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Neurological soft signs significantly differentiate schizophrenia patients from healthy controls

Fountoulakis KN, Panagiotidis P, Gonda X, Kimiskidis V, Nimatoudis I. Neurological soft signs significantly differentiate schizophrenia patients from healthy controls.

Objective: Neurological soft signs (NSS) are a group of minor non-localisable neurological abnormalities found more often in patients with schizophrenia. The aim of the current study was to test for the effect of gender, age, parental age, age at onset and clinical symptomatology on NSS.
Material and methods: The study sample included 133 patients suffering from schizophrenia according to DSM-IV-TR (77 males and 56 females; aged 33.55 ± 11.22 years old) and 122 normal controls (66 males and 56 females; aged 32.89 ± 9.91 years old). The assessment included the Neurological Evaluation Scale (NES), and a number of scales assessing the clinical symptoms and adverse effects especially extrapyramidal. The statistical analysis included exploratory *t*-test, simple linear regression analysis, analysis of covariance and the calculation of correlation coefficients.
Results: The results of the current study confirm that NSS are more frequent in patients with schizophrenia in comparison with normal controls (Wilks = 0.622, $p < 0.0001$), but do not support an effect of gender, age, age at onset, paternal or maternal age, education, medication status or clinical subtype of schizophrenia on NES scores.
Discussion: Overall these results suggest that NSS constitute an independent (from the rest of symptoms), core (present in the vast majority of patients) and trait (unrelated to age and probably to the stage of schizophrenia) symptom of schizophrenia which could be of value in the clinical assessment and research of schizophrenia. Overall these results are not in full accord with the literature, but they could serve to fill in gaps and inconsistencies observed so far.

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Keywords: motor coordination; neurological abnormalities; schizophrenia; soft neurological signs

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Significant outcomes

- Neurological softs signs (NSS) are highly significantly more frequent in schizophrenia patients compared with healthy controls.
- Medication, gender, age, age at onset, education, clinical subtype and paternal or maternal age do not influence neurological soft signs.
- NSS could be used as an auxiliary tool in the diagnosis of schizophrenia patients.

Limitations

- All the subjects have been previously hospitalised which may represent a more severe form of schizophrenia.
- Also, all patients were under antipsychotic and some also under benzodiazepine medications.
- Patients with comorbid somatic disorders were excluded which may decrease generalisability of results.

Introduction

NSS are a group of minor non-localisable neurological abnormalities. Mainly they include dysfunction in simple motor coordination, complex motor sequencing, and in integration, but also lateralisation variability (1,2). While they are not 'psychomotor' *per se*, it is important to note that psychomotor abnormalities are highly prevalent phenomena in schizophrenia and have to be considered as a heterogeneous construct, often including or misidentifying NSS (3).

NSS are found more often in patients with schizophrenia in comparison with the normal population, even during the first episode (4–10), while they are also present in relatives of patients and in general in individuals at risk to develop psychosis (11–13). This means they could be of value as endophenotypes (14–16). Medication of any type seem to have little or no impact at all (7,17–21). Whether they are specific to schizophrenia is a matter of debate (20,22–24).

The Neurological Evaluation Scale (NES) (4) and the Cambridge Neurological Inventory (25) are the two most frequently used measures for NSS in schizophrenia and other neuropsychiatric disorders but a number of other instruments also exist (26–30).

It should be noted that there are methodological issues resulting in inconsistencies in these studies comparing the prevalence of NSS in schizophrenia and other neuropsychiatric disorders. A major issue is that most of these studies have not controlled for confounding variables such as age, education and IQ. It has been shown that education (7,25) is inversely associated, whereas age is positively associated (7,15) with NSS in patients with schizophrenia and healthy controls. Moreover, the different assessment tools used to measure NSS might have confounded the results in the literature.

Aim of the study

The aim of the current study was to establish neurological soft signs in patients with different clinical manifestations of schizophrenia and healthy controls, and test for the effect of gender, age, parental age, age at onset and clinical symptomatology on neurological soft signs in patients with schizophrenia in comparison with normal control subjects.

