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Validity Evidence for the Use of Automated Neuropsychologic Assessment Metrics As a Screening Tool for Cognitive Impairment in Systemic Lupus Erythematosus

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Objective. Screening for cognitive impairment in systemic lupus erythematosus (SLE) conventionally relies on the American College of Rheumatology (ACR) neuropsychologic battery (NB), which is not universally available. To develop a more accessible screening approach, we assessed validity of the Automated Neuropsychological Assessment Metrics (ANAM). Using the ACR NB as the gold standard for cognitive impairment classification, the objectives were 1) to measure overall discriminative validity of the ANAM for cognitive impairment versus no cognitive impairment, 2) to identify ANAM subtests and scores that best differentiate patients with cognitive impairment from those with no cognitive impairment, and 3) to derive ANAM composite indices and cutoffs.

Methods. A total of 211 consecutive adult patients, female and male, with SLE were administered the ANAM and ACR NB. 1) For overall discriminative validity of the ANAM, we compared patients with cognitive impairment versus those with no cognitive impairment on 4 scores. 2) Six ANAM models using different scores were developed, and the most discriminatory subtests were selected using logistic regression analyses. The area under the receiver operating characteristic curve (AUC) was calculated to establish ANAM validity against the ACR NB. 3) ANAM composite indices and cutoffs were derived for the best models, and sensitivities and specificities were calculated.

Results. Patients with no cognitive impairment performed better on most ANAM subtests, supporting ANAM's discriminative validity. Cognitive impairment could be accurately identified by selected ANAM subtests with top models, demonstrating excellent AUCs of 81% and 84%. Derived composite indices and cutoffs demonstrated sensitivity of 78–80% and specificity of 70%.

Conclusion. This study provides support for ANAM's discriminative validity for cognitive impairment and utility for cognitive screening in adult SLE. Derived composite indices and cutoffs enhance clinical applicability.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem chronic autoimmune disease (1), and the nervous system is commonly affected by SLE and includes 19 neuropsychiatric SLE syndromes, as defined by the American College of Rheumatology (ACR) (2,3). Studies on neuropsychiatric SLE have identified 2 principal mechanisms: inflammatory/immune and thrombotic/ischemic-vascular injury (3,4). Cognitive impairment is one of the most common manifestations of neuropsychiatric SLE, with reported frequencies ranging from 20% to 80% (5–7) and a pooled prevalence of 38% (5). Common deficits are found in the domains of attention, memory, executive dysfunction, and psychomotor speed (8–13). Cognitive impairment may occur in the absence

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SIGNIFICANCE & INNOVATIONS

- This study provides validity evidence to support the use of Automated Neuropsychological Assessment Metrics (ANAM) as a screening tool for cognitive impairment in patients with systemic lupus erythematosus (SLE).
- We identified the most discriminating subtests and scores of ANAM to be able to identify cognitive impairment.
- The derived composite index and cutoff score for ANAM enhance the applicability and interpretation of ANAM results.
- ANAM can be implemented as a clinically relevant cognitive impairment screening test in adult patients with SLE.

of active SLE or other neuropsychiatric SLE manifestations (4,8, 13–15) and is known to have a significant effect on patients' everyday functioning, employment status, and quality of life (8,9,14,16,17). The course of cognitive impairment in SLE may be one of fluctuation, persistence, or progression (5,18,19).

Conventionally, the assessment of cognitive impairment in adult patients with SLE is carried out with the validated ACR neuropsychologic battery (NB) (2,20). The battery includes protected tests that necessitate specialized personnel, and it requires approximately 1 hour to administer, plus additional time for scoring and interpretation. For many clinics, these are notable barriers to accessing cognitive impairment assessment, because health care payers do not cover these costs (12,21). Other batteries, such as the Montreal Cognitive Assessment (22,23), and discrete tests such as the Controlled Oral Word Association Test and the Hopkins Verbal Learning Test–Revised (HVLT-R) (24,25) have been examined in SLE studies, but while briefer, they also require specialized personnel for administration and interpretation and cannot be self administered. In addition, their validity for the screening for cognitive impairment in SLE has not been well established. Thus, there is an unmet need for a screening assessment for cognitive impairment that is validated for SLE and that can be applied in an ambulatory clinic setting without specialized personnel (26). A screening assessment without specialized personnel would allow for a better rationalization of resources, which might in turn enable more comprehensive neuropsychologic assessment by specialists as needed. Moreover, a cost-effective screening approach that does not require specialized personnel would permit widescale and early screening for cognitive impairment. Such screening would improve identification of patients in need of enhanced clinical management for cognitive impairment, which may prevent the accrual of long-term damage and disability (7,27) and would enable such patients to participate in treatment research trials.

The Automated Neuropsychological Assessment Metrics (ANAM) was designed as a library of computer-based, self-administered, automated tasks assessing various aspects of cognitive functioning, and its longest battery (ANAM [v4] general neuropsychological screening [GNS]) requires 30–40 minutes or less to complete (21), including automated scoring. The ANAM v4 GNS consists of 15 subtests representative of 7 cognitive domains (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24096/abstract). It has been used to screen cognitive performance in diverse clinical contexts (28–30). Studies of the ANAM in patients with SLE are promising (6,11,31,32); however, validated cognitive impairment thresholds for adult SLE are lacking. The ANAM generates an enormous amount of data, and developing a composite index that encompasses selected subtests and appropriate scores as a method for data reduction, simplification, and display is needed to facilitate its use in a clinical setting and the interpretation of its scorings (28).

