Are Cognitive and Olfactory Dysfunctions in Neuropsychiatric Lupus Erythematosus Dependent on Anxiety or Depression?

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ABSTRACT. ***Objective.*** Depressed mood and cognitive impairments are common findings in systemic lupus erythematosus (SLE) and frequently coexist. We assessed the neuropsychological functioning of patients with SLE and investigated its association with psychopathological symptoms.

Methods. A total of 85 patients with SLE (28 with neuropsychiatric syndromes: NPSLE) and 85 healthy control subjects with similar demographic characteristics were asked to perform a series of neuropsychological tests. A self-report questionnaire (the Hospital Anxiety and Depression Scale) was used to screen for psychopathology symptoms. Patients with SLE underwent a neurological examination.

Results. Patients with NPSLE were more depressed and were more frequently impaired in cognitive and olfactory functions than controls or non-NPSLE patients. The NPSLE group remained statistically different from the other 2 groups on a series of neuropsychological measures (the Auditory Verbal Learning Test, Trail Making Test – Part A, Nine-Hole Peg Test, and Brief Smell Identification Test) even after control for elevated anxiety and depressed mood. Non-NPSLE and control groups were not significantly different regarding either psychopathological symptoms or neuropsychological functioning.

Conclusion. Verbal memory, psychomotor speed, and olfaction are particularly vulnerable to dysfunction in NPSLE; impairment in these neuropsychological domains is not completely explained by psychopathology symptoms. (First Release March 1 2012; J Rheumatol 2012;39:770–6; doi:10.3899/jrheum.110574)

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Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disorder with heterogeneous clinical manifestations and a fluctuating course. It affects mostly women (~10/1 ratio) and most often begins during young adulthood[1,2]. Neuropsychiatric manifestations (NPSLE) such as mood disturbances and cognitive impairments are relatively common in SLE[3,4,5,6,7] and have a negative influence on patients' daily functioning[8] and quality of life[9]. The estimated prevalences vary widely[3,10,11], reflecting methodological differences. The best assessment instruments and the most adequate criteria to identify mood disturbance and to classify impairment in cognition in SLE remain a matter of debate.

Cognitive impairments have been documented in SLE patients with NPSLE and without NPSLE (non-NPSLE). However, the reported prevalence of cognitive dysfunction in patients with SLE is higher for NPSLE than non-NPSLE patients[10]. The areas of cognitive dysfunction vary somewhat across studies, but verbal memory deficits and slow psychomotor speed are relatively common findings[4,10,12,13,14,15,16].

In a recent study, Shoenfeld and colleagues[17] explored the olfactory functions in patients with SLE and found that history of neuropsychiatric manifestations and higher disease activity were associated with decreased sense of smell.

Studies with rodents have provided evidence suggestive of a significant association between depressive symptoms in SLE and olfactory disturbances[18,19]. Katzav and colleagues[18] proposed a rodent model of NPSLE by injecting antiribosomal-P antibodies from the serum of a depressive patient with SLE directly into the ventricles of the brains of naive mice. The mice developed depressive-like behaviors (i.e., increased immobility time in the forced swim test) and presented diminished sense of smell on a threshold test. These findings suggest an association between depressive mood and olfactory disturbance mediated by autoantibodies in SLE.

The pathological mechanisms of cognitive and olfactory dysfunction in SLE are still largely unknown. It has been suggested that cognitive impairments in SLE might result from coexisting psychopathology[10,20]. However, some studies found no significant association between cognitive dysfunction and depressed mood[21,22,23]. Other pathogenic candidates for cognitive and olfactory dysfunction in SLE [e.g., positive antiphospholipid antibodies (aPL), higher disease activity, and regular use of prednisone] have also been suggested. However, the evidence has been inconsistent[10,13,14,17,22,23,24,25].

It is well established that major depression, not related to SLE, affects cognition, particularly memory functions and psychomotor speed[26,27]. And there are indications that major depression may damage olfactory functions[28,29].

