# Screening for Cognitive Impairment in Systemic Lupus Erythematosus

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***ABSTRACT.*** ***Objective***. We examined the association between responses on a screening questionnaire and objective performance on a computer-administered test of cognitive abilities in systemic lupus erythematosus (SLE).

***Methods.*** The Cognitive Symptom Inventory (CSI) and Hospital Anxiety and Depression Scales (HADS) questionnaires were compared in patients with SLE or rheumatoid arthritis (RA). The Automated Neuropsychological Assessment Metrics (ANAM) was used to evaluate cognitive performance in patients with SLE. Efficiency of performance was measured by "throughput" (number of correct responses per minute) and "inverse efficiency" (response speed/proportion of correct responses). Linear regression was applied to log-transformed CSI scores to examine their associations with ANAM scores and other factors.

***Results.*** Patients with SLE (n = 68) or RA (n = 33) were similar in age, sex, ethnicity, and education status ($p > 0.05$). Patients with SLE had higher total CSI scores (33.6 ± 10.5 vs 29.4 ± 6.8, respectively; $p = 0.041$) and attention/concentration subscale CSI scores (15.7 ± 5.3 vs 13.3 ± 3.4; $p = 0.016$) compared to patients with RA. In patients with SLE there was a positive association between CSI scores and neuropsychiatric (NP) events at the time of testing ($p = 0.0006$), HADS anxiety ($p < 0.0001$), and depression ($p < 0.0001$) scores. After adjustment for age, education, disease duration, and NP events at the time of testing, there was no significant association ($p > 0.05$) between ANAM and CSI scores in patients with SLE. The results were similar using either "throughput" or "inverse efficiency" or the number of impaired ANAM subscales after adjustment for simple reaction time.

***Conclusion.*** The CSI self-report questionnaire of cognitive symptoms does not reliably screen for efficiency of cognitive processing in patients with SLE. Rather, cognitive complaints reported in the CSI are influenced by the presence of anxiety and depression. (First Release June 1 2012; J Rheumatol 2012;39:1371–7; doi:10.3899/jrheum.111504)

*Key Indexing Terms:*
SYSTEMIC LUPUS ERYTHEMATOSUS — COGNITIVE IMPAIRMENT
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Nervous system disease is common in patients with systemic lupus erythematosus (SLE), encompassing a wide range of manifestations of which roughly 30% to 40% are attributable to SLE[1]. Cognitive impairment is one of the more common neuropsychiatric (NP) events and has been reported in a higher frequency in patients with SLE compared to healthy individuals and sometimes compared to disease controls. There is no pattern of cognitive dysfunction that is specific for SLE, and the characteristics include overall cognitive slowing, decreased attention, impaired working memory, and executive dysfunction (e.g., difficulty with multitasking, organization, and planning). Sometimes profound in individual cases, the majority of patients with SLE have subtle and frequently subclinical cognitive deficits that are evanescent rather than progressive over time[2,3,4,5]. The mild, intermittent, and unpredictable expression of cognitive impairment in SLE frequently presents a diagnostic challenge to clinicians.

Formal neuropsychological assessment by a trained neuropsychologist is the "gold standard" for diagnosing cognitive impairment. The American College of Rheumatology (ACR) has proposed a battery of neuropsychological tests for the assessment of cognitive function in patients with SLE[6]. Although comprehensive, there are several factors that limit the widespread use of these neuropsychological test batteries in every patient. For example, they are

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time-consuming, require specialized training to administer, and are subject to large practice effects. Computerized neuropsychological testing permits more rapid evaluation that can also be administered by non-experts and is particularly sensitive to reduced cognitive efficiency. A useful adjunct to both forms of testing would be a validated screening questionnaire for cognitive symptoms to identify patients who would benefit from a complete neuropsychological assessment.

