Neuropsychiatric Lupus: Classification Criteria in Neuroimaging Studies

Tania M. Netto, Nicolle Zimmermann, Fernanda Rueda-Lopes, Bernardo C. Bizzo, Rochele P. Fonseca, Emerson L. Gasparetto

ABSTRACT: This systematic review described the criteria and main evaluations methods procedures used to classify neuropsychiatric systemic lupus erythematous (NPSLE) patients. Also, within the evaluations methods, this review aimed to identify the main contributions of neuropsychological measurements in neuroimaging studies. A search was conducted in PubMed, EMBASE and SCOPUS databases with the terms related to neuropsychiatric syndromes, systemic lupus erythematous, and neuroimaging techniques. Sixty-six abstracts were found; only 20 were completely analyzed and included. Results indicated that the 1999 American College of Rheumatology (ACR) criteria is the most used to classify NPSLE samples together with laboratorial, cognitive, neurological and psychiatric assessment procedures. However, the recommended ACR assessment procedures to classify NPSLE patients are being used incompletely, especially the neuropsychological batteries. Neuropsychological instruments and neuroimaging techniques have been used mostly to characterize NPSLE samples, instead of contributing to their classifications. The most described syndromes in neuroimaging studies have been seizure/cerebrovascular disease followed by cognitive dysfunctions as well as headache disorder.


Neuropsychiatric manifestations occur with frequency in systemic lupus erythematous (NPSLE)1. However, attribution of these manifestations to SLE are considered one of the greatest challenges among behavioural and neuroimaging studies2. There still seems to be a long way towards a comprehension of the neuropsychiatric (NP) syndromes in SLE, even though the American College of Rheumatology (ACR) has started to facilitate and to enhance clinical research by developing standards for terminology, definitions and some assessment methods to describe 19 NP syndromes in SLE3. Nevertheless, it is still quite a challenge to differentiate the NPSLE from the non-NPSLE, mainly due to the heterogeneity of assessments even after ACR recommendations, not sufficiently reported or unreported methods to classify each syndrome. American College of Rheumatology proposed nomenclature for NPSLE is mainly intended for didactic purposes, clinical research and reporting rather than clinical setting3. The general SLE is a recurrent, chronic, systemic, autoimmune disease which causes morbidity in between 161,000 to 322,000 adults4. The NPSLE is a set of neurologic syndromes of the central and peripheral nervous system and/or of psychiatric syndromes observed in patients with SLE in which other causes are excluded3,5,6, by clinical, laboratory, neuroimaging and neuropsychological tests3. These syndromes include twelve manifestations from the central nervous system, as follows, “aseptic meningitis, cerebrovascular disease, demyelinating syndrome, headache (including migraine and benign intracranial hypertension), movement disorder (chorea), myelopathy, seizure disorders, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, psychosis” and seven manifestations related to the peripheral nervous system, “acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré

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syndrome), autonomic disorder, mononeuropathy, single/multiplex, myasthenia gravis, neuropathy, cranial, plexopathy, polyneuropathy\(^3\). The neuropsychiatric manifestations can occur as single or multiple events at any time during the course of SLE\(^7\). These manifestations have been considered very frequent among SLE patients, with occurrences varying from 57% to 91%, being up to two-thirds of patients with this disease\(^6-8\). Among the 19 neuropsychiatric syndromes in SLE, the four most reported ones have been cognitive impairment (ranging from 70 to 80%), mood disorders (from 60 to 70%), headache (from 50 to 60%) and cerebrovascular disease (from 20 to 40%)\(^7,9,10\). This variability is due, in part, to methodological differences among studies such as inclusion criteria of samples, type of design (retrospective), heterogeneous procedures of assessments and lack of reporting procedures\(^6\).

Neuroimaging techniques have been continuously improving and ACR considers them to be important complementary tools for some case definitions in NPSLE and to rule out evidence of other disorders\(^5,11\), being useful for differential diagnosis. Some reviews have shown that advanced magnetic resonance imaging (MRI) techniques are able to detect white matter changes, which is frequently present in NPSLE\(^1\). However, advanced MRI techniques are still not clearly established as essential tools contributing to the diagnosis of NP syndromes in SLE\(^12,13\).

The ACR had also considered a neuropsychological battery based on formal instruments important to identify one of the most frequent syndromes, cognitive impairment, which also can contribute to the classification of NP in SLE. In spite of these recommendations by ACR, 1999, several studies have not presented homogeneity on this method of cognitive measurement\(^10,12,14,15\). Among the main advantages of using neuroimaging and neuropsychological tools for complementary diagnosis of NPSLE are that they can be non-invasive as well as sensitive in detecting central nervous system manifestations\(^13\).

The correct attribution of NP events to SLE or to other causes is still very challenging, and methodological approaches for assessment are a problem that still remain unresolved, lacking explicit case and terms definitions, comprehension of their pathogenesis, and pathognomonic tests findings, amongst other consequences that have been hampering the possibilities to compare results, reproduce methods, test hypotheses or conduct intervention studies\(^3\). Considering these difficulties, it seems very relevant to systematically review data generated in studies of neuropsychiatric syndromes classification in SLE\(^2\). Although the ACR system of classification for the 19 neuropsychiatric syndromes has been traditionally used, there still seems to be a lack of methodological homogeneity in the classification of NP in SLE.

In addition to the ACR consensus in 1999, as far as we know, only six general reviews or critical analyses have been published related to NPSLE\(^7,12,16-19\). However, none of them had systematically reviewed the factors contributing to inclusion criteria, sample’s characteristics, assessment methods and heterogeneous outcomes, for NPSLE descriptions which consider neuroimaging studies.

The present systematic review aims to verify and to describe the criteria and main methods of assessment procedures employed to classify NP syndromes in SLE patients in neuroimaging studies. Also, within the assessment procedures, this review aims to identify the main contributions of neuropsychological tests in these neuroimaging studies. According to Popescu and Kao’s\(^20\) review, the development of treatments for NPSLE is still a great challenge, due to the broad spectrum of manifestations of these syndromes and limitations in diagnostic tests. Since ACR considered neuroimaging evaluations important enough to change the direction and to enhance clinical investigations in NPSLE classification\(^3\), this systematic review may point out some important issues to better understand how neuroimaging study methods characterize and differentiate NPSLE from non-NPSLE samples. Regarding neuropsychological evaluations in neuroimaging studies, Borchers et al’s\(^13\) review brings out two important issues that may limit improvements in NPSLE treatment: one is the limited knowledge of the pathophysiology of this disease and the other is the fact that patients have simultaneously more than one NP syