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ORIGINAL PAPER

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Neurological soft signs in patients with schizophrenia and their unaffected siblings: frequency and correlates in two ethnic and socioeconomic distinct populations

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Abstract Recent studies have suggested that ethnicity and socioeconomic status may have an impact on the frequency and significance of neurological soft signs (NSS). However, this impact has not been adequately assessed. The objectives were to determine the NSS scores in patients with schizophrenia and their unaffected siblings and to examine the clinical and therapeutic correlates of NSS in two ethnic and socioeconomic distinct populations. Two independent replicate studies were carried out: (1) a French Caucasian sample of 69 patients with schizophrenia, 43 of their unaffected siblings and 108 control subjects; (2) a Tunisian sample of 66 patients with schizophrenia, 31 of their unaffected siblings and 60 control subjects. NSS were assessed with a multidimensional scale, previously validated in drug-naïve and treated samples of patients with schizophrenia. Both patient groups were assessed with the positive and negative syndrome scale (PANSS), the clinical global impressions (CGI) and the global assessment of functioning. NSS total scores were significantly higher in patients with schizophrenia comparatively to siblings and to controls in both studies. The two sibling groups had also higher NSS scores than controls. In addition, NSS total scores were correlated to the PANSS negative and disorganization sub-scores, to the CGI-severity of illness and to a low educational level in both studies. These studies provide a confirmation in two distinct samples of the high prevalence of NSS in patients with schizophrenia, and in their biological relatives, independently of their respective ethnic and socioeconomic origins.

Key words neurological soft signs · replication study · schizophrenia · siblings · gene × environment

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Introduction

Neurological soft signs (NSS) are subtle neurological signs indicating non-specific cerebral dysfunction. Several studies have found an excess of NSS in patients with schizophrenia compared to healthy subjects [7, 21, 41, 43, 49]. In addition, the presence of NSS in first degree relatives of patients with schizophrenia suggests that they could be associated with the genetic liability [7, 10, 15, 22, 49]. Although NSS have been consistently reported in patients with schizophrenia, their clinical relevance and their relation to functional impairments, severity of disease and impact of antipsychotic medications are not well clarified. This could be explained by assessment tool diversity, but also by heterogeneity of the studied populations.

Previous studies have suggested that ethnicity and socioeconomic status may have an impact on the frequency and significance of NSS [5, 8]. However, this impact has not been adequately assessed. Inconclusive results have been reported regarding the influence of socioeconomic status. Griffiths et al. [16] reported an inverse correlation between social class and NSS, while Gupta et al. [18] found that NSS are not related to socioeconomic status of patients. Only a few studies have examined the role of ethnicity [6, 8].

Buchanan and Heinrichs [6] have found that both African–American patients and controls showed more neurological abnormalities than Caucasian ones. This finding has been also reported in siblings of patients with schizophrenia [10]. In another study, non-Caucasian patients including African–American and other ethnic groups had more cognitive/perceptual neurological abnormalities [26]. Studies exploring the interactions among those different variables are needed [5]. Indeed, these variables could influence not only the prevalence of NSS but also their relationship with clinical and functional impairments.

The aims were to determine the NSS scores in patients with schizophrenia and their unaffected siblings and to examine the clinical and therapeutic correlates of NSS in patients with schizophrenia in two ethnic and socioeconomic distinct populations.

Subjects and methods

Subjects

Two independent replicate case–control studies were carried in a French Caucasian sample of 224 subjects and a Tunisian sample of 157 subjects in two distinct countries. On each site, three groups were, respectively, recruited: 69 patients with schizophrenia, 43 of their unaffected siblings and 108 control subjects without family psychiatric history recruited in Sainte-Anne Hospital (Paris, France) and 66 patients with schizophrenia, 31 of their unaffected siblings and 60 control subjects without family psychiatric history, recruited in the University hospital of Monastir (Tunisia).

All subjects were informed about procedures of both studies and gave their informed written consent before participating to the study. All study procedures were approved by the local ethical committee, in agreement with the respective national regulation, and followed the ethical principles of the Declaration of Helsinki.

Patients with schizophrenia were consecutively recruited from the inpatients and outpatients clinics of both study sites. For inclusion in the previously mentioned studies, the patients were examined by trained psychiatrists and had to meet the diagnostic and statistical manual of mental disorders (DSM-IV) [1] criteria for schizophrenia. In the French study, diagnostic of schizophrenia were conducted through semi-standardized interview: the French version of the Diagnostic Interview for Genetic Studies (DIGS 3.0) [39].

The exclusion criteria were an age superior to 65 years, presence of co-morbid psychiatric disorder of axis I of DSM-IV [1], including dependence on alcohol or psychoactive substances (except tobacco dependence) and current (but not former) abuse and personal history of severe somatic or neurological disorder.

Real siblings (i.e. those having the same mother and father and not half siblings) accompanied the schizophrenic patients during consultations or attended upon invitation by the research team. One sibling for each patient was to be included. When more than one healthy sibling was available, the one who was of the same gender and nearest in age to the patient was asked to participate. Further, some of the patients in both studies had no unaffected siblings available, or had siblings who refused to participate in the study.

Control subjects were mostly recruited among nursing and technical or security hospital staff, and, in the French Study, by advertisement for half of the subjects. Control subjects had a negative family history of psychiatric disorders in their first-degree relatives. Psychiatric disorders were ruled out among siblings of schizophrenic patients and control subjects by direct assessment, conducted by trained psychiatrists according to the DSM-IV checklist [1] in Tunisian study and, in French study, using the DIGS 3.0 [39] for siblings and the structured clinical interview for DSM-III-R, non-patients (SCID-NP) [46] for controls.

The demographic, clinical and therapeutic characteristics of the patients with schizophrenia, siblings and controls are summarized in Table 1. In each study, the three groups were equivalent for age. The sex ratio was the same between the three groups in the Tunisian study ($P = 0.44$) while there were more female in siblings that in patients and controls in the French study ($P = 0.003$). In both studies, the school level was lower in the patients group ($P < 0.05$).

In addition, the French and Tunisian samples of patients with schizophrenia had the same range for age (16–57 years in French sample and 15–47 years in Tunisian sample), and the mean age at onset was comparable (22.1 ± 4.9 years in French sample and 21.2 ± 4.8 years in Tunisian sample). Age at onset was defined as age at first psychotic episode. Thus, they were mostly chronic patients with duration of illness longer than 12 months (88.4% in French sample vs. 92.4% in Tunisian sample). Moreover, in the two samples, the drug-naïve patients had a shorter duration of disease (11.6 and 7.6%, respectively) (Table 1).

However, the two samples differ for ethnic origin: in the French study, all subjects were Western European Caucasians, while in the Tunisian study, subjects were Arab, Berber or, most of the time, mixed between those two ethnical origins. The socioeconomic status of the patients estimated in reference to the respective overall socioeconomic level of the country was different in the two samples (Inferior: 26.1%, Middle: 42.0%, High: 31.9% in the French sample vs. Inferior: 25.8%, Middle: 69.7% and High: 4.5% in the Tunisian sample).

There were also differences in the clinical and therapeutic features of the two patient groups. The French patients were predominantly inpatients (60.3%), usually seen, however, just before their discharge, while the majority of Tunisian patients were outpatients (86.4%). In line with that, their mean duration of disease was longer in the Tunisian sample than in the French one (9.9 ± 4.6 vs. 6.2 ± 6.9 years). The mean duration of exposure to antipsychotic was only available for the French sample 45.6 ± 59.6 months. The distribution of the clinical sub-type of schizophrenia was different in the two samples with paranoid (27.0 vs. 36.4%), disorganized (23.8 vs. 33.3%) and undifferentiated (46.0 vs. 30.3%). Moreover, Tunisian patients were treated more frequently by first generation antipsychotic agents (74.2 vs. 21.7%) and more frequently by anticholinergic medication (62.1% vs. 17.4) (Table 1).

Procedures

Neurological soft signs were assessed with Krebs et al. [29] NSS scale previously validated in drug-naïve and treated samples of patients with schizophrenia, bipolar disorder and healthy controls. It is a comprehensive and standardized scale composed by 23 items rated from 0 to 3. Five factors were isolated using a Principal Component Analysis: motor coordination, motor integration, sensory integration, quality of lateralization, and involuntary movements (Table 2). The Simpson and Angus scale (SAS) [45] for extra pyramidal symptoms and the abnormal involuntary movement scale (AIMS) [19] were also rated. Clinical assessment of the patients with schizophrenia was conducted using French versions of the positive and negative syndrome scale (PANSS) [25, 31], the clinical global impressions (CGI) [17, 19] and the global assessment of functioning (GAF) [1, 17]. All the investigators on both side were fully trained for the ratings of those classical scales and the inter rater homogeneity has been checked prior to this study. In addition, the homogeneity of rating between the French and Tunisian team has been checked by simultaneous rating of patients during the different stays of AM in Paris.

