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A preliminary study on similarities and dissimilarities of Neurological Soft Signs in schizophrenic and obsessive-compulsive disorders suggests a common maldevelopmental model

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Summary. Aim. Neurological Soft Signs (NSS) represent minor neurological signs related to non-specific cerebral alterations. They have been documented in many psychiatric disorders including schizophrenia (SCZ) and obsessive-compulsive disorder (OCD). Aim of this study was to determine and compare the incidence and severity of NSS in patients with SCZ, in patients with OCD, and healthy control subjects (HCs). **Methods.** Using the Neurological Evaluation Scale (NES), this study investigated NSS in 15 SCZ patients, 14 OCD patients, and 15 HCs. PANSS and Y-BOCS were used to evaluate clinical picture in both groups. **Results.** Patients with SCZ showed significantly higher scores compared to HCs in the NES total and each of the three NES subscales (Integrative Sensory Function, Motor Coordination, and Sequencing of Complex Motor Acts). Patients with OCD also showed significantly higher scores compared to HCs in the NES total, Motor Coordination and Sequencing of Complex Motor Acts, but not in Integrative Sensory Function. No significant differences emerged in the NES total and the various subscales scores between the two patients' groups. **Conclusions.** Our results seem to confirm the presence of NSS in both SCZ and OCD. The different types of NSS presented by the two patients' groups versus HCs further supports the findings of widespread cerebral alterations in SCZ, on the other hand, with a preferential involvement of prefrontal and frontal cortex in OCD.

Key words. Cerebral maldevelopment, neurodevelopment, neurological soft signs, obsessive-compulsive disorder, schizophrenia.

Lo studio preliminare sulle similitudini e differenze dei Neurological Soft Signs suggerisce un comune modello di alterazione dello sviluppo nei disturbi schizofrenici e ossessivo-compulsivi.

Riassunto. Scopo. I Neurological Soft Signs (NSS) rappresentano dei segni neurologici cosiddetti minori correlati ad alterazioni cerebrali non specifiche. I NSS sono presenti in molti disturbi psichiatrici inclusi la schizofrenia (SCZ) e il disturbo ossessivo-compulsivo (OCD). Obiettivo dello studio è stato quello di determinare e comparare l'incidenza e la gravità dei NSS in pazienti con schizofrenia e in pazienti con OCD confrontandoli con controlli sani. **Metodi.** I NSS sono stati valutati in 15 pazienti schizofrenici, 14 pazienti con OCD e 15 controlli sani, attraverso la somministrazione della Neurological Evaluation Scale (NSS). La sintomatologia clinica è stata misurata attraverso la somministrazione della PANSS e della Y-BOCS. **Risultati.** I pazienti con schizofrenia hanno valori significativamente più alti nella NES totale e in tre sottoscale (Integrative Sensory Function, Motor Coordination e Sequencing of Complex Motor Acts) rispetto ai controlli sani. Anche i pazienti con OCD hanno, rispetto ai controlli sani, valori più alti nella NES totale e in due sottoscale (Motor Coordination e Sequencing of Complex Motor Acts) ma non nella Integrative Sensory Function. Nessuna significativa differenza è emersa tra i due gruppi di pazienti nel valore totale e nelle sottoscale della NES. **Conclusioni.** I risultati del nostro studio confermano la presenza di NSS in entrambi i gruppi di pazienti. Inoltre, i differenti tipi di NSS presenti nei due gruppi di pazienti studiati, rispetto ai controlli sani, supportano il dato di diffuse alterazioni cerebrali nei pazienti con schizofrenia e di un coinvolgimento preferenziale della corteccia frontale e prefrontale nei pazienti con OCD.

Parole chiave. Alterato sviluppo cerebrale, disturbo ossessivo-compulsivo, neurological soft signs, neurosviluppo, schizofrenia.

Introduction

Neurological Soft Signs (NSS) are subtle but observable impairments in motor and sensory functions that are not restricted to a characteristic of any specific neurological condition[1] and typically, they are classified into signs relating to sensorimotor integration, motor coordination, sequencing of complex motor tasks, and disinhibition[2].

