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Metrics and definitions used in the assessment of cognitive impairment in systemic lupus erythematosus: A systematic review

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ABSTRACT

Objective: To review: 1) degree of conformity to the American College of Rheumatology neuropsychological battery (ACR-NB) among studies that used a NB, 2) review definitions of cognitive impairment (CI) from studies that used a NB, and 3) characterize measurement tools used to assess CI in systemic lupus erythematosus (SLE).

Methods: The literature search was conducted in Ovid Medline, Embase, and PsycINFO for articles on CI in adult SLE patients. We reviewed studies that used a NB and compared their tests to the ACR-NB to assess the degree of conformity. Definitions of CI from studies that used a NB were reviewed when sufficient information was available. We reviewed and categorized CI measurement tools into four broad categories: NB, screening, incomplete/mixed batteries, and computerized batteries.

Results: Of 8727 references, 118 were selected for detailed review and 97 were included in the final analysis. Of 43 studies that used a NB, none of the studies used the ACR-NB exactly as published. Many studies supplemented with other tests. Overall, there was inconsistent use of ACR-NB tests. Definitions for CI varied, with cut-offs ranging from 1 to 3 standard deviations below normative values on domains/tests varying in type and number. The most frequently used measurement tool for assessing CI in SLE was a NB. Use of screening tests and computerized batteries have also increased over the last decade.

Conclusion: The assessment and definition of CI in SLE remains heterogeneous. A consensus meeting to address existing inconsistencies should be considered to harmonize the field of CI in SLE.

Introduction

Cognitive impairment (CI) is a common manifestation in patients with Systemic Lupus Erythematosus (SLE). Our previous systematic review assessing the prevalence of objective CI reported a range of 3–81% from studies that described the use of a CI measurement tool [1], and a pooled prevalence of 38% (95% confidence interval: 33–43%) from studies that used a comprehensive neuropsychological battery (NB) [1], which is recommended for detecting CI.

By CI, we are referring to a decrement in a person's cognitive functioning relative to their pre-morbid status; this is optimally measured by objective, performance-based metrics that take estimated level of pre-morbid IQ and relevant socio-cultural and demographic factors into consideration. The American College of Rheumatology (ACR) Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature

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operationally defined cognitive dysfunction as "significant deficits in any or all of the following main cognitive functions: complex attention, executive skills (e.g., planning, organizing, sequencing), memory (e.g., learning, recall), visual–spatial processing, language (e.g., verbal fluency), and psychomotor speed" [2].

Assessment of CI in patients with SLE can include screening tests, a NB, or combinations of the two. While screening tests and NBs have been traditionally administered by pen and paper, computerized versions are also available. A screening test is a brief (typically 5–10 min) assessment tool that assesses one or more cognitive domains and can be helpful in determining whether administration of a NB is warranted; popular, widely used screening tests include the Montreal Cognitive Assessment (MoCA) [3] and Mini-Mental State Examination (MMSE) [4]. A NB is a more comprehensive set of neuropsychological tests plus associated normative data that can take many hours to administer, score and interpret. It may be used for diagnostic purposes, to determine the nature and severity of cognitive deficits and to help guide treatment and rehabilitation. A NB may vary according to the needs of a specific context or they may be "fixed", with a combination of tests that are always employed together, usually across a given population [5,6].

In 1999, the ACR committee proposed a brief, 1-hour fixed NB to provide a more in depth assessment of cognitive functioning than screening measures (which are insensitive to milder cognitive deficits) while minimizing time and financial burden [2]. The ACR-NB consists of the following neuropsychological tests: the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol Substitution Test [7], Trail Making Test (Parts A and B) [8], Stroop Color and Word Test [9], California Verbal Learning Test (CVLT) learning trials and short delay free recall [10], Rey-Osterrieth Complex Figure Test (RCFT) delayed and immediate recall [11], Wechsler Adult Intelligence Scale-III (WAIS-III) Letter Number Sequencing [12], Controlled Oral Word Association Test (COWAT) [13], Animal Naming Test [13], and the Finger Tapping Test [8] (Table 1).

The ACR-NB measures a variety of cognitive domains shown to be affected in SLE, including attention and speed of processing, language processing, learning and memory (visuospatial and verbal), executive functioning, and manual motor speed [2]. The ACR committee provided an operational definition of CI in SLE for the ACR-NB, which was $\geq$2 standard deviations (SD) below the estimated population mean in the domains of attention, memory, and psychomotor speed [14]. In 2004, Kozora et al., provided evidence on the validity of the ACR-NB for idendifying CI in SLE against a longer 4 hour NB, with an overall agreement of 90% (sensitivity 86%, specificity 91%, κ = 0.75) [15]. In addition, adequate reliability of the ACR-NB was demonstrated with intraclass correlation coefficients tests ranging from 0.40 to 0.90 [15].

Table 1
ACR-NB domains and tests.

NB Domains	NB Tests
Manual Motor Speed	Finger Tapping Test (dominant and non-dominant hand)
Attention and Processing Speed	Stroop Colour and Word Test (interference score) Trails A and Trails B
Language processing	
Letter fluency	COWAT
Category fluency	ANIMALS
Learning and Memory	
Visuospatial	RCFT (delayed recall, immediate recall)
Verbal	CVLT (learning trials 1–5, short delay free recall)
Auditory	WAIS-III Letter-Number Sequencing
Executive Function	Stroop Colour and Word Test (interference score) WAIS-R Digit Symbol Substitution Test Trails B

Abbreviations: Trails A: Trail Making Test Part A; Trails B: Trail Making Test Part B; WAIS: Wechsler Adult Intelligence Scale [versions R (revised) and III (3rd edition)]; COWAT: Controlled Oral Word Association Test (phonemic fluency); ANIMALS: Animal Naming Test (verbal fluency); RCFT: Rey Complex Figure Test; CVLT: California Verbal Learning Test.

The ACR-NB and its corresponding CI definition were proposed for the purpose of standardizing the assessment of CI in SLE [2]. However, use of the ACR-NB has been adapted in many studies, with deletions or additions of neuropsychological tests to the original battery [16–19]. Similarly, definitions of CI have been variable, e.g., employing different thresholds for impairment.

Due to the inconsistencies found among the measurement tools and definitions of CI in SLE, this systematic review aimed to summarize how CI is being assessed in patients with SLE with the long-term goal of creating recommendations to update the proposed ACR-NB and its CI definitions in SLE. Therefore, the objectives of the review were to: (1) assess the degree of conformity to the ACR-NB among studies that used a NB, (2) review definitions of CI from studies that used a NB, and (3) characterize measurement tools used to assess CI in SLE.