For the neurological assessment, the raters were trained in advance (DG and MOK; AM and HS) and the inter rater reliability assessed on 16 and 20 patients, for the French and Tunisian study, respectively. The intra-class correlation coefficient of the NSS total

Table 1 Demographic, clinical and therapeutic characteristics of French and Tunisian study groups (mean ± SD), range (min–max)

	French study			Tunisian study		
	Patients $n = 69$	Siblings $n = 43$	Controls $n = 108$	Patients $n = 66$	Siblings $n = 31$	Controls $n = 60$
Age (years)	28.2 ± 7.2 (16–57)	29.2 ± 9.4 (15–64)	28.2 ± 7.5 (18–54)	31.2 ± 7.2 (15–47)	32.2 ± 5.9 (23–48)	30.8 ± 6.7 (16–46)
Gender (male: female)	51:18*	17:26	68:40	50:16	22:9	40:20
School level (years)	12.4 ± 2.7** (7–18)	13.8 ± 3.3 (5–22)	13.5 ± 2.9 (7–22)	8.5 ± 3.6*** (5–16)	10.6 ± 4.3 (5–17)	9.8 ± 3.2 (6–17)
Age of onset (years)	22.1 ± 4.9 (11–35)	–	–	21.2 ± 4.8 (13–33)	–	–
Duration of illness (years)						
<1	12.3	–	–	7.6	–	–
1–5	45.2	–	–	34.8	–	–
6–10	23.3	–	–	19.7	–	–
>10	19.2	–	–	37.9	–	–
Mean duration of illness	6.1 ± 6.9	–	–	9.9 ± 4.6		
First degree family history of psychiatric disorders (%)	56.7	100	0	34.8	100	0
Clinical sub-types (%)						
Paranoid schizophrenia	27.0	–	–	36.4	–	–
Disorganized schizophrenia	23.8	–	–	33.3	–	–
Undifferentiated schizophrenia	46.0	–	–	30.3	–	–
Catatonic schizophrenia	3.2	–	–	0.0	–	–
PANSS total	86.5 ± 20.3 (43–145)	–	–	76.6 ± 16.2 (49–126)	–	–
CGI-severity	5.2 ± 0.8 (3–7)	–	–	3.9 ± 0.8 (2–5)	–	–
GAF	39.5 ± 11.9 (25–85)	–	–	40.7 ± 15.3 (20–90)	–	–
SAS	3.9 ± 3.2 (0–13)	–	–	2.0 ± 2.1 (0–8)	–	–
Antipsychotic agents (%)						
Second-generation agent	55.1	–	–	3.0	–	–
First-generation agent	21.7	–	–	74.2	–	–
Both a first-generation and a second-generation agents	4.3	–	–	3.0	–	–
Drug-naïve	13.0	100	100	7.6	100	100
Untreated	5.8	–	–	12.1	–	–
Daily dosage of antipsychotics (mg CPZ equivalents) [3]	528 ± 449 (25–2500)	–	–	464 ± 428 (25–2600)	–	–
Anticholinergic medication (%)	17.4	–	–	62.1	–	–

SD standard deviation, *PANSS* positive and negative syndrome scale, *CGI* clinical global impressions, *GAF* global assessment of functioning, *SAS* Simpson and Angus scale for extra pyramidal symptoms, *CPZ* chlorpromazine

*$\chi^2 = 13.4$, $P = 0.001$

**ANOVA: $F_{2,219} = 4.2$, $P = 0.015$

***ANOVA: $F_{2,154} = 3.92$, $P = 0.02$

Table 2 Factorial structure of a Krebs et al. [29] neurological soft signs scale

Factor	Items
Motor coordination	Hand dysrhythmia
	Finger opposition
	Fist edge-palm
	Foot dysrhythmia
	Alternative movements: foot speed
	Alternative movements: hand speed
	Standing heel-to-toe
Motor integration	Romberg
	Apraxia
	Tandem walk
	Finger-to-nose
	Gait
	Tongue protrusion
Sensory integration	Stereognosia
	Hand-face
	Constructive apraxia
	Graphesthesia
	Right/left recognition
Quality of lateralizonati	Right/left confusion
	Lateral preference
	Right/left asymmetry
Involuntary movements	Abnormal movement and posture
	Mirror movements

score (SPSS: two-way Mixed Effect Model, confidence interval = 95%) was 0.72 [0.51–0.95] and 0.90 [0.77–0.95], respectively, in the two studies.