NSS have been proposed to be a marker of abnor-

mal brain development[3,4], and are known to correlate with a wide range of neurocognitive and neuroanatomical abnormalities, and it has been proposed that they represent an underlying defect in neural integration[5].

NSS have been reported in excess in SCZ, where they are considered a neuro-dysfunction associated to this disorder[6], with frequency ranging from 50% to 65% in contrast to 5% in normal population[7,8] and they have been described both in first-episode *drug-naïve* and treated patients[9-11]. They have been associated with negative or deficit symptoms, cognitive functioning, an earlier onset of the illness and a poorer long-term outcome[5,7,12]. The neural substrates of NSS in SCZ remain poorly understood. Basal ganglia and cerebellum, as somatomotor and somatosensory regions, would seem to be involved in impairment in visual processing and spatial orientation, as well as dysfunction of frontoparietal and cerebellar networks would seem to be implicated in the pathophysiology of NSS. It remains unclear if white matter integrity deficits or neurometabolic alterations contribute to NSS in the illness. Furthermore, only little is known about the temporal evolution of NSS, and in antipsychotic medication-naïve patients These data are very important gaps in the knowledge of NSS[13].

On the whole, the etiology of NSS is uncertain; Tsuang et al.[14] have argued that they might reflect genetic and non-genetic processes underpinning the predisposition to psychotic illness. Corroborating this assumption, NSS have well been documented in subjects genetically at risk of developing SCZ[15]. Indeed, according to the "Neurodevelopmental model", SCZ is believed to be the result of an interaction between genetic and environmental factors. More specifically, this model hypothesizes that, in subjects with SCZ, cerebral damage – caused by non-genetic factors, such as obstetric complications – eventually interacts with genetic liability to cause neurodevelopmental abnormalities; thus, the onset of SCZ in adult life might ensue when the brain matures sufficiently to call into operation the damaged system[16].

With regard to OCD, controversial reports are present in the literature about the relationship between OCD and NSS. Some Authors have found a higher prevalence of NSS in patients with OCD[17-19] and cognitive deficits in the domains of visuospatial ability, executive function, attention, and working memory in these patients compared to controls[20-22] yet other studies have failed to detect such differences[23-25]. Moreover, whilst some Authors[17,25] suggest NSS as indicators of non-structural brain damage, which may cause OCD symptoms[17], other Authors believe that NSS are likely to be related to both structural and functional brain abnormalities, especially regarding left basal ganglia and insula, and a disorder-specific fronto-striato-insular dysregulation in the form of poor frontal control over overactive basal ganglia[26], and that the affected regions of the brain for NSS probably resemble those in OCD[27]. Whether NSS can be consider a marker of a deviant neurodevelopment in patients with OCD, as for patients with SCZ, is still a matter of debate[25].

Considering the former, the aim of the present pilot study was to determine the incidence and severity of NSS in patients with SCZ as compared with patients with OCD and a control group, and to evaluate differences in the expression of NSS in SCZ compared with OCD.

Materials and methods

Three groups of subjects took part in this study: 1) 15 patients with chronic SCZ, 2) 14 patients with OCD, and 3) 15 HCs. Psychiatric diagnoses were determined according to DSM-V criteria. Demographic information and past and current symptom history of all patients were obtained in semi-structured interviews. Clinical status was assessed by using the Scale for the Assessment of Positive and Negative Syndrome Scale (PANSS)[28] and the Yale Brown Obsessive Compulsive Scale (Y-BOCS)[29]. Subjects were matched for age, sex and other demographic variables. Informed consent was obtained from all participants. In order to evaluate a possible correlation between NSS and previous and/or ongoing antipsychotic medications, a careful investigation was carried out with regard to the antipsychotic treatment throughout the illness course. Patients were recruited from the Unit of Psychiatry A. Fiorini Hospital in Terracina (Sapienza University, Rome). Inclusion criteria for all subjects were: 1) 15-60 years of age (in order to avoid bias due to degenerative diseases); 2) no previous or ongoing substance abuse; and 3) no previous or ongoing neurological disorders (such as intellectual disability, dementia, and/or history of traumatic brain injury with loss of consciousness).

NSS were assessed using an Italian version of the Neurological Evaluation Scale (NES)[2]. This is a twenty-six items check list, fourteen of which are bilateral, and consists of three subscales relatively to the three different NSS cluster categories and their most likely, putative neuroanatomical localization[7]. Each item, except for the *snout reflex* and the *suck reflex* (evaluated with a score of 0 or 2), has a score scaled three points: 0= no anomaly; 1= slight presence of anomaly; 2= marked presence of anomaly. The NES has been employed following the instructions provided by the Authors. We took into consideration the score obtained at the NES total, as an index of global NSS seriousness, and the scores obtained at the three NES subscales: Integrative Sensory Function (the score of which is the sum of the items tactile extinction on bi-

lateral stimulation, graphestesia, stereognosis, right/left confusion and audio-visual integration); Motor Coordination (the score of which is the sum of the items tandem walk, finger-to-nose test, finger-thumb opposition and dysdiachokinesis); and Sequencing Of Complex Motor Acts (the score of which is the sum of the items fist-ring test, fist-edge-palm test and Ozeretski's test).

Statistical analyses

Analyses were carried out using SPSS V17 (SPSS Inc., Chicago, IL, USA). Sociodemographic clinical variables were described and compared amongst the three groups (OCD, SCZ, and HCs) with t tests, one-way ANOVAs or chi-square tests as appropriate. Pearson's correlations between the NES, the PANSS, and the Y-BOCS total and subscales scores were computed after testing data for normality and linearity distributions.

Because of the possible influence of antipsychotic treatment on NSS and because there was a significant difference in the age ratio, ANCOVAs, with age and lifetime antipsychotic treatment (duration of illness by the chlorpromazine equivalent units of current daily antipsychotic dose) as covariates, were performed for the NES total and subscales scores to evaluate contrasts amongst the groups. When data could not be transformed to meet the assumptions of normality, Kruskal-Wallis tests or Mann-Whitney tests were used as appropriate. The critical level for statistical significance was set at $p<0.05$. The exploratory nature of the study and the small sample size, which might have easily lead to a Type II error, argued against the application of correction for multiple comparisons.

Results

Demographic and clinical characteristics of the study participants are shown in table 1. SCZ patients were significantly older than the OCD patients and the HCs [$F(2,42)=4.297$, $p=.020$. Post-hoc test: SCZ vs OCD: $p=.020$; SCZ vs HC: $p=.012$]. Age at onset was significantly earlier [$t(27)=2.636$, $p=.014$] in the OCD group than in the SCZ group. In the SCZ group, all patients were currently on antipsychotics. In the OCD group, 69.23% of patients (N=9) were currently on antidepressants and 30.77% (N=4) were currently being treated with antipsychotics. There were no significant differences for the remaining descriptive variables amongst the three subjects' groups [sex: $\chi^2(2)=.968$, $p=.616$; educational level: $F(2,42)=.908$, $p=.412$; and duration of illness: $t(27)=-.593$, $p=.558$].

In the SCZ patients, the NES total score was positively correlated with the PANSS General Psychopathology Symptoms score ($r=.808$, $p=.028$). A positive correlation was also found between the right-sided tests score of the Integrative Sensory Function subscale of the NES and the PANSS-Negative symptoms score ($r=.839$, $p=.018$) and even between the right-sided tests score of the Integrative Sensory Function subscale of the NES and the PANSS total score ($r=.952$, $p=.028$). In the OCD patients, the NES total

Table 1. Characteristics of patients and control subjects.

