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Research article

Motor sequencing abnormalities are the trait marking neurological soft signs of schizophrenia

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HIGHLIGHTS

- 84 Black Africans with first-episode schizophrenia were studied.
- We investigated the one year profile of neurological soft signs (NSS).
- We examined whether NSS are stable despite changes in psychopathology.
- Motor sequencing exhibited trait marking features.
- Other NSS marked the psychopathology state.

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ABSTRACT

We describe the profile of NSS across the one-year course of schizophrenia in 84 Nigerian first-episode patients. They were assessed at baseline and 3 monthly for 12 months using the Neurological Evaluation Scale and the Positive and Negative Syndrome Scale (PANSS), and treated with flupenthixol decanoate. The pattern of NSS total and sub-category scores obtained from repeated measurements were investigated for responders (≥50% reduction of baseline PANSS scores) and non-responders using the method of repeated measures analysis of variance. Trait-like features of NSS categories were quantified using intraclass correlation coefficients (ICCs). NSS were present in 96.4% of the patients at baseline (mean 21.5 ± 11.1). The motor-sequencing sub-category was found unrelated to changes in schizophrenia psychopathology with treatment (positive, $r = 0.19$, $p = 0.136$., negative, $r = 0.12$, $p = 0.350$; disorganization, $r = 0.16$, $p = 0.245$; overall, $r = 0.20$, $p = 0.112$). Regardless of decrements in psychopathology, motor-sequencing scores remained relatively unchanged across the course of the disease (main effects: 'responders' $F = 2.44$, $p = 0.930$, 'poor responders' $F = 0.27$, $p = 0.764$, entire sample $F = 1.87$, $p = 0.160$). ICC was "substantial" at 0.8 (95% C.I = 0.6–0.9). Only the motor-sequencing NSS appear to be trait marker of schizophrenia in this sample. Other NSS seem to reflect symptomatic states of the disorder.

1. Introduction

Neurological soft signs (NSS) are subtle but clinically measurable abnormalities that are now recognized as part of the expression of schizophrenia [1,2]. They have been theoretically grouped into three major categories derived from the neurological evaluation scale (NES) [3]: sensory integration, motor co-ordination and motor sequencing. These signs are attractive as potential trait markers for the disorder because the pattern of their occurrence suggests they have been present before the onset of the schizophrenia phenotype [4].

An ideal trait marker would be expected to exhibit a degree of stability across the course of the relevant disease. This characteristic of NSS has been demonstrated in Caucasian and mixed samples of patients with schizophrenia [5,6]. These studies have often examined stability without exploring the pattern of change in NSS according to the different levels of response to treatment. Yet, investigation of the temporal stability of NSS in relation to longitudinal changes in psychopathology among first episode schizophrenia patients may clarify the groups of NSS that are

Abbreviations: SIN, sensory integration; MCN, motor co-ordination; MSN, motor sequencing.

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markers of vulnerability to the disease, and those that reflect the different expressions of the overt phenotype. In the absence of specific genes for schizophrenia, such information may be of value for the understanding of gene functions in the disorder. In particular, the study of a homogenous racial group may improve the contextual validity of such information.

There are presently no studies of the longitudinal profile of NSS in a homogeneous group of indigenous Africans with first episode schizophrenia. The present report aimed at describing the profile of both the total and the sub-categories of NSS in mostly medication naïve Black African patients showing good or poor response to biomedical treatment across the one-year course of schizophrenia. We hypothesized that regardless of changes in psychopathology, the scores for groups of NSS will remain relatively unchanged across the one year course of the disease.

2. Materials and methods

Ethical approval for the study was obtained from the University of Ibadan ethics committee. Participants provided written consent before interviews were conducted.

The study was conducted among patients presenting for treatment for the first time as in- or out-patients at the two general hospitals with psychiatric units in Ibadan, Nigeria.