Statistical analysis

Statistical analysis was carried out with SPSS 11.0 software. Results were expressed as mean ± SD. To compare sociodemographic variables between groups in each study, ANOVA and Chi-squared tests were used for continuous and categorical variables, respectively. Differences in the NSS scores between studies groups were tested by performing an ANOVA for Tunisian study and ANCOVA adjusted by gender for French study (because the sex ratio was not the same in the three groups and it was a possible confounding effect), following by post hoc Tukey-test. The correlations between NSS scores and demographical, clinical and therapeutic characteristics were calculated using Pearson correlation coefficients. Finally, multiple regression analysis of relationship between demographical, clinical and therapeutic characteristics and NSS total score was conducted separately for each study using forward stepwise method. The independent variables for the multiple regression analysis were those significantly associated with NSS in bivariate analysis.

Results

Neurological soft signs scores

In both studies, patients with schizophrenia had significantly higher NSS total scores than sibling and control groups ($P < 0.001$) (Table 3). The NSS total scores of the siblings were intermediate between those of the patients with schizophrenia and those of the control subjects ($P < 0.001$), though in the French study, the comparison between siblings and control subjects was not significant ($P = 0.07$) (Table 3).

Table 3 Neurological soft signs scores in French and Tunisian study groups (mean ± SD), range (min–max)

NSS scores	French study				Tunisian study			
	Patients $n = 69$	Siblings $n = 43$	Controls $n = 108$	ANCOVA[a] $df = 2,216$	Patients $n = 66$	Siblings $n = 31$	Controls $n = 60$	ANOVA $df = 2,154$
Motor coordination	7.2 ± 4.3 (0–16.5)	4.3 ± 3.3 (0–14)	2.7 ± 2.0 (0–8)	$F = 45.8$ $P < 0.001$	9.2 ± 3.0 (4–18)	5.0 ± 1.8 (2–9)	2.0 ± 1.5 (0–6)	$F = 151.6$ $P < 0.001$
Motor integration	3.1 ± 2.8 (0–16)	1.4 ± 1.2 (0–4)	0.7 ± 1.1 (0–4.5)	$F = 34.9$ $P < 0.001$	3.5 ± 1.8 (1–9)	1.7 ± 1.0 (0–4)	0.6 ± 0.8 (0–4)	$F = 70.8$ $P < 0.001$
Sensory integration	2.9 ± 2.6 (0–11)	1.3 ± 1.1 (0–3.5)	1.4 ± 1.4 (0–5)	$F = 17.6$ $P < 0.001$	4.5 ± 1.8 (0–9)	2.7 ± 1.1 (0–5)	1.0 ± 1.0 (0–4)	$F = 87.1$ $P < 0.001$
Quality of laterality	1.2 ± 1.5 (0–5)	0.7 ± 1.1 (0–3)	0.6 ± 1.0 (0–4)	$F = 4.9$ $P = 0.009$	1.6 ± 1.4 (0–5)	1.1 ± 1.0 (0–4)	0.4 ± 0.7 (0–3)	$F = 17.3$ $P < 0.001$
Involuntary movements	0.6 ± 0.6 (0–2)	0.3 ± 0.5 (0–2.5)	0.4 ± 0.7 (0–3)	$F = 2.8$ $P = 0.06$	0.6 ± 1.0 (0–4)	0.3 ± 0.4 (0–1)	0.1 ± 0.3 (0–2)	$F = 8.5$ $P < 0.001$
Total score	15.0 ± 7.9 (1–36)	8.0 ± 4.0 (2–17.5)	5.8 ± 3.3 (0–18)	$F = 63.3$ $P < 0.001$	19.5 ± 5.2 (11–32)	10.8 ± 3.4 (5–17)	4.2 ± 2.1 (2–10)	$F = 235.7$ $P < 0.001$

NSS neurological soft signs, *SD* standard deviation
[a]ANOVA adjusted for gender

In both studies, patients with schizophrenia had significantly higher sub-scores for motor coordination, motor integration and sensory integration than siblings and controls ($P < 0.001$ for all post hoc comparisons patients vs. siblings and patients vs. controls) (Table 3).