The aim of this study was to assess the performance of the ANAM as a screening tool for cognitive impairment in patients with SLE, employing the ACR NB as the gold standard for classifying patients into cognitive impairment versus no cognitive impairment groups. Our objectives were: 1) to measure overall discriminative validity of the ANAM v4 GNS battery for cognitive impairment versus no cognitive impairment, 2) to determine the best subtests and scores to differentiate patients with cognitive impairment from no cognitive impairment, and 3) to derive composite indices and appropriate cutoffs to enhance the interpretability of the ANAM in the screening for cognitive impairment in SLE.

PATIENTS AND METHODS

Study population. A total of 211 adult patients with SLE who attended the University of Toronto Lupus Clinic between July 2016 and October 2018 participated in the study. Inclusion criteria were fulfillment of the revised ACR criteria for SLE classification (33) or meeting 3 criteria and a supportive biopsy result (1), age between 18 and 65 years, and ability to give informed consent. Exclusion criteria were mental or physical disability preventing participation in the study and low fluency in English, precluding completion of verbal items of the ACR NB. Of the 738 screened patients, 702 were eligible for participation, and 373 patients provided informed consent. Of the 373 patients, 24 withdrew from the study (citing duration and stress of visits) and 211 patients actively participated (117 have yet to participate). This project was approved by the University Health Network Research Ethics Board.

Procedures and outcome measures. All patients were administered the ACR NB followed by the ANAM on the same day. Patients' scores on the ACR NB were compared to normative data stratified for age and sex, yielding standardized scores that were used in analyses. Patients were classified on the ACR NB as impaired, unimpaired, or indeterminate using the following criteria: cognitive impairment (Z score of less than or equal to –1.5

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in 2 or more domains), no cognitive impairment (Z scores in all domains greater than –1.5), and indeterminate (Z score of less than or equal to –1.5 in only 1 domain). In this study we excluded the indeterminate group from the analysis to reduce heterogeneity within the groups of patients and to enable the comparison of 2 well-defined groups of patients (definite cognitive impairment, definite no cognitive impairment).

ACR NB. The battery consisted of 11 cognitive tests representative of 6 cognitive domains (i.e., manual motor speed, simple attention and processing speed, visual-spatial construction, language processing, learning and memory [visuospatial and verbal], and executive functioning [untimed and timed]) (Table 1). A domain was defined as impaired if a Z score of less than or equal to –1.5 was reached in at least 1 test in the following domains: manual motor speed, simple attention and processing speed, visual-spatial construction, and language processing or a Z score of less than or equal to –1.5 in ≥2 tests in the domains learning and memory and executive functioning. The ACR NB was identical to the ACR-recommended cognitive battery for adults with SLE (10,20), except that the HVLT-R was substituted for the California Verbal Learning Test (CVLT) (34), and the trail making test part A (35) was added.

ANAM. The ANAM v4 GNS battery consists of 15 subtests (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24096/abstract). For each ANAM subtest, 4 scores are provided: accuracy, operationalized as the percentage of correct responses (PCT) on a task; mean reaction time (MR; in seconds); throughput, a measure of cognitive efficiency, operationalized as the number of correct responses per minute (36); and coefficient of variation of reaction time (CV), an index of the consistency of a test-taker's response speed within a given timed subtest, a derived score (SD of MR divided by MR). Higher PCT and throughput scores and lower MR and CV scores indicate better cognitive performance.

Note that for 4 subtests (simple reaction time, tower puzzle, and tapping left and right hand) there is no PCT score because these subtests do not allow for incorrect responses. For 2 subtests (tower puzzle and go/no go), in which throughput cannot be derived, the ANAM provides instead the following scores: MeanScore (derived from a combination of accuracy, speed, and problem difficulty) and NumIncRsp (the number of incorrect responses, or false positives), which were used in analyses.

Statistical analyses. Demographic and clinical characteristics were summarized and statistical significance was set at an alpha level of *P* value less than 0.05.

Discriminative construct validity (objective 1). Using the ACR NB to classify patients as having cognitive impairment or no cognitive impairment, we hypothesized that patients without cognitive impairment would perform better on the majority of the ANAM subtests compared to those with cognitive impairment. For each subtest, we compared the 4 ANAM scores (PCT, MR, throughput, and CV, whenever applicable) between patients

Table 1. Comparison of domains/subtests of ACR neuropsychologic battery (ACR NB) and the Automated Neuropsychological Assessment Metrics (ANAM)*

Domains	ACR NB subtest	Domains	ANAM subtest
Manual motor speed	Finger tapping test: dominant hand and nondominant hand	Fine motor processing	1. Tapping right hand 2. Tapping left hand
Simple attention and processing speed	Trail A Stroop Color Naming Stroop Word Reading	Attention and processing speed	3. Running memory 4. Procedural reaction time 5. Two-choice reaction time 6. Simple reaction time 7. Simple reaction time–repeated
Visual-spatial construction	RCFT copy	Visual-spatial perception	8. Spatial processing
Language processing	COWAT Animal Naming Test	Language processing	9. Logical relations
Learning and memory			10. Code substitution–learning
Visuospatial	RCFT delay recall RCFT delay recognition	Learning	11. Code substitution–delay 12. Match to sample
Verbal	HVLT-R delayed recall HVLT-R recognition HVLT-R total recall	Memory	
Executive functioning Untimed	Stroop (interference score) WAIS letter-number Consonant trigrams (used lower value from 18 second or 36 second)	Executive functioning	13. Math processing 14. Go/no go hits 15. Tower test
Executive timed	WAIS-III digit symbol Trail B		

* Detailed description of the ANAM is found in Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24096/abstract. ACR = American College of Rheumatology; RCFT = Rey Complex Figure Test; COWAT = Controlled Oral Word Association Test; HVLT-R = Hopkins Verbal Learning Test–Revised; WAIS-III = Wechsler Adult Intelligence Scale, 3rd ed.

