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# Proposing the short Neurological Evaluation Scale

Ojagbemi A, Emsley R, Gureje O. Proposing the short Neurological Evaluation Scale.

**Objectives:** The time required in completing the 26 items of neurological examinations in the standard Neurological Evaluation Scale (NES) may limit its utility in pragmatic clinical situations. We propose the Short Neurological Evaluation Scale (S-NES) for use in busy clinical settings, and in research.
**Methods:** Using confirmatory factor analyses, we identified 12 items of neurological examination showing significant overlap with previously reported theoretical and empirical categories of neurological soft signs (NSS) in schizophrenia. This provided justification for the development of a shorter version of the NES based on the empirically identified NSS. In the present study, we relied on existing data to present an initial validation of the S-NES against the referent standard 26-item NES.
We determined sensitivity, specificity, and likelihood ratios. Posterior-test probability was estimated using a Bayesian nomogram plot.
**Results:** Using data derived from 84 unmedicated or minimally treated patients with first-episode schizophrenia, 12 empirically determined items of neurological examinations showed high agreement with the 26 items in the standard NES battery (sensitivity = 96.3%, specificity = 100%, and posterior-test probability = 100%).
**Conclusions:** Within limitations of validity estimates derived from existing data, the present results suggest that the design of the S-NES based on empirically identified 12 items of neurological examination is a logical step. If successful, the S-NES will be useful for rapid screening of NSS in busy clinical settings, and also in research.

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Keywords: biological markers; endophenotypes; psychometric analyses; screening tools

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**Significant outcomes**

- The clinical utility of neurological soft signs (NSS) may be improved by simplifying their measurement.
- 12 items of neurological examination overlapping with previously described categories of NSS in schizophrenia were identified by factor analyses.
- The 12 items showed high agreement with the referent standard 26-item Neurological Evaluation Scale (NES) in initial validation analyses.
- The design and standardisation of a short-NES (S-NES) based on empirically identified 12 items of neurological examination in an independent study is justified.

**Limitations**

- Analyses were based on existing data collected using the standard 26-item NES.
- Given the heterogeneous nature of both NSS and schizophrenia, the possibility exists that the identified 12 items of neurological examination are specific to the studied sample, thus limiting generalisation.

## Introduction

NSS are subtle but observable neurological abnormalities. They include impairments in fine motor and sensory functions, as well as persistence of some primitive reflexes on neurological examination. These signs are often associated with abnormalities

in widespread cortical and sub-cortical brain connections (1–7). They may also be indicative of both vulnerability (8–12) and clinical course characteristics of a variety of neuropsychiatric disorders (12–15).

NSS are documented to be in excess in schizophrenia patients at various stages of disease (14,16), their unaffected first-degree relatives (17), and those with schizophrenia spectrum disorders (18). They are thus an important subset in the heterogeneous manifestation of schizophrenia, and satisfy consensus criteria as endophenotypes of the disease (10,19).

Endophenotype markers may represent more accessible readout of gene functions in the effort to identify genes conferring vulnerability to schizophrenia. In this way, they could be used in ordinary clinical settings to establish that an individual had progressed along the neuro-developmental pathway to schizophrenia. The presence of higher rates of NSS may therefore have the potential to augment the predictive power of psychopathological tests for individuals at risk of developing the disease. The clinical importance of NSS in schizophrenia is that they may also allow us to define a specific subset of patients with a distinct course of illness and specific requirements regarding treatment interventions.

Among available measures of NSS, the most fully described and widely employed in adult psychiatry is the NES (20). Other scales that have been developed for this purpose include the quantified neurological scale (21), Heidelberg scale (22), Cambridge neurological inventory (23), and brief motor scale (24). Apart from the brief motor scale designed specifically for motor soft signs, other batteries are composed of a heterogeneous inventory of neurological examination abnormalities, including behavioural observations. As such, different items contribute to the composite NSS scores of the various instruments. This limits interpretation as to the meaning of NSS in categories of patients with schizophrenia.

In our previous exploratory (25) and confirmatory (26) factor analyses of the standard (26 items) NES in a sample of 84 unmedicated or minimally treated patients with first-episode schizophrenia, we identified 12 items showing significant overlap with previous theoretical (27) and empirical categories (28–32). This raised the possibility for the development of a shorter version of the NES (S-NES) based on the 12 empirically identified items of NSS. In the present study, we investigate the validity of the 12 items of NSS within existing data on first-episode schizophrenia to determine whether there is sufficient merit in proceeding from factor analysis to the design of the S-NES from the standard (26 items) NES in an independent study.