Nevertheless, differences also were found between the two studies. In particular, siblings were more similar to controls in the French study (post hoc P value significantly only for motor coordination = 0.01), while all post hoc comparison were significantly different between siblings vs. controls in the Tunisian study ($P \leq 0.001$).

More complicated patterns were found for the remaining NSS dimensions. For quality of laterality, again, siblings had intermediate sub-scores between corresponding patients or controls in both studies. However, post hoc comparisons lead to significant P values in the Tunisian sample only (patients vs. siblings: $P = 0.05$; patients vs. controls: $P < 0.001$; siblings vs. controls: $P = 0.03$), while differences were not significant between patients and siblings and between siblings and controls in the French sample (respective P values: patients vs. siblings: $P = 0.07$; patients vs. controls: $P = 0.004$; siblings vs. controls: $P = 0.93$). Regarding involuntary movements, the sole significant difference in post hoc comparison was between patients and controls in the Tunisian sample (Tunisian sample: patients vs. siblings $P = 0.12$; patients vs. controls: $P < 0.001$; siblings vs. controls: $P = 0.33$; French sample: patients vs. siblings $P = 0.06$; patients vs. controls: $P = 0.38$; siblings vs. controls: $P = 0.39$). This could be due to the low level of involuntary movements in the two studies (maximal range between 0 and 4) (Table 3).

Table 4 Correlation coefficients between neurological soft signs total score and demographic and clinical characteristics in French and Tunisian patients with schizophrenia

	French study	Tunisian study
Age	0.15	0.05
School level	−0.37**	−0.41**
Age of onset	−0.07	0.06
PANSS positive	0.09	−0.05
PANSS negative	0.50***	0.43***
PANSS disorganization	0.53***	0.38**
PANSS total	0.39**	0.35**
CGI-severity	0.32**	0.50***
GAF	−0.24	−0.35**
SAS	0.39**	0.19

PANSS positive and negative syndrome scale, *CGI* clinical global impressions, *GAF* global assessment of functioning, *SAS* Simpson and Angus scale for extra pyramidal symptoms
**$P < 0.01$
***$P < 0.001$

Table 5 Multiple regression analysis of relationship between clinical and therapeutic characteristics and neurological soft signs total score in French and Tunisian patients with schizophrenia (forward stepwise method of variable selection used)

	Beta	*t*	*P*
French study			
PANSS disorganization	0.88	4.12	0.000
SAS	0.29	2.99	0.004
First-degree family history of psychiatric disorders	0.24	2.44	0.017
Tunisian study			
CGI-severity	0.38	3.85	0.000
School level	0.34	−3.58	0.001
PANSS negative	0.26	2.62	0.011

PANSS positive and negative syndrome scale, *CGI* clinical global impressions, *SAS* Simpson and Angus scale for extra pyramidal symptoms

Clinical and therapeutic correlates of neurological soft signs

In both studies, the NSS total scores were positively correlated with the PANSS negative and disorganization sub-scores and the CGI-severity of illness. The NSS total scores were negatively correlated with the school level. No correlation was found between the NSS total scores, age, age at onset and the PANSS positive sub-score (Table 4).

In the French study, the NSS total score was higher in female patients than in male patients (17.6 ± 8.7 vs. 14.0 ± 7.6, $F_{1,67} = 2.7$, $P = 0.11$), and was associated with first-degree family history of psychiatric disorders (17.4 ± 7.9 in presence vs. 11.8 ± 6.9 in absence of first-degree family history of psychiatric disorders, $F_{1,67} = 9.2$, $P = 0.004$) and medication status (15.9 ± 8.1 in treated vs. 10.9 ± 6.1 in untreated patients, $F_{1,67} = 4.4$, $P = 0.04$. In addition, the NSS total score was correlated with the SAS score (Table 4). Moreover, no significant difference concerning the NSS total score was found between patients treated with first or second generation of antipsychotic medications in this study.