Material and methods

Study sample

The study sample included 133 patients suffering from schizophrenia according to DSM-IV-TR (77 males and 56 females; aged 33.55 ± 11.22 years old) and 122 normal controls (66 males and 56 females; aged 32.89 ± 9.91 years old) aged between 18 and 65 years.

A total of 35 (26.31%) of patients were not under medication while the rest were receiving medication with an average dosage in haloperidol equivalents of 6.25 ± 6.05 mg/day (range 0–33). Some patients were also receiving benzodiazepines at the time of assessment due to the widespread use of benzodiazepines in general hospitals.

In terms of schizophrenia subtypes, 70 (52.63%) belonged to the paranoid subtype, five (3.75%) to the disorganized, none to the catatonic, 15 (11.27%) to the residual and 43 (32.33%) to the undifferentiated subtype.

In terms of education, patients with schizophrenia included 1 (0.75%) person who had no education at all, 25 (18.80%) with <6 years of education, 23 (17.29%) with 6–9 years, 51 (38.35%) with 9–12 years, 31 (23.31%) with a university degree, and 2 (1.50%) with post-graduate education. The corresponding numbers for controls were 0 (0.00%), 7 (5.74%), 12 (9.84%), 42 (34.43%), 55 (45.08%) and 6 (4.92%).

Patients were recruited from local hospitals and the diagnosis was made by two of the authors (K.N.F. and P.P.) with the use of the Mini-International Neuropsychiatric Interview (M.I.N.I.) and after consensus. The exclusion criteria for the present study included (1) a history of neurological disorder; (2) presence of any somatic disorder; (3) a lifetime prevalence of substance abuse; (4) IQ estimate lower than 70; and (5) age below 18 or above 65.

Controls came from the community, and their exclusion criteria included (1) presence of any mental disorder; (2) past history of any mental disorder; (3) family member with any mental disorder; and (4) age below 18 or above 65.

The study received ethical approval from the Ethics Committee of the School of Medicine, Aristotle University of Thessaloniki, Greece. Written informed consent was obtained from all participants before the administration of NES and related measures. 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.

Assessment tools

The NSS were assessed with the use of the NES (4) which includes four main subscales in addition to the total NES score: sensory integration, motor coordination, sequencing of complex motor acts and a fourth subscale with all other signs. Concerning the scoring

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of lateralising items, some researchers used the mean score while others kept the highest side score (31–34). We chose to use the sum of both (35). Two additional scores were used, the sum of all items concerning the left and the sum concerning the right side of the body.

The clinical symptoms of schizophrenia were assessed with the Positive and Negative Syndrome Scale (36), depression with the use of the Calgary Depression Scale (37,38) and the Montgomery-Asberg Depression Rating Scale (39), anxiety with the State-Trait Anxiety Inventory form Y, State and Trait subscales (40–43), and manic symptoms with the Young Mania Rating Scale (44). For the assessment of extrapyramidal signs which could affect the performance on the NES the following scales were used: The Simpson-Angus Rating Scale (45), and the Extrapyramidal Symptom Rating Scale (46). The Udvalg for Kliniske Undersøgelser (UKU) Side Effects Rating Scale (47) was used for the assessment of adverse events. The General Assessment of Functioning scale was used for the assessment of general functioning and impairment (48) and the Annett Hand Preference Questionnaire (49) for the assessment of general functional lateralization (eye, hand, leg, etc.).

Statistical analysis

The statistical analysis included three steps. In the first step, exploratory *t*-tests were performed in order to determine the categorical variables to include in the second step. These exploratory analyses included gender separately in schizophrenic patients and healthy controls, any clinical subtype versus all the others together, and drug free versus medicated patients in terms of NES scores. Exploratory *t*-tests were performed with education transformed as a two-level variable (above vs. below 6 years of education) separately in schizophrenic patients and healthy controls, while analysis of variance was used to test for the effect of education (independent variable; six levels) on NES scale and subscales. Because of the great number of comparisons and in spite of the exploratory nature of this part of the analysis, the $p < 0.01$ was chosen as the level of significance. If at least one significant effect concerning any of the NES scores was detected, then this specific grouping variable would be included with the grouping variables in the analysis of covariance (ANCOVA) which would follow.

