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Neurological soft signs as trait markers of a subset of patients with obsessive-compulsive disorder with low insight and altered cognitive abilities

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ABSTRACT

Neurological soft signs (NSS) are subtle motor control impairments that include involuntary movements and abnormalities of motor coordination, sensory integration and lateralization. They engage different brain networks, including the prefrontal networks that support the higher cognitive functions that are dysfunctional in obsessive-compulsive disorder (OCD). This study investigated the relationships between the presence of NSS and patients' severity of OCD symptoms, insight, and treatment resistance in a sample of 63 patients. Treatment-resistance was assessed considering all the treatments the patients received during the course of their disease. The four dimensions of OCD defined in the dimensional obsessive-compulsive scale were considered. Links between the patients' cognitive abilities and NSS were assessed using tests targeting specifically the core components of executive functions.

As expected, OCD patients displayed more NSS than individually matched control participants. In OCD patients, high NSS scores were associated with poor insight and lower cognitive abilities. Multiple regression analysis identified worse visuospatial working memory, attentional control, and verbal fluency as predictive factors of high NSS scores among cognitive functions. Unexpectedly, the patients displaying symptoms in the contamination/washing dimension displayed less NSS than the other patients. In contrast, neither the severity of OCD symptoms nor long-range treatment resistance was significantly related to patients' NSS scores. Altogether, our findings suggest that high NSS scores may be a trait marker of a subset of OCD patients with low insight and particularly altered cognitive abilities who would not express the contamination/washing dimension of the pathology.

1. Introduction

Neurological soft signs (NSS) are subtle motor control impairments that include abnormalities of motor coordination, sensory integration and lateralization, as well as involuntary movements (Guz and Aycin, 2004; Hirjak et al., 2016; Krebs et al., 2000). They can be quickly

assessed in clinical examinations (Schröder et al., 1991) but cannot be associated with any specific brain lesion (Hirjak et al., 2016). NSS were first described in schizophrenia (Danion, 2014; Krebs et al., 2000), where the presence of NSS is associated with strong executive deficits (Herold et al., 2020; Whitty et al., 2009).

Most authors agree that OCD patients display more NSS than control

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participants (Çeşmeci et al., 2017; Jaafari et al., 2013; Tapancı et al., 2018). However, OCD patients display less frequent and less severe NSS than patients with schizophrenia (Hollander et al., 1990; Jaafari et al., 2011; Mergl and Hegerl, 2005; Toro and Schröder, 2019). The presence of NSS in OCD patients has been positively related to the severity of the illness (Bolton et al., 2000; Hollander et al., 2005; Tapancı et al., 2018) and, more precisely, to obsession severity (Hollander et al., 1990). However, other studies (Jaafari et al., 2011, 2013; Karadag et al., 2011) failed to confirm this link. OCD patients with poor insight into their pathology exhibit more NSS than those with higher insight, particularly during motor coordination and sensory integration tasks (Ekinci and Ekinci, 2016; Karadag et al., 2011). Finally, about half of OCD patients are resistant to treatments (Denys, 2006; Gupta et al., 2019; Hantouche and Demonfaucon, 2008), and several studies reported that NSS intensity in OCD was positively related to treatment resistance (Bloch et al., 2011; Hollander et al., 2005; Mergl and Hegerl, 2005). Hence, an assessment of NSS could help characterize subsets of OCD patients together with clinical interviews and questionnaires.

According to recent models (Friedman and Miyake, 2017; Miyake and Friedman, 2012; Himi et al., 2019; Karr et al., 2018), adults' executive functions stand mostly on three fundamental components: inhibition, set-shifting, and working memory updating (Miyake and Friedman, 2012). In addition, the inhibition component includes two distinct sub-components, inhibition of prepotent responses (self-control or behavioral inhibition) and resistance to interference from distracting information (attentional control; Friedman and Miyake, 2004; Rey-Mermet et al., 2018).

Many experimental studies have assessed OCD patients' cognitive abilities. Recent reviews and/or meta-analyses (Abramovitch et al., 2013; Gruner and Pittenger, 2017; Shin et al., 2014; Snyder et al., 2015) demonstrated that OCD patients exhibit broad impairments of moderate effect size across all domains of executive functions. The intensity of OCD patients' NSS has been positively related to the strength of patients' cognitive impairment (Conde López et al., 1990; Dhuri and Parkar, 2016; Mataix-Cols et al., 2003). More precisely, OCD patients who display strong NSS during motor coordination and sensory integration tasks would show lower executive and working memory abilities, with dysfunctions of attentional control, visuospatial working memory, and verbal fluency (Dhuri and Parkar, 2016; Hollander et al., 1990; Hymas et al., 1991; Mataix-Cols et al., 2003; Ozcan et al., 2016).