In the Tunisian study, the NSS total score was negatively correlated with the GAF score (Table 4). However, no association was found between the NSS total score, gender, family history of psychiatric disorders and medication status.

A multiple regression analysis was conducted in both studies including gender, school level, first-degree family history of psychiatric disorders, PANSS negative and disorganization sub-scores, CGI-severity, medication status and SAS. This regression led to distinct results. In the French study, the regression results showed an association between the NSS total score and the PANSS disorganization sub-score, the SAS score and the first-degree family history of psychiatric disorders. In the Tunisian study, the NSS total score was associated with the CGI-severity of illness, the low educational level and the PANSS negative sub-score (Table 5).

Discussion

These studies provide a confirmation in two distinct samples of the high scores of NSS in patients with schizophrenia, and in their biological relatives, independently of their respective geographic origins. These results were found despite differences between the two studied populations concerning ethnic (Caucasian in the French sample vs. Arab or Berber in the Tunisian sample) [14], socioeconomic level of the patients in addition to the overall difference between the two countries (7th for France vs. 60th place for Tunisia in term of Gross Domestic Product) [48], clinical and therapeutic features (French patients were treated more frequently by second-generation antipsychotics vs. first-generation antipsychotics for the Tunisian patients). These findings thus confirm those of previous studies [7, 8, 13, 21, 22, 49] and strongly support that NSS are intrinsic features of schizophrenia and a reliable intermediate phenotype. In addition, the high prevalence of NSS in the siblings of patients with schizophrenia further support that neurological impairment in schizophrenia may be familial and trait-like in nature [9, 15, 22, 49].

Our results show that motor coordination anomalies are more discriminative to differentiate patients with schizophrenia and their relatives from healthy subjects. It reinforces the idea that motor abnormalities are genetically mediated and may constitute reliable markers of vulnerability, as already suggested [5, 15] although we cannot exclude that this difference between NSS dimensions could be due measurement factors (more items than in the other factors). The two studies also revealed different pattern regarding sensory integration and laterality sub-scores, which were not different between siblings and control subjects in the French study in contrast to the Tunisian study. Similar inconsistent results are found in the literature: sensory integration abnormalities in siblings were reported at the same level than in patients with schizophrenia [22, 49] or comparable to controls subjects [7, 10]. This suggests the variability in the intra-familial transmission of NSS dimensions, while assessment bias cannot be excluded.

Several bivariate correlates were found in the two schizophrenic patient groups with demographic and clinical variables. An inverse correlation was found between NSS and school level in both patient groups. Similar results were reported by some authors [37, 41, 44], while other studies failed to find a relationship between NSS and educational level [12, 18, 35, 36]. In addition, we did not find correlation between NSS and age at onset in both studies. This result was consistent with those reported by other studies [28, 30, 32], while some authors [35, 38] found that early onset schizophrenia is more clearly associated with neurodevelopmental abnormalities, including the NSS. Some clinical issues and methodological consideration might account for those differences: depending on the study, age at onset can be age at first positive symptoms, age at first psychotic episode, age at first admission, age when criteria A for schizophrenia was first met, including negative symptoms of schizophrenia.

The association of NSS with negative and disorganization symptoms of schizophrenia in the two studies has already been reported in the literature. Several studies have examined the relationship between neurological impairments and symptoms of schizophrenia [2, 9, 13, 21, 23, 27, 30, 34, 37, 42, 43, 49]. The majority of these studies have suggested that negative symptoms and, less often disorganization, could be correlated to NSS, especially frontal function (motor) signs and parietal function (sensory integration) signs, whereas positive symptoms consistently appear unrelated to NSS [5]. An association between NSS and some clinical dimensions of schizophrenia may explain which neurological dysfunction is an intrinsic characteristic of the illness [47].

In addition, the association of NSS with CGI-severity of illness in the two patient groups suggests that neurological impairments could characterize more severe psychopathological processes of schizophrenia, resulting in poorer functional outcome. Indeed, functional outcome in schizophrenia is multidimensional and mainly predict by psychopathological symptoms [20].

Previous studies of the literature led to inconclusive results regarding a relationship between neurological impairments and family history of psychosis [16, 21]. The association of NSS with first-degree family history of psychiatric disorders found only in French patients with schizophrenia supports that the relative weight of genetic factors on the neurological signs could be more important in this population. However, this result also could be explained by the recruitment of patients with more family history of psychiatric disorders in the French sample compared to the Tunisian one.