The second step aimed at investigating for possible differences between the two diagnostic groups concerning the NES scores. It included ANCOVA with diagnosis and education (below and above 6 years) as grouping variables, age and maternal and paternal age as covariates and NES subscales as dependent variables. The Scheffe test was used as *post hoc* test.

The third step aimed to detect whether NES scores could be explained by the presence of other variables (e.g. clinical or side effects). It included simple linear regression analysis (SLRA) with forward stepwise method with NES subscales and total NES as dependent variables (seven separate regressions) and all clinical and extrapyramidal scales as independent variables. Finally, the Pearson correlation coefficient was used to explore correlations between NES subscales and clinicodemographic variables as an exploratory technique additionally to the SLRAs.

Table 1. Means, standard deviations of clinical and demographic variables in the two diagnostic groups

	Patients with schizophrenia		Normal controls	
	Mean	SD	Mean	SD
Age	33.55	11.22	32.89	9.91
Paternal age	31.95	5.70	26.65	3.80
Maternal age	27.37	5.28	24.07	3.40
Age at onset	23.07	6.19		
PANSS-P	16.22	5.81	7.00	0.00
PANSS-N	18.17	7.37	7.00	0.00
PANSS-G	26.20	7.03	15.00	0.00
PANSS-EP	7.40	3.23	5.00	0.00
CDS	1.53	3.37	0.00	0.00
MADRS	6.71	8.46	0.17	0.49
STAI-S	49.87	11.44	21.87	1.06
STAI-T	50.08	11.44	20.39	0.62
YMRS	2.61	6.07	0.00	0.00
GAF	49.86	12.08	95.47	2.46
AHPQ	13.83	12.72	19.26	8.89
UKU	7.07	5.33		
SARS	0.61	2.00		
ESRS-Parkinsonism	0.77	2.17		
ESRS-Hypokinesia	0.42	1.42		
ESRS-Hyperkinisia	0.35	0.99		
ESRS-Akathisia	0.06	0.32		
ESRS-Dystonia	0.02	0.26		
ESRS-Dyskinesia	0.05	0.37		
ESRS-total score	1.17	3.26		
ESRS-CGI-Dyskinesia	0.03	0.27		
ESRS-CGI-Parkinsonism	0.11	0.51		
ESRS-CGI-Dystonia	0.20	0.61		
ESRS-CGI-Akathisia	0.02	0.15		
NES-sensory integration	4.29	3.09	0.14	0.41
NES-motor coordination	3.89	2.84	0.19	0.52
NES-complex motor acts	6.67	3.50	0.53	0.84
NES-others	4.68	3.51	0.21	0.68
NES-right	6.05	3.35	0.34	0.78
NES-left	6.02	3.29	0.61	0.94
NES-total score	19.54	9.48	1.07	1.41

AHPQ, Annett Hand Preference Questionnaire; CDS, Calgary Depression Scale; ESRS, Extrapyramidal Symptom Rating Scale; GAF, General Assessment of Functioning; MADRS, Montgomery-Asberg Depression Rating Scale; NES, Neurological Evaluation Scale; PANSS, Positive and Negative Syndrome Scale; SARS, Simpson-Angus Rating Scale; STAI, State-Trait Anxiety Inventory; YMRS, Young Mania Rating Scale.

