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

SARA CAVACO, ANA MARTINS da SILVA, ERNESTINA SANTOS, ESTER COUTINHO, ANTÓNIO MARINHO, INÉS MOREIRA, ALEXANDRA GONÇALVES, CLÁUDIA PINTO, ARMANDO TEIXEIRA-PINTO, and CARLOS VASCONCELOS

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)

Key Indexing Terms: SYSTEMIC LUPUS ERYTHEMATOSUS NEUROLOGICAL MANIFESTATIONS NERVOUS SYSTEM DISEASES

From the Laboratory of Neurobiology of Human Behavior, Centro Hospitalar do Porto, Hospital de S. António, Porto; and Universidade do Porto, Biomedical Investigation Multidisciplinary Centre, Porto, Portugal.

S. Cavaco, PhD, Laboratory of Neurobiology of Human Behavior, Centro Hospitalar do Porto, Hospital de S. António, Biomedical Investigation Multidisciplinary Centre, Porto, Portugal; A. Martins da Silva, MD, Laboratory of Neuropsychology, Centro Hospitalar do Porto, Hospital de S. António, Biomedical Investigation Multidisciplinary Centre, Porto, Portugal; E. Santos, MD, E. Coutinho, MD, Neurology Department, Centro Hospitalar do Porto, Hospital de S. António; A. Martinho, MD, Clinical Immunology Unit, Internal Medicine Department, Centro Hospitalar do Porto, Hospital de S. António; I. Moreira, MSc, Laboratory of Neurobiology of Human Behavior, Centro Hospitalar do Porto, Hospital de S. António; A. Gonçalves, MSc; C. Pinto, MSc, Laboratory of Neurobiology of Human Behavior, Centro Hospitalar do Porto, Hospital de S. António, Biomedical Investigation Multidisciplinary Centre, Instituto Ciências Biomédicas Abel Salazar, Universidade do Porto; A. Teixeira-Pinto, PhD, Department of Health Information and Decision Sciences, CINTESIS, Faculdade de Medicina, Universidade do Porto; C. Vasconcelos, MD, PhD, Biomedical Investigation Multidisciplinary Centre, Instituto Ciências Biomédicas Abel Salazar, Universidade do Porto, Clinical Immunology Unit, Internal Medicine Department, Centro Hospitalar do Porto, Hospital de S. António.

Address correspondence to S. Cavaco, Hospital S. António, Serviço de Neurologia, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal.

E-mail: saramscavaco@gmail.com

Accepted for publication December 22, 2011.

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. Neuropsychiatric manifestations (NPSLE) such as mood disturbances and cognitive impairments are relatively common in SLE and have a negative influence on patients’ daily functioning and quality of life. The estimated prevalences vary widely, 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. The areas of cognitive dysfunction vary somewhat across studies, but verbal memory deficits and slow psychomotor speed are relatively common findings. In a recent study, Shoenfeld and colleagues 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. Katzav and colleagues 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. However, some studies found no significant association between cognitive dysfunction and depressed mood. 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.

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

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 Zung and Snith, a cutoff score of > 11 was used to classify elevated anxiety on the anxiety subscale and depressed mood on the depression subscale.

Neuropsychological tests. 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-
The Brief-Smell Identification Test consists of scratching odor strips and matching the sniffed odorant to 1 of 4 possible odorant names. These items were selected from the University of Pennsylvania Smell Identification Test, because they were considered to be familiar in different cultures. 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.

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).

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

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; persistent aPL: persistent antiphospholipid antibodies as defined by elevated anticardiolipin antibodies, lupus anticoagulant, and/or B2-glycoprotein I antibodies on 2 different occasions; headaches without clinical or neuro-radiological evidence of central nervous system involvement.
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).

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

* 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 signifi-
cantly higher for SLE subjects relative to controls after adjust-
ment 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 fre-
cently depressed (p < 0.001) than controls. However, the fre-
quency of elevated anxiety (p = 0.122) was not statistically
different (Table 2). The total number of impaired neuropsy-
chological 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 neu-
ropsychological 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 anx-
xiety 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 neuropsychologi-
cal 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 differ-
ences were investigated further with multiple logistic regres-
sions. The comparison between non-NPSLE and NPSLE on
each of these neuropsychological measures was adjusted for
demographic characteristics (age, education), clinical vari-
ables (age at onset, disease duration, history of headaches,
diagnosis of APS, persistent aPL, and current intake of acetyl-
salicylic acid, benzodiazepines, hydroxychloroquine, hypo-
coagulant, immunosuppressant, and prednisone), and psy-
chopathology screening results (elevated anxiety and
depressed mood). For each regression model we used a for-
dward stepwise procedure to select the significant covariates.

DISCUSSION
Our study demonstrates that poor neuropsychological func-
tioning in NPSLE is not dependent of psychopathological
symptoms. Consistent with previous reports4,10,12,13,14,15,16,
verbal memory and psychomotor speed were particularly vul-
nerable to dysfunction in patients with NPSLE. Our results
provide additional evidence for an association between
decreased olfaction and NPSLE.

Similar to Shoenfeld and colleagues’ study17, 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
NPSLE18,19. These findings reinforce the notion of a close
interaction among immune system, central nervous system
(CNS), and olfactory systemm17. In addition, it was recently
proposed that olfactory dysfunction in Parkinson’s disease
may also be the result of autoimmune mechanisms38. Accumu-
lating evidence confirms that olfactory disturbance is
functions are relatively common in patients with SLE, but logical measures may reflect a lack of statistical power. Larger
Parkinson’s disease. 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 neuropsycho-
logical measures may reflect a lack of statistical power. Larger samples might have produced significant findings.

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

REFERENCES