Nevertheless, the involvement of NSS in the etiopathogenesis of OCD is still poorly understood. NSS have not yet been measured in a large population of OCD patients for which a detailed assessment of both clinical variables and cognitive abilities was available. In particular, no study ever evaluated whether NSS were associated with particular dimensions of OCD or with the patients' "overall treatment-resistance" that was assessed considering the clinical outcomes of all the drugs and psychological treatments the patients received during the course of their disease. Indeed, most of the studies that assessed treatment-resistance in OCD patients only assessed the patients' resistance to one treatment or set of treatments over a relatively brief period (for review, see Doolub et al., 2023).

Hence, this study aimed at investigating in a sample of 63 OCD patients the relationships between the presence of NSS and patients' severity of OCD symptoms, insight and overall treatment resistance. The four dimensions of OCD defined in the dimensional obsessive-compulsive scale (Abramowitz et al., 2010) were considered: contamination/washing, symmetry/ordering, responsibility/checking, and unacceptable thoughts/mental rituals. Another originality of the study was that potential links between the patients' cognitive abilities and NSS were assessed using tests targeting one or several of the core components of executive functions, according to Miyake and Friedman (2012). Finally, the NSS scores of a subset of 48 patients were compared with those of individually matched controls.

The hypotheses were that among patients with OCD, poor insight (hypothesis 1), more severe symptoms (hypothesis 2), and higher

treatment resistance (hypothesis 3) should be associated with higher NSS scores. Since no previous study searched for potential links between OCD dimensions and NSS scores, no specific hypothesis could be made regarding this question. Higher NSS scores should also be associated with greater alterations in patients' executive functions and working memory (hypothesis 4). Finally, patients with OCD should display more NSS than matched controls (hypothesis 5).

2. Material and methods

2.1. Participants

Sixty-three consecutive outpatients with a primary diagnosis of OCD (Tables 1 and 2) were enrolled at a psychiatric hospital after clinical examination by psychiatrists. Patients were interviewed according to the Mini International Neuropsychiatric Interview (version 5.0.0) and their medical files were reviewed to affirm the presence of obsessive-compulsive symptoms according to DSM-IV TR criteria, and to assess any comorbid psychiatric condition (Sheehan et al., 1998). All patients had a score of 16 or greater on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), which measures the severity of OCD on a 0 to 40 (maximum severity) scale (Mollard et al., 1989). Participants with current or former severe or decompensated mood disorders, schizophrenia, and/or addictive disorders (except tobacco smoking) were excluded. All patients were under medication at the time of testing as detailed in Table 1.

The NSS scores of 48 patients were compared with those of control participants (Table 2). The prior power analysis that was conducted to

Table 1

Summary of patients' treatments at inclusion. SSRI: selective serotonin reuptake inhibitors, CBT: cognitive behavioral therapy, rTMS: repetitive transcranial magnetic stimulation, tDCS: transcranial direct current stimulation, DBS: deep brain stimulation.

	All OCD patients (n = 63)	OCD patients with matched controls (n = 48)
Drug treatment	63	48
SSRI	9	6
SSRI + antipsychotics	2	2
SSRI + anxiolytics	4	3
SSRI + other classes of antidepressants	2	1
SSRI + antipsychotics and anxiolytics	4	4
SSRI + antipsychotics + anxiolytics + other classes of antidepressants	17	15
SSRI + antipsychotics + anxiolytics + other classes of antidepressants + mood stabilizers	11	7
SSRI + other classes of antidepressants + antipsychotics	1	0
SSRI + other classes of antidepressants + anxiolytics	6	4
SSRI + other classes of antidepressants + anxiolytics + mood stabilizers	2	2
Other classes of antidepressants	2	1
Other classes of antidepressants + antipsychotics + anxiolytics	2	2
Other classes of antidepressants + antipsychotics + mood stabilizers	1	1
At least one non-drug therapy	60	46
CBT or other type of psychotherapy	22	19
CBT or other type of psychotherapy + rTMS	15	14
CBT or other type of psychotherapy + tDCS	5	1
CBT or other type of psychotherapy + rTMS + tDCS	13	7
Deep brain stimulation (DBS)	1	1
DBS + CBT	1	1
DBS + CBT + rTMS	2	2
DBS + CBT + tDCS	1	1

Table 2

Mean values \pm standard deviations (SD) of patients' and controls' sociodemographic and clinical features at the time of testing (except otherwise stated). N/A: not applicable.