	SCZ (N=15)		OCD (N=14)		HCs (N=15)		p
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	41.47	12.48	32.14	9.37	31.36	8.72	0.02
Educational level (years)	11.47	2.80	12.57	3.06	12.93	3.32	0.41
Onset	38.93	15.58	28.93	8.50			0.01
Duration of illness (months)	31.33	25.10	37.71	32.561	-	-	0.56
Y-BOCS - Obsessions - Compulsions - Total	 - - -	 - - -	 13.36 9.36 22.73	 2.38 3.58 5.31	 - - -	 - - -	-
PANSS - Positive - Negative - Total	17.00 27.71 92.71	5.164 5.678 15.861	- - -	- - -	- - -	- - -	-
Antipsychotic treatment	15		9		0		-

Legend: SCZ= patients with schizophrenia; OCD= patients with obsessive-compulsive disorders; HCs= healthy controls; Y-BOCS= Yale-Brown Obsessive Compulsive-Scale (subscores and total scores); PANSS= Positive And Negative Syndrome Scale (subscores and total scores).

and subscales scores did not correlate significantly with the Y-BOCS total or subtotal scores for obsessions or compulsions.

The NES total and subscales scores were significantly different amongst the three groups [NES total: F(2,42)=6.693, p=.003; Integrative Sensory Function: H(2)=15.514, p<.001; Motor Coordination: H(2)=12.945, p=.002; and Sequencing Of Complex Motor Acts: H(2)=13.326, p=.001] (table 2). Post-hoc tests revealed that the NES total score was significantly higher in both SCZ and OCD patients' groups than in the HCs group (respectively, p=.002 and p=.008).

With regard to SCZ patients, they performed higher than HCs at each of the three NES subscales scores (Integrative Sensory Function: U=19.500, z=-3.858, p<.001; Motor Coordination: U=34.000, z=-3.405, p=.001; and Sequencing Of Complex Motor Acts: U=21.000, z=-3.780, p<.001) and also at each of their right- (Integrative Sensory Function: U=56.000, z=-2.857, p=.004; Motor Coordination: U=56.000, z=-2.857, p=.004; and Sequencing Of Complex Motor Acts: U=42.000, z=-3.360, p=.001) and left-sided tests scores (Integrative Sensory Function: U=56.000, z=-2.861, p=.004; Motor Coordination: U=56.000, z=-2.851, p=.004; and Sequencing Of Complex Motor Acts: U=46.000, z=-2.890, p=.004). Apart from the Integrative Sensory Function subscale score, OCD patients performed higher than HCs at the various NES subscales scores (Motor Coordination: U=59.000, z=-2.170, p=.030 and Sequencing ff Complex Motor Acts: U=52.000, z=-2.267, p=.023). Interestingly, significant differences were found in both the right- and left- tests of the Sequencing of Complex Motor Acts (U=56.000, z=-2.695, p=.007 and U=53.500, z=-2.403, p=.016, respectively), whereas, with regard to the Motor Coordination, this difference was seen only for the tests assessing the left side (U=56.000, z=-2.696, p=.007).

OCD and SCZ patients did not differ significantly in total scores on the NES or in any of the individual tests.

Discussion and conclusions

The first major finding of this study is the presence of NSS in both SCZ and OCD patients, although with significant differences in the type of NSS presented by the two patients' groups when compared to HCs.

According to previous studies[5], the performances of SCZ patients were significantly worse than HCs in the NES total and each of the three NES subscales (Integrative Sensory Function, Motor Coordination, and Sequencing of Complex Motor Acts). Sequencing of Complex Motor Acts reflects the functions of the prefrontal cortex[7]; Motor Coordination signs are reported to be hypothetically related to fronto-cerebellar impairments[7,30] and Integrative Sensory Function reflects the functions of the parietal lobe[7,30].

With regard to OCD patients, they also showed significantly higher scores compared to HCs in the NES total, Motor Coordination and Sequencing of Complex Motor Acts, but not in Integrative Sensory Function.

Such results seem to suggest widespread cerebral alterations in SCZ, on the other hand, with a preferential involvement of prefrontal and frontal cortex in

Table 2. Scores on the Neurological Evaluation Scale (NES) in patients with schizophrenia, in patients with obsessive-compulsive disorders and in control subjects.