Our aim was to determine the agreement between self-reported symptoms of cognitive impairment on a screening questionnaire and objective performance on a computer-administered neuropsychological test battery for the detection of cognitive impairment in ambulatory patients with SLE. The Cognitive Symptom Inventory (CSI) questionnaire[7] was used to record perceived abilities to perform several cognitive functions. Studies have found an association between such subjective complaints and impairment, at least among patients with clinically overt neuropsychiatric SLE (NPSLE)[8]. To determine the specificity of abnormal CSI responses for patients with SLE, we compared their CSI scores to those in patients with rheumatoid arthritis (RA), a chronic autoimmune rheumatic disease with similar treatments and clinical manifestations as in SLE, with the exception of primary nervous system involvement. The Automated Neuropsychological Assessment Metrics (ANAM)[9,10] was used to objectively measure cognitive function. In previous studies, the ANAM has demonstrated reasonable associations with the findings from the ACR neuropsychological test battery in a sample of patients with SLE[11]. The accuracy of self-reported cognitive functioning has been found to be affected by mood in conditions such as multiple sclerosis (MS)[12], an autoimmune disease similar to SLE in its demographic characteristics as well as in its chronic and often unpredictable course. Thus, we also sought to examine the relationship between cognitive complaints and symptoms of depression and anxiety as reported by patients with SLE on the Hospital Anxiety and Depression Scales (HADS)[13,14].

## MATERIALS AND METHODS

*Patients*. All subjects provided informed consent following procedures approved by the Capital District Health Authority Research Ethics Board, Halifax, Nova Scotia, Canada. Sixty-eight patients with SLE and 33 patients with RA participated. The patients were recruited from the Dalhousie Lupus Clinic and general rheumatology clinics, respectively, in the Division of Rheumatology. All patients fulfilled the ACR classification criteria for SLE and RA, respectively. Global SLE disease activity was measured with the SLE Disease Activity Index (SLEDAI)[15] and cumulative organ damage by the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index[16]. In patients with RA, disease activity and effect was assessed by the number of tender and swollen joints, erythrocyte sedimentation rate, C-reactive protein, and Health Assessment Questionnaire. All participants had normal or corrected-to-normal vision and reported no vision problems at the time of the study.

The following data were collected on all participants: age, sex, ethnicity, education, and medication use. NP events were characterized using the ACR case definitions and were diagnosed by clinical evaluation supported with appropriate investigations, as per the ACR glossary[6].

*ANAM testing*. The ANAM test battery[17] takes 30–45 min to administer and includes a variety of tasks designed to assess neurocognitive efficiency through measures of response time and accuracy. Most ANAM tasks resemble commonly used neuropsychological tests but have been modified to require a relatively simple subject-computer interface in which the required responses are either a yes/no or a same/different discrimination, indicated by pressing 1 of 2 mouse buttons. The ANAM consists of 7 subtests, each preceded by practice trials that include visual feedback regarding response accuracy. Test trials do not include feedback. Two Simple Reaction Time tasks (20 trials each) are administered at the beginning and at the end of the ANAM, in which participants are asked to respond as quickly as possible to a cue ("*") in the center of the screen. Subtests (i) and (ii): learning and recall are examined using 2 code substitution subtests (CDS and CDD) where participants are first asked to determine whether a series of number/symbol pairings are consistent with a standard set provided at the top of the screen (CDS; 76 trials), and later to discriminate correct pairings from incorrect without the answer key (CDD; 36 trials). Subtests (iii) and (iv): working memory is assessed using both the Mathematical Processing subtest (20 trials), which requires participants to solve a series of mathematical operations and to determine whether the answer is > or < 5; and using a version of the Sternberg Memory Scanning paradigm (30 trials) that requires participants to memorize a fixed set of 6 upper-case letters and to determine whether letters presented later are part of this set. Subtest (v): sustained attention is measured using a Continuous Performance subtest (81 trials), where individuals are presented with single digits at the rate of 950–1200 ms and are asked to indicate whether each digit is the same as or different from the one that directly preceded it. Subtest (vi): visual-spatial processing is tested using the Matching Grids subtest (20 trials), where participants are presented with two 4 × 4 block-grid designs and are asked to indicate whether they are the same or different. Subtest (vii): the Match to Sample subtest (20 trials) is used to assess short-term memory, attention, and visual-spatial discrimination. It requires participants to memorize a 4 × 4 block-grid design and then determine which of 2 designs, presented after a delay of 5000–5100 ms, is the same as that studied.