Our study pursued the following questions: (1) are cognitive and olfactory functions in SLE related to psychopathology (i.e., anxiety and depression); and (2) are cognitive and olfactory dysfunction in NPSLE dependent on elevated anxiety and depressed mood?

MATERIALS AND METHODS

Subjects. Eighty-five patients with SLE were selected from Centro Hospitalar do Porto's Clinical Immunology Unit and Neuroimmunology Outpatient Clinic. The inclusion criteria for the SLE group were definite diagnosis of SLE according to the American College of Rheumatology (ACR) criteria[30]; no history of flare in the previous month; and age > 18 years. These patients were mostly women (95.3%), of mean age 41.02 years (SD 11.91), with an average 11.24 years of education (SD 4.98), and 15 (17.6%) were current smokers (Table 1).

Based on the neurological examination and medical chart review, the SLE group was subdivided into the following groups: patients with (n = 28) and without (n = 57) neuropsychiatric manifestations according to the ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature[31]. The recorded syndromes were cerebrovascular disease (n = 5), headache (n = 11), movement disorder (n = 4), myelopathy (n = 1), seizure disorders (n = 4), anxiety disorder (n = 1), cognitive dysfunction (n = 2), mood disorder (n = 13), psychosis (n = 2), neuropathy (n = 1), and polyneuropathy (n = 2). Some patients had more than 1 syndrome. The cognitive dysfunction syndrome was defined as dementia.

Eighty-five community-dwelling individuals with no history of psychiatric, neurological, or autoimmune disorder composed the healthy comparison control group. To assure the sociodemographic similarities of the SLE and control groups, propensity scores (with 2 margins) based on sex, age, education, and smoking habit were used to select the control subjects from our healthy subjects database. Thus, this group had the same proportion of women (95.3%), with similar ages (mean 40.76 yrs, SD 10.45) and education level (mean 11.84 yrs, SD 5.03), and about the same proportion of smokers (18.8%) as the SLE group.

Subjects were excluded if they had a history of posttraumatic or upper respiratory infection-induced olfactory loss, head injury, or other medical condition that could alter their olfactory function. All subjects provided written informed consent, in accord with the Declaration of Helsinki.

Procedures. Patients with SLE and controls underwent a comprehensive neuropsychological evaluation and answered psychopathology and quality-of-life questionnaires. Experienced psychologists administered these tests in a standardized manner in a single session. Within a week from this assessment, the patients with SLE underwent a neurological examination and performed the Mini-Mental State Examination[32].

Psychopathology questionnaire. The Hospital Anxiety and Depression Scale contains 14 multiple-choice items, 7 for anxiety and 7 for depression. For each item, the participant is asked to choose, from 4 options, the response that best describes how he/she felt during the previous week. Higher scores indicate more psychopathology symptoms. Based on Zigmond and Snaith[33], a cutoff score of > 11 was used to classify elevated anxiety on the anxiety subscale and depressed mood on the depression subscale.

Neuropsychological tests[34]. The Attentive Matrices test consists of asking the participant to use a pencil to mark out all the numbers that match the ones at the top of the paper, from an array of numbers. The task score is the completion time. Lower scores correspond to better results.

The Digit Span test consists of repeating a series of digits that are read by the examiner, initially in the same order (forward) and then in the reverse order (backward). Two trials are given per sequence of digit length. If at least 1 of these is repeated correctly, the next 2 trials of an increased length are administered. The task score is the sum of the longest lists the participant can remember in forward order and backward order. Higher scores correspond to better results.

The Corsi Block-Tapping Test consists of tapping a series of cubes in the same order immediately after the examiner has finished. Two trials are given per sequence of the same length. If at least 1 of these is repeated correctly, the next 2 trials of a sequence of increased length are administered. The task score is the length of the longest sequence the participant can reproduce. Higher scores correspond to better results.

Judgment of Line Orientation consists of asking the participant to match pairs of full or partial angled lines that appear on the stimulus card to 2 of the 11 numbered lines on the reference card. The task score is the number of correct responses. Higher scores correspond to better results.