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Table 2. Results of exploratory *t*-tests comparing subjects according to different groupings

	Mean	SD	Mean	SD		
	Females with schizophrenia ($n=56$)		Males with schizophrenia ($n=77$)		*t*-value	*p*
NES-sensory integration	4.39	2.95	4.22	3.21	−0.316	0.753
NES-motor coordination	4.13	2.61	3.73	3.00	−0.796	0.427
NES-complex motor acts	7.14	3.26	6.32	3.65	−1.335	0.184
NES-others	4.45	3.04	4.86	3.82	0.666	0.507
NES-right	6.13	3.00	5.99	3.60	−0.234	0.816
NES-left	6.09	3.20	5.96	3.38	−0.221	0.826
NES-total score	20.11	8.96	19.13	9.88	−0.585	0.559
	Controls					
	Females ($n=56$)		Males ($n=66$)			
NES-sensory integration	0.18	0.46	0.09	0.35	1.236	0.219
NES-motor coordination	0.20	0.50	0.18	0.54	0.194	0.846
NES-complex motor acts	0.53	0.88	0.54	0.79	−0.036	0.972
NES-others	0.23	0.74	0.20	0.62	0.248	0.805
NES-right	0.39	0.80	0.27	0.75	0.891	0.375
NES-left	0.68	1.03	0.52	0.83	0.959	0.340
NES-total score	1.14	1.42	1.00	1.40	0.531	0.596
	Patients with schizophrenia					
	Education <6 years ($n=26$)		Education >6 years ($n=107$)			
NES-sensory integration	4.15	3.21	4.33	3.08	0.255	0.799
NES-motor coordination	3.96	3.08	3.88	2.79	−0.133	0.894
NES-complex motor acts	7.73	3.87	6.41	3.37	−1.737	0.085
NES-others	6.08	3.15	4.35	3.52	−2.294	0.023
NES-right	5.69	3.22	6.13	3.39	0.597	0.551
NES-left	5.96	3.28	6.03	3.31	0.092	0.927
NES-total score	21.92	10.68	18.96	9.13	−1.434	0.154
	Controls					
	Education <6 years ($n=7$)		Education >6 years ($n=115$)			
NES-sensory integration	0.00	0.00	0.15	0.42	0.919	0.360
NES-motor coordination	0.00	0.00	0.20	0.53	0.989	0.325
NES-complex motor acts	0.14	0.38	0.56	0.85	1.276	0.204
NES-others	0.00	0.00	0.23	0.70	0.849	0.397
NES-right	0.14	0.38	0.35	0.80	0.675	0.501
NES-left	0.00	0.00	0.64	0.96	1.772	0.079
NES-total score	0.14	0.38	1.13	1.43	1.817	0.072
	Drug free ($n=98$)		Medicated ($n=35$)			
NES-sensory integration	4.48	3.11	3.77	3.01	1.16	0.246
NES-motor coordination	3.94	2.75	3.77	3.12	0.30	0.766
NES-complex motor acts	6.68	3.38	6.63	3.88	0.08	0.937
NES-others	5.24	3.58	3.11	2.79	3.19	0.002
NES-right	6.02	3.27	6.11	3.60	−0.14	0.887
NES-left	6.16	3.13	5.60	3.74	0.87	0.387
NES-total score	20.35	9.47	17.29	9.28	1.65	0.101
	Other subtypes ($n=63$)		Paranoid ($n=70$)			
NES-sensory integration	3.80	3.02	4.84	3.10	−1.96	0.052
NES-motor coordination	3.80	2.94	4.00	2.75	−0.40	0.687
NES-complex motor acts	6.49	3.64	6.87	3.35	−0.64	0.526
NES-others	4.27	3.37	5.14	3.62	−1.44	0.153
NES-right	5.64	3.10	6.49	3.58	−1.47	0.145
NES-left	5.61	3.18	6.46	3.38	−1.49	0.140
NES-total score	18.36	9.59	20.86	9.26	−1.53	0.129
	Other subtypes ($n=128$)		Disorganized ($n=5$)			
NES-sensory integration	4.28	3.07	4.60	4.10	−0.23	0.822
NES-motor coordination	3.84	2.80	5.40	3.78	−1.21	0.228
NES-complex motor acts	6.62	3.51	8.00	3.39	−0.87	0.388
NES-others	4.63	3.52	6.20	3.19	−0.99	0.326
NES-right	5.92	3.23	9.20	5.07	−2.18	0.031
NES-left	5.92	3.22	8.40	4.67	−1.66	0.099
NES-total score	19.36	9.38	24.20	12.03	−1.12	0.264
	Other subtypes ($n=90$)		Undifferentiated ($n=43$)			
NES-sensory integration	4.03	3.16	4.84	2.91	4.03	3.16
NES-motor coordination	3.89	2.94	3.91	2.64	3.89	2.94
NES-complex motor acts	6.80	3.66	6.40	3.17	6.80	3.66
NES-others	4.71	3.41	4.63	3.74	4.71	3.41
NES-right	5.91	3.35	6.33	3.37	5.91	3.35
NES-left	5.99	3.43	6.07	3.03	5.99	3.43
NES-total score	19.43	9.90	19.77	8.65	19.43	9.90
	Other subtypes ($n=118$)		Residual ($n=15$)			
NES-sensory integration	4.21	3.04	4.93	3.51	−0.85	0.397
NES-motor coordination	3.91	2.86	3.80	2.76	0.14	0.892
NES-complex motor acts	6.52	3.45	7.87	3.76	−1.41	0.160
NES-others	4.48	3.50	6.27	3.28	−1.87	0.063
NES-right	6.04	3.34	6.07	3.51	−0.03	0.979
NES-left	5.90	3.22	6.93	3.84	−1.15	0.253
NES-total score	19.12	9.36	22.87	10.12	−1.45	0.150