*Cognitive symptoms, mood, and quality of life*. A number of self-report questionnaires were completed by all patients on the day of ANAM testing. The CSI[7] consists of 21 questions that enquire about an individual's perceived ability to perform several cognitive tasks. This provides a total CSI score in addition to 4 subscales, as described[7], that provide information on attention/concentration, pattern recognition/activity management, intermediate memory, and initiation of executive functions. A higher score on each of these scales indicates greater perceived cognitive impairment. Symptoms of depression and anxiety were assessed by the HADS[13,14]. Scores of 11–21 on the HADS subscales indicate anxiety or depression[13,14]. Self-reported health-related quality of life (HRQOL) was assessed by the Medical Outcomes Study Short Form-36 (SF-36)[18,19].

*Data analysis*. Summary statistics and logistic discriminant analyses were used to examine differences in demographic and clinical characteristics of the SLE and RA groups. As described[20], cognitive performance on each of the ANAM subtests was evaluated using different measures. These included simple reaction time in addition to "throughput" and adjusted "inverse efficiency" scores for each of the 7 ANAM subtests, as well as the number of impaired ANAM subtests after adjustment for simple reaction time. We examined the associations of CSI total score and the CSI attention/concentration subscale score with the ANAM scores (standardized) and other covariates [sex, age, education, ethnicity, years since disease diagnosis (disease duration), SLEDAI, SLICC damage index, NP events at the time of testing, disease group, HADS depression and anxiety scores, SF-36 subscales, and mental component summary (MCS) and physical component summary scores (PCS)] by linear regression. The CSI attention/concentration subscale was the only subscale examined because it includes 9 of the 21 CSI questions and accounts for 28.8% of the common variance[7]. The

remaining 3 subscales each consist of 2–4 of the 21 questions and account for only 3.4%–5.7% of the common variance. Because the data for the CSI total score and attention/concentration subscale score were right-skewed, log-transformation was applied to reduce the skewness. Analyses based on receiver-operating characteristic (ROC) curves were also performed to assess the prediction accuracy of the CSI scores for objective cognitive impairment as defined by the ANAM scores.

## RESULTS

*Patients*. Demographic characteristics, by group, are shown in Table 1. There were no significant differences in sex, age, ethnicity, years of education, or disease duration between SLE and RA patients. Patients with SLE had mild disease activity and low cumulative organ damage as indicated by SLEDAI and SLICC/ACR Damage Index scores. The disease-specific summary scores for RA also indicated low disease activity and disability.

*Cognitive symptoms, depression, anxiety, and HRQOL*. Patients with SLE had significantly higher total CSI and attention/concentration subscale scores compared to patients with RA ($p < 0.05$), with other subscale score comparisons not achieving this level of significance. There was no significant difference in any of HADS-depression, HADS-anxiety, or SF-36 subscales and summary scores between the 2 groups of patients (Table 2).

Univariate linear regression analyses with the logarithm of total CSI score as the outcome variable for patients with SLE (detailed results not shown) established additional associations of higher total CSI scores with NP events at the

*Table 1*. Demographic and clinical characteristics of SLE and RA patients (mean ± SD).