Copy of the Complex Figure consists of asking the participant to copy the Rey-Osterrieth Complex Figure. Following a 30-min interval, in which the participant performs other psychometric testing, he/she is asked to draw the figure from memory. The examiner assesses the accuracy of the reproduction. The test score ranges from 0 to 36, higher scores indicating better results.

The Auditory Verbal Learning Test consists of reading to the participant a list of 15 highly frequent, unrelated words at the rate of 1 word/s and then asking the subject to recall as many of the words as he/she can. This procedure is repeated for each of the 5 immediate recall trials. After a 30-min interval, in which the participant performs other psychometric testing, he/she is asked to remember as many words as possible from the previously presented list. Upon completion of the 30-min recall test, the participant is presented with a 30-word list (i.e., the 15 words from the original list and 15 foils randomly ordered) and is asked to judge whether each word is or is not from the original list. The number of words correctly remembered is the dependent measure for the 30-min recall trial. The score on the recognition trial corresponds to the number of correct judgments. Higher scores correspond to better results.

Sentence Repetition consists of asking the participant to repeat sentences of increasing length and complexity. Any error in repeating the sentences is scored as an error. After 3 consecutive failures the test is stopped. The test score ranges from 0 to 14, higher scores indicating better results.

Semantic Fluency consists of asking the participant to name as many animals that he/she can think of. The participant is instructed that sex or devel-

Table 1. Demographic and clinical characteristics of patients with systemic lupus erythematosus (SLE) and comparison between the SLE subgroups: patients with (NPSLE) and without (Non-NPSLE) neuropsychiatric syndromes. The data are frequencies (%) or mean (SD).

Characteristics	SLE Group, n = 85	Non-NPSLE, n = 57	NPSLE, n = 28	Non-NPSLE vs NPSLE, p
Demographic				
Female (%)	81 (95.3)	55 (96.5)	26 (92.9)	0.595
Age, yrs	41.02 (11.9)	39.2 (11.1)	44.8 (12.8)	0.058
Education, yrs	11.2 (5)	11.8 (4.8)	10.2 (5.3)	0.224
Current smoking habit (%)	15 (17.6)	11 (19.3)	4 (14.3)	0.764
Mini-Mental State Examination	28.1 (2.2)	28.5 (1.5)	27.3 (2.9)	0.073
Clinical chart review				
Age at onset, yrs	29.3 (11.9)	28.1 (11.3)	31.7 (13.1)	0.293
Disease duration, yrs	11.8 (7.8)	11.1 (7.7)	13.2 (7.9)	0.191
History of headaches (%)	53 (62.4)	35 (61.4)	18 (64.3)	0.797
APS (%)	14 (16.5)	6 (10.5)	8 (28.6)	0.059
Persistent aPL (%)	33 (38.8)	19 (33.3)	14 (50)	0.138
Current medication (%)				
Acetylsalicylic acid	22 (8.2)	15 (26.3)	7 (25)	0.896
Antidepressant	31 (36.5)	19 (33.3)	12 (42.9)	0.391
Benzodiazepine	35 (41.2)	18 (31.6)	17 (60.7)	0.010
Hydroxychloroquine	59 (69.4)	42 (73.7)	17 (60.7)	0.223
Hypocoagulant	7 (8.2)	5 (8.8)	2 (7.1)	> 0.999
Immunosuppressant	13 (15.3)	10 (17.5)	3 (10.7)	0.531
Prednisone	56 (65.9)	36 (63.2)	20 (71.4)	0.450

Chi-square test or Fisher's exact test (when applicable) were used for all group comparisons, except for age, education, Mini-Mental State, age at onset, and disease duration, in which the Mann-Whitney U Test was used. APS: secondary clinical antibody antiphospholipid syndrome according to international consensus criteria[36]; persistent aPL: persistent antiphospholipid antibodies as defined by elevated anticardiolipin antibodies, lupus anticoagulant, and/or ß$_2$-glycoprotein I antibodies on 2 different occasions; headaches without clinical or neuroradiological evidence of central nervous system involvement.

opmental stage variations of the same species are not allowed. The task score is the total number of animals named within 60 seconds. Higher scores correspond to better results.