As NSS appear to identify a group of patients who may have a more severe schizophrenia as well as poorer response to treatment, the S-NES will be especially useful for rapid examination of NSS in busy clinical settings to provide information, in addition to history and gross findings on physical examination, that an individual had progressed along a more neurobiological pathway to the disease. This is of considerable importance in clinical practice when formulating aetiological models, planning both pharmacological and psychosocial interventions, and assessing the likelihood of adverse effects, including longer term prognosis. In addition to the clinical utility, the S-NES will save valuable research time by enabling a relatively rapid, but accurate, assessment of NSS in investigating variations in the risk of schizophrenia.

## Material and methods

The present study is part of an investigation of the socio-demographic, clinical, biological, and treatment aspects of schizophrenia (and related disorders) in patients presenting for biomedical treatment for the first time as out- or in-patients in two general hospitals with psychiatric units in Nigeria. Ethical approval was obtained from the University of Ibadan ethics committee.

### Subjects

The sample examined for the present study has been fully described (8,25,26); we give a brief overview here. Patients were mostly anti-psychotic naive or had received minimal treatment (6.0% had <12 weeks of lifetime oral anti-psychotic exposure). They comprised of 47 males and 37 females, aged between 16 and 45 years. Participants were consecutively recruited between April 2009 and June 2011 (about 26 months). They were from the Yoruba ethnic group and were resident within and around Ibadan.

Patients were approached after they had been seen by the clinician, usually a consultant psychiatrist who was responsible for their routine clinical assessment at presentation. Only those who were assessed by the clinician to have a psychotic illness were approached for possible participation in the study. Written informed consent was obtained from all patients and/or their guardians after the data collection procedure was explained to them in either English or the local Yoruba language. The structured clinical interview for diagnostic and statistical manual for mental disorders – fourth edition (DSM-IV) patients edition (33) was employed to provide for a standardised assessment of patients after a semi-structured interview. The diagnosis of schizophrenia or schizophreniform disorder was then verified using criteria from the DSM-IV (34).



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Patients meeting inclusion criteria were cross-sectionally evaluated as far as possible before anti-psychotic medications were prescribed. A wash-out period of 1 week was allowed for the five patients who had a lifetime exposure to oral antipsychotics. We obtained baseline information on demographic, personal, medical, and psychiatric history, as well as family history.

### Assessment of NSS

NSS in the sample of 84 patients with confirmed DSM-IV diagnosis of schizophrenia or schizophreniform disorder were assessed using the standard 26-item NES (20). The measure includes tests such as tandem walk, rapid alternation movements, finger-to-thumb opposition, the finger-to-nose test, audio-visual integration, stereognosis, graphesthesia, extinction, right-to-left confusion, the first-ring, first-edge-palm, Ozeretski, and rhythm tapping tests (Table 1). The other signs assessed by the NES include cerebral dominance, short-term memory, frontal release, and eye movement signs. The NES items are scored with reference to the descriptive anchors provided on a three-point scale (no abnormality = 0; mild, but definite impairment = 1; marked impairment = 2) with the exception of 'suck' and 'snout' reflexes which are scored 0 or 2. In the present study, marked neurological abnormality was defined as the rating of 2 on any one item on the NES.

The tests were administered by two independent raters (both psychiatrists) after a total of 18 h of training spread across 3 days, including practical sessions on administering the 26-item NES and inter-rater reliability (IRR) measurements. Assessments were conducted in English and/or the Yoruba language. Each item was assessed according to a fixed order. The IRR conducted after training ranged from $\kappa = 0.62$ to 0.82, whereas the intra-class correlation (ICC) across the measurements of NSS after the study was 0.98 [95% confidence interval (CI) = 0.97–0.98].

Table 1. Items in the referent standard 26-item Neurological Evaluation Scale with conceptually defined subscales

| Sensory-integration subscale | Motor-coordination subscale | Motor-sequencing subscale |
|---|---|---|
| Audio-visual integration | Tandem walk | Fist-ring test |
| Stereognosis | Rapid alternation movements | Fist-edge palm |
| Graphaesthesia | Finger-thumb opposition | Ozeretski test |
| Extinction | Finger-nose test | Rhythm tapping test B |
| Right/left confusion | | |
| | 'Other' subscale | |
| Adventitious flow | Rhythm tapping test A | Glabellar tap reflex |
| Rhomberg test | Mirror movements | Snout reflex |
| Tremor | Synkinesis | Grasp reflex |
| Memory (5 min) | Convergence | Suck reflex |
| Memory (10 min) | | |

### Data analyses

Analyses were conducted using SPSS version 18.0 and AMOS 18.0. Descriptive statistics such as means and standard deviations were used to summarise quantitative variables, whereas frequencies and proportions were used for discrete variables.