| Characteristic | SLE, n = 68 | RA, n = 33 | p |
|---|---|---|---|
| Female:male | 63:5 | 32:1 | 0.40 |
| Age, yrs | 45.5 ± 13.4 | 49.8 ± 10.2 | 0.11 |
| Ethnicity, % | | | |
| White | 92.6 | 93.9 | 0.63 |
| Other | 7.4 (8.8) | 6.1 | |
| Education, yrs | 14.9 ± 2.5 | 14.4 ± 3.2 | 0.40 |
| Disease duration, yrs | 11.9 ± 9.5 | 12.0 ± 11.0 | 0.95 |
| HADS-D scores | 3.9 ± 4.2 | 4.6 ± 4.2 | 0.47 |
| HADS-A scores | 6.0 ± 4.2 | 5.6 ± 4.2 | 0.60 |
| Cumulative NP events, % patients | 66.2 | 42.4 | 0.05 |
| Cumulative NPSLE events, % patients | 32.4 | — | |
| NP events < 4 weeks of assessment, % patients | 45.6 | 30.3 | 0.15 |
| NPSLE events < 4 weeks of assessment, % patients | 25.0 | — | |
| SLEDAI | 4.4 ± 4.2 | — | |
| SLICC/ACR damage index | 1.3 ± 1.9 | — | |
| Tender joint count | — | 1.8 ± 3.7 | |
| Swollen joint count | — | 1.9 ± 3.1 | |
| ESR | — | 14.5 ± 13.7 | |
| CRP | — | 3.9 ± 3.7 | |
| HAQ | — | 1.0 ± 1.1 | |
| SF-36 MCS score | 48.1 ± 13.8 | 51.9 ± 11.9 | 0.19 |
| SF-36 PCS score | 38.2 ± 13.4 | 35.6 ± 12.3 | 0.35 |
| Current medications, % patients | | | |
| Prednisone | 16.2 | 6.1 | 0.17 |
| Average daily dose of prednisone, mg | 13.0 ± 18.9 | 5.8 ± 2.7 | 0.64 |
| Biologics* | 0 | 33.3 | NA |
| ASA (low-dose) | 25 | 0 | NA |
| NSAID | 16.2 | 42.4 | 0.01 |
| COXIB | 1.5 | 9.1 | 0.11 |
| Antimalarials | 48.5 | 45.5 | 0.77 |
| Methotrexate | 14.7 | 63.6 | < 0.0001 |
| Azathioprine | 10.3 | 0 | NA |
| Mycophenolate | 4.4 | 0 | NA |
| Cyclophosphamide | 2.9 | 0 | NA |

* TNF-α inhibitors (etanercept, infliximab, adalimumab). NA: not available because could not be estimated. HADS: Hospital Anxiety and Depression Scales questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NP: neuropsychiatric; SLE: systemic lupus erythematosus; SLICC: Systemic Lupus International Collaborating Clinics; SLEDAI: SLE Disease Activity Index; HAQ: Health Assessment Questionnaire; SF-36: Medical Outcomes Study Short Form-36; MCS: mental component summary; PCS: physical component summary; NSAID: nonsteroidal antiinflammatory drugs; COXIB: cyclooxygenase inhibitors; RA: rheumatoid arthritis; ACR: American College of Rheumatology; ASA: acetylsalicylic acid; TNF-α: tumor necrosis factor-α.

*Table 2.* Self-report cognition, depression, anxiety, and health-related quality of life scores in SLE and RA patients (mean ± SD).

| Measure | SLE, n = 68 | RA, n = 33 | p |
|---|---|---|---|
| CSI scores* | | | |
| Total CSI score | 33.6 ± 10.5 | 29.4 ± 6.8 | 0.05 |
| CSI subscale 1 | 15.7 ± 5.3 | 13.3 ± 3.4 | 0.02 |
| CSI subscale 2 | 5.2 ± 1.7 | 4.6 ± 1.0 | 0.07 |
| CSI subscale 3 | 3.3 ± 1.2 | 3.0 ± 1.2 | 0.35 |
| CSI subscale 4 | 2.4 ± 0.7 | 2.6 ± 0.8 | 0.20 |
| HADS-D scores** | 3.9 ± 4.2 | 4.6 ± 4.2 | 0.47 |
| HADS-A scores | 6.0 ± 4.2 | 5.6 ± 4.2 | 0.60 |
| SF-36 subscale and summary scores | | | |
| Bodily pain | 56.9 ± 24.7 | 56.8 ± 21.8 | 0.99 |
| General health | 53.2 ± 25.9 | 51.7 ± 20.0 | 0.77 |
| Physical function | 67.6 ± 26.1 | 59.4 ± 29.4 | 0.16 |
| Role — physical | 56.3 ± 42.2 | 59.4 ± 44.3 | 0.73 |
| Physical component summary | 38.2 ± 13.4 | 35.6 ± 12.3 | 0.35 |
| Role — emotional | 74.5 ± 39.5 | 77.1 ± 37.3 | 0.76 |
| Social function | 73.2 ± 28.0 | 75.0 ± 25.2 | 0.75 |
| Vitality | 50.1 ± 25.6 | 57.7 ± 24.9 | 0.17 |
| Mental health | 74.9 ± 17.6 | 78.9 ± 16.4 | 0.28 |
| Mental component summary | 48.1 ± 13.8 | 51.9 ± 11.9 | 0.19 |