Letter-Word Fluency consists of asking the participant to name all the words that he/she can think of beginning with the letters "M," "R," and "P." Sixty seconds are allowed for each letter. The participant is instructed that proper names (e.g., names of people or places) and plurals are not allowed. Perseverative responses, intrusions, and close variations of the same word are not credited. The test score corresponds to the sum of the 3 letter trials. Higher scores correspond to better results.

The Wisconsin Card Sorting Test – Nelson's modified version consists of asking the participant to sort 48 cards in accordance with an unknown principle using only error feedback. The number of categories correctly identified and the number of perseverative errors are the task measures. Higher number of categories and lower number of perseverative errors correspond to better results.

The Trail Making Test (TMT) consists of asking the participant to draw a line connecting consecutive numbers from 1 to 25 (TMT-A). For TMT-B, the participant is required to draw a similar line, connecting alternating numbers and letters in sequence (i.e., 1-A-2-B and so on) from 1 to 13. TMT-B is discontinued after 4 errors. For each part, time to completion is the task score.

The Nine-Hole Peg Test consists of asking the participant to place 9 pegs in 9 holes, twice with the dominant hand and then twice with the nondominant hand. The task score corresponds to the sum of time to place and remove all pegs on the 4 trials. Lower scores correspond to better results.

The Brief-Smell Identification Test consists of scratching odor strips and matching the sniffed odorant to 1 of 4 possible odorant names. The test consists of 6 food-related odorants (banana, chocolate, cinnamon, lemon, onion, pineapple) and 6 nonfood-related odorants (gasoline, paint thinner, rose, soap, smoke, turpentine). These items were selected from the University of Pennsylvania Smell Identification Test, because they were considered to be familiar in different cultures[35]. There is no time constraint to perform the test. The test score is the number of correct choices. The test score ranges from 0 to 12, higher scores indicating better ability to identify odors.

Statistical analysis. Mann-Whitney U test was used for univariate comparison between groups of continuous measurements. Chi-square and Fisher's exact tests were applied to categorical variables. The neuropsychological test scores were adjusted for age and education using multiple linear regression (the normality assumption of the regression residuals is not required in this setting because the purpose here is to "remove" age and education effect from the test scores rather than make inference about those effects). Based on the regression coefficients for age and education of the control group, the raw scores of all participants on the neuropsychological measures were adjusted for age and education. The estimated fifth percentile of the adjusted score was then used to identify deficit on each measure. Logistic regressions were used to compute OR while adjusting for other covariates.

RESULTS

Demographic and clinical characteristics. The demographic characteristics (sex, age, education, and smoking habits) were not significantly different between groups (i.e., controls vs SLE; controls vs non-NPSLE; controls vs NPSLE; non-NPSLE vs NPSLE). Regarding patients' clinical characteristics (Table 1), patients with NPSLE were more frequently treated with benzodiazepines (p = 0.010). The odds of taking benzodiazepines (adjusted OR 2.892, 95% CI 1.099, 7.609) remained significantly higher for patients with NPSLE after adjustment for age.