Materials and methods

Search strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement [20]. We used the same broad search strategy (Appendix A) as our previous systematic review, which focused on studying the prevalence of CI in SLE in studies that used objective neuropsychological tests [1]. The original search strategy was a broad search covering CI in SLE, which was conducted by an expert medical librarian [1] and included three databases: Ovid Medline (1946 to August 15, 2016), Embase (1974 to August 15, 2016), and PsycINFO (1806 to August 15, 2016). For this systematic review, we updated the search using identical search strategies in these databases on July 3, 2019, conducted by a second expert librarian (MA). Update searches were limited to material added to databases between August 16, 2016 and July 3, 2019. Previous and new search results were then combined. Due to the similar inclusion and exclusion criteria and same search strategy between our previous systematic review and the present review, we streamlined the screening process by only screening included studies from our previous systematic review [1] (76 studies of 5536 references), and all references from the new search (673 references) to total 749 records. Complete strategy is described in Appendix A. For Medline we used the MeSH terms cognitive dysfunction, cognitive impairment, systemic lupus erythematosus, neurocognitive, and neuropsychological and relevant keywords. For Embase, we used Entree terms lupus erythematosus, cognition disorders, cognition, cognitive defect, psychological test, mental function assessment, neurocognitive, and neuropsychological as well as relevant keywords. For PsycINFO we used lupus, SLE, cognitive impairment, psychological assessment, measurement, and relevant keywords.

Inclusion criteria

Inclusion criteria were as follows: evaluation of CI; an abstract published in the English language; human studies of adult patients with SLE older than 16 years of age; CI measured with performance based outcomes that are either (i) a single neuropsychological test (e.g., the Rey Auditory Verbal Learning Test [RAVLT]), (ii) a screening test (e.g., Montreal Cognitive Assessment [MoCA]), (iii) any kind of NB (e.g., Halstead-Reitan Battery; ACR-NB; Automated Neuropsychological Assessment Metrics [ANAM]; or one created for the purpose of the study).

Exclusion criteria

Studies were excluded if any of the following were met: 1) case reports, 2) cohorts with <20 patients, 3) non-primary studies (e.g., reviews), 4) non-peer reviewed studies (i.e., dissertations).

Study selection and assessment

In the first step of the review, establishment of agreement between two reviewers (KY and VLK) was undertaken. This involved scanning the title and abstracts of articles. The two reviewers scanned 100 articles at a time and discussed any discrepancies that arose. Discrepancies were resolved by consensus between the two reviewers. Whenever there was disagreement between the two reviewers, it was resolved by consensus and involvement of a third reviewer (ZT). After 200 articles and less than 5 discrepancies, the two reviewers continued to screen the remaining 549 articles. In the next step of the review process, selected articles were then screened at the full text level by the same reviewers (KY and VLK) who assessed them for eligibility independently based on the inclusion and exclusion criteria. After reviewing the updated search, the two reviewers (KY and VLK) proceeded to review the 76 articles at the full text level from the previous search.

Data extraction

A standardized data collection form was developed and included relevant variables to extract data from the selected articles. Based on our study objectives, the form included the following variables: [1] study information (title, author, year of publication), and [2] information related to CI (CI definition, CI prevalence, category of measurement [NB, screening, incomplete/mixed, and computerized], and neuropsychological tests in the battery [if a NB was used]). Neuropsychological tests were recorded as reported by studies. Subtests of neuropsychological tests (e.g., immediate recall, delayed recall, etc. of RCFT) were also recorded since studies may use different subtest scores of a test for assessing CI. However, for the ease of comparing tests in NBs, subtests of tests were just counted as a single test (e.g., if a study reported RCFT immediate recall and delayed recall it was counted as RCFT). We categorized the assessment of CI in patients with SLE into four approaches: NB, screening tests, incomplete/mixed, and computerized batteries. The ***NB category*** constituted a well described NB, where studies used the terms "battery" or a variant, with the use of ≥ 4 neuropsychological tests and >2 cognitive domains. The ***screening category*** consisted of studies that used one or more screening tools (e.g., MoCA, MMSE, etc.). The ***incomplete/mixed category*** consisted of studies using either a combination of screening tools and neuropsychological tests that did not meet our definition for the NB category, or a combination of a computerized battery with neuropsychological tests. The ***computerized category*** consisted of studies that used only a computerized battery (e.g., CANTAB, ANAM).

Two reviewers (KY and VLK) extracted data from the included articles independently. Any discrepancies were resolved by the senior author (ZT). Based on the precedent of solely reviewing the metrics used in the assessment of CI and definitions of CI, a quality assessment was not carried out.

Results

There were 673 references identified from this search. From our previous systematic review, 76 references were included in the final review from 8054 references. Those 76 references were added to the 673 references from the current search (totalling 749 references), 118 were selected for detailed review and 97 were included in this systematic review (Fig. 1).

***Objective* 1: Assess the degree of conformity to the American College of Rheumatology Neuropsychological Battery (ACR-NB)**

We identified 62 studies that used a NB following the criteria of ≥4 tests and >2 cognitive domains. Fifty-eight NBs from 57 of those