*Background factor analyses.* The methods, results, and interpretation of the initial factor analyses leading to the present study have been fully described (25,26). Briefly, we conducted exploratory factor analysis (EFA) on NES items that were abnormal in >10% of the entire sample of 84 patients. Items testing for cerebral dominance were excluded from the analyses. Factors obtained following initial maximum-likelihood exploration were further rotated using the varimax procedure. Factors were recorded when they have eigenvalues greater than unity and contributed a minimum of 10% to the cumulative variance (35). For the factor extraction, loadings of ≥0.5 were considered meaningful. Following EFA, maximum-likelihood estimation of confirmatory factor analyses (CFA) was next conducted. For this, four competing models based on the four categories in EFA which, in theory, may provide good fit to the data were considered. Incremental fit statistics were used to provide information on the relative goodness-of-fit of each model (36).

The background EFA generated a four factor loading comprising of 12 NES items; audio-visual integration, fist-edge palm, rhythm tapping tests, extinction, right-left confusion, synkinesis, convergence, gaze impersistence, tandem walk, adventitious flow, graphaesthesis, and stereognosis. In CFA, a final three correlated factor structure in which stereognosis is prescribed to load into a 'Perceptual and motor sequencing' category (audio-visual integration, fist-edge palm, rhythm tapping, extinction, and right-left confusion) provided the best fit to the data ($\chi^2$ goodness-of-fit test = 1.25; comparative fit index = 0.95; root square means error of approximation <0.05). The other two factors were: 'Eye movement' (synkinesis, convergence, gaze impersistence) and 'Motor co-ordination and graphaesthesia' (tandem walk, adventitious flow, graphaesthesia).

*The present psychometric analyses.* For the present study, we compared the phenomena of being positive for NSS using the referent standard 26-item



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NES versus being positive using the 12 empirically determined NES items. For this, we first classified the entire sample of 84 patients into four groups using the result of the referent standard, and that for the S-NES. We then determined subjects showing positive result for the referent standard (total abnormal) and those showing negative results (total normal). We next determine participants showing positive tests (true positive) and those showing negative results using S-NES (false negative) among the 'total abnormal' group. Among participants belonging in the 'total normal' group, we determined 'true negative' when participants show negative S-NES results and 'false positive' when they show positive results using the same screening.

Next, we calculated sensitivity (number of 'true positive' participants divided by number of participants in the 'total abnormal' group), and specificity (number of 'true negative' participants divided by number of participants in the 'total normal' groups). We also estimated likelihood ratios (LR) for positive and negative S-NES tests and plotted these values against the proportion of 'total abnormal' NSS (pre-test probability) in the sample to determine the posterior-test probabilities of abnormal NSS when using the S-NES for the sample. The Bayesian plot of the LR, pre-test, and posterior-test probabilities is presented.

## Results

Out of 89 patients meeting criteria for the present study, five refused to participate out of their initiatives or those of their parents/guardians. Among those agreeing to participate, the mean ages at onset schizophrenia and presentation for treatment were 24.6 (±8.2) and 28.7 (±6.4) years, respectively. The mean duration of untreated psychosis was 38.9 months, with a median of 26.0 months. The baseline characteristics of the study sample are presented in Table 2.

The mean NES score of the subjects was 21.5 ± 11.1, with 81 (96.4%) subjects having marked impairment in NSS using the referent standard NES test (Fig. 1). In the same figure, the number of patients with and without marked NSS who test positive and negative for the S-NES is also presented.

The items in the S-NES, their sub-categories determined using CFA, and mean severity scores is presented in Table 3. The S-NES items showed high agreement with the referent standard NES with a sensitivity rate of 96.3% and specificity of 100% (Table 3). The result of the Bayesian nomogram plot indicates a posterior-test probability of 100% when using the S-NES (Fig. 2).