Controls versus SLE. The prevalence of elevated anxiety ($p = 0.041$) and depressed mood ($p = 0.002$) was significantly higher for patients with SLE compared to controls (Table 2). Among the SLE group, patients with elevated anxiety had significantly less education ($p = 0.034$), more frequently had history of headaches ($p = 0.013$), and had current intake of antidepressants ($p = 0.017$). No significant association ($p > 0.05$) was found between SLE subjects' anxiety and age, age at onset, disease duration, NPSLE diagnosis, diagnosis of antiphospholipid syndrome (APS), persistent aPL, or current intake of acetylsalicylic acid, benzodiazepines, hydroxychloroquine, hypocoagulant, immunosuppressant, or prednisone. SLE subjects' depressed mood was significantly associated with higher age ($p = 0.044$), lower education level ($p < 0.001$), diagnosis of NPSLE ($p = 0.0498$), and current intake of antidepressants ($p = 0.001$) and benzodiazepines ($p = 0.001$). It was not statistically related ($p > 0.05$) to age at onset, disease duration, history of headaches, diagnosis of APS, persistent aPL, or current intake of acetylsalicylic acid, hydroxychloroquine, hypocoagulant, immunosuppressant, or prednisone. Among patients with NPSLE, no significant associations were found between current elevated anxiety or depressed mood and specific neuropsychiatric syndromes recorded on the clinical chart ($p > 0.05$). Among controls, elevated anxiety and depressed mood were not related to subject's age or education level.

The total number of impaired neuropsychological measures was higher ($p = 0.001$) for SLE subjects (mean 2.21, SD 2.79) than for controls (mean 0.94, SD 1.32). Three or more impaired measures were found in 10.6% of controls and 29.4% of patients with SLE ($p = 0.002$).

Patients with SLE were statistically more impaired than controls on 6/18 neuropsychological measures (Table 2): Attentive Matrices ($p = 0.028$), Auditory Verbal Learning Test – immediate recall ($p = 0.013$), 30-min recall ($p = 0.002$) and 30-min recognition ($p = 0.001$), Sentence Repetition ($p = 0.007$), and Nine-Hole Peg Test ($p = 0.028$). These significant group differences were investigated further with multiple logistic regressions. Comparisons between controls and SLE on each of these neuropsychological measures was adjusted

Table 2. Psychopathology and impaired neuropsychological performance. Due to logistical problems, the following data were not collected: Judgment of Line Orientation (5 non-NPSLE and 2 NPSLE), Complex Figure – copy (2 non-NPSLE) and 30-min recall (3 non-NPSLE), Sentence Repetition (1 non-NPSLE), Semantic Fluency (1 control and 3 non-NPSLE), Trail-making Test – Part A and Part B (1 non-NPSLE).

	Controls, n = 85 %	SLE Total, n = 85 %	Non-NPSLE n = 57 %	NPSLE n = 28 %	Group Comparisons*, p
Psychopathology					
Hospital Anxiety and Depression Scale					
Anxiety ≥ 11	21.2	35.3	35.1	35.7	a
Depression ≥ 11	4.7	20.0	14.0	32.1	a, c, d
Neuropsychological tests					
Attentive Matrices	5.9	16.5	12.3	25.0	a, c
Digit Span	4.7	8.2	7.0	10.7	
Corsi-Block Tapping Test	7.1	15.3	14	17.9	
Judgment of Line Orientation	4.7	10.3	7.7	15.4	
Complex Figure					
Copy	4.7	3.5	1.8	7.1	
30-min recall	4.7	10.6	7.0	17.9	c
Auditory Verbal Learning Test					
Immediate recall	4.7	16.5	10.5	28.6	a, c
30-min recall	4.7	20	12.3	35.7	a, c, d
30-min recognition	4.7	21.2	8.8	46.4	a, c, d
Sentence Repetition	4.7	17.9	14.3	25.0	a, c
Semantic Fluency	4.7	12.9	11.1	17.9	c
Letter-Word Fluency	4.7	5.9	1.8	14.3	d
Wisconsin Card Sorting Test					
No. categories	4.7	9.4	10.5	7.1	
No. perseverative errors	5.9	4.7	3.5	7.1	
Trail Making Test					
Part A	4.7	11.9	3.6	28.6	c, d
Part B	8.2	9.5	5.4	17.9	
Nine-Hole Peg Test	5.9	16.5	5.3	39.3	a, c, d
Brief-Smell Identification Test	4.7	11.8	5.3	25.0	c, d

* Chi-square test or Fisher's exact test (when applicable) were used for group comparisons; a: controls vs SLE; b: controls vs non-NPSLE; c: controls vs NPSLE; d: non-NPSLE vs NPSLE; such marked groups represent $p < 0.05$. SLE: systemic lupus erythematosus.