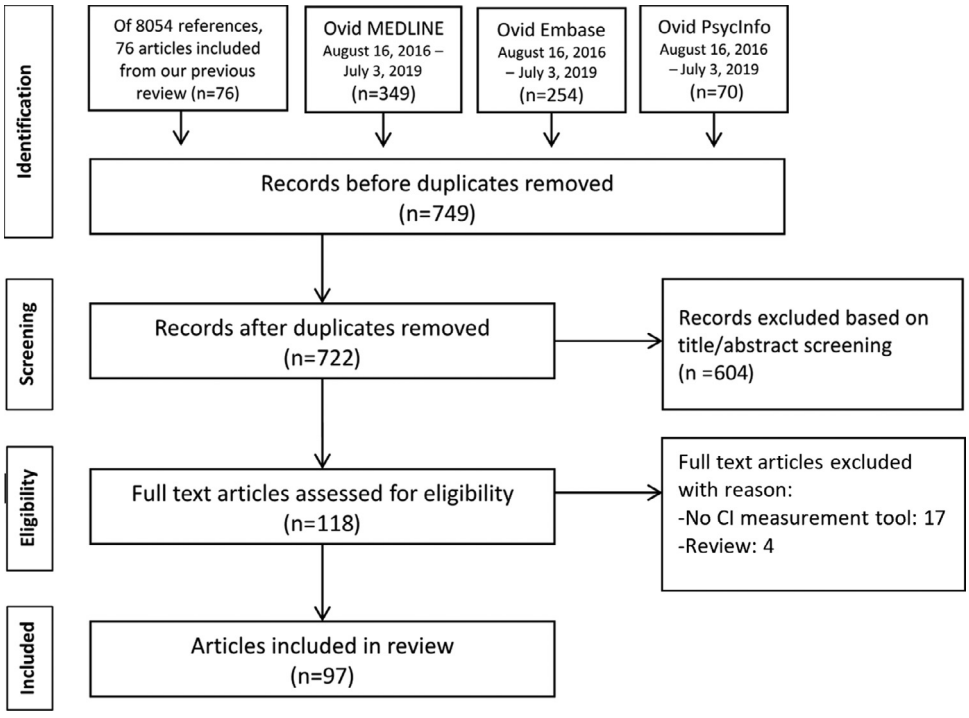

Fig. 1. Flow chart illustrating study selection of updated search.
Abbreviations: CI: cognitive impairment.

studies listed the neuropsychological tests included in their NB (one study was the 2004 validation study with two NBs [15]), and 43 of those studies occurred after the introduction of the ACR-NB in 1999. The proportion of ACR-NB tests and non-ACR-NB tests in each NB following the introduction of the ACR-NB in 1999 is displayed in Fig. 2.

After the introduction of the ACR-NB in 1999, 0 of the 43 studies used the ACR-NB exactly as published. Three out of 43 studies used all of the ACR-NB tests except for Trails A (the validation study conducted by Kozora et al. [15], and two of their other studies [21,22]). Kozora et al., had 6 other studies [17,18,22–25] that used the ACR-NB, but with the addition of four tests: the Paced Auditory Serial Addition Test (PASAT) [26], Digit Vigilance Test [27], WAIS-III Block Design [12] and the Category Test [8]. All other studies used a varying number of tests from the ACR-NB and often included other tests. The total number of neuropsychological tests used in each battery ranged from 5 to 28, with an average of 11 tests. The ACR-NB consists of 10 tests, and the number of ACR-NB tests used in the studies ranged from 0 to 9, with an average of 5 tests. The number of non-ACR-NB neuropsychological tests ranged from 0 to 21, with an average of 6 tests. One study did not use any tests from the ACR-NB [28].

A summary of all neuropsychological tests used from the 58 NBs (from 1986 to 2018) as reported by the study authors and their frequency can be seen in Table 2; a summary of neuropsychological tests and subtests can be seen in Appendix B, Table B.1. Overall, the pattern of ACR-NB tests used in NBs fluctuated overtime with no increased uptake of ACR-NB tests following its introduction and validation.

***Objective* 2: Review definitions of CI from studies that used a NB**

Of the 97 studies included in this review, 62 used a NB, 58 of which reported a definition of CI which is summarized in Table 3.

In defining CI, studies included thresholds ranging from −1 SD to −3 SD compared to normative data from each neuropsychological test or control group (usually age or age and education matched). The number of domains or tests used to classify CI was variable across studies. Five studies used a threshold of −1 SD, 6 studies used −1.5 SD, 16 studies used −2 SD, 5 studies (all studies by Hanly et al. [29–33]) used a range from −1 to −3 SD depending on the test, 10 studies used a T-score < 40 (which is the same as < 1 SD); 9 of those studies were by Kozora et al., and 16 studies used a definition that did not correspond to any of the aforementioned SD thresholds ("Other" in Table 3). Along with the thresholds, the number of domains required to determine CI varied. Some studies employed a minimum number of domains at a given level of impairment (e.g., −2 SD in at least 2 cognitive domains). In addition to a dichotomous classification of CI vs. no-impairment, some studies provided more fine-grained categories of impairment, using a combination of test performance and number of domains (e.g., mild CI if −2 SD in <3 domains, moderate if in 3–4 domains, severe if at least 5 domains). Definitions of CI varied widely across studies.

***Objective* 3: Characterize the measurement tools used to assess cognitive impairment (CI)**

Cognitive impairment measurement tools used in SLE from 1986 to 2019 were reviewed. Of the 97 included studies, four studies included two measurement approaches, therefore the measurement tool categories total to 101, even though there are 97 studies (Fig. 3).

Including the four validation studies, there were 62 NBs [15,17–19,21–25,28–30,32–80], 15 screening tools [81–95], 9 incomplete/mixed batteries [96–104] (Appendix B, Table B.2), and 15 computerized batteries [61,82,86,105–116] reported (9 ANAM, 4 Cambridge Neuropsychological Test Automated Battery [CANTAB], 2 CNS Vital Signs [CNS-VS]) to total 97 measurement tools. Of note,

