The nature of such variations is unknown. It appears that the assessment and the rating processes are not likely to be sources of variation, as both the linguistic and the conceptual demands involved in NSS evaluation are relatively simple, and it is possible to achieve good interrater reliability regardless of the ethnic origin of the subjects and the raters.

A more likely source for ethnic variation in NSS could be of a biological rather than cultural nature. Studies of NSS among healthy subjects in different ethnic groups are important for addressing this issue. In this context it is interesting to note that Gureje\textsuperscript{21} speculated that increased NSS in the Nigerian control subjects might relate to the level of obstetric care.

While we found no overall ethnic difference in NSS between Chinese and Caucasian samples, an inherent limitation is the cross-ethnic comparability of intelligence.\textsuperscript{38} Likewise, the lack of comparable data between the Chinese and Caucasian schizophrenic patient groups has limited the scope of comparison between the two clinical groups. These issues require further examination, probably by comparing the cross-ethnic presence of NSS in patients, their siblings, and healthy controls matched for intelligence and age.

**Effects of Age**

The relationship between age and NSS varies in previous studies. Several studies found no relationship between age and NSS\textsuperscript{3,5,35,36} while others have\textsuperscript{7,18,37,39} Different age ranges among studies was considered as a potential contributor to the inconsistency.\textsuperscript{1} We found a linear trend for NSS to increase with age in the patient group, but not in the control group. However, the effect became nonsignificant after covariance analysis controlled for education. This highlights the possibility that different approaches to address potential confounding variables could have contributed to the inconsistencies in previous findings.
Illness Duration

Data addressing the relationship between NSS and illness duration also conflict. In Kolakowska et al.,38 found patients with NSS had longer illness duration than those without. However, when stratified into smaller groups, according to illness duration, the proportion of those with NSS was not significantly different. Flashman et al.32 found patients with NSS had a longer illness duration (younger age of onset and same current age). Cuesta et al.7,18 also found frontal signs were related to duration of illness.

Others have failed to find a relationship.10,11 Flyckt et al.8 compared motor tests (including NSS) between first-episode psychotic patients and chronic patients and found no significant difference. In our sample, we found a linear trend for increased NSS with illness duration. This effect appears to be particularly prominent for the motor coordination subgroup of signs.

The relationships between NSS and age and illness duration are important. Although NSS is known to be present in high-risk subjects and first-episode patients, it is important to ascertain whether NSS also progresses with age and illness duration. This issue is important in clarifying whether NSS, as a target feature, reflects those factors only affected by the neurodevelopmental mechanisms of the disorder or whether it is also vulnerable to potential progressive processes. In addition, it is important to distinguish between changes in NSS associated with illness progression from effects of aging. Our analysis suggests there is an increase in NSS with both age and illness duration. It is difficult, however, to distinguish which is the more important factor. In this regard, one particular limitation is that in a cross-sectional study, age usually is correlated with illness duration.

Longitudinal studies are required to resolve some of these issues, and to date, few have been carried out. Smith et al.40 demonstrated NSS in a sample of middle-aged chronic patients remained stable. However, Chen et al.41 studied a sample of slightly older patients and found evidence of progression. Longitudinal studies with a larger sample and longer follow-up will be required to learn whether there is longitudinal change in NSS at specific stages of the illness.

CONCLUSION

Neurological soft signs are important target features of schizophrenia that may reflect the presence of genetic and non-genetic vulnerability to schizophrenia. In order to fully appreciate the significance and meaning of NSS, it is important to examine their relationship to ethnic, demographic, and clinical correlates in healthy and schizophrenic patient populations.

We analyzed NSS data (using the CNI) from studies of Chinese and Caucasian schizophrenic patient and healthy control samples to address these issues. The results confirm a robust relationship between NSS and intelligence not only for patients, but also for healthy controls. Although the overall NSS level did not differ between Chinese and Caucasian subjects, results suggest ethnic variation in subscale scores may exist. The data also revealed a gender difference in the pattern of symptom correlation, i.e., NSS association with negative symptoms appears to be specific only for female subjects. Neurological soft signs also probably increase with age and illness duration. Clarification of these NSS relationships may increase our understanding of NSS in schizophrenia and facilitate appropriate design and control in future studies.

REFERENCES


38. Greenfield FM. You can’t take it with you: why ability assessments don’t cross cultures. Am Psychol. 1998;52:1115-1124.