2.1. Subjects

The sample comprised mostly anti-psychotic naive patients with first episode schizophrenia (5 participants had less than 12 weeks lifetime oral antipsychotic exposure). For inclusion, they had to meet criteria in the fourth revision of the diagnostic and statistical manual of mental disorders (DSM-IV) [7] following a semi-structured interview conducted by a psychiatrist. Patients also had to be aged between 16 and 45 years. We excluded patients with previous depot antipsychotics treatments, current substance abuse [7], significant physical illnesses (e.g., open tuberculosis), and clinical history suggestive of intellectual disability. On the bases of these criteria we recruited 84 patients consecutively between April 2009 and June 2011. They were evaluated as far as possible before antipsychotic medication was prescribed.

2.2. Measures

Diagnostic assessment was conducted with the structured clinical interview for DSM-IV- patients' edition (SCID-P) [8].

2.3. Neurological assessment

NSS were evaluated using the NES [3]. The scale includes subscales which reflect signs of motor co-ordination (tandem walk, rapid alternation, finger-to-thumb opposition, and finger-to-nose test), sensory integration (audiovisual integration, stereognosis, graphesthesia, extinction, and right-to-left confusion tests), and motor sequencing (first-ring, the first-edge-palm, Ozeretski, and rhythmic tapping tests). The items are scored with reference to the descriptive anchors provided on a three-point scale (no abnormality = 0; mild, impairment = 1; marked impairment = 2). Similar to criteria in previous studies [9], a neurological abnormality was defined as a rating of 2 on any item on the NES. The tests were administered by a psychiatrist who had been trained in the use of the NES. The assessments conducted at baseline, 6 and 12 months are the focus of this report.

2.4. Psychiatric assessment

The severity of the baseline psychopathology was evaluated with the Positive and Negative Syndrome Scale (PANSS) [10]. The PANSS five factor solution [11] was adopted for this study based on its stability and superior validity when compared to the older three factor model [10]. It includes factors for positive (delusions, hallucinations, unusual thought content, suspiciousness, and grandiosity), negative (lack of spontaneity, blunted affect, emotional withdrawals, social withdrawals, motor retardation, poor rapport, and social avoidance), disorganization (stereotyped thinking, poor attention, disorientation, disorganization, and poor abstraction), excitement/hostility (impulsivity, excitement, hostility, and uncooperativeness), and emotional distress (anxiety, depression, guilt, and tension).

The overall clinical status was assessed using Clinical Global Impression (CGI-severity) [12], while pre-morbid adjustments, depression, and extrapyramidal symptoms (EPSE) were explored using the pre-morbid adjustment scale (PAS) [13], Calgary depression scale for schizophrenia (CDSS) [14], and extrapyramidal symptom rating scale (ESRS) [15], respectively. These measures have been used for the assessments of African patients with schizophrenia in previous studies [16].

2.5. Treatment

A wash-out period of one week was allowed for the 5 participants who had lifetime oral anti-psychotic exposures. After ruling out hypersensitivity, flexible doses of deep intramuscular flupenthixol injections starting from 5 mg or 10 mg in two or four weekly intervals were administered, with increases of up to a maximum of 30 mg depending on age, tolerability or response. Concomitant medications such as lorazepam, benzhexol, and propranolol, for sedation, EPSE and akathisia, respectively, were allowed at the discretion of the investigators. Depot antipsychotic was chosen for this study to rule out covert non-adherence, a common phenomenon in first episode schizophrenia [17]. Additional measure to improve adherence included the incorporation of a multi-disciplinary assertive monitoring team in the design of this study.

Duration of untreated psychosis (D.U.P) was defined as the period in months from the onset of psychotic phenomena to first presentation for biomedical treatment. Onset of psychosis was defined as the presence for one week or more of psychotic symptoms with marked deterioration of functioning.

In all cases, pre-morbid functioning was the retrospective rating of patients' functioning up to six months before the defined onset of psychosis.

2.6. Outcome

Outcome was assessed in terms of symptom reduction between baseline and month 12. Response was defined as 50% or more reduction in the PANSS scores from baseline to month 12.