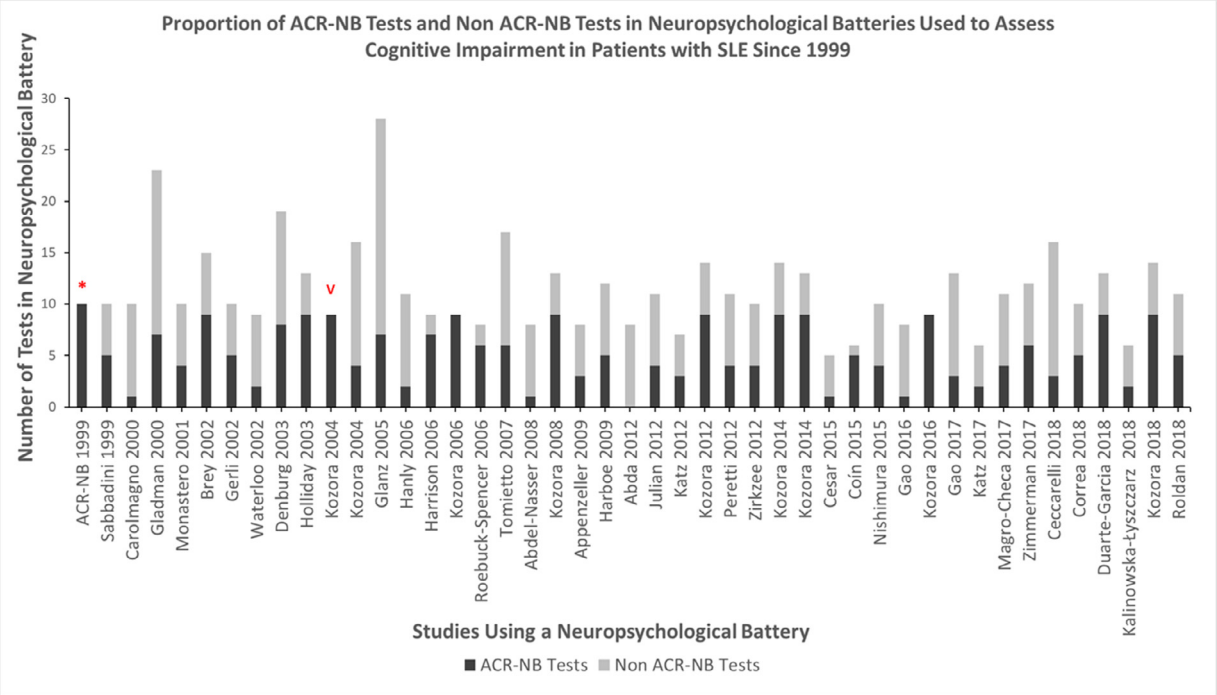

Fig. 2. Proportion of neuropsychological tests in different NBs since the introduction of the ACR-NB in 1999.

* = introduction of ACR-NB in 1999; *V* = validation of ACR-NB in 2004.

Forty-four NBs were included in this graph from 43 studies following the introduction of the ACR-NB in 1999. One study (Kozora 2004) compared the ACR-NB to a longer NB. This figure highlights the proportion of ACR-NB tests used in each battery from 1999 to 2018. The ACR-NB consists of the following neuropsychological tests: the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol Substitution Test [7], Trail Making Test Parts A and B (Trails A, B) [8], Stroop Color and Word Test [9], California Verbal Learning Test (CVLT) learning trials and short delay free recall [10], Rey-Osterrieth Complex Figure Test (RCFT) delayed and immediate recall [11], Wechsler Adult Intelligence Scale-III (WAIS-III) Letter Number Sequencing [12], Controlled Oral Word Association Test (COWAT) [13], Animal Naming Test [13], and the Finger Tapping Test [8,15].

Abbreviations: ACR-NB: American College of Rheumatology Neuropsychological Battery; NB: neuropsychological battery.

Table 2
Frequency of Neuropsychological Tests Used Among all 58 Neuropsychological Batteries from 1986 to 2018.

Neuropsychological Test	Frequency (# of NBs)
ACR-NB Tests	
Trails B	39
WAIS-R Digit Symbol	37
COWAT	32
Trails A	30
Stroop	30
CVLT	26
RCFT	26
ANIMALS	25
FTT	19
WAIS-III Letter Number Sequencing	13
Non ACR-NB Tests	
WAIS Block Design	27
WAIS Digit span backward	25
WAIS Digit span forward	24
WAIS Similarities	21
RAVLT	15
WAIS Picture Completion	13
WAIS Information	12
Category Test, WAIS-R Comprehension, WMS	10
DVT	9
Grooved pegboard, PASAT, Verbal Fluency Test, WCST	8
Corsi Block Test, Raven's matrices, WMS logical memory	7
MMSE, WMS Paired Associates, WMS visual reproduction	6
Design Fluency Test, WAIS	5
NART, WMS-III spatial span backward, WMS-III spatial span forward, WMS-R mental control	4
BVRT, Category Naming Test, Digit Cancellation Test, Rey's 15-word memory Test, WAIS Arithmetic, WAIS-R Object Assembly, WAIS-R Vocabulary, Wechsler Test of Adult Reading (FSIQ), WMS-R Digit Span Backward, WMS-R Digit Span Forward	3
Bells Cancellation Test—Omissions (time 1), Brazilian Brief Neuropsychological Assessment Battery constructive praxis task, BVMT-R, Complex Figure Test, Color Trails Test, Complex Material from Boston Diagnostic Aphasia Exam, Consonant Trigrams, DKEFS Card Sorting (*total correct*), DKEFS Colour Word, DKEFS Trail Making Test (*shifting condition*), DKEFS Design Fluency Test, Handwritten copies of perspective/geometric figures, Hayling Test, Figure Memory Test, Reading Peabody, Ruff Figural Fluency Test, Seashore Rhythm Test, SDMT, Story Memory Test, Tactual Performance Test, Token Test, WAIS-R Picture Arrangement, WMS Delayed Recall Drawings, WMS Delayed Recall Stories, WRAT-3	2
15-word list recall test, Analogies Test, Attention to Detail Test, Attentive Matrices, Boston Naming Test, Copy with Landmark Test, Copying drawings without elements, copying drawings with elements, Denomination of Aachener Aphasie Test, DKEFS, Facial Recognition Test, Fused Rhymed Words Test, Grip Strength, HVLT-R, Immediate Visual Memory Test, Joint Line Orientation, Kimura recurring figures test, Kramer Two Group Card Test, NAART, Phrase construction, Rey's Word-List learning immediate, Ruff 2&7 selective attention test, Simple copy, Spontaneous word list generation test, SBST. Symbol Cancellation Test, Time and Weight Estimation Test (STEP), Verbal Recall Task of Grober and Buschke, Vocabulary Scale, WAIS Block Span, WAIS Symbol Search, WAIS-III Digit Symbol Incidental Learning, WMS-III Digit Symbol Incidental Learning, WMS-III Letter Number Sequencing, WMS-R Associate Learning, Woodcock-Munoz Test	1

Due to variable reporting of neuropsychological tests and editions for the Wechsler Memory Scale (WMS) and Wechsler Adult Intelligence Scale (WAIS), all editions were grouped together if more than one version was used among studies or they did not report a version. Versions of the WAIS include WAIS, WAIS-III, WAIS-IV, WAIS-R. Versions of the WMS include WMS, WMS-III, WMS-R.
Abbreviations: WAIS: Wechsler Adult Intelligence Scale; COWAT: Controlled Oral Word Association Test (phonemic fluency); RCFT: Rey Complex Figure Test; FTT: Finger Tapping Test; CVLT: California Verbal Learning Test; RAVLT: Rey Auditory Verbal Learning Test; PASAT: Paced Auditory Serial Addition Test; WMS: Wechsler Memory Scale; DVT: Digit Vigilance Test; MMSE: Mini-Mental State Examination; WCST: Wilson Card Sorting Test; DKEFS: Delis-Kaplan Executive Function System; BVRT: Benton Visual Retention Test; FSIQ: full scale intelligence quotient, SDMT: Symbol Digit Modalities Test; WRAT-3: Wide Range Achievement Test 3; BVMT: Brief Visuospatial Memory Test; AAT: Aachen Aphasia Test; HVLT-R: Hopkins Verbal Learning Test Revised; NAART: North American Adult Reading Test; NART: National Adult Reading Test; SBST: Stanford-Binet Subset Testing; STEP: Time and Weight Estimation Test; SDMT: Symbol Digit Modalities Test.

studies that used the CANTAB [110,111,114] and CNS-VS [115,116] were from the same center. The trend and proportion of CI neuropsychiatric measurement tools used in SLE is illustrated in Fig. 3. The most frequently used measurement approach was the NB; however, the use of screening tools (e.g., MoCA) and computerized batteries (e.g., ANAM) has increased over time. Between 1997–2007, two studies used a screening tool, but between 2008 and 2019, the use of screening tools increased to 13. Similarly, between 1997 and 2007, a computerized battery was used in two studies, which increased to 13 between 2008 and 2019. Furthermore, the number of studies has approximately doubled each decade.