	SCZ (N=15)		OCD (N=14)		HCs (N=15)		p	
Domain	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**SCZ vs. HCs**	**OCD vs HCs**
Sensory Integration								
- right-sided tests	0.73	0.88	0.50	0.76	0.00	0.00	0.004	n.s.
- left-sided tests	0.93	1.10	0.93	1.07	0.00	0.00	0.004	n.s.
- total score	3.67	2.74	1.71	1.90	0.43	0.85	<0.001	n.s.
Motor Coordination (fronto-cerebellar)								
- right-sided tests	0.73	0.88	0.21	0.43	0.00	0.00	0.004	n.s.
- left-sided tests	1.00	1.31	0.57	0.76	0.00	0.00	0.004	0.007
- total score	2.33	2.13	0.93	1.14	0.14	0.36	0.001	0.030
Motor sequencing (prefrontal)								
- right-sided tests	1.40	1.55	0.86	1.10	0.00	0.00	0.001	0.007
- left-sided tests	1.53	1.46	1.14	1.23	0.21	0.58	0.004	0.016
- total score	4.47	3.78	3.29	3.50	0.50	0.85	<0.001	0.023
Total NES score	16.60	11.10	9.64	6.18	2.43	2.03	0.002	0.008

Legend: SCZ= patients with schizophrenia; OCD= patients with obsessive-compulsive disorders; HCs= healthy controls; SD= standard deviation; n.s.: not significant.

OCD. As regards to laterality and cerebral dominance, our research did not identify an unequivocal laterality pattern of neurological signs in SCZ. Indeed, patients with SCZ performed worse than HCs in both the right- and left-sided tests. With regard to OCD patients, they also showed significant differences in both the right- and left-sided tests of Sequencing of Complex Motor Acts, whereas in Motor Coordination this difference was significant only for tests assessing the left side.

Some studies have reported for SCZ a predominance of neurological abnormalities on the right side of the body, but there are conflicting reports of higher scores for NSS on the left side of the body[31].

Regarding OCD, few studies have investigated the laterality of NSS in these patients. Confirming our results, a trend for higher scores of the NSS on the left side, especially motor signs, was reported[32].

The second major finding of our study is the lack of any significant differences in the NES total and/or the various subscales scores between the two patients' groups. SCZ and OCD are disorders involving the prefrontal-striato-thalamic pathway, even though the cortical areas implicated in these illnesses are different: in SCZ, the main cortical area involved is the dorsolateral prefrontal cortex, in OCD it is the orbitofrontal cortex[33]. The NES scale does not specifically assess orbitofrontal cortex functions and this could explain the lack of significant differences between the two groups.

As would be expected, the two patients' groups were different with respect to psychotropic administration. ANCOVAs, with age and lifetime antipsychotic treatment (duration of illness by the chlorpromazine equivalent units of current daily antipsychotic dose) as covariates did show an absolute independence of NSS from antipsychotic treatment. This result seems to confirm other studies that found no influence of medication on NSS in either SCZ or OCD[9,11,17].

NSS are considered signs of impaired neurodevelopment[14,19,25], thus the lack of any significant differences in the NES total and/or the various subscales scores between the two patients' groups seems to support a neurodevelopmental origin not only for SCZ, but also for OCD. It can be assumed that these neurological signs may depend on some functional brain abnormalities, potentially involved as substrate for SCZ and/or OCD. Genetic and non-genetic factors may cause brain alterations responsible for slight neurological abnormalities, then – in high-risk patients – they may precipitate a psychotic or an OCD symptomatology[14,16,19].

To conclude, both SCZ and OCD are associated with an increased rate of NSS, though with significant differences in the type of NSS presented by the two patients' groups when compared to HCs. The lack of any significant differences in the NES total and/or the various subscales scores between the two patients' groups may support a common neurodevelopmental origin.

The main limit of this study is the small sample size and the impossibility to completely exclude a potential confounding effect of psychotropic medication in patients with SCZ. Yet, our study confirms previous research further suggesting a possible extension of the "Neurodevelopmental Model" to SCZ, OCD and other mental diseases.

Conflict of interests: the authors have no conflict of interests to declare.

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