for age, education, elevated anxiety, and depressed mood. The odds of having impaired performance on the Auditory Verbal Learning Test – immediate recall (adjusted OR 3.696, 95% CI 1.119, 12.205), 30-min recall (adjusted OR 5.408, 95% CI 1.683, 17.379) and 30-min recognition (adjusted OR 4.433, 95% CI 1.385, 14.187), and on the Sentence Repetition (adjusted OR 3.627, 95% CI 1.105, 11.903) remained significantly higher for SLE subjects relative to controls after adjustment for age, education level, elevated anxiety, and depressed mood.

Non-NPSLE versus controls. Non-NPSLE and control groups did not differ significantly regarding elevated anxiety ($p = 0.066$), depressed mood ($p = 0.066$), or frequency of deficit on each of the neuropsychological measures (Table 2). The total number of impaired neuropsychological measures was not statistically higher ($p = 0.081$) for the non-NPSLE group (mean 1.40, SD 1.87) than for the controls (mean 0.94, SD 1.32). Three or more impaired measures were found in 10.6% of controls and 17.5% of non-NPSLE patients ($p = 0.233$).

Controls versus NPSLE. Patients with NPSLE were more frequently depressed ($p < 0.001$) than controls. However, the frequency of elevated anxiety ($p = 0.122$) was not statistically different (Table 2). The total number of impaired neuropsychological measures was higher ($p < 0.001$) for the NPSLE group (mean 3.86, SD 3.58) than for controls (mean 0.094, SD 1.32). Three or more impaired measures were found in 10.6% of controls and 53.6% of non-NPSLE patients ($p < 0.001$).

Patients with NPSLE were more impaired than controls on 10/18 neuropsychological measures (Table 2): Attentive Matrices ($p = 0.009$), Complex Figure – 30-min recall ($p = 0.040$), Auditory Verbal Learning Test – immediate recall ($p = 0.001$), 30-min recall ($p < 0.001$) and 30-min recognition ($p < 0.001$), Sentence Repetition ($p = 0.005$), Semantic Fluency ($p = 0.042$), Trail Making Test – Part A ($p = 0.001$), Nine-Hole Peg Test ($p < 0.001$), and Brief-Smell Identification Test ($p = 0.005$). These significant group differences were investigated further with multiple logistic regressions. The comparison between controls and NPSLE subjects on each of these neuropsychological measures was adjusted for age, education, elevated anxiety, and depressed mood. The odds of having impaired performance remained significantly higher for NPSLE patients compared to controls, even after adjustment for age, education level, elevated anxiety, and depressed mood, on the Auditory Verbal Learning Test – immediate recall (adjusted OR 7.240, 95% CI 1.747, 29.999), 30-min recall (adjusted OR 12.088, 95% CI 2.989, 48.877) and 30-min recognition (adjusted OR 13.643, 95% CI 3.629, 51.291), Sentence Repetition (adjusted OR 5.206, 95% CI 1.201, 22.569), Trail Making Test – Part A (adjusted OR 6.469, 95% CI 1.337, 31.306), Nine-Hole Peg Test (adjusted OR 6.392, 95% CI 1.757, 23.262), and the Brief-Smell Identification Test (adjusted OR 6.135, 95% CI 1.169, 32.186).

Non-NPSLE versus NPSLE patients. The frequency of depressed mood ($p = 0.0498$) was lower for non-NPSLE than NPSLE participants. However, the frequency of elevated anxiety was not statistically different ($p = 0.955$) between groups (Table 2). The total number of impaired neuropsychological measures was lower for the non-NPSLE group (mean 1.40, SD 1.87) than for the NPSLE group (mean 3.87, SD 3.58; $p = 0.001$). Impaired performance on 3 or more neuropsychological measures was found in 17.5% (10/57) of non-NPSLE patients and 53.6% (15/28) of patients with NPSLE ($p = 0.001$).