Discussion

Cognitive impairment is common in patients with SLE, yet the metrics and definitions in the literature do not always follow the recommendations of the ACR committee. Cognitive functioning includes a complex set of constructs associated with vast literatures on its assessment and definitions. Efforts by the ACR committee were made to unify CI in SLE, however the literature has shown variable adherence to committee recommendations [2,14]. In this review, we aimed to examine adherence or lack thereof to the ACR-NB, summarize the definitions of CI based on different NBs, and characterize the measurement approaches that have been used to assess CI in patients with SLE.

It has been almost two decades since the introduction of the ACR-NB in 1999 and its validation in 2004 yet use of the ACR-NB in its original form is rare, with studies including a highly variable number of other neuropsychological tests along with the traditional ACR-NB tests. Surprisingly, there were no studies that used the ACR-NB exactly as published following its introduction in 1999. There was also no clear trend demonstrating increased uptake of the ACR-NB tests following its introduction and validation. Studies often acknowledged the ACR-NB but used other neuropsychological tests [15,17–19,21,23–25,51,58,61,65,69,73,74,80,117]. Several tests that are not part of the ACR-NB were commonly used, including WAIS-R tests such as Block Design, Digit Span forward and backwards, and Similarities. However, there are many possible reasons for deviations

Table 3
Cognitive impairment definitions from 58 NBs.

	Studies	# Domains/tests involved/scoring
−1SD	Katz, 2017 [65]	At least one-third of tests
	Julian, 2012 [121]	Impairment on at least 5 of 16 indices. Analogous impairment index: impairment on any of 3 domains
	Tomietto, 2007 [77]	Impairment: at least 1 function (1 domain impaired). Normal (0 impaired), mild (3 functions, 2 domains), or moderate/severe (3 functions, 2 domains)
	Roebuck-Spencer, 2006 [73]	Z-score < −1.0 and −1.99 on 2 domains or average Z-score < −2.0 on 1 cognitive domain
	Carlomagno, 2000 [41]	−1 Z-score based on Mental Deterioration Battery
−1.5 SD	Correa, 2018 [45]	Based on composite score of specific subtest scores, or in ≥2 test variables
	Gao, 2016 [51]	On any of the tests
	Coin, 2015 [44]	Based on ACR guidelines
	Katz, 2012 [64]	Impairment on at least one-third of indices in each battery (total, memory, or executive function)
	Harrison, 2006 [58]	Used a mean Z-score derived from all tests
	Sailer, 1996 [76]	At least 2 tests
−2 SD	Duarte-Garcia, 2018 [49]	At least 2 cognitive domains
	Gao, 2017 [50]	Memory deficits: ≥ 1 tests in memory domain < −2 SD, CI if ≥ 1 cognitive domain < −2 SD
	Zimmermann, 2017 [80]	At least 1/8 dimensions. Specific scoring for reasoning/problem-solving
	Lapa, 2017 [68]	In any of 8 domains. Mild CI: deficits <3 dimensions, moderate: 3–4 dimensions, severe: ≥5 dimensions
	Cesar, 2015 [43]	Based on ACR guidelines
	Nishimura, 2015 [71]	At least 2 of the 7 neurocognitive domains
	Appenzeller, 2009, 2007, 2005 [36–38]; Ainiala, 2004 [35]	In any of 8 domains. Mild CI: deficits in <3 dimensions, moderate: 3–4 dimensions, severe: ≥5 dimensions
	Harboe, 2009 [57]	Mild CI: deficits <3 domains, moderate: 3–4 domains, severe: ≥5 domains
	Gladman, 2000 [53]	Any summary score below threshold; CI: ≥3 or more summary scores impaired (based on Carbotte, 1986)
	Glanz, 1997 [55]	CI: summary score ≥2 units below premorbid/best estimate were impaired. Test profile designated impaired if ≥3 summary scores met this criterion.
	Hay, 1994, 1992 [59,60]	Based on test norms. Specific scoring for WAIS score.
	Carbotte, 1986 [40]	Mean Z-score on each summary score was compared to estimate premorbid level of functioning; any summary score ≥2SD below premorbid level was significant CI
Range from −1 – −3SD	Hanly, 2006, 1997, 1994, 1993, 1992 [29-33]	Used norm referenced criteria and individualized assessment criteria. Cut-offs:1–3SD depending on the test. CI: impairment in at least 3/7 areas of function
T score <40	Kozora, 2018, 2016, 2014, 2014, 2012, 2008, 2006, 2004, 1996 [15,17,18,21–25,66]	T-scores < 40 were considered impaired. ACR-CI index ranges from 0 to 12; higher number representing greater CI
	Peretti, 2012 [72]	Global CI: 4 T-scores < 40 in tests. CI: T-score <40 in tests. Significant global CI: at least 2 T-scores <40 in 4 domains. Significant CI: T-score <40, in specific domains compared to normal control women.
Other	Ceccarelli, 2018 [42]	Z-score for each domain converted into Domain Cognitive Dysfunction score (DCDs). Higher values meant more impairment. Sum of DCDs across 5 domains = Global Cognitive Dysfunction score and converted to Global Cognitive Dysfunction category
	Roldan, 2018 [74]	Total Z-score computed (combined sum of all measures). Individual and global Z-scores computed using controls as reference.
	Kalinowska-Lyszczarz, 2018 [63]	Test scores indicated impairment if worse than median for the given test. Composite score: 0 (all test results above median) to 6 (all test results below median)
	Magro-Checa, 2017 [69]; Zirkzee, 2012 [19]	Norms based on Spreen & Strauss, 1998
	Glanz, 2005 [54]	10th and 25th percentiles were cut-off points for the index. Scores below the cut-off points were impaired.
	Denburg, 2003, 1987 [46,48]	17 different summary scores were compared to the premorbid estimate level. Any summary score >2 units below premorbid level reflected significant impairment
	Holliday, 2003 [61]	T-scores using published age and education corrected norms. CI ratings: 0 no CI, 1 mild, 2 moderate, 3 severe for specific domains as well as a global impairment
	Brey, 2002 [39]	Used age and education corrected norms. CI ratings: 0-no CI, 1-mild, 2-moderate, 3-severe, specific domains
	Gerli, 2002 [52]	Based on norms reported by each test in battery
	Waterloo, 2002 [78]	T-scores calculated using published means and SDs for normative samples
	Monastero, 2001 [70]	Scored based on published procedures. CI: score < 5th percentile of normal population in ≥2 tests
	Sabbadini, 1999 [75]	Based on norms for each test
	Denburg, 1997 [47]	CI: ≥3 individual cognitive summary scores < *Z*-score of −1.64 (5th percentile)
	Wekking, 1991 [79]	Scores on tests expressed in 25 subscores (Lezak, 1995)