Significant are those results with $p<0.001$ because of multiple corrections.

Results

The descriptive statistics (means and standard deviations) for each variable in the two groups are shown in Table 1.

Exploratory *t*-tests revealed no significant differences between drug free and medicated patients, between genders in either the schizophrenic patients or healthy control group and between clinical subtypes in terms of NES subscales. There was a nominally significant difference for NES other signs between groups defined by education above versus below 6 years in the schizophrenic patients but not in the healthy control group; however, this did not survive correction for multiple testing (Table 2).

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The ANOVA results revealed no significant differences between the six groups of subjects by diagnosis in terms of NES scores. Exploratory *t*-test with education as grouping variable (cut-off 6 years of education) detected only one significant comparison, for patients with schizophrenia concerning the NES-others subscale at the level of $p < 0.05$. However, this would not survive correction for multiple comparisons.

Table 3. Investigating the effect of diagnosis and education on Neurological Evaluation Scale (NES) scores with parental age and age as covariates (analysis of covariance)

	Wilks value	*F*	Effect (df)	Error (df)	*p*
Age	0.968	1.36	6	243	0.232
Paternal age	0.953	2.02	6	243	0.064
Maternal age	0.960	1.71	6	243	0.120
Diagnosis	0.622	24.59	6	243	<0.001
Education	0.970	1.25	6	243	0.282
Diagnosis × education	0.955	1.91	6	243	0.079

The ANCOVA results suggested a significant effect for diagnosis but not for education or for their interaction. There was no significant effect of age or parental age (Table 3). Scheffe test suggested that all NES subscales differed between the two diagnostic groups ($p < 0.05$).

The results of SLRA returned significant results for all NES subscales. The models explained 12.3–33.2% of the variance of individual NES subscales (Table 4).

Correlations between NES subscales and clinicodemographic variables are shown in Table 5.

Discussion

Summary of main findings

The results of the current study confirm that NSS are more frequent in patients with schizophrenia in comparison with normal controls. No control subject had a NES total score above 6 and only 11 (8.3%) of patients had scores below this level. The difference is so big that the NES could be used as an auxiliary

Table 4. Results of the simple linear regression analysis (SLRA) with each of the Neurological Evaluation Scale (NES) subscales as dependent and all the clinical variables as independent