2.7. Statistical analysis

Descriptive statistics such as means and standard deviations were used to summarize quantitative variables. Characteristics of the study sample who met criteria for response (good responders) were compared with those not meeting such criteria (poor responders) using the chi-square test or *t*-test, for categorical or continuous variables, respectively. Reduction in PANSS score was calculated by subtracting the total PANSS scores for each participant at months 12 from the scores at baseline. The correlations

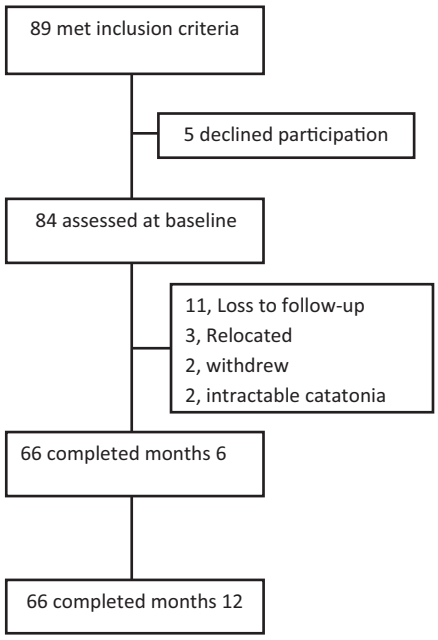

Fig. 1. Study flow chart.

between NES scores and indices of clinical profile at baseline and follow-up were then tested using the Pearson's correlation method.

The repeated measures analysis of variance (rANOVA) was used to compare differences in the observed NES scores, with time as the within subject factor (three levels: baseline, months 6, and 12). We compared the differences in the observed total NES scores across the three measurements, followed by a comparison of the differences in the observed sub-scale scores. The Mauchly's sphericity assumption was tested to ensure the equality of variance of the between pairs values, and in cases where the assumption was violated, the Greenhouse-Geisser correction was applied. We next investigated the effect of antipsychotic response on changes in NES total scores. For this, the type of response; good or poor, was entered as the between subject factor in the repeated measures analyses. Post-hoc correction was conducted using the method of Fisher's protected least significant difference (LSD). The stability of NSS categories was further quantified using intraclass correlations coefficients (ICCs). This was calculated as the between subject variance divided by sum of the within and between subject variances. 95% confidence intervals for ICCs were calculated using the exact method.

Data analyses were performed using SPSS version 15.0 [SPSS Inc.]. A significant level of <0.05 was used throughout the study.

3. Results

Fig. 1 shows the flow chart for the study, while Table 1 shows the baseline characteristics of the sample. The mean ages at onset of psychosis and at presentation for treatment were 24.6 (±8.2) and 28.7 (±6.4) years, respectively. The mean D.U.P was 38.9 months, with a median of 26.0 months. The mean NES score of the subjects was 21.5 ± 11.1, with 81 (96.4%) subjects having marked impairment in NSS at baseline.

The signs were generally associated with disease severity (Table 2). Motor-sequencing was not associated with the major psychopathology dimensions at baseline (positive, $r = 0.21$, $p = 0.055$., negative, $r = 0.07$, $p = 0.535$., disorganization symptoms, $r = 0.17$, $p = 0.115$), or changes in psychopathology over-time (positive, $r = 0.19$, $p = 0.136$., negative, $r = 0.12$, $p = 0.350$., disorganization, $r = 0.16$, $p = 0.245$). The other NSS were associated with mostly negative and disorganisation psychopathology at baseline and follow-up (Table 2). NSS were negatively correlated with EPSE during follow-up.

In Fig. 2, motor-sequencing scores remained relatively unchanged across the 12 months course of the disease regardless of the level of response to treatment. The ICC was 'substantial' at 0.8 (95% C.I = 0.6–0.9) [18]. The mean scores for the remaining categories, including the total NES changed significantly across the same time frame.

4. Discussion

In this study, NSS were already present in 96.4% of patients before they were exposed to antipsychotics. Motor-sequencing NSS were not associated with the major psychopathology dimensions of schizophrenia at baseline and follow-up. Scores for this category of NSS also remained relatively unchanged over the course of the study with robust ICC. This was regardless of patients' response to treatment. In contrast, the other NSS categories demonstrated significant decreases in intensity as patients experienced symptomatic improvements. They were mostly associated with severe negative and disorganization psychopathologies throughout the course of the disease. Motor co-ordination NSS was associated with excitement/hostility symptoms at baseline only.

An important innovation in this study is the description of these changes in both the entire sample and in patients showing good response to treatment, in comparison with those with poor response. We replicate the findings of previous studies showing an increased prevalence of NSS in patients with first episode schizophrenia [9,19]. This observation, together with the absence of a positive correlation between NSS and EPSE in this study, would suggest that these signs were not due to the effect of antipsychotics.

The interpretation of the rates of NSS reported in this study may be complicated by our failure to include a comparison group of healthy individuals. Also, a direct comparison of our results with those of studies from samples around the world is made difficult by the observation in the literature that different studies have used different measures in the evaluation of NSS in schizophrenia. Cut-offs for defining NSS have also varied from one study to another. Nevertheless, studies that have used a cut-off point similar [9], or higher [20] than that used in this study in defining abnormal NSS have often reported similarly high prevalence.

The finding of significant association between non motor-sequencing NSS and negative, disorganisation, or excited/hostility psychopathologies had been expected, as this relationship has been well documented in samples around the world [5,21]. The pattern where signs and symptoms that may be characteristic of the active disease process fluctuates, but dominate the picture in the acute phase of never treated first episode schizophrenia is also recognised in the literature [22].

Some of the acute phase symptoms may affect the performance of patients on tests requiring complex repetitive movements [23]. Motor-sequencing, as an example, involves intricate repetition of hand and finger movements. The performance on motor-sequencing tasks is known to be affected by motivation [3], and regulated within the same fronto-basal ganglia circuits that have been associated with the neurodevelopmental process of schizophrenia [24]. In line with this observation, we found at baseline only, a statistically significant, and a non-significant ($p = 0.055$) tendency towards the correlation of motor-sequencing NSS and emotional distress (depression/anxiety), and positive symptoms, respectively. It is unclear whether these interactions are solely the results of interference with the performance on the motor-sequencing tests by, for example, disturbances of motivation in depressed schizophrenia patients during the acute phase before

Table 1
Characteristics of subjects.

Characteristics	Good-responders ($n=50$) n/%	Poor-responders ($n=16$) n/%	χ^2/p-value
Gender			
Male	26/52.0	10/62.5	0.5/0.463
Female	24/48.0	6/37.5	
Education			
Elementary	11/22.0	6/37.5	1.9/0.390
Secondary	20/40.0	4/25.0	
Tertiary	19/38.0	6/37.5	
Marital status			
Never married	35/70.0	13/81.3	0.8/0.379
Ever married	15/30.0	3/18.8	
Family history of psychoses	5/10.0	1/6.3	0.2/0.650
Psychopathology change			
Positive	45/69.7	20/30.0	8.7/0.003
Negative	41/63.6	24/36.5	18.8/<0.001
Disorganised	51/78.8	13/21.2	4.7/0.030
Excited	44/66.7	22/33.3	4.8/0.028
Emotional distress	12/18.2	53/81.8	3.2/0.073

Characteristics	Mean/±SD	Mean/±SD	t-Test/p-value
Age in years			
At onset of psychosis	24.0/9.2	24.8/8.1	0.3/0.778
At presentation	24.0/9.2	30.0/7.3	1.0/0.334
D.U.P in months (range)	33.2/57.2 (32.5)	56.9/47.8 (50.9)	1.5/0.138
Baseline PANSS	77.0/15.0	66.5/19.0	2.3/0.026
CGI-severity	5.3/0.7	4.8/1.0	2.6/0.010
NES score	22.9/11.0	17.5/13.1	1.6/0.110
ESRS (range)			
Baseline	0.4/0.8 (3.0)	0.7/0.3	1.4/0.157
Month 6	0.4/1.0 (5.0)	0.5/1.6 (6.0)	0.1/0.892
Month 12	0.4/1.0 (6.0)	0.2/0.6 (2.0)	0.7/0.520

D.U.P = duration of untreated psychosis; CGI = clinical global impression; NES = neurological evaluation scale; ESRS = extrapyramidal symptom rating scale.