* Cognitive Symptom Inventory provides a total score and 4 subscale scores[7] that provide information on attention/concentration (subscale 1), pattern recognition/activity management (subscale 2), intermediate memory (subscale 3), and initiation of executive functions (subscale 4). ** Hospital Anxiety and Depression Scales for depression (D) and anxiety (A). SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SF-36: Medical Outcomes Study Short Form-36.

time of testing (coefficient = 0.27, 95% CI 0.10, 0.35; p = 0.0006) and higher HADS-depression (coefficient = 0.04, 95% CI 0.03, 0.05; p < 0.0001) and HADS-anxiety (coefficient = 0.03, 95% CI 0.02, 0.05; p < 0.0001) scores. Further, negative associations between higher total CSI scores and lower SF-36 subscale and summary scores were found for patients with SLE (MCS score coefficient = –0.011, 95% CI –0.015, –0.006; p < 0.0001). Results for CSI attention/concentration subscale scores were similar. In multivariate analyses, the significant associations of CSI scores with HADS-depression scores, HADS-anxiety scores, and SF-36 MCS scores remained if they were included separately in models in addition to the SF-36 PCS scores, which were also significant (Table 3, columns 1–3). If all 3 of the HADS-depression, HADS-anxiety, and SF-36 MCS scores were included in the regression, significant relationships at the 0.05 level were not achieved because of the high correlation between them (Table 3, column 4).

*Cognitive symptoms and cognitive function*. The association between total CSI score and cognitive performance on ANAM testing in patients with SLE was examined by multiple linear regressions as summarized in Table 4. There was no evidence of a relationship between CSI scores and any ANAM measure, with or without adjustment for age and education (Table 4, columns 1 and 2), 2 variables that were previously found to correlate with ANAM scores[20] as well as years since disease diagnosis and NP events at the time of testing (Table 4, columns 1 and 2). Further adjustment for HADS and SF-36 scores did not alter this finding. For this purpose, because HADS-depression and HADS-anxiety scores and SF-36 MCS scores were highly correlated, they were included separately and in addition to the SF-36 PCS scores. Column 3 of Table 4 gives the results for the inclusion of SF-36 mental component and physical component summary scores together with other important covariates.

The results of these analyses were similar regardless of whether simple reaction time, throughput, or adjusted inverse efficiency scores was used for each of the 7 ANAM subtests or the number of impaired ANAM subtests, after adjustment for simple reaction time. Positive associations of total CSI scores with NP events at the time of testing, the HADS-depression, and HADS-anxiety scores and negative associations of total CSI scores with SF-36 mental and physical component summary scores remained in multiple regression analyses. Identical results were obtained when the analysis was repeated using the attention/concentration subscale of the CSI.

In additional analyses, the ANAM subtest performances of patients with SLE were classified as impaired if their Z score differed from healthy controls by 1.5 or more (i.e., performance was 1.5 or more SD worse than the mean performance of a previously examined healthy control group[21]). Sensitivity analyses were conducted in which overall cognitive impairment was defined either as impaired performance on ≥ 2 or on ≥ 3 of the 7 ANAM subtests. Using adjusted inverse efficiency scores for ANAM subtests, a total of 21 and 10 patients with SLE, respectively, had cognitive impairment using these definitions. The frequency of impairment was almost identical using throughput ANAM scores with 20/21 (95%) and 8/10 (80%) of the patients with SLE impaired, respectively. ROC analyses were performed for the total CSI score and its attention/concentration subscale score as continuous predictors for these criteria of cognitive impairment. In all these scenarios, the areas under the ROC curve were close to 0.5 (Table 5), indicating poor prediction by CSI scores for objectively defined cognitive impairment. These results are consistent with the multiple regression analyses in illustrating that the CSI questionnaire did not reliably screen for cognitive impairment as defined by ANAM performance in our sample of patients with SLE.