The most important difference between the two studies was the association of NSS with antipsychotic medication status and antipsychotic-related effects in French schizophrenic patients, but not in Tunisian patients. The relationships of NSS with antipsychotic medication status or side effects remain under discussion. The majority of studies have reported a lack of association between antipsychotic medication and NSS frequency [2, 7, 13, 16, 21, 30, 37, 40, 42], whereas, several studies found a significant association between NSS and extra pyramidal symptoms [11, 12, 18, 49]. These latter studies point towards a possible relationship between poorer performance on tasks involving motor dexterity and the presence of extra pyramidal symptoms. However, other studies failed to find an association with extra-pyramidal symptoms [35, 37, 42, 43].

The more frequent association with anticholinergic medication in this population could explain the surprising lack of correlation between NSS and SAS scores in the Tunisian patients, despite the fact they received conventional antipsychotic. A lower susceptibility to extra pyramidal effects in Tunisian could also explain this result, but studies with more homogeneous antipsychotic treatments (type and dosage) are needed to further document this latter hypothesis.

Even though the majority of the bivariate correlations were reproduced in the two studies (with school level, negative and disorganization symptoms, CGI-severity), multiple regression analysis failed to find similar pattern between the two samples. While NSS were significantly related with the family history and medication effects in the French patients with schizophrenia, they were mainly related to the school level and severity of illness in the Tunisian patients with schizophrenia. These different results could reflect the complex interrelationship between the NSS and the clinical and therapeutic features of schizophrenia and the possible intervention of potential confounder factors. It appears clearly that the ethnic or socioeconomic origin has no major influence on the presence of NSS in patients with schizophrenia per se. However, the French and Tunisian samples differed concerning the influence of medication and, possibly, of genetic versus environmental factors. The relation between NSS and family history of psychiatric disorders in the French Caucasian patients suggest the prominent weight of genetic factor. In addition, the susceptibility to the antipsychotic medication effects could also be linked to genetic characteristics in Caucasian schizophrenic patients [24]. In contrast, those features did not appear to prominently influence NSS scores in the Tunisian sample, suggesting that the relative weight of environmental factors could be more important in the Tunisian patients. This is in line with the known frequency of obstetric complications in this population [33] and remains to be directly addressed in future studies.

Several limitations should be considered when interpreting these findings. First, although, we attempt to reproduce as much as possible the same procedures in Tunisia and France and the fact that the main Tunisian investigator was trained within the French group, there were differences between the two studies, depending on the type of referral, place of recruitment and socioeconomic characteristics. The recruitment of the patients with schizophrenia was limited to patients admitted or followed in the Tunisian university hospital, with a large outpatient clinic while for the French sample it was both from a University Department and first line psychiatric department. There were several differences in the type of patients enrolled. The proportion of inpatients versus outpatients differed between the two samples and inpatients can differ from outpatients in the severity of symptomatology. In fact, NSS may reflect the severity of the disease psychopathological process [4]. The recruitment of unaffected siblings was not exhaustive, considering the lack of availability of some and the refusal to participate by others. The recruitment of controls from hospital staff may represent another limitation, although, all procedures respected the confidentiality of the psychiatric interview done, in the French study, by an independent psychologist. They were not fully match to the patients, in particular regarding the level of study. The inclusion of technical staff in both samples and of subjects recruited via advertisement in the French study enabled us to limit the bias and the controls were not different for the level of study from the siblings, and in turn to the family socioeconomic level of the patients. A last limitation was that raters were not blind to diagnosis for the neurological assessment, but it is, however, hardly feasible.

Conclusion

The findings of these parallel studies confirm the frequency of NSS in patients with schizophrenia and their unaffected siblings further supporting that neurological abnormalities are a reliable phenotypic vulnerability marker for schizophrenia, in particular motor coordination abnormalities. In addition, we found a significant association between the NSS scores and the negative and the disorganization symptoms contrasting with the lack of relationship with the positive symptoms and the age at psychosis onset. The difference observed between the two studies in the multiple regression analysis could reflect differences in the relative importance of genetic and environmental factors and the possible influence of other variables such as ethnicity, socioeconomic origin and medication effects. These findings highlight the need to take into account the ethnic and socioeconomic status in clinical researches in schizophrenia.

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