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Table 2. Differences in Automated Neuropsychological Assessment Metrics (ANAM) performance according to cognitive function based on the ACR neuropsychologic battery (NB)*

ANAM score and subtest	Cognitive status based on ACR NB: No cognitive impairment (n = 52, 24.6%)	Cognitive status based on ACR NB: Cognitive impairment (n = 96, 45.5%)	P
Percentage of correct responses			
Code substitution–learning	97.70 ± 1.96	97.3 ± 3.6	NS
Procedural reaction time	97.30 ± 4.46	94.4 ± 10.1	0.049†
Math processing	94.62 ± 6.09	92.0 ± 8.4	NS
Matching to sample	91.25 ± 13.32	88.1 ± 12.3	NS
Code substitution–delayed	90.22 ± 11.66	81.7 ± 13.0	<0.001‡
Go/no go	95.18 ± 2.99	92.6 ± 6.1	0.004‡
Logical reactions	92.87 ± 10.77	86.2 ± 16.8	0.011‡
Spatial processing	97.31 ± 5.09	95.0 ± 6.6	0.031‡
Two-choice reaction time	95.48 ± 8.93	94.9 ± 10.6	NS
Running memory	93.58 ± 13.69	88.4 ± 16.8	NS
Mean reaction time			
Simple reaction time	0.31 ± 0.07	0.35 ± 0.12	0.041†
Code substitution–learning	1.29 ± 0.26	1.50 ± 0.35	<0.001‡
Procedural reaction time	0.65 ± 0.13	0.78 ± 0.24	<0.001‡
Math processing	2.73 ± 0.72	3.10 ± 0.99	0.018†
Matching to sample	2.06 ± 0.58	2.31 ± 0.72	0.037†
Code substitution–delayed	1.56 ± 0.41	1.74 ± 0.57	0.045†
Simple reaction time–repeated	0.31 ± 0.06	0.37 ± 0.19	0.021†
Go/no go	0.37 ± 0.04	0.40 ± 0.06	<0.001‡
Logical reactions	2.44 ± 0.66	2.78 ± 0.96	0.025†
Spatial processing	2.46 ± 0.62	2.83 ± 0.89	0.009†
Tower puzzle	2.82 ± 0.67	3.27 ± 1.11	0.033†
Tapping right	0.17 ± 0.02	0.27 ± 0.72	0.336†
Tapping left	0.18 ± 0.02	0.21 ± 0.06	0.007†
Two-choice reaction time	0.48 ± 0.07	0.51 ± 0.12	NS
Running memory	0.71 ± 0.14	0.79 ± 0.17	0.008†
Throughput			
Simple reaction time	207.04 ± 36.10	186.8 ± 39.8	0.003†
Code substitution–learning	47.48 ± 8.74	41.1 ± 9.6	<0.001‡
Procedural reaction time	94.52 ± 17.14	79.7 ± 21.0	<0.001‡
Math processing	22.21 ± 6.11	19.8 ± 6.9	0.032‡
Matching to sample	28.46 ± 8.63	24.4 ± 8.5	0.007†
Code substitution–delayed	37.19 ± 13.57	30.2 ± 12.3	0.002‡
Simple reaction time–repeated	207.65 ± 35.64	181.6 ± 42.3	<0.001‡
Logical reactions	24.81 ± 7.88	21.0 ± 8.3	0.007†
Spatial processing	25.06 ± 6.14	22.0 ± 6.5	0.006†
Two-choice reaction time	124.75 ± 29.70	116.8 ± 22.4	0.07†
Running memory	81.67 ± 24.00	68.5 ± 26.4	0.003‡
Coefficient of variation of reaction time			
Simple reaction time	0.25 ± 0.16	0.34 ± 0.29	0.035†
Code substitution–learning	0.31 ± 0.06	0.32 ± 0.07	NS
Procedural reaction time	0.34 ± 0.21	0.37 ± 0.20	NS
Math processing	0.32 ± 0.09	0.33 ± 0.09	NS
Matching to sample	0.41 ± 0.17	0.42 ± 0.13	NS
Code substitution–delayed	0.50 ± 0.19	0.49 ± 0.15	NS
Simple reaction time–repeated	0.33 ± 0.27	0.42 ± 0.29	NS
Go/no go	0.24 ± 0.05	0.26 ± 0.06	0.028†
Logical reactions	0.42 ± 0.12	0.44 ± 0.16	NS
Spatial processing	0.35 ± 0.09	0.33 ± 0.08	NS
Tower puzzle	0.73 ± 0.16	0.66 ± 0.16	0.012†
Tapping right	0.15 ± 0.11	0.20 ± 0.31	NS
Tapping left	0.17 ± 0.08	0.16 ± 0.09	NS
Two-choice reaction time	0.27 ± 0.15	0.27 ± 0.13	NS
Running memory	0.33 ± 0.07	0.35 ± 0.09	NS
NumIncRsp: go/no go	4.88 ± 2.45	5.51 ± 3.63	NS
MeanScore: tower puzzle	1,673.84 ± 352.6	1,523.75 ± 419.3	0.033†

* Values are the mean ± SD unless indicated otherwise. Cognitive status was defined as follows: no cognitive impairment = no domains with Z scores less than or equal to –1.5; cognitive impairment = ≥2 domains with Z score less than or equal to –1.5. ACR = American College of Rheumatology; NS = not significant.
† Statistically significant.
‡ Statistically significant based on the Holm-Bonferroni adjustment.