## DISCUSSION

Cognitive complaints are frequent in patients with SLE. Objective evidence of cognitive impairment in patients with SLE that is consistent with the ACR case definition requires confirmation by assessment with a battery of neuropsychological tests[6]. However, in many of these cases cognitive impairment can be subtle and evanescent, and access to formal neuropsychological services is limited by personnel and

*Table 3*. Association between total Cognitive Symptom Inventory scores (log-transformed) for SLE patients with Hospital Anxiety and Depression Scale (HADS) depression scores, HADS anxiety scores, and SF-36 scores as indicated by regression coefficient estimates and their standard errors (SE) in multiple linear regression analyses.

| Variables | Analysis I | | Analysis II | | Analysis III | | Analysis IV | |
|---|---|---|---|---|---|---|---|---|
| | Estimate (SE) | p | Estimate (SE) | p | Estimate (SE) | p | Estimate (SE) | p |
| Intercept | 3.376 (0.104) | < 0.001 | 3.421 (0.108) | < 0.001 | 4.193 (0.131) | < 0.001 | 3.566 (0.334) | < 0.001 |
| HADS depression score | 0.038 (0.007) | < 0.001 | | | | | 0.022 (0.013) | 0.099 |
| HADS anxiety score | | | 0.032 (0.007) | < 0.001 | | | 0.010 (0.010) | 0.317 |
| SF-36 mental component summary score | | | | | –0.011 (0.002) | < 0.001 | –0.003 (0.004) | 0.476 |
| SF-36 physical component summary score | –0.001 (0.002) | 0.550 | –0.004 (0.002) | 0.108 | –0.006 (0.002) | 0.010 | –0.003 (0.003) | 0.335 |

SLE: systemic lupus erythematosus; SF-36: Medical Outcomes Study Short Form-36.

*Table 4*. Association between total CSI scores (log-transformed for SLE patients) with ANAM performance and SF-36 scores as indicated by regression coefficient estimates and their standard errors (SE) in multiple linear regression analyses.

| Variables | Analysis I | | Analysis II | | Analysis III | |
|---|---|---|---|---|---|---|
| | Estimate (SE) | p | Estimate (SE) | p | Estimate (SE) | p |
| Intercept | 3.526 (0.251) | < 0.0001 | 4.020 (0.394) | < 0.0001 | 4.051 (0.360) | < 0.0001 |
| Age | | | –0.003 (0.004) | 0.482 | –0.001 (0.003) | 0.687 |
| Education | | | –0.024 (0.015) | 0.125 | –0.002 (0.016) | 0.900 |
| Years since disease diagnosis | | | –0.004 (0.004) | 0.334 | –0.001 (0.004) | 0.762 |
| NP events at the time of testing | | | 0.254 (0.076) | 0.002 | 0.184 (0.072) | 0.014 |
| SF-36 mental component summary score | | | | | –0.007 (0.003) | 0.008 |
| SF-36 physical component summary score | | | | | –0.006 (0.003) | 0.036 |
| Simple reaction time throughput | | 0.345* | | 0.369* | | 0.700* |
| Average | –0.0004 (0.001) | 0.754 | –0.001 (0.001) | 0.417 | 0.000 (0.001) | 0.938 |
| Difference | 0.002 (0.001) | 0.164 | 0.001 (0.001) | 0.277 | 0.001 (0.001) | 0.406 |
| ANAM subset throughput† | | 0.827* | | 0.455* | | 0.649* |
| ST6 | 0.009 (0.042) | 0.832 | –0.022 (0.031) | 0.404 | 0.022 (0.039) | 0.567 |
| MTH | –0.027 (0.039) | 0.488 | –0.002 (0.031) | 0.299 | 0.044 (0.039) | 0.260 |
| MSP | –0.068 (0.057) | 0.239 | –0.036 (0.038) | 0.073 | –0.082 (0.050) | 0.107 |
| CPT | –0.003 (0.040) | 0.933 | –0.024 (0.033) | 0.741 | 0.008 (0.036) | 0.817 |
| CDS | 0.004 (0.051) | 0.932 | 0.004 (0.046) | 0.313 | –0.035 (0.048) | 0.462 |
| CDD | –0.030 (0.047) | 0.523 | –0.037 (0.041) | 0.968 | –0.004 (0.042) | 0.923 |
| MTG | 0.073 (0.048) | 0.130 | 0.071 (0.039) | 0.341 | 0.034 (0.042) | 0.425 |