Abbreviations: WAIS = Wechsler Adult Intelligence Scale.

from the ACR-NB, such as ease at which a preferred test measuring the same cognitive domain can be substituted, availability of tests in a given clinic or lab, familiarity with a test, availability of alternate forms, psychometric properties, limited funding (some tests are licensed and must be purchased) etc. Furthermore, additional tests can be added to a NB for more comprehensive cognitive evaluation. The majority of studies assessed in this review included a subset of the recommended ACR-NB tests and supplemented with additional measures.

Definitions of CI used in the SLE literature typically consist of a normative threshold and a minimum number of domains or tests reaching that threshold [51,66,73], however, current definitions vary widely in terms of the threshold and number of domains or tests involved. As a result, this heterogeneity makes it challenging to set criteria for classifying patients with SLE as CI, to compare results across studies, and to share clinical experiences. Different cut-offs used in CI definitions can also cause variability in sensitivity, specificity and predictive values for CI in patients with SLE as was seen in a study investigating the validity of the HVLT-R for use with patients with dementia. In this study, sensitivity and specificity of the HVLT-R were 95% and 83% respectively when using a cut-off of 1 SD to classify patients with impairment, with a positive predictive value (PPV) of 84% and negative predictive value (NPV) of 94% [118]. A stricter cut-off of 2 SD resulted in a sensitivity of 67%, specificity of 98%, PPV of 97% and NPV of 76%. Thus, the current heterogeneity of CI definitions needs to be addressed, as it makes the assessment and classification

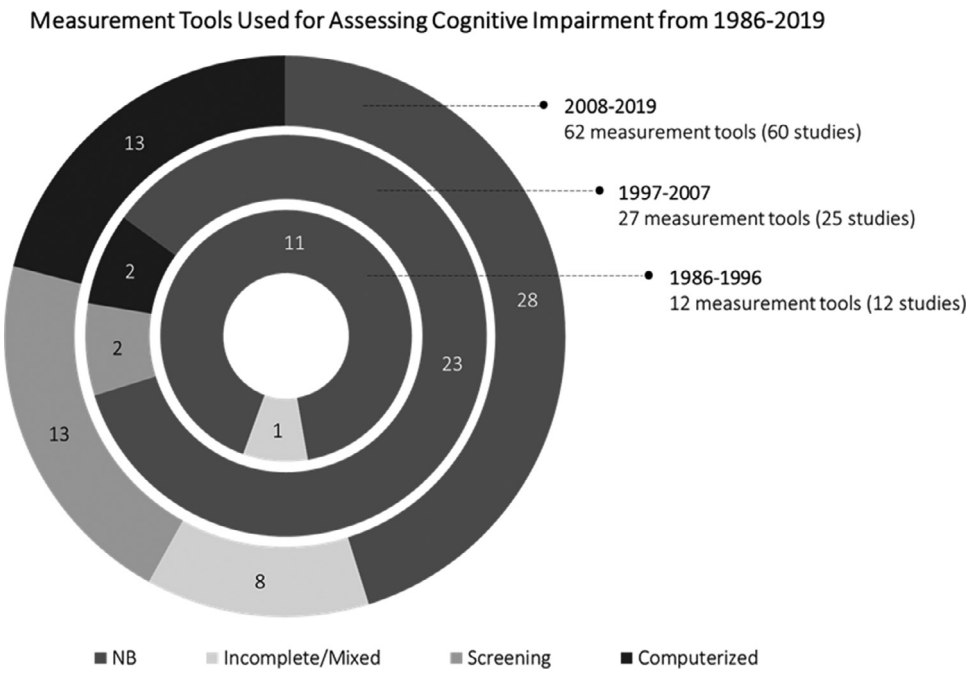

Fig. 3. Measurement tools used for assessing cognitive impairment from 1986 to 2019.

Between 1986–1996, there were 11 NBs and 1 incomplete/mixed battery used among 12 studies. Between 1997–2007, there were 23 NBs, 2 computerized batteries and 2 screening tools used among 24 studies. Between 2008–2019, there were 28 NBs, 13 screening tools, 13 computerized batteries and 8 incomplete/mixed batteries used among 60 studies. Over the years, there has been an increase in the use of screening tools and computerized batteries.

of CI in patients with SLE elusive and unclear. However, it is important to note that the definition of CI provided by the ACR was for the purpose of clinical trials, therapeutic or rehabilitative studies [2,14]. The types of studies included in this review may differ, which may explain the heterogeneity surrounding this definition.

To review the CI measurement tools used in SLE, we used four categories: NB, screening, incomplete/mixed, and computerized. Of these, a NB continues to be used most frequently in CI studies in SLE patients. However, computerized batteries and screening tools have gained popularity over the past 10 years. The ANAM is a popular computerized self-administered battery that is quick to administer (30–40 min), created by the U.S. military to rapidly and precisely assess cognitive processing [119]. The ANAM has been gaining popularity over the years for use in several clinical populations including SLE, and several studies comparing the ANAM against the NB have found it to have validity evidence in screening for CI in SLE [16,61,73]. The CANTAB and CNS-VS are less commonly used in SLE but were designed to be clinical CI screening tools. Tools such as the MoCA and MMSE were commonly used as well (for screening purposes); however, validation studies for both the MoCA and MMSE in SLE have shown mixed results and require further research to confirm its validity in SLE [3,91,120]. Nonetheless, the increased use of both screening and computerized tools may be attributed to aims in reducing assessment time, financial limitations, and/or advancements in technology.