	All OCD patients (n = 63)	OCD patients with matched controls (n = 48)	Healthy controls (n = 48)
Age (yrs)	38.4 \pm 13.1	37.6 \pm 13.0	37.3 \pm 12.5
Gender (F/M)	35/28	26/22	26/22
Age at onset of pathology (yrs)	16.7 \pm 11.4	16.8 \pm 11.6	N/A
Educational level (yrs)	12.3 \pm 2.6	12.2 \pm 2.4	12.2 \pm 2.5
Y-BOCS score	27.9 \pm 4.5	27.0 \pm 4.4	N/A
BABS score (insight)	7.8 \pm 4.5	7.9 \pm 4.2	N/A
HAM-A score	13.8 \pm 5.5	11.5 \pm 3.0	N/A
Number of comorbidities	1.1 \pm 1.3	1.2 \pm 1.3	N/A
Characterization of OCD dimensions			
Contamination/washing	41 patients	32 patients	N/A
Symmetry/ordering	25 patients	19 patients	N/A
Responsibility/checking	31 patients	22 patients	N/A
Unacceptable thoughts/mental rituals	31 patients	22 patients	N/A
Current comorbidity	49 patients	39 patients	None
Anorexia nervosa	6 patients	6 patients	None
Bipolarity	1 patient	1 patient	None
Generalized anxiety disorder	12 patients	8 patients	None
Mild depressive episode	13 patients	9 patients	None
Obsessive compulsive personality disorder	7 patients	6 patients	None
Sleep disorders	21 patients	16 patients	None
Social phobia	4 patients	4 patients	None
Tics	6 patients	6 patients	None

estimate the number of patients and control participants to include in the comparison, assuming an expected medium effect size of 0.50 (Cohen's *d*, see Abramovitch et al., 2013), a power of 0.80, and a significance level set at 0.05, yielded a minimum sample size of 27. The controls were selected from a larger population of control participants recruited for another larger-scale study. They were individually matched with the patients by sex, age (to within five years), and educational level. They were recruited from the general population by word of mouth and had no psychiatric or neurological illness history. All participants gave informed consent to participate in the study, and the local ethics committee approved the experimental protocol.³

2.2. Assessment of neurological soft signs

The NSS were assessed using the Neurological Soft Signs Examination (NSSE, Krebs et al., 2000), which consists of 23 items that evaluate five dimensions of neurological dysfunction.

- motor coordination (finger opposition, fist-edge-palm, speed of alternate movements of foot and hand, hand and foot dysrhythmia);
- motor integrative function (Romberg test, finger to nose, gait, tandem walk, tongue protrusion, apraxia, standing heel-to-toe);
- sensory integration (stereognosia, hand-face, constructive apraxia, graphesthesia, right-left recognition);
- involuntary movements (mirror movements, abnormal movements);
- quality of lateralization (lateral preference, right/left confusion, and asymmetry).

³ 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.

Ratings range from 0 to 3 for every item. A total NSS score ranging from 0 (absence of any sign) to 69 is obtained by adding the 23 sub-scores.

2.3. Assessment of patients' clinical variables

The Department of Medical Information of the psychiatric hospital approved access to the patients' medical files. Each file was anonymized, and the data collected were classified in an Excel® workbook. The medical data were listed according to clinical observations and the checklist of symptoms of the Y-BOCS. The treatment inventory included all the treatments that patients had received and their clinical outcomes.

During the pre-inclusion visit, participants were administered French versions of the Hamilton Anxiety Rating Scale (HAM-A, Hamilton, 1959), which measures anxiety levels on a 0 to 56 (maximum severity) scale, and of the Brown Assessment of Beliefs Scale (BABS, Eisen et al., 1998), which assesses patients' insight by a score ranging from 0 (excellent insight) to 24 (no insight).

Treatment resistance was assessed considering all the psychotropic drugs and psychological treatments the patients received from the appearance of obsessive-compulsive symptoms until the testing time (Tables 1 and 2). We used adapted versions of the two scales of treatment resistance designed by Pallanti and Quercioli (2006), i.e., the "levels of non-response to treatments" (LNRT) and "stages of response to treatments" (SRT) scales.

The LNRT scale includes ten levels of successive treatments that ought to be prescribed to patients with OCD up until clinical response is observed, according to the staging of successive treatments for OCD (Albert et al., 2018; Skapinakis et al., 2016; Van Ameringen et al., 2014). The SRT scale classifies treatment outcomes into seven levels based on the evolution of the patients' Y-BOCS scores (Busner and Targum, 2007). In both cases, large numbers reflect higher treatment resistance.