	NES-sensory integration	NES-motor coordination	NES-complex motor acts	NES-others	NES-right	NES-left	NES-total
R^2	0.297	0.332	0.123	0.347	0.237	0.247	0.314
p-level	<0.001	<0.001	0.004	<0.001	<0.001	<0.001	<0.001
% of variance explained	29.7%	33.2%	12.3%	34.7%	23.7%	24.7%	31.4%
PANSS-P	–	–	–	–	–	–	–
PANSS-N	0.18	0.18	–	–	–	–	–
PANSS-G	–	–	0.21	–	–	–	–
PANSS-EP	–	–	–	–	–	–	–
CDS	–	–0.38	–0.26	–	–0.28	–0.37	–0.36
MADRS	–	0.44	–	0.47	–	–	0.38
STAI-S	–	–	–	–	–	–	–
STAI-T	–	–	–	–0.34	–	–	–
YMRS	–	–	–	–	–	–	–
GAF	–	–	–	–	–0.19	–	–
AHPQ	–	–	–	–	–0.23	–0.20	–
UKU	0.30	–	0.28	–	0.26	0.26	0.22
SARS	–	–	–	0.43	–	–	0.54
ESRS-Parkinsonism	–	–	–	-0.52	–	–	–
ESRS-Hypokinesia	–	–	–	–	–	–	–
ESRS-Hyperkinisia	–	–	–	0.40	–	–	–
ESRS-Akathisia	–	–0.43	–	–	–	–	–
ESRS-Dystonia	–	–	–	–	–	–	–
ESRS-Dyskinesia	–	–	–	–	–	–	–
ESRS-total score	–	–	–	–	–	–	–
ESRS-CGI-Dyskinesia	–	–0.82	–	–	–	–	–
ESRS-CGI-Parkinsonism	–	–0.43	–	–	–	–	–0.45
ESRS-CGI-Dystonia	–	–	–	–	–	–	–
ESRS-CGI-Akathisia	–	–	–	–	–	–	–

AHPQ, Annett Hand Preference Questionnaire; CDS, Calgary Depression Scale; ESRS, Extrapyramidal Symptom Rating Scale; GAF, General Assessment of Functioning; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SARS, Simpson-Angus Rating Scale; STAI, State-Trait Anxiety Inventory; YMRS, Young Mania Rating Scale.
The results include variables in each model, R^2, *p*-level and β coefficients.

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Table 5. Pearson correlation coefficients between clinical and demographic variables and Neurological Evaluation Scale (NES) subscales

	NES-sensory integration	NES-motor coordination	NES-complex motor acts	NES-others	NES-right	NES-left	NES-total
Age	−0.03	−0.02	0.10	***0.22***	−0.04	0.05	0.10
Paternal age	−0.06	0.06	0.04	0.15	0.05	0.00	0.07
Maternal age	−0.05	−0.07	0.03	0.08	0.04	−0.06	0.00
Age at onset	−0.02	0.08	0.11	0.07	0.01	0.08	0.08
PANSS-P	−0.02	−0.06	0.09	0.16	−0.03	−0.02	0.07
PANSS-N	***0.28***	***0.26***	0.13	***0.25***	***0.20***	***0.27***	***0.31***
PANSS-G	0.07	−0.04	0.15	***0.26***	0.11	0.09	0.16
PANSS-EP	0.00	***−0.17***	0.11	0.07	0.03	−0.01	0.01
CDS	0.09	−0.05	−0.05	0.10	−0.01	−0.05	0.03
MADRS	***0.20***	0.16	0.11	***0.29***	0.15	***0.18***	***0.26***
STAI-S	−0.08	−0.06	0.00	***−0.30***	−0.03	−0.10	−0.16
STAI-T	−0.10	−0.01	−0.09	***−0.34***	−0.06	−0.14	***−0.20***
YMRS	−0.06	−0.07	−0.01	***0.18***	−0.06	−0.02	0.02
GAF	***−0.23***	***−0.24***	−0.16	***−0.18***	***−0.29***	***−0.25***	***−0.27***
AHPQ	***−0.29***	−0.06	−0.11	***0.20***	***−0.23***	***−0.17***	−0.08
UKU	***0.37***	***0.24***	***0.21***	***0.25***	***0.32***	***0.33***	***0.36***
SARS	−0.01	***0.31***	−0.01	***0.32***	0.10	0.13	***0.20***
ESRS-Parkinsonism	0.03	***0.31***	0.03	***0.33***	0.13	***0.17***	***0.24***
ESRS-Hypokinesia	0.02	***0.32***	0.05	***0.26***	0.14	0.15	***0.22***
ESRS-Hyperkinisia	0.03	***0.22***	−0.02	***0.37***	0.08	0.15	***0.21***
ESRS-Akathisia	−0.09	0.02	−0.05	0.14	−0.07	−0.02	0.01
ESRS-Dystonia	−0.01	0.03	0.06	0.16	0.05	0.03	0.09
ESRS-Dyskinesia	−0.03	−0.08	0.08	−0.03	−0.02	−0.03	−0.01
ESRS-total score	−0.01	***0.29***	0.02	0.32	0.11	0.15	***0.21***
ESRS-CGI-Dyskinesia	−0.06	−0.10	0.05	−0.04	−0.06	−0.07	−0.05
ESRS-CGI-Parkinsonism	−0.07	***0.24***	−0.04	***0.20***	0.06	0.09	0.11
ESRS-CGI-Dystonia	0.07	***0.23***	0.09	***0.35***	0.13	0.16	***0.25***
ESRS-CGI-Akathisia	−0.10	0.06	−0.09	0.13	−0.06	−0.03	0.00