This review is not without limitations. The most challenging aspect was setting criteria to delineate between measurement tools (NB and non-NB) in a field where criteria itself was the topic of interest. For example, when comparing the neuropsychological tests in different NBs to the ACR-NB (objective 2), we decided to define NBs as $\geq$4 tests and $>$2 cognitive domains. We felt that this definition would encompass a more representative sample of NBs to compare to the ACR-NB. As a result, studies that may have reported the use of a NB but did not meet our prescribed definition for a NB were not included in this comparison. However, including such studies would have yielded even more heterogeneity. It was difficult to report on the tests within NBs because there was so much variability. For example, some studies reported the use of the CVLT as a whole, while others reported components of the CVLT (e.g., CVLT recognition only). We recorded tests and subtests as listed by the authors because the learning 1–5 trials and short delay free recall scores of the CVLT and the immediate and delayed recall scores of the RCFT of the ACR-NB were used in the 2004 validation study [15]. However, due to this variability, grouping was difficult and as a result, studies that mentioned components from a single test were counted as the single test (e.g., CVLT recognition would just be counted as CVLT). This could have affected our evaluation of the proportion of ACR-NB tests used in each study, as many studies stated they used the ACR-NB, but their exact list of tests (or subtests) were not identical to the ACR-NB. We came across a similar roadblock with respect to Trails A and B. Usually when completing the Trail Making Test, both Trails A and B are completed. However, some studies stated the use of both Trails A and B, while others reported only one. Thus, we could not assume that the mention of one of the tests also meant the other was completed. This was reflected in our results, as Trails A was reported 30 times and Trails B was reported 39 times (Table 2).

Due to the wide variety of cognitive measurement tools and variability in NBs, it is not surprising that the assessment of CI and estimates of CI in SLE are heterogeneous. Although the ACR committee created the ACR-NB and corresponding definition of CI for SLE specifically, it has only been used precisely in three studies. Furthermore, studies that claimed to use the ACR-NB or a battery akin to it, often did not adhere to the prescribed definition [15,17–19,21,23–25,51,58,61,65,69,73,74,80,117]. This non-conformity makes it apparent that both the definition of CI and the ACR-NB as a measurement tool should be revisited. As a first step, a survey directed to researchers in the field querying on the rationale for deviating from the ACR-NB would be helpful. Once responses are collated, a consensus meeting of experts in the field of cognition and SLE could be convened to create an updated and agreed upon battery of tests. Finally, a task force can be assembled to meet routinely and continually update recommendations. Responses would help in achieving a

more harmonized approach to cognitive assessment and assess researchers in understanding barriers or limitations. As cognition research in SLE continues to grow, it is imperative to develop a comprehensive and standardized methodology for defining and assessing CI that is both clinically feasible and standardized within the field.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2021.05.018.

Appendix A. Complete Search Strategy

Database(s): **Embase Classic+Embase** 1947 to 2019 July 02
Search Strategy:

#	Searches	Results
1	exp Lupus/	3695
2	lupus*.mp,kw.	142,062
3	sle.mp.	53,952
4	1 or 2 or 3	147,334
5	exp cognition/	2,205,538
6	exp cognitive defect/	462,541
7	exp psychologic test/	179,267
8	exp mental function assessment/	90,099
9	cognit*.mp,kw.	631,573
10	neurocognit*.mp,kw.	30,224
11	neuropsych*.mp,kw.	162,026
12	neuro psych*.mp,kw.	2821
13	or/5–12	2,803,345
14	4 and 13	9494
15	limit 14 to english language	8943
16	limit 15 to (book or book series or chapter or conference abstract or conference paper or conference proceeding or "conference review" or letter or note)	4062
17	15 not 16	4881
18	(201,608* or 2017* or 2018* or 2019*).dd.	2,490,699
19	17 and 18	254

Database(s): **Ovid MEDLINE(R) ALL** 1946 to July 02, 2019
Search Strategy:

#	Searches	Results
1	Lupus Erythematosus, Systemic/	52,636
2	Glomerulonephritis/	25,598
3	limit 2 to yr="1966 - 1986″	11,794
4	exp Lupus Nephritis/	6058
5	exp Lupus Vasculitis, Central Nervous System/	770
6	lupus*.mp,kw.	85,535
7	sle.mp.	32,096
8	1 or 3 or 4 or 5 or 6 or 7	98,508
9	exp Cognition Disorders/	86,950
10	exp Cognition/	149,750
11	exp Psychological Tests/	302,556
12	cognit*.mp,kw.	411,221
13	neurocognit*.mp,kw.	27,868
14	neuro cognit*.mp,kw.	493
15	neuro psych*.mp,kw.	1597
16	neuropsych*.mp,kw.	144,403
17	or/9–16	733,477
18	8 and 17	2443
19	limit 18 to english language	2224
20	(201,608* or 2017* or 2018* or 2019*).ed.	2,560,407
21	19 and 20	349

Database(s): **PsycINFO** 1806 to June Week 4 2019
Search Strategy:

#	Searches	Results
1	exp Lupus/	775
2	lupus*.mp,id.	1492
3	sle.mp,id.	824
4	1 or 2 or 3	1742
5	exp cognitive impairment/	34,223
6	exp Cognitive Processes/	677,376
7	exp Cognition/	35,608

(*continued*)

(*Continued*)

#	Searches	Results
8	exp cognitive ability/	117,663
9	exp Psychological Assessment/	103,947
10	exp Measurement/	407,737
11	exp Cognition/	35,608
12	cognit*.mp,id.	567,149
13	neurocognit*.mp,id.	18,936
14	neuro psych*.mp,id.	971
15	neuropsych*.mp,id.	133,020
16	or/5–15	1,367,759
17	4 and 16	606
18	limit 17 to english language	572
19	(201,608* or 2017* or 2018* or 2019*).up.	464,081
20	18 and 19	70

Appendix B. Additional tables

Tables B.1 and B2.

Table B.1
Frequency of Subtests of Neuropsychological Tests Used Among Neuropsychological Batteries.

Neuropsychological Test	Frequency (# of NBs)
Stroop	**30**
Color-Word Interference (30), Word Reading (10), Color Naming (7)*	
CVLT	**26**
CVLT learning trials 1–5 (16), long delay free recall (14), short delay free recall* (7), recognition (5), list A trial 1 (3), immediate cued (1), immediate recall (1), list A trial 5 (1), list B (1), long delay cued (1)*	
RCFT	**26**
Delayed recall (21), copy (13), immediate recall* (12), Figure B reproduction (2), figure B recall (2), figure B reproduction and recall (2), recall (1), recognition (1)*	
RAVLT	**15**
Trial A-4 (3), trial B-1 (3), A-4 delayed (2), Trial A-1 (2), Trials A1–4 (2), Delayed recall (1), learning over trials (1), pro delayed recall (1), pro interference (1), recognition (1), retroactive delayed recall (1), retroactive interference (1), total recall (1), trials 1–5 (total) (1)	
Digit Vigilance Test	**9**
Total errors (3), total time (3)	
WCST	**8**
# essays to start first category/completed categories (1), perseverative (1), perseverative errors (1)	
Corsi Block Test	**7**
Backward (1), forward (1)	
Raven's matrices	**7**
Coloured progressive matrices (4), progressive matrices (3)	
WMS logical memory	**7**
Delayed (4), immediate (1), recognition (1)	
MMSE	**6**
Reverse Numerical Sequence (MMSE) (2)	
WMS Paired Associates	**6**
Delayed paired associates (5), paired associates total (3), trial 1 (3)	
WMS visual reproduction	**6**
Delayed (4), immediate (1), recognition (1)	
Design Fluency Test	**5**
Fixed (2), free (2)	
DKEFS Colour Word	**3**
Inhibition-inhibition (3), inhibition-switching (2)	
DKEFS Design Fluency Test	**3**
Shifting condition (2)	
BVRT	**3**
BVRT A # correct (3), # errors (3)	
BVMT-R	**2**
delayed recall (1), recognition (1), total recall (1)	
color trails test	**2**
Interference index (1), trial 1 (1), trial 2 (1)	
Complex Figure Test	**2**
Copy (1), delayed (1)	
Hayling Test	**2**
Errors/15 (2), errors/45 (2), time B-A (2), time parts A (1)	
Figure Memory Test	**2**
Delayed (2), learning (2)	
Story Memory Test	**2**
Delayed (2), learning (2)	

(*continued*)

Table B.1 (*Continued*)

Neuropsychological Test	Frequency (# of NBs)
HVLT-R *Delayed recall (1), total learning (1)*	**1**
SBST *4th ed vocabulary (1), bead memory (1), comprehension (1), memory for sentences (1), pattern analysis (1), quantitation (1)*	**1**

* indicates this component score was used in the ACR-NB. Subtests/components of tests are italicized.
Abbreviations: CVLT: California Verbal Learning Test; RCFT: Rey Complex Figure Test; RAVLT: Rey Auditory Verbal Learning Test; WCST: Wilson Card Sorting Test; HVLT-R: Hopkins Verbal Learning Test Revised; SBST: Stanford-Binet Subset Testing.

Table B.2
Studies categorized as "incomplete/mixed".

Reference	Tests Used
Shulman S, Shorer R, Wollman J, Dotan G and Paran D. Retinal nerve fiber layer thickness and neuropsychiatric manifestations in systemic lupus erythematosus. *Lupus*. 2017;26(13):1420–1425. doi:10.1177/0,961,203,317,703,496	NeuroTrax and RAVLT
Zhang XD, Jiang XL, Cheng Z, et al. Decreased Coupling Between Functional Connectivity Density and Amplitude of Low Frequency Fluctuation in Non-Neuropsychiatric Systemic Lupus Erythematosus: a Resting-Stage Functional MRI Study. Mol Neurobiol. 2017;54(7):5225–5235. doi:10.1007/s12035–016–0050–9	MMSE, MoCA, NCT-A, Digit Symbol
Mahdavi Adeli A, Haghighi A, Malakouti SK. Prevalence of Cognitive Disorders in Patients with Systemic Lupus Erythromatosus; a Cross-sectional Study in Rasoul-e-Akram Hospital, Tehran, Iran. Arch Iran Med. 2016;19(4):257–261.	MMSE, Clock Drawing Test, Trails A
El-Shafey, A. M., Abd-El-Geleel, S. M., & Soliman, E. S. Cognitive impairment in non-neuropsychiatric systemic lupus erythematosus. *Egypt Rheumatol*. 2012;34(2):67–73. doi:10.1016/j.ejr.2012.02.002	MoCA, Trails A, Trails B
Ginsburg KS, Wright EA, Larson MG, et al. A controlled study of the prevalence of cognitive dysfunction in randomly selected patients with systemic lupus erythematosus. Arthritis Rheum. 1992;35(7):776–782. doi:10.1002/art.1780350711	NES2 Computerized Cognitive Test Battery and Stroop
Montero-López E, Santos-Ruiz A, Navarrete-Navarrete N, Ortego-Centeno N, Pérez-García M, Peralta-Ramírez MI. The effects of corticosteroids on cognitive flexibility and decision-making in women with lupus. Lupus. 2016;25(13):1470–1478. doi:10.1177/0961203316642313	Cognitive flexibility was measured with the Trail Making Tests A and B; decision-making was measured with the Iowa Gambling Task.
Bizzo BC, Sanchez TA, Tukamoto G, Zimmermann N, Netto TM, Gasparetto EL. Cortical Thickness and Episodic Memory Impairment in Systemic Lupus Erythematosus. J Neuroimaging. 2017;27(1):122–127. doi:10.1111/jon.12394	RAVLT
Said MSM, Bin Shudim SS, Mohamad K, Shaharir SS, Tong NKC, Ali RA. Subclinical memory dysfunction in Malaysian systemic lupus erythematosus patients: association with clinical characteristics and disease activity – a pilot study. Egypt Rheumatol. 2016;38:189–194. https://doi.org/10.1016/j.ejr.2015.12.001	Weschler Memory Scale (WMS-IV)
Maciel RO, Ferreira GA, Akemy B, Cardoso F. Executive dysfunction, obsessive-compulsive symptoms, and attention deficit and hyperactivity disorder in Systemic Lupus Erythematosus: Evidence for basal ganglia dysfunction?. J Neurol Sci. 2016;360:94–97. doi:10.1016/j.jns.2015.11.052	MMSE, MoCA, FAB, COWAT, ANIMALS

Abbreviations: MoCA: Montreal Cognitive Assessment; NES2: Neurobehavioral Evaluation System 2; MMSE: Mini-Mental State Examination; FAB: Frontal Assessment Battery; RAVLT: Rey Auditory Verbal Learning Test.

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