2.4. Experimental procedure and assessment of patients' cognitive functions

Most of the patients (50 out of 63) performed seven tests assessing their working memory (2 tests) and executive abilities (5 tests), always in the same order as described below. Ten patients who were enrolled at the beginning of the study were only asked to perform the two working memory tests. Participants began with three pen-and-paper tests.

- A verbal, semantic fluency test, in which participants must cite a maximum of exemplars of the "animals" category within 60 s. The score is the number of different animal names given by the participant. Performance on semantic fluency tests would tap the updating component of executive functions but would also depend on language abilities.
- The color and word Stroop test (Stroop, 1935; Golden, 1978) assesses the inhibition of automatic/prepotent responses. Performance on the Stroop test was evaluated using Golden's inhibition score. Positive and negative scores indicate higher or lower than average inhibition abilities, respectively.
- The d2 attention control test (Brickenkamp and Zillmer, 1998) assesses sustained attention and resistance to interference from distracting information. The test consists of 658 characters, either "p" or "d", with one, two, or three dashes presented around each character. Participants must mark as many as possible "d" characters with exactly two dashes within a limited period. Performance is evaluated by assessing the error rate and counting the number of correctly processed characters.

The four other tests were computerized.

- The reading span test (Desmette et al., 1995) evaluates participants' ability to maintain and update information in verbal working

memory. Participants are instructed to read aloud sets of several unrelated sentences, which are presented one by one, and to memorize the final word of each set sentence. The score is the number of correctly recalled final words, with a maximum possible score of 100

- The Hayling sentence completion test (Burgess and Shallice, 1996), in which participants must complete a series of 32 sentences from which the last word is omitted. In the completion condition (16 sentences), which taps the updating component of executive functions, participants are required to give a word that completes the sentence in a meaningful way as quickly as possible. In the inhibition condition (16 sentences), participants must produce a word unrelated to the sentence. In that condition, response times and error rates indicate participants' ability to inhibit prepotent responses.
- Monsell and Mizon's (2006) task-switching test taps both the set-shifting and resistance to interference components of executive functions. Participants' response times are collected on each trial and averaged according to the nature of the stimuli and whether they are task-repetition or task-switch trials. Participants' set-shifting ability is evaluated by measuring the task-switching cost, i.e., the difference between reaction times to task-switch and task-repetition trials. Participants' ability to resist interference is evaluated by measuring the incongruency cost, i.e., the difference between reaction times to incongruent and congruent trials.
- The backward location span test (Fournier-Vicente et al., 2008) evaluates participants' ability to maintain and update information in visuospatial working memory. On each trial, participants are shown a grid in which a sequence of randomly located cells turns black one after the other. Then, participants are requested to reproduce it in the opposite order. The participant's visuospatial span score is the total number of correctly recalled cells, with a maximum possible score of 176.

For the Hayling test and the task-switching test, E-Prime® 2.0 software was used to control the presentation of stimuli, timing operations, and behavioral data collection. Response times were measured using a voice key for the Hayling test and a serial response box for the task-switching test.

2.5. Data analysis

All statistical analyses were performed with Statistica® 14.0.0.15 software, with the significance threshold set at 5%. To test hypotheses 1, 2, and 3, a multivariate regression model was designed to assess the links between the demographic and clinical variables of OCD patients and their total NSS score, and to check whether this score depended on the number of comorbidities they displayed or on the treatments they received.

Potential links between the dimensions of OCD and the patients' total NSS score were assessed by designing another multivariate regression model, which used the presence or absence in each patient of each one of the four dimensions of OCD symptoms defined by Abramowitz et al. (2010) as categorical predictors.

To test hypothesis 4, raw correlations were assessed between the patients' scores on executive and working memory tests and their total NSS score. Because numerous statistical tests increase the risk of erroneously finding significant correlations, Benjamini and Hochberg's (1995) procedure was used to control the false discovery rate, and a multivariate regression model was then designed to assess which of the patients' cognitive scores were the most related to their NSS score.

Finally, to test hypothesis 5, t-tests for paired samples were performed to compare the NSS scores of a subset of 48 patients with OCD with their matched controls. Effect sizes were evaluated with Cohen's d. Again, correction for multiple comparisons was performed using Benjamini and Hochberg's (1995) procedure.

3. Results

The NSS scores obtained for the 63 OCD patients included in this study are displayed in Table 3. The treatment-resistance scores of patients with OCD were heterogeneous. The LNRT score was $M \pm SD = 5.9 \pm 3.3$, but individual scores covered the whole range of the scale, from 1 to 10. The SRT score was 4.8 ± 2.0 , with individual scores covering the whole range of the scale, from 1 to 7.

A multivariate regression model was built to assess whether the patients' total NSS score could be predicted by one or several of the following variables: the patients' insight and Y-BOCS scores, their treatment-resistance scores on the LNRT and SRT scales, and their age, gender and number of comorbidities. The most significant regression model ($F(1,60) = 3.97, p < 0.05$) included only one significant predictor, namely the patients' insight score, which explained 6.2 percent of the variance in NSS score. As expected (hypothesis 1), there was a positive relationship between the patients' insight score and their total NSS score, such that the patients with poor insight exhibited higher NSS scores ($b^* = 0.25, SE = 0.13, p < 0.05$). When considering the different subscales of NSS, the correlation was significant for the motor integration ($r = 0.30, p < 0.05$) and involuntary movements ($r = 0.32, p < 0.05$) subscales, marginally significant for the quality of lateralization ($r = 0.27, p < 0.05$) subscale after applying Benjamini and Hochberg's (1995) correction for multiple testing, but not significant for the motor coordination ($r = 0.07, p = 0.59$) and sensory integration ($r = 0.20, p = 0.12$) subscales.

None of the other predictors significantly impacted on the patients' total NSS score, as confirmed by simple correlational analyses or t-tests. Hence, contrary to what was expected (hypothesis 2), the patients' total NSS score was not significantly related to their Y-BOCS score ($r = 0.05, p = 0.69$) and, thus, did not depend on the severity of the pathology. In addition, the patients' total NSS score was not significantly related to the patients' age ($r = 0.07, p = 0.56$), gender ($t(61) = 0.02, p = 0.98$), or number of comorbidities ($r = 0.02, p = 0.87$). Finally, contrary to expectations (hypothesis 3), there was no significant link between the patients' treatment resistance scores and total NSS score (LNRT $r = 0.01, p = 0.93$, SRT $r = 0.06, p = 0.62$). The absence of any significant relationship between the patients' LNRT score and their total NSS score indicates that the presence and amount of NSS displayed by OCD patients did not depend on the type of treatment they received according to the staging of successive treatments prescribed for OCD (Pallanti and Quercioli, 2006).

To further confirm that the patients' NSS score was not significantly related to the pharmacological treatments they received, Mann-Whitney U tests were performed to compare, for each possible pharmacological treatment, the NSS score of patients receiving this treatment with the scores of the patients who did not receive it. Non-parametric tests were used because of the low number of patients displaying some comorbidities. No significant difference was obtained between the different groups of patients. Similarly, to confirm that the patients' total NSS score was not significantly related to the presence of particular comorbidities, Mann-Whitney U tests were performed to compare, for each comorbid pathology, the NSS scores of patients displaying this comorbidity with the scores of the patients who did not display it. Again, no significant difference was obtained between the different groups of

Table 3
Mean values, standard deviations and range of patients' NSS scores. mps = maximum possible score.

	M	SD	Range
Total NSS score (mps = 69)	8.98	5.70	1 to 24
Motor coordination score (mps = 18)	3.18	2.29	0 to 8
Motor integration score (mps = 21)	1.55	1.51	0 to 6
Sensory integration score (mps = 15)	3.17	2.08	0 to 9
Involuntary movements score (mps = 6)	0.39	0.64	0 to 2
Quality of lateralization score (mps = 9)	0.67	0.64	0 to 2

patients.

Regarding the dimensions of OCD (Table 2), a multivariate regression model was built to assess whether the patients' total NSS score could be predicted by the presence or absence in each patient of each one of the dimensions of OCD symptoms. The most significant regression model ($F(2,60) = 4.67, p < 0.05$) included only one significant predictor, namely the contamination/washing dimension, which explained 8.5 percent of the variance in NSS score ($b^* = -0.32, SE = 0.12, p < 0.01$). The patients who did not express the contamination/washing dimension displayed higher NSS scores than those who expressed this dimension (see Table 4). After applying Benjamini and Hochberg's (1995) correction for multiple testing, the difference between these two groups of patients was significant for the motor coordination and quality of lateralization subscales, marginally significant for the motor integration and involuntary movements subscales, but not significant for the sensory integration subscale (Table 2).