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with cognitive impairment and with no cognitive impairment using unpaired *t*-tests and Holm-Bonferroni adjusting for multiple comparisons.

Selective ANAM subtests construct validity (objective 2). We hypothesized that selected ANAM subtests and scores would identify cognitive impairment with good-to-excellent performance (based on the area under the receiver operating characteristic [ROC] curve [AUC]), employing the ACR NB as the gold standard for classification of patients as having cognitive impairment or no cognitive impairment. To employ the ANAM as a screening test, sensitivity is prioritized over specificity (37), and we hypothesized that ANAM sensitivity of ≥0.90 would be achieved. To test this hypothesis, we first constructed 6 ANAM models; 4 models included 1 ANAM score each, and 2 additional models combined multiple scores. Each model included all the relevant ANAM subtests. Model 1 encompassed PCT scores, model 2 encompassed CV scores, model 3 encompassed MR scores, model 4 encompassed throughput scores, model 5 encompassed PCT, CV, and MR scores, and model 6 encompassed PCT, CV, MR, and throughput scores.

For each model, a backward elimination variable selection method was used (38) while adjusting for age in a logistic regression analysis. Variables with the highest *P* values were dropped one-by-one until the best-fit model was reached, while adjusting for age. The best-fit models were determined by Akaike's information criterion (38). Parameters that were selected for each model were assessed for collinearity. This approach allowed the identification of the 6 most parsimonious models with the best discriminatory subtests and the corresponding scores. For models 5 and 6, subtests were allowed to appear only once in each model, to prevent redundancy, and in the case of recurring subtests with different scores within a model, the subtests with the higher *P* values were removed from the models.

Second, we assessed the ability of all ANAM models to accurately identify cognitive impairment. The AUC was calculated, and sensitivity and specificity were determined under a preferred threshold approach. Values of the AUC can be interpreted as outstanding, excellent, good, fair, and poor performance for identifying cognitive impairment, corresponding to values of 1.0–0.91, 0.81–0.90, 0.71–0.80, 0.60–0.70, and <0.60, respectively (39).

Derivation of the composite indices for the best ANAM models (objective 3). The best ANAM models (with the highest AUCs) were used for deriving the candidate ANAM composite indices. The composite index included the sum of the selected subtests with their selected corresponding scores, multiplied by their parameter estimate from the logistic regression (40). The performance of the candidate ANAM composite indices in the identification of cognitive impairment as classified by the ACR NB was evaluated using ROC curve analysis. The proposed cutoff value of the composite index was determined by a combination approach for sensitivity ≥75% and the highest Youden index. The performance of the candidate composite indices was also compared between patients with neuropsychiatric lupus (ever) and patients without neuropsychiatric lupus (2).

RESULTS

Study participants and cognitive battery testing. Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24096/abstract, provides the demographic and clinical characteristics of the cohort. A total of 211 patients were enrolled. Cognitive impairment was diagnosed by the ACR NB in 45.5% of patients (n = 96), no cognitive impairment in 24.6% of patients (n = 52), and indeterminate in 29.9% of patients (n = 63). There were no significant differences in demographic and clinical characteristics between patients with cognitive impairment and no cognitive impairment.

Hypothesis testing for discriminative construct validity (objective 1). Comparing the 4 scores (PCT, CV, MR, and throughput, whenever applicable) for each ANAM subtest between patients with cognitive impairment and no cognitive impairment, we confirmed the hypothesis that patients with no cognitive impairment performed significantly better on the majority of the ANAM subtests compared to those with cognitive impairment (Table 2). This difference was most prominent for throughput and MR, with statistically significant differences in 11 of 11 subtests and 14 of 15 subtests, respectively, and less for PCT and CV, with 5 of 10 subtests and 3 of 15 subtests, respectively.

Hypothesis testing for the selective ANAM subtests construct validity (objective 2). Table 3 provides the 6 parsimonious models of the ANAM with the most discriminatory subtests and corresponding scores. Four subtests were selected in model 5 (code substitution–learning, code substitution–delayed memory, spatial processing, and tapping left hand), and an additional 4 subtests were selected in model 6 (simple reaction time–repeated, go/no go, tower puzzle, and two-choice reaction time), for a total of 8 subtests. Six subtests were not selected by any of the models (including simple reaction time, mathematical processing, matching to sample, logical relations, tapping right hand, and running memory) (Table 3). The selected ANAM subtests in model 6 represent 5 of the 6 domains of the ACR NB (Table 1). The only domain that was not represented in model 6 was language processing, which was the least impaired domain in our cohort (<3% of patients).

The ROC curve analysis confirmed the hypothesis that the selected ANAM models could accurately identify cognitive impairment compared to the ACR NB (Figure 1A and Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24096/abstract). As hypothesized, all models were able to reach high sensitivity

Table 3. Variable selection of the Automated Neuropsychological Assessment Metrics (ANAM) with the discriminatory subtests and corresponding scores*

ANAM: subtest and score	Model 1: PCT		Model 2: CV		Model 3: MR		Model 4: TP		Model 5: PCT, CV, MR†		Model 6: PCT, CV, MR, TP‡	
	Slope ± SE	*P*	Slope ± SE	*P*	Slope ± SE	*P*	Slope ± SE	*P*	Slope ± SE	*P*	Slope ± SE	*P*
1. Code substitution–learning												
MR	–	–	–	–	2.5454 ± 0.86	0.003§	–	–	2.4374 ± 0.96	0.011§	–	–
TP	–	–	–	–	–	–	–	–	–	–	−0.0576 ± 0.034	0.09
2. Procedural reaction time												
TP	–	–	–	–	–	–	−0.0363 ± 0.013	0.004§	–	–	–	–
3. Code substitution–delay												
PCT	−0.0524 ± 0.02	0.003§	–	–	–	–	–	–	−0.0468 ± 0.02	0.020§	−0.0587 ± 0.02	0.010§
TP	–	–	–	–	–	–	−0.0368 ± 0.019	0.052	–	–	–	–
4. Simple reaction time–repeated												
TP	–	–	–	–	–	–	–	–	–	–	−0.0195 ± 0.01	0.03§
5. Go/no go												
PCT	−0.1072 ± 0.05	0.039§	–	–	–	–	–	–	–	–	−0.1401 ± 0.08	0.063
CV	–	–	8.6883 ± 3.87	0.025§	–	–	–	–	–	–	–	–
6. Spatial processing												
CV	–	–	−6.4267 ± 2.46	0.009§	–	–	–	–	−8.4039 ± 2.91	0.004§	−9.9252 ± 3.22	0.002§
7. Tower puzzle												
CV	–	–	−2.2736 ± 1.23	0.064	–	–	–	–	–	–	–	–
MeanScore	–	–	–	–	–	–	−0.0008 ± 0.0005	0.142	–	–	−0.0008 ± 0.0007	0.25
8. Tapping left hand												
CV	–	–	−3.5085 ± 1.70	0.174	–	–	–	–	–	–	–	–
MR	–	–	–	–	12.5314 ± 7.05	0.076	–	–	9.8734 ± 6.83	0.179	9.7445 ± 7.10	0.17
9. Two-choice reaction time												
CV	–	–	–	–	–	–	–	–	–	–	−6.3786 ± 3.16	0.044§
Intercept	15.3564 ± 5.01	0.002	3.0657 ± 1.70	0.071	−4.189 ± 1.48	0.005	8.0134 ± 1.994	<0.001	19.80 ± 8.4	0.019	31.8509 ± 9.08	<0.001

* Parameters that were selected for each model were assessed for collinearity. PCT = percentage of correct responses; CV = coefficient of variation of reaction time; MR = mean reaction time; TP = throughput.
† CV score for tapping left hand was removed from the final model 5 because the MR score for the same subtest was selected with lower *P* value.
‡ The model included TP scores for all available subtests and NumIncRsp for go/no go subtest and MeanScore for tower puzzle subtest. NumIncRsp score for go/no go subtest was removed from final model 6 because the CV score for the same subtest was selected with a lower *P* value.

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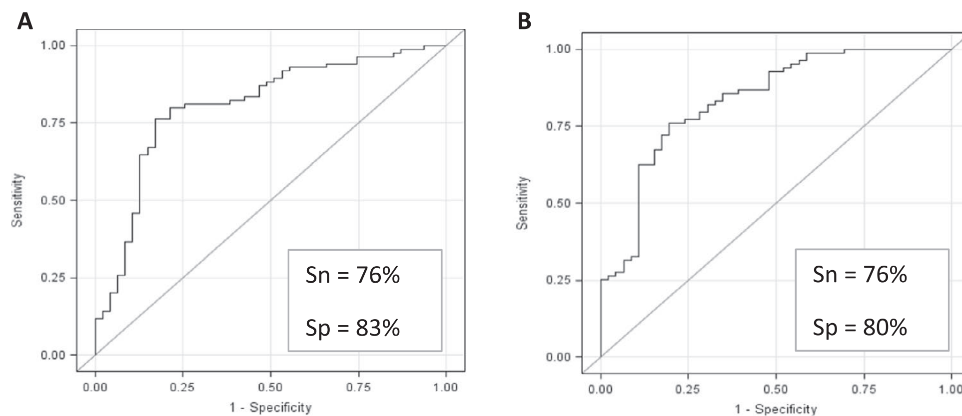

Figure 1. Receiver operating characteristic (ROC) curves for identifying cognitive impairment based on the performance of Automated Neuropsychological Assessment Metrics models 5 and 6. **A**, Model 5 (AUC = 81%): ROC curve of stepdown selected subtests using the percentage of correct responses (PCT), coefficient of variation of reaction time (CV), and mean reaction time (MR); **B**, Model 6 (AUC = 84%): ROC curve of stepdown selected subtests using PCT, CV, MR, and throughput with NumIncRsp for go/no go, and MeanScore for tower puzzle. AUC = area under the curve; Sn = sensitivity; Sp = specificity.

of ≥90%. The 2 best models were model 5, encompassing 3 scores, including PCT, CV, and MR, with an excellent AUC of 81% (95% confidence interval [95% CI] 0.79–0.83), sensitivity of 76%, and specificity of 83% (at the highest Youden index), and model 6, encompassing all 4 scores (PCT, CV, MR, and throughput, or NumIncRsp and MeanScore where applicable) with an excellent AUC of 84% (95% CI 0.84–0.87), sensitivity of 76%, and specificity of 80% (at the highest Youden index). Models that encompassed only 1 score, including model 4, which used only the throughput score, performed worse than the 2 models using combination scores.

Derivation of the composite indices for the best ANAM models (objective 3). Composite indices were derived for the 2 best models: model 5 and model 6, which we have named ANAM-index$_5$ and ANAM-index$_6$. The model 5 composite index was calculated according to the formula:

$$\text{ANAM} - \text{index}_5 = 3.88 - 0.05 \times \text{PCT/CSD} - 8.4 \times \text{CV/SP} + 2.44 \times \text{MR/CSL} + 9.87 \times \text{MR/TL}$$

The model 6 composite index was calculated according to the formula:

$$\text{ANAM} - \text{index}_6 = 31.85 - 0.06 \times \text{PCT/CSD} - 0.14 \times \text{PCT/GNG} - 9.93 \times \text{CV/SP} - 6.38 \times \text{CV/TCRT} + 9.74 \times \text{MR/TL} - 0.06 \times \text{throughput/CSL} - 0.02 \times \text{throughput/SRTR} - 0.0008 \times \text{MS/TPZ}$$

(CSD = code substitution–delay, SP = spatial processing, CSL = code substitution–learning, TL = tapping left hand, GNG = go/no go, TCRT = two-choice reaction time, SRTR = simple reaction time–repeated, MS = MeanScore, TPZ = tower puzzle). The composite index for each model was able to significantly differentiate between patients with cognitive impairment and no cognitive impairment, with mean ± SD ANAM-index$_5$ of 3.0 ± 1.5 for patients with cognitive impairment compared to 1.6 ± 1.3 for no cognitive impairment and mean ± SD ANAM-index$_6$ of 3.8 ± 2.3 for patients with cognitive impairment compared to 1.6 ± 1.9 for no cognitive impairment ($P < 0.0001$ for both ANAM composite indices).

The overall performance of the ANAM composite indices at identifying cognitive impairment is summarized in Table 4 (for ROC curves see Supplementary Figure 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24096/abstract). The scores showed good ability to identify cognitive impairment, with an AUC of 78% (95% CI 0.69–0.86) for model 5 and 79% (95% CI 0.71–0.88) for model 6. The proposed cutoffs showed good performance, with a sensitivity of 78% and 80% for model 5 and model 6, respectively, specificity of 70% for both models, positive predictive value (PPV) of 83% for both, and negative predictive values (NPV) of 64% and 65%, respectively. Figure 2 shows the performance of each composite index over different cutoff values.

The performance of ANAM-index$_5$ and ANAM-index$_6$ was similar among patients with neuropsychiatric lupus (ever) (n = 53) and patients without neuropsychiatric lupus (n = 95). The scores showed good ability to identify cognitive impairment for ANAM-index$_5$ (accuracy of 72% for patients with and without neuropsychiatric lupus) and for ANAM-index$_6$ (accuracy of 70% for patients without neuropsychiatric lupus and 64% for patients with neuropsychiatric lupus).

DISCUSSION

In this study, we showed that the ANAM battery can be used accurately as a screening test to differentiate between SLE patients

Table 4. Performance of the candidate Automated Neuropsychological Assessment Metrics (ANAM) composite indices*

	AUC	Cutoff value	Sensitivity†	Specificity	PPV	NPV
ANAM-index$_5$	78	1.96/1.32	78/91	70/51	83/77	64/75
ANAM-index$_6$	79	2.17/1.61	80/89	70/54	83/78	65/74

* Values are percentages unless indicated otherwise. Each model is presented with 2 sets of performance values based on 2 sets of cutoff values. Model 5 composite index was calculated according to the ANAM-index$_5$ formula (see Results). Model 6 composite index was calculated according to the ANAM-index$_6$ formula (see Results). AUC = area under the receiver operating characteristic curve; PPV = positive predictive value; NPV = negative predictive value.
† Only sensitivities of ≥75% were considered for the higher cutoff and of ≥89% for the lower cutoff.

with and without cognitive impairment, and moreover, that specific subtests of the ANAM, along with their selected scores, can identify cognitive impairment in patients with SLE. This approach not only enables us to use a cost-effective screening approach without specialized personnel, but we have reduced the duration of the ANAM battery itself. The ANAM v4 GNS full battery requires approximately 40 minutes to administer, while our analyses enable us to limit the number of ANAM subtests used, shortening the testing duration to 20 minutes. We developed candidates for the ANAM composite indices to serve as a summary measure of cognitive screening for patients with SLE on the ANAM, thus increasing the usefulness of the ANAM as a screening test in day-to-day clinical practice.