Table 2
Pearson correlation of baseline NSS and the clinical characteristics of schizophrenia.

Clinical characteristics	Sensory integration	Motor coordination	Motor sequencing	Total
Age at onset	−0.224*	−0.034	0.202	−0.004
D.U.P	−0.006	−0.005	0.016	−0.005
PAS				
CHILDHOOD (Social/academic)	0.029/0.010	0.051/0.136	0.031/0.158	0.034/0.101
ADOLESCENT (Social/academic)	0.031/0.069	0.116/−0.082	0.088/0.061	0.039/-0.081
PANSS(Baseline/change over-time)				
Positive	−0.020/0.004	−0.102/-0.055	0.211/0.117	−0.075/-0.008
Negative	0.412**/0.251*	0.493**/0.448**	0.069/0.186	0.456**/0.401**
Disorganized	0.463**/0.276*	0.567**/0.372**	0.173/0.145	0.559**/0.345*
Excited/hostility	0.030/0.007	0.272*/0.178	0.145/0.076	0.228*/0.134
Emotional distress	0.128/0.049	0.107/0.140	0.293**/0/239	0.169/0.157
CGI-severity (clinician impression)	0.388**	0.555*	0.420**	0.566**
CDSS	0.155	−0.004	0.137	0.095
ESRS				
Month 6	−0.135	−0.099	−0.269*	−0.154
Month 12	0.077	−0.038	−0.265*	−0.056

* $P<0.05$.
** $P<0.01$.

treatment. We conducted the motor-sequencing tests 3 monthly for 12 months, and did not find these interactions beyond the baseline measurements. Moreover, the tendency for a relationship between the motor-sequencing NSS and some symptoms at the baseline does not appear to fit into the overall behaviour of the NSS category in this study. For instance, despite significant decrements in the dimensions of psychopathology overtime, we found relatively stable scores for motor-sequencing. The scores for this NSS category also demonstrated a tendency towards worsening between months 6 and 12, especially among poor responders.

The pattern where the initial response of the florid acute phase symptoms to the introduction antipsychotics may result in decrement of the NSS that are associated with such symptoms is in keeping with previous studies on the temporal stability of NSS in first episode schizophrenia [6]. In this way, trait marking signs, which are inherently more stable, may become more prominent as acute phase symptoms stabilize [22]. These signs may also become relatively worse overtime [25]. Our methodology has allowed us to take a closer look at this characteristic of NSS in both the entire sample and in patients with different degrees of response to treatment.