The descriptive data for the patients' executive and working memory tests are given in Table 5. Following hypothesis 4, the patients' total NSS score was negatively correlated with their performance on the working memory tests (reading span test $r = -0.56, p < 0.001$; backward location span test $r = -0.49, p < 0.001$) and on several executive tests, including the verbal fluency test ($r = -0.40, p < 0.01$) and the d2 test ($r = -0.48, p < 0.001$). Patients' total NSS score was also negatively correlated with the Stroop test ($r = -0.31, p < 0.05$) and positively correlated with the task-switching cost evaluated by Monsell and Mizon's (2006) task-switching test ($r = 0.29, p < 0.05$). However, these correlations were only marginally significant after applying Benjamini and Hochberg's (1995) correction for multiple testing. Finally, there was no significant correlation between the patients' total NSS score and their performance in the Hayling test, their reaction time and incongruency cost in the task-switching test and their error rates in the d2 test and task-switching test ($-0.03 < r < 0.26, p > 0.06$ in all cases).

The multivariate regression model that was built to assess to which cognitive test the patients' total NSS score was the most related was highly significant ($F(5,40) = 6.04, p < 0.001$) and explained about 36% of the variance of NSS. As expected (hypothesis 4), higher NSS scores were associated with worse visuospatial working memory as assessed by the backward location span test ($b^* = -0.45, SE = 0.16, p < 0.05$), weaker performance in attentional control as assessed by the d2 performance score ($b^* = -0.52, SE = 0.17, p < 0.01$) and worse verbal fluency scores ($b^* = -0.27, SE = 0.13, p < 0.05$).

After applying Benjamini and Hochberg's (1995) correction, the

Table 4

Mean values, standard deviations and results of the *t*-tests for independent samples comparing NSS scores between the 41 patients who expressed the Contamination/washing dimension (CWD) and the 22 patients who did not. The asterisks (*) indicate significant differences between the two groups of patients after applying Benjamini and Hochberg's (1995) correction for multiple testing.

	CWD		No CWD		<i>t</i>	<i>p</i>	Cohen's <i>d</i>
	Mean	SD	Mean	SD			
Total NSS score	7.8	5.0	11.2	6.4	2.38	<0.05*	0.59
Motor coordination score	2.7	2.0	4.1	2.5	2.39	<0.05*	0.62
Motor integration score	1.3	1.5	2.1	1.5	2.06	<0.05	0.53
Sensory integration score	3.0	2.0	3.6	2.3	1.06	0.29	–
Invol. movements score	0.28	0.57	0.59	0.73	1.86	0.07	0.47
Quality of later. Score	0.54	0.64	0.93	0.58	2.42	<0.05*	0.52

Table 5

Mean values and standard deviations of patients' scores on executive and working memory tests. Sixty patients performed the reading span and backward location span tests, whereas 50 of them performed the other tests. Hayling = Hayling sentence completion test, Task-switching = task-switching test, RT = response time.

Dependent Variable	Patients with OCD	
	<i>M</i> ± <i>SD</i>	Range
Verbal fluency score	20.2 ± 5.6	9 to 36
Stroop test score (Golden's score)	-0.2 ± 9.9	-22.2 to 22.8
d2 test score	363 ± 104	160 to 603
d2 error rate (%)	6.2 ± 7.1	0.0 to 37.0
Hayling RT (ms), completion condition	1045 ± 510	519 to 3720
Hayling RT (ms), inhibition condition	2993 ± 1718	1002 to 8752
Number of errors in the inhibition condition	9.9 ± 2.2	4 to 13
Task-switching RT (ms), all trials	1249 ± 638	534 to 3479
Task-switching, switching cost (ms)	198 ± 234	-111 to 1215
Task-switching, incongruency cost (ms)	320 ± 406	-125 to 2268
Task-switching, error rate (%)	4.3 ± 4.7	0.0 to 22.2
Reading span scores	52.2 ± 14.9	25 to 86
Backward location span scores	111.4 ± 23.5	57 to 157

backward location span score was negatively correlated with the patients' scores on all NSS subscales except the involuntary movements subscale ($-0.64 < r < -0.32, p < 0.02$ in all cases), for which the correlation was only marginally significant ($r = -0.24, p = 0.07$). For the d2 score, the negative correlation was significant for the four first subscales ($-0.43 < r < -0.29, p < 0.04$ in all cases), but not significant for the quality of lateralization subscale ($r = -0.22, p = 0.13$). For the verbal fluency score, the negative correlation was significant for the motor coordination ($r = -0.40, p < 0.01$) and motor integration ($r = -0.38, p < 0.01$) subscales, marginally significant for the sensory integration subscale ($r = -0.26, p = 0.06$), but not significant for the involuntary movements ($r = -0.19, p = 0.18$) and the quality of lateralization ($r = -0.19, p = 0.19$) subscales.