† ANAM scores were standardized such that their sample means were zero and sample standard deviations were one. * Values for global tests. CSI: Cognitive Symptom Inventory; ANAM: Automated Neuropsychological Assessment Metrics; NP: neuropsychiatric; ST6: Sternberg Memory Scanning paradigm; MTH: Mathematical Processing subtest; MSP: Match to Sample subtest; CPT: Continuous Performance subtest; CDS/CSS: code substitution subtests; MTG: Matching Grids subtest; SF-36: Medical Outcomes Study Short Form-36.

*Table 5*. Area under the receiver-operating characteristic (ROC) curve with 95% confidence limits (CL) for the total CSI score and its attention/concentration subscale score as predictors of cognitive impairment defined by ANAM scores in SLE patients.

| Gold Standard | Predictor | ROC Area | Standard Error | Lower CL | Upper CL |
|---|---|---|---|---|---|
| Impaired item in IE ≥ 3 | Total CSI score | 0.4302 | 0.1059 | 0.2226 | 0.6377 |
| Impaired item in IE ≥ 3 | Attention/concentration subscale score | 0.4233 | 0.1115 | 0.2047 | 0.6419 |
| Impaired item in TPT ≥ 3 | Total CSI score | 0.4854 | 0.1441 | 0.2030 | 0.7678 |
| Impaired item in TPT ≥ 3 | Attention/concentration subscale score | 0.4844 | 0.1441 | 0.2019 | 0.7668 |
| Impaired item in IE ≥ 2 | Total CSI score | 0.4883 | 0.0763 | 0.3388 | 0.6379 |
| Impaired item in IE ≥ 2 | Attention/concentration subscale score | 0.4944 | 0.0773 | 0.3430 | 0.6458 |
| Impaired item in TPT ≥ 2 | Total CSI score | 0.5089 | 0.0821 | 0.3479 | 0.6698 |
| Impaired item in TPT ≥ 2 | Attention/concentration subscale score | 0.5021 | 0.0838 | 0.3379 | 0.6662 |

CSI: Cognitive Symptom Inventory; ANAM: Automated Neuropsychological Assessment Metrics; SLE: systemic lupus erythematosus; IE: inverse efficiency; TPT: throughput.

financial constraints. Thus the use of a validated self-report questionnaire in routine clinical care could be a helpful first step in the assessment of patients with SLE reporting cognitive difficulties. Confirmation and characterization of reported cognitive deficits through objective computerized cognitive testing could then provide an efficient triage system to identify those patients with SLE requiring a formal comprehensive clinical neuropsychological assessment. Our study compared a self-report Cognitive Symptom Inventory that was originally developed for patients with rheumatic diseases to cognitive performance on a brief, automated battery of tests of neurocognitive efficiency. However, the results indicated no significant association between CSI scores and objective test performance. Rather, cognitive complaints in our sample of patients with SLE were associated with self-reported symptoms of anxiety and depression.

Linkage between subjective cognitive complaints and objective performance on neuropsychological tests has been investigated in a variety of populations. In some studies of elderly individuals, self-report questionnaires and clinical interviews have been found to correlate with objective cognitive performance and decline over time, although here too potential confounding factors include symptoms of depression/anxiety, psychosocial stressors, and poor quality of life as well as demographic variables such as education[22,23,24]. Other studies in the elderly found no relationship between subjective cognitive complaints and objective test performance, but only strong associations of such complaints with mood, psychosocial stress, and demographic variables[25,26,27]. Similar results have been reported in studies of patients with traumatic brain injury[28,29,30] and in patients with human immunodeficiency virus[31]. As noted above, findings on this topic in patients with MS were of particular interest because MS is an autoimmune disorder that directly affects the central nervous system and has a chronic and unpredictable course, similar to SLE. Subjective complaints of executive dysfunction by patients with MS were found to be associated with objective neuropsychological deficits and functional disability in one study[32]. Another study of mildly impaired patients with MS found that subjective reports of cognitive impairment accurately reflected problems with processing speed and immediate memory that were independent of fatigue, mood, and physical functioning[33]. On the other hand, the accuracy of self-reported cognitive functioning in MS does appear to be significantly affected by other factors, particularly mood[12].

We have previously reported higher CSI scores in SLE compared to patients with RA, but only when patients had a history of clinically overt NP events[34]. In the current study, CSI scores were higher in the SLE compared to the RA group, regardless of NP history. However, because the elevated CSI scores among patients with SLE were not attributed to cognitive impairment on ANAM, how does one interpret such findings? One possibility is that, because of its cyclical and unpredictable course, SLE is a more distressing illness to live with than RA and that this distress is manifest in additional cognitive concerns. Compared to RA, at least some patients with SLE may have a heightened awareness, acquired from publicly available sources of information, of the potential for SLE to cause cognitive decline and thus may be prone to "overstate" their symptoms in self-report instruments. If this is the case, then it is important to correctly identify such patients and reassure them of the optimistic outlook for their cognitive status. In the current study, we did not set out to examine SLE patients with known, clinically overt NP disease or to compare those with and without cognitive impairment as determined by standard clinical neuropsychological measures. As shown by Kozora, *et al*[8], patients with clinically overt NPSLE may report greater cognitive deficits and may indeed have poorer neurocognitive functioning. However, as a screening procedure, our findings clearly indicate the need for caution in interpreting subjective complaints of cognitive impairment from patients with SLE when seen for routine clinical care.

There are a number of limitations to our study. First, we used a single self-report questionnaire to screen for cognitive symptoms. Although the CSI was originally designed for use in patients with various rheumatic diseases, it is nonetheless possible that an alternative questionnaire would have been more discerning. Second, although it provides an objective measure of cognitive efficiency and has reasonable associations with the ACR neuropsychological test battery[11], the ANAM is a screening tool that does not comprehensively evaluate specific cognitive abilities (e.g., attention, memory, executive functions) over and above cognitive efficiency. Thus, associations between subjective complaints and objective performance, as reported in some studies[20,21,30,31,32], may be seen in some groups of patients with SLE if they are assessed using a detailed battery of clinical neuropsychological tests rather than the ANAM. Regardless, our findings clearly do not support the use of the CSI as a means of identifying those patients with SLE in routine care who are most likely to demonstrate objective evidence of cognitive impairment on a comprehensive neuropsychological assessment. The fact that our study population consisted primarily of patients with quiescent SLE of relatively long duration is a limitation, in that the findings may not be applicable to newly diagnosed patients or those with more active disease. Nonetheless, for many patients with SLE seen in routine practice, screening for cognitive impairment by self-report instruments such as the CSI appears to be problematic.

Our study indicates that the CSI questionnaire alone is insufficient to accurately determine the likelihood of significant cognitive impairment in SLE patients with quiescent disease during the course of routine followup. Subjective cognitive complaints and objective, reaction time-based measures of cognitive efficiency appear to be independent sources of information in such individuals, and their role(s)

and relative importance as screening instruments in patients with SLE will require further study. In patients seen for routine clinical care, high CSI scores indicate the need for further clinical evaluation to initially determine the presence of clinically significant symptoms of anxiety and/or depression.

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