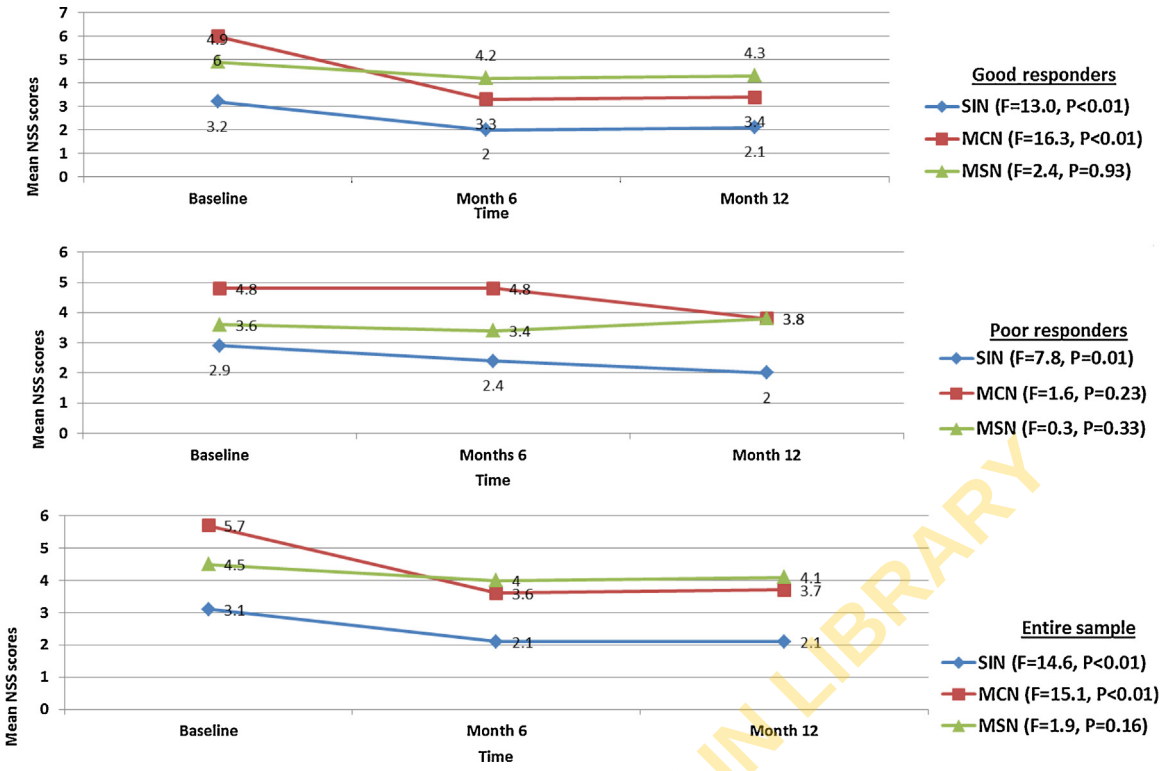

Fig. 2. Repeated measures ANOVA of NSS categories across the study. SIN = Sensory integration, MCN = Motor co-ordination, MSN = Motor sequencing.

In this sample, the behaviour of the motor-sequencing signs, but not the broad categories of NSS, may be interpreted as an indication of their origin: genetic, neuro-developmental, or pre-morbidly acquired. Motor-sequencing NSS has been suggested as possible evidence of pre-morbidly acquired permanent deficits, in so far as they correlated positively with an excess of obstetric complications and pre-morbid deterioration in psycho-social functioning in a previous study [26]. Other evidence in support of motor-sequencing NSS as intrinsic marker of schizophrenia can be found in studies demonstrating their heritability [27].

This study has some important limitations. The investigators were not blind to the clinical state of the subjects. This may have introduced an observer bias in the measurement of NSS. In the same vein, some of the improvements observed may have been due to learning effects on some of the tests. Also, the analysis of the outcome in terms of psychopathology and NSS was based on the per protocol data. The inclusion of the last observations of the drop-out subjects may have revealed a more pragmatic picture, such as a higher number of poor responders. This is because some of the attritions were due to poor efficacy. In this regard, there is a possibility that our inability to demonstrate a decrease in NSS scores among the 'poor responders' may have been due to their relatively small numbers.

In concluding, it would appear that NSS show differential relationships with the short to medium term course of psychopathology in this sample of African patients. While the motor sequencing NSS exhibited significant stability regardless of the degree of response to treatments, other signs appear to reflect symptomatic state of the disorder. The evidence from this finding and others in the literature lends credence to the conceptualization of motor sequencing abnormalities as the trait marking NSS in schizophrenia. Motor sequencing NSS can be elicited quickly, reliably and cheaply, and may therefore, find relevance in research and clinical practice, especially in settings where resources for more elaborate testing of biochemical markers in schizophrenia are limited.

Conflict of interest

None to declare.

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