Table 2. Characteristics of 84 patients with first episode schizophrenia

| Characteristics | % |
|---|---|
| Gender | |
| Male | 54.8 |
| Female | 45.2 |
| Marital status | |
| Never married | 73.8 |
| Married | 26.2 |
| Family history of psychoses | |
| No | 90.5 |
| Yes | 9.5 |
| Employment | |
| Unemployed | 92.9 |
| Employed | 7.1 |
| DUP (months) | |
| <12 | 38.1 |
| ≥12 | 61.9 |
| | Mean (SD) |
| Age in years | |
| At onset of psychosis | 24.6 (8.2) |
| At presentation | 28.7 (6.4) |
| DUP (months) | 38.9 (47.7) |
| Median | 26.0 |
| Pre-morbid adjustment (PAS) | |
| Childhood (social/academic) | 1.8 (2.9)/3.2 (2.7) |
| Range | 0–11/0–12 |
| Early adolescent (social/academic) | 3.8 (4.1)/3.3 (2.8) |
| Range | 0–15/0–12 |
| Total PANSS scores | 73.3 (15.9) |
| CGI-severity | 5.1 (0.9) |
| Functioning (SOFAS) | 44.2 (4.7) |

DUP, Duration of untreated psychoses; PAS, pre-morbid adjustment scale; PANSS, positive and negative syndrome scale; CGI, clinical global impression; SOFAS, social and occupational functioning scale.

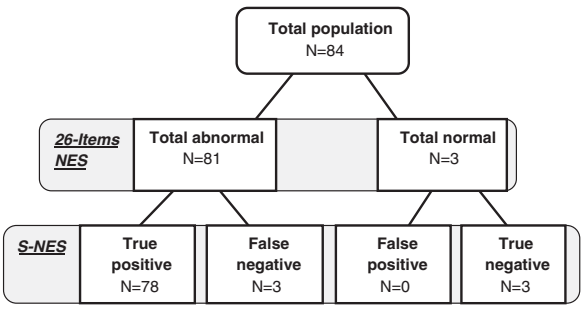


*Fig. 1.* Number of patients with or without marked neurological soft signs who test positive using the 12-item Neurological Evaluation Scale (NES). S-NES, 12-item short NES.

## Discussion

We found in the present study that within existing data from a fairly large sample of minimally medicated or never treated patients with first episode schizophrenia, empirically determined 12 items of neurological examination showed high agreement with the traditional 26-item NES battery. These results would suggest that the design of a short



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Table 3. Prevalence and severity scores of items in the short Neurological Evaluation Scale (S-NES), its properties in comparison with the referent standard 26-item NES in 84 patients with first episode schizophrenia

| S-NES items | % | Mean (SD) |
|---|---|---|
| Perceptual and motor-sequencing subscale | | |
| Audio-visual integration | 53.6 | 1.2 (0.9) |
| Fist-edge palm | 71.4 | 1.6 (0.80 |
| Rhythm tapping-B | 56.0 | 1.3 (0.9) |
| Extinction | 38.1 | 0.9 (0.9) |
| Right-left confusion | 48.1 | 1.2 (0.9) |
| Stereognosis | 17.9 | 0.5 (0.8) |
| Eye movements subscale | | |
| Synkinesis | 26.2 | 0.7 (0.9) |
| Convergence | 26.2 | 0.8 (0.9) |
| Gaze impersistence | 35.7 | 0.9 (0.9) |
| Motor-coordination and graphaesthesia subscale | | |
| Tandem walk | 16.7 | 0.5 (0.8) |
| Adventitious flow | 6.0 | 0.2 (0.6) |
| Graphaesthesia | 52.4 | 1.3 (0.9) |
| | | % |
| Properties of the S-NES | | |
| Pre-test probability | | 96.4 |
| Sensitivity rate | | 96.3 |
| Specificity rate | | 100.0 |

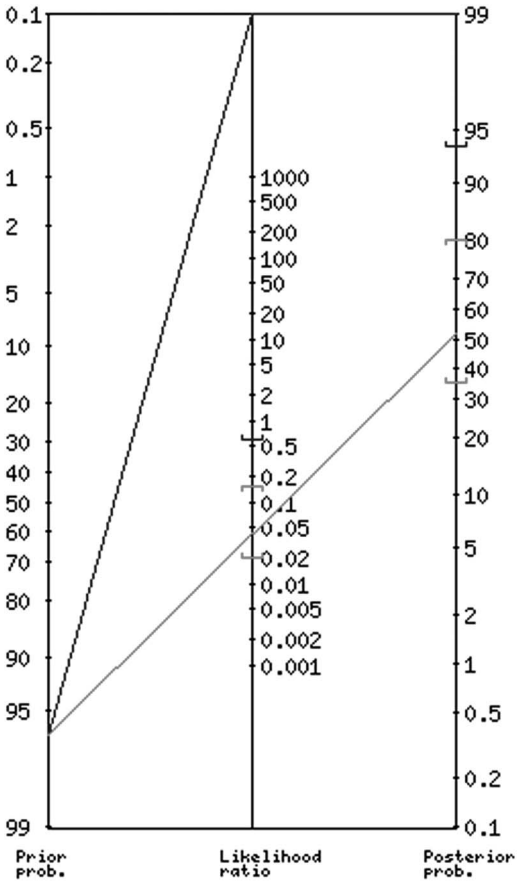


*Fig. 2.* Probability that a patient has a neurological soft sign after testing positive or negative on the Neurological Evaluation Scale 12.