Patients with NPSLE were statistically more impaired than non-NPSLE on 6/18 neuropsychological measures (Table 2), namely Auditory Verbal Learning Test – 30-min recall ($p = 0.011$) and 30-min recognition ($p < 0.001$), Letter-Word Fluency ($p = 0.039$), Trail Making Test – Part A ($p = 0.002$), Nine-Hole Peg Test ($p < 0.001$), and Brief-Smell Identification Test ($p = 0.013$). These significant group differences were investigated further with multiple logistic regressions. The comparison between non-NPSLE and NPSLE on each of these neuropsychological measures was adjusted for demographic characteristics (age, education), clinical variables (age at onset, disease duration, history of headaches, diagnosis of APS, persistent aPL, and current intake of acetylsalicylic acid, benzodiazepines, hydroxychloroquine, hypocoagulant, immunosuppressant, and prednisone), and psychopathology screening results (elevated anxiety and depressed mood). For each regression model we used a forward stepwise procedure to select the significant covariates. Table 3 shows that even after adjustment for demographic, clinical, and psychopathological variables, the odds of impairment were significantly higher for patients with NPSLE relative to non-NPSLE patients on the Auditory Verbal Learning Test – 30-min recall and 30-min recognition, Letter-Word Fluency, Trail Making Test – Part A, Nine-Hole Peg Test, and the Brief-Smell Identification Test.

DISCUSSION

Our study demonstrates that poor neuropsychological functioning in NPSLE is not dependent of psychopathological symptoms. Consistent with previous reports[4,10,12,13,14,15,16], verbal memory and psychomotor speed were particularly vulnerable to dysfunction in patients with NPSLE. Our results provide additional evidence for an association between decreased olfaction and NPSLE.

Similar to Shoenfeld and colleagues' study[17], deficits in odor identification abilities were found only in patients with diagnosis of NPSLE. Smell defects in patients with NPSLE are consistent with reports of olfactory dysfunction induced by brain-specific antibodies in the rodent model of NPSLE[18,19]. These findings reinforce the notion of a close interaction among immune system, central nervous system (CNS), and olfactory system[37]. In addition, it was recently proposed that olfactory dysfunction in Parkinson's disease may also be the result of autoimmune mechanisms[38]. Accumulating evidence confirms that olfactory disturbance is

Table 3. The odds of impaired neuropsychological performance for non-NPSLE vs NPSLE. OR are adjusted for demographic, clinical, and psychopathological variables.

	Adjusted OR (95% CI)	p
Auditory Verbal Learning Test – 30-min recall	4.454 (1.166–17.013)	0.029
Auditory Verbal Learning Test – 30-min recognition	9.404 (2.725–32.454)	< 0.001
Letter-Word Fluency	17.250 (1.486–200.183)	0.023
Trail Making Test – Part A	10.800 (2.111–55.244)	0.004
Nine-Hole Peg Test	10.728 (1.768–65.091)	0.010
Brief-Smell Identification Test	7.061 (1.529–32.606)	0.012

one of the most common and early manifestations of Parkinson's disease[39].

Our study also confirms previous reports of more cognitive impairments in patients with NPSLE than non-NPSLE patients. The prevalence of impaired neuropsychological functioning in our NPSLE group was similar to that reported by others[3,10]. But the frequency of impairment in the non-NPSLE group was somewhat lower than expected. The absence of significant differences between the non-NPSLE and control groups on the psychopathology and neuropsychological measures may reflect a lack of statistical power. Larger samples might have produced significant findings.

Depressed mood, elevated anxiety, and mild cognitive dysfunctions are relatively common in patients with SLE, but often do not reflect overt CNS lupus activity[40]. They can be a secondary response to a chronic illness and/or the result of certain treatment options. The etiopathology of these symptoms in SLE is an important matter of debate, with implications for patient classification and clinical management. Our study contributes to better understanding of the mechanisms that mediate cognitive and olfactory dysfunction in SLE.

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