As expected (hypothesis 5) and as displayed in Table 6, the total NSS score of patients with OCD was larger than the controls' score. When considering the different subscales of NSS, this was true for the motor coordination, motor integration, and sensory integration subscales but not for the involuntary movements and quality of lateralization subscales.

4. Discussion

In accordance with the literature, which states that the medication status of OCD patients does not have any significant impact on either the level of NSS they display (Bolton et al., 2000; Jaafari et al., 2013; Karadag et al., 2011) or their performance on cognitive tests (Abramovitch et al., 2013; Mataix-Cols et al., 2002; Shin et al., 2014), there was no evidence in this study that the patients' treatment status impacted their NSS or cognitive abilities. Similarly, the patients' NSS scores were not significantly related to their comorbidities. Hence, the type of treatment received by the patients and their comorbidities were not considered in the following discussion.

Following hypothesis 1, high NSS scores were associated with poorer patients' insight, as previously demonstrated (Ekinici and Ekinici, 2016; Karadag et al., 2011). However, Karadag et al. (2011) found that the patients with poor insight exhibited more NSS than those with good insight during motor coordination and sensory integration tasks. In contrast, in the present study the correlation between NSS and insight was significant for the motor integration and involuntary movements subscales, but not for the quality of lateralization, motor coordination or sensory integration subscales. This discrepancy may result from using different instruments to assess the patients' NSS, i.e., the Neurological Evaluation Scale in Karadag et al.'s study versus the NSSE (Krebs et al., 2000) in the present study.

Hypothesis 2 was not verified because the patients' NSS scores were

Table 6

Mean values, standard deviations and results of the *t*-tests for independent samples comparing NSS scores between 48 of the patients with OCD and their matched controls.

	Patients with OCD		Controls		<i>t</i>	<i>p</i>	Cohen's <i>d</i>
	Mean	SD	Mean	SD			
Total NSS score	8.6	5.7	3.7	2.0	5.63	<0.001	1.15
Motor coordination score	2.7	2.2	1.3	1.2	3.94	<0.001	0.79
Motor integration score	1.3	1.2	0.64	0.72	3.42	<0.001	0.67
Sensory integration score	3.5	2.1	1.0	1.1	7.16	<0.001	1.49
Invol. movements score	0.34	0.61	0.34	0.53	0.00	1.00	–
Quality of later. Score	0.72	0.64	0.46	0.82	1.73	0.09	–

not significantly related to their Y-BOCS scores. Hence, the data did not confirm the relationship between the presence of NSS and the severity of OCD symptoms reported in some studies (Bolton et al., 2000; Hollander et al., 2005; Tapancı et al., 2018), but were following other studies which failed to find this relationship (Jaafari et al., 2011, 2013; Karadag et al., 2011). As Jaafari et al. (2011) pointed out, the absence of a significant relationship between the NSS score and the severity of OCD suggests that the presence of NSS may be a trait-marker of a particular OCD subtype. Altogether, the presence or absence of relationships between the patients' Y-BOCS and NSS scores may depend on the size and composition of the sample of OCD patients included in each study.

Hypothesis 3, which assumed that NSS intensity would positively relate to treatment resistance, was not verified either. Indeed, the data did not confirm the relationship between the presence of NSS and treatment resistance reported by some authors (Bloch et al., 2011; Hollander et al., 2005; Mergl and Hegerl, 2005), but were following Bolton et al.'s (2000) results, which found no significant link between the presence of NSS and patients' response to cognitive behavioral treatment. This discrepancy may result from the fact that in the present study, patients' treatment resistance was evaluated by considering the clinical outcomes of all the treatments received during their disease, i.e., over the years. In contrast, in Hollander et al.'s (2005) study, treatment resistance was assessed only over 12 weeks during a single treatment trial. Bloch et al. (2011) did not assess treatment resistance per se but investigated whether high NSS scores could predict the persistence of pediatric-onset obsessive-compulsive disorder into adulthood.

For the first time, the present data show that one of the four main dimensions of OCD may be linked to the presence or absence of NSS. Indeed, the patients displaying symptoms in the contamination/washing dimension displayed *less or marginally less* NSS than the other patients, except for the sensory integration subscale. This finding confirms that, as stated by Mataix-Cols et al. (2004, 2005), the different obsessive-compulsive symptom dimensions would be mediated by distinct components of the dysfunctional fronto-striato-thalamic circuits in OCD (Abramowitz et al., 2010, 2013; Çeşmeci et al., 2017). In addition, this result fits well with the data reported by Çeşmeci et al. (2017). They found that in OCD patients, schizotypy was mainly associated with sexual and/or religious obsessions, order/symmetry obsessions, and pathological doubt, but not with the contamination/washing dimension.