In keeping with previous studies on the performance of the ANAM in adult and pediatric patients with SLE (21,31,32,40–43), we showed that the ANAM scores of patients with SLE with no cognitive impairment were significantly different from the scores of patients with cognitive impairment. We also showed that specific subtests are associated with cognitive impairment in patients with SLE, including code substitution–learning, code substitution–delayed memory, spatial processing, tapping left hand, simple reaction time repeated, go/no go, tower puzzle, and two-choice

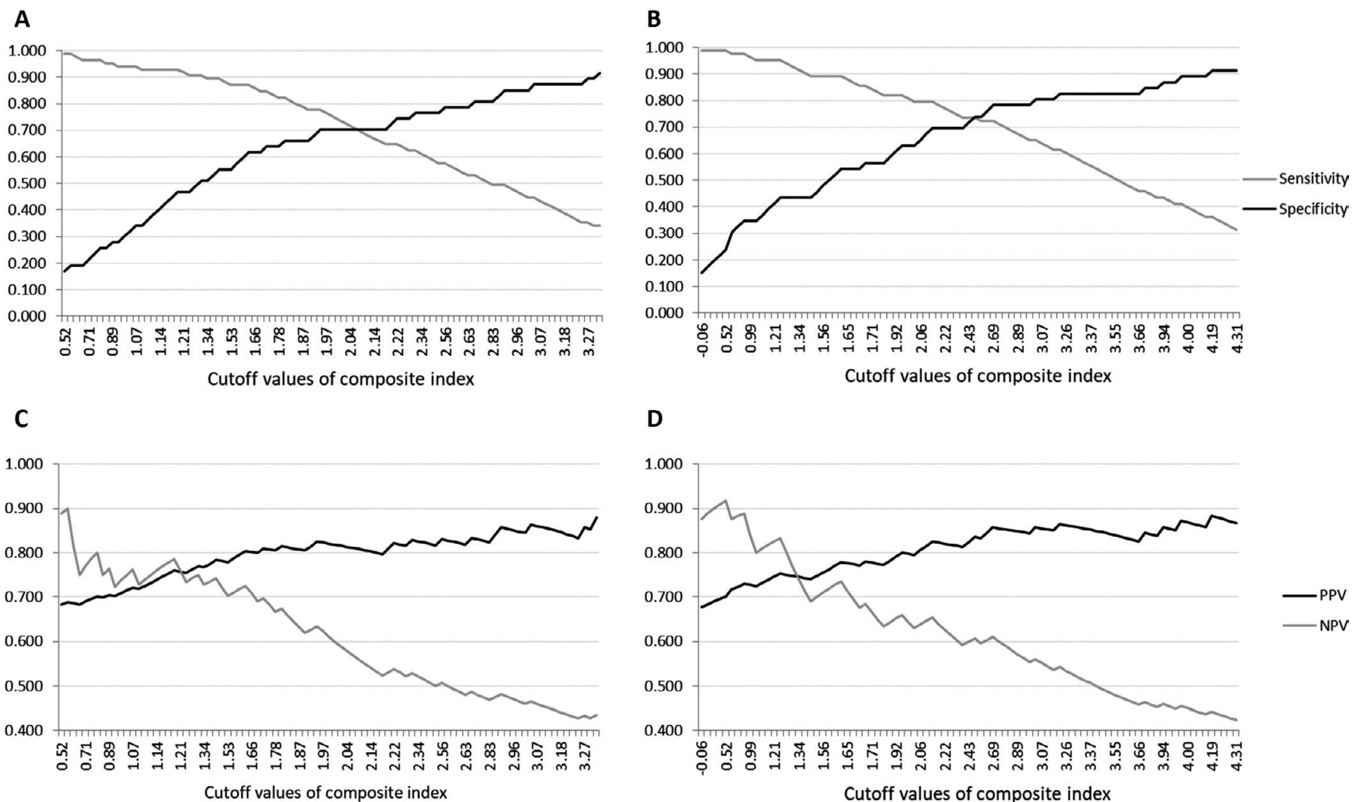

Figure 2. Performance of the candidate Automated Neuropsychological Assessment Metrics (ANAM) composite indices for identifying cognitive impairment over different cutoff values. **A**, Sensitivity and specificity over ANAM-index$_5$ values; **B**, Sensitivity and specificity over ANAM-index$_6$ values; **C**, Positive predictive value (PPV) and negative predictive value (NPV) over ANAM-index$_5$ values; **D**, PPV and NPV over ANAM-index$_6$ values.

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reaction time. These selected subtests represent 5 of 6 cognitive domains, excluding language processing (comprising a phonemic and a semantic fluency test), which was the least impaired domain in our cohort (<3% of patients). Three of the most affected cognitive domains among the patients with cognitive impairment in this cohort, as well as in previous studies, were learning and memory, visual-spatial construction, and simple attention and speed of processing (8,10,11), and these domains were represented by 2 ANAM subtests each (except for visual-spatial construction, which includes only 1 ANAM subtest). Comparable pediatric ANAM subtests evaluating memory, attention, and visual-spatial construction (including code substitution–delayed, continuous performance test, matching to sample, and spatial processing) were selected using similar methods in pediatric populations (43). Our findings can be further validated through prospective studies with different SLE cohorts.

While the ANAM automatically generates several performance scores for each subtest, the majority of studies on ANAM performance in adult patients with or without SLE used the throughput as a single outcome (21,31,32). The throughput score has been widely used in clinical research employing the ANAM, because it is considered one of the most sensitive metrics to evaluate cognitive performance (28,36). Under conditions in which both speed and accuracy decline (or improve), throughput will be a more sensitive index of performance than either measure alone (21,28,31,36). An agreement on interpretation of the throughput score by itself and validated normative data for patients with SLE are lacking, and thus most studies have used it in comparison to a control group. Using this method, studies on the performance of the ANAM in patients with SLE found only moderate associations between ANAM subtests and analogous traditional neuropsychologic tests (32). In a previously study using this method (40), we found moderate ANAM sensitivity of 52%, good specificity of 73%, and PPV and NPV values of 70% and 55%, respectively.

One study, which used the throughput score in 60 patients with SLE using logistic regression models revealed higher sensitivity (76%) and specificity (83%) for the ANAM after controlling for premorbid levels of cognitive ability (31). However, using throughput as a single score has a limitation, because it does not allow for differentiation between sensorimotor efficiency and mental processing efficiency. Thus, the utility of exclusively using throughput to differentiate clinically meaningful groups of subjects who differ in their cognitive efficiency has limitations (21). Furthermore, in SLE populations, in whom the musculoskeletal system is commonly affected, reaction time may be potentially influenced by pain and joint restriction. Studies in pediatric patients with SLE using all 4 scores generated from the ANAM were better at assessing cognitive impairment than the throughput score alone and allowed for the detection of moderate or severe cognitive impairment with 100% sensitivity and 86% specificity (43). Accordingly, we found that using all 4 scores for ANAM interpretation yielded good sensitivity, specificity, PPV, and NPV. Furthermore, models using a combination of the scores (models 5 and 6, with AUCs of 81% and 84%, respectively) showed superiority over the model using throughput alone (model 4, with an AUC of 74%).

We developed candidate ANAM composite indices to further increase the clinical usefulness of the ANAM. We found that the proposed scores differentiated individuals' cognitive status with good ability, as exemplified by a 78–79% AUC. A similar method was used by Brunner et al (43) in pediatric patients with SLE. Their scores performed slightly better, with an AUC of 89%, sensitivity of 92%, and specificity of 66% for detecting moderate-to-severe cognitive impairment. The smaller cohort of Brunner et al (80 patients), which also included 50% of healthy children with a different definition of cognitive impairment (>1 domain with a Z score less than –2 or >2 domains with Z scores less than –1), may explain this difference. Although the performances of our 2 proposed ANAM composite indices are similar, we favor the use of ANAM-index$_6$, which contains 8 of 15 ANAM subtests and represents the ACR NB to a greater extent (i.e., represents 5 of 6 cognitive domains of our ACR NB battery).

Our findings suggest the usefulness of the ANAM composite indices for screening of cognitive impairment in patients with SLE with the proposed cutoffs. A lower cutoff to achieve a higher sensitivity may be used, allowing primarily for screening patients and encouraging more comprehensive testing by specialists. Choosing a higher cutoff with a high PPV will improve the specificity over sensitivity and can be applied in specific settings, as shown in Figure 2.

Factors contributing to a relatively high prevalence (45.5%) of cognitive impairment in our cohort may include referral bias, because our clinic serves as a tertiary center. Comparison of patients who agreed to participate (n = 211) to patients who refused to participate (n = 353) revealed a significant difference in the age of the patients and SLE duration, which could have introduced participation bias (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24096/abstract). The prevalence of cognitive impairment in our cohort is comparable with some studies, because the prevalence of cognitive impairment ranges widely, between 15% and 79% (5), a range that has been attributed partly to lack of standardization in the definitions of cognitive impairment in SLE (5).

A limitation of our study, reducing generalizability of the findings, is that it evaluated only individuals with sufficient English ability for completion of the ACR NB. We also excluded patients with indeterminate cognitive status from the analysis. We reasoned that they represented a nonhomogeneous group, and without a clear consensus on the definition of cognitive impairment in patients with SLE (5), we chose to concentrate on the more clearly defined cognitive impairment in SLE. We also found that grouping together the intermediate group with the no cognitive impairment group dropped the performance of the ANAM and its ability to discriminate between patients with cognitive impairment

and no cognitive impairment. Another possible limitation is practice effects, because the ANAM was completed after the ACR NB. Despite measuring the same cognitive functions, the tasks of the ACR NB and the ANAM are not similar; therefore, practice effects are unlikely. On the other hand, order effects are possible, with greater fatigue on the ANAM tasks because they were completed second, which may have decreased the cognitive performance on the ANAM. Our battery is slightly different from the ACR NB, because we have substituted the CVLT (34) by the HVLT-R. The HVLT-R is shorter and an easier test compared to CVLT, which could have rendered our battery less sensitive than the original ACR NB.

In this study, we used a rigorous process to achieve a high-quality study while avoiding the risk of bias and maintaining a favorable applicability of the assessed tool, the ANAM, to meet the requirement of the Quality Assessment of Diagnostic Accuracy Studies (44). This study provides evidence of the usefulness of the ANAM as a clinical tool for screening for cognitive impairment in patients with SLE. We first demonstrated the ANAM's ability to identify cognitive status accurately compared to the ACR NB. Second, we identified the best model along with the most discriminating subtests and scores to be able to identify cognitive impairment. Third, we developed a composite index for the best model and derived a cutoff score to enhance the applicability and interpretation of ANAM results. Thus, the ANAM can be implemented as a clinically relevant cognitive impairment screening test in adult patients with SLE.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Touma had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Tayer-Shifman, Green, Beaton, Ruttan, Wither, Tartaglia, Kakvan, Lombardi, Anderson, Su, Bonilla, Zandy, Choi, Fritzler, Touma.

Acquisition of data. Tayer-Shifman, Green, Beaton, Ruttan, Wither, Tartaglia, Kakvan, Lombardi, Anderson, Su, Bonilla, Zandy, Choi, Fritzler, Touma.

Analysis and interpretation of data. Tayer-Shifman, Green, Beaton, Ruttan, Wither, Tartaglia, Kakvan, Lombardi, Anderson, Su, Bonilla, Zandy, Choi, Fritzler, Touma.

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