AHPQ, Annett Hand Preference Questionnaire; CDS, Calgary Depression Scale; ESRS, Extrapyramidal Symptom Rating Scale; GAF, General Assessment of Functioning; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SARS, Simpson-Angus Rating Scale; STAI, State-Trait Anxiety Inventory; YMRS, Young Mania Rating Scale.
The values in bold italics are significant at $p<0.05$ (patients with schizophrenia only).

diagnostic tool in the clinical assessment of schizophrenia. The results of this study do not support an effect of gender, age, age at onset, paternal or maternal age, education, medication status or clinical subtype of schizophrenia on NES scores. They also suggest that although there are some correlations between NES subscales and clinical features, especially with the negative symptoms of schizophrenia and depression as well as with extrapyramidal side effects of medications, these correlations are weak and most of NES variability is independent of these factors.

Relevance of the results of the current study to the existing literature, and implications for future research and clinical practice

Overall these results suggest that NSS constitute an independent (from the rest of symptoms), core (present in the vast majority of patients) and trait (unrelated to age and probably to the stage of schizophrenia) symptom of schizophrenia which could be of value in the clinical assessment and research of schizophrenia.

Although overall our present results are not in full accord with the literature, they could serve to fill in gaps and inconsistencies observed so far.

Past research suggests a rather complex and unstable correlation with age and a strong correlation with clinical status (13,50,51). Most studies support a correlation with negative symptoms and report that NSS are more frequent in patients with a 'deficit syndrome' (52–58). Our findings suggest a weak correlation of negative symptoms with NES sensory integration and motor coordination but overall are negative for the effect of age and clinical variables and are in accord with some other studies which, however, constitute the minority (51,59). Other studies report no relationship with lower cognitive ability, while the rates in normal controls are low (20,60). Some authors suggest NSS are suitable for the staging of schizophrenia (56,61) which again is not in accord with the results of the current study.

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As NES is unrelated to gender, symptomatology, age at onset, paternal or maternal age, education, medication status and clinical subtype of schizophrenia, with only weak and rather sporadic correlation with negative symptoms, depression and adverse effects of medication, it is reasonable to suggest that NSS include a core biological–neurological deficit which constitutes a trait marker probably present already at disease onset and it is of neurodevelopmental origin. There are a number of papers in the literature which agree with these conclusions (62,8,63–66).

Strengths and limitations of the present study

One of the advantages of the current study is that it is the first to report on the possible relationship of NSS with gender, parental age and medication status and one of the very few reporting on the role of education and age. It explored the data first with exploratory analysis and then with multivariate techniques which include correction for multiple testing.

The limitations of the current study include the fact that all patients have been previously hospitalised which means they represent maybe a more severe form of schizophrenic illness.

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Conflicts of Interest

None.

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