version of the NES (S-NES) based on 12 items of neurological examination investigated in the present study is a logical step. If successful, the S-NES will be particularly useful for rapid screening of NSS in busy clinical settings, and also in research.

Observations from over three decades of research on the subject of NSS in schizophrenia suggest that the wide variation of items of neurological examination in the standard 26-item NES makes it too heterogeneous to identify specific aspects of the neurobiological underpinnings of the disease process (37). This is because different items are likely to contribute to the total score at different stages of the disease. This observation has added to persisting uncertainty about the meaning of NSS in schizophrenia (38,39). For example, in a previous study by our team using the 26-item NES (8), we observed that while some NSS categories exhibited trait marking characteristics, other abnormalities, including the total NES score, did not reflect significant vulnerability marking potentials. The length of time required in completing the 26 items of neurological examinations in the standard NES battery may also limit its utility in pragmatic clinical situations.

Starting with their organisation into sensory integration, motor co-ordination, and motor sequencing NSS based on 13 items presumed to have 'meaningful' theoretical underpinnings (27), there have been many previous effort to distil the multiplicity of neurological abnormalities measured in the standard NES battery into more parsimonious categories. This includes a total of 13, mostly exploratory, factor-analytic studies in the literature (26–31,35,40–45). Progress beyond factor analyses to the development of a shorter version of the standard NES battery has often been hindered because each subsequent factor-analytic study has often failed to replicate any of the preceding studies (35,40). The nearest approximation to replicating a previous factor analysis has been achieved by studies relying on similar items or number of items hand-picked from the standard (26 items) NES battery. For instance, Goldstein et al. (31) and Keshavan et al. (30) included the same 13 items previously used by the Sanders et al. (29) factor analysis. Similarly, Emsley et al. (41) used 13 items that bore similarities with those of Keshavan et al. (28,30). It is noteworthy that apart from Emsley et al. (41), the other studies reviewed have relied on the same sample for their analysis (28–31), thus making the findings of such studies difficult to generalise. In the CFA conducted by our group using the entire 26 items in the standard NES battery, NSS loaded into a three factor structure with significant overlaps with previously described categories (25,26). This provided support for the findings in the present psychometric analyses of 12 empirically identified



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items in comparison with the 26 items in the standard NES battery (20).

We are mindful of the limitations of the present study. The tests of validity were conducted within data collected using the 26 items NES, rather than independently using the two versions; 12 items versus 26 items. This methodology is likely to produce high agreements between the two versions and introduce contamination, as it were, to the results derived from such analyses. Contrariwise, we reasoned that as the results are derived from neurological examinations according to a standard procedure, the observations made by an expert clinician as to whether a patient has neurological abnormality, or not, may not be very different from those derived using 12 or 26 items. As an example, the ICC conducted across ratings using the 26-item NES was 0.98 (95% CI = 0.97–0.98). The near perfect ICC would suggest a consensus of measurements between raters. Therefore, the results of the present study provide support for further development of the S-NES through an investigation comparing the proposed S-NES with the standard (26 items) NES among patients at different stages of the schizophrenia spectrum: first episode unmedicated, medicated patients and/or those with chronic schizophrenia, including first-degree relatives of patients. Such investigation will also generate reliability data for both the individual items and empirically determined sub-categories of the proposed S-NES, including cut-off scores providing the best balance between sensitivity and specificity.

In concluding, we believe that the clinical utility of NSS can be improved by further simplifying their assessment using a shorter version of the standard 26-item NES. This is because these specific NSS have an established profile as viable intermediate phenotypes of schizophrenia (8,14,17,41,46), and may be relevant to establish that an individual had progressed along the neuro-developmental pathway to the disease. Given observations that NSS may identify a group of patients with schizophrenia who may have a more severe illness and poorer treatment response, the S-NES will be especially useful for rapid examination of NSS in busy clinical settings. This will be of considerable importance in clinical practice when planning both pharmacological and psychosocial interventions, and assessing the likelihood of adverse effects.

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#### Conflicts of Interest

None.

#### Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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