Following hypothesis 4, high NSS scores were associated with lower executive and working memory abilities. Patients' total NSS scores were negatively correlated with their performance on the working memory tests and on several of the executive tests encompassing all main components of executive functions (Friedman and Miyake, 2017; Miyake and Friedman, 2012), i.e., inhibition of prepotent responses (Stroop test), resistance to interference (d2 test), working memory updating (verbal fluency test) and set-shifting (task-switching test). More precisely, the cognitive tests on which the patients' NSS scores depended the most were the visuospatial working memory test, the verbal fluency test, and the d2 attention test. The patients' scores on these three tests were correlated with their scores on almost all NSS subscales, which suggests that all types of NSS may be markers of cognitive deficits in OCD. The strong link between the presence of NSS and dysfunctions of

visuospatial working memory, attentional control, and verbal fluency confirms previous results (Bolton et al., 2000; Dhuri et al., 2016; Hollander et al., 1990; Mataix-Cols et al., 2003). The data are also in line with the idea that NSS are associated with alterations of the cerebello-thalamo-prefrontal brain networks (Kong et al., 2020; Thomann et al., 2015; Zhao et al., 2014) that are known to support executive dysfunction in OCD (Gruner and Pittenger, 2017; Snyder et al., 2015).

Following hypothesis 5, OCD patients displayed more NSS than controls, except for the involuntary movements and quality of lateralization subscales, which confirms what was consistently reported in the literature (Dhuri and Parkar, 2016; Guz and Aygun, 2004; Hollander et al., 1991; Jaafari et al., 2013; Mataix-Cols et al., 2003; Ozcan et al., 2016).

Regarding the neurobiological alterations of executive brain networks that may underlie high NSS scores in OCD patients, one hypothesis can be made by extending findings reported in schizophrenia. In this pathology, the presence of NSS and impairments of executive functions might result from premature brain aging, which would lead to a progressive decrease of grey matter volume coupled with an expansion of white matter (Herold et al., 2020). Indeed, decreased grey matter volumes were recently described in OCD patients in several of the critical brain areas involved in OCD, such as the basal ganglia, thalamus, cingulate cortex and orbitofrontal cortex (Boedhoe et al., 2018; Bowen et al., 2021; Koch et al., 2021).

This study has several limitations that must be considered to interpret the data. First, although a relatively high number of OCD patients was included in this study, the number of patients included in the regression analyses involving executive and working memory tests (50) was relatively low. Moreover, the patients' treatment resistance scores were very heterogeneous, and about 75% of the patients were resistant to first- and second-line treatments, which is higher than the 40–60% of resistant patients reported in the literature (Denys, 2006; Gupta et al., 2019; Hantouche and Demonfaucon, 2008). Hence, the sample of patients included in this study may represent a somewhat atypical population of OCD patients.

In conclusion, although NSS are present in other psychiatric pathologies, the present data suggest that they are involved in the psychopathology of OCD independently of the severity of the illness and patients' treatment resistance. High NSS scores may characterize a particular subset of patients with poor insight and substantial alterations of working memory and attention control who do not express the contamination/washing dimension of the pathology.

In clinical settings, NSS assessment might thus be used to get a quick overview of the patients' executive dysfunctions and insight into their pathology without resorting to time-consuming questionnaires or neuropsychological tests. A high NSS score (>10) would indicate that the patient is likely to have low insight and strongly impaired cognitive abilities. The psychiatrist could then use this information to adapt the follow-up of the patients. Ultimately, as Hollander et al. (2005) suggested, a quick screening tool for NSS might help guide treatment selection or suggest alternate procedures for patient care. In addition, since general practitioners or advanced medical students can easily assess NSS, NSS assessment could be particularly useful in developing

countries with only a few psychiatrists and neuropsychologists. Further studies targeting more specifically the subset of OCD patients with high NSS scores are needed to check the validity of this approach.

Author's statement

Damien Doolub: article writing, protocols, design set-up, proof-reading, data analysis, data interpretation, article submission, reviewing.

Nicolas Vibert: article writing, protocols, design set-up, proof-reading, data analysis, data interpretation, article submission, reviewing.

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Issa Wassouf: proofreading, experimentation, Bruno Millet: proof-reading, advisor, design conception.

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Declaration of competing interest

None of the authors have any conflict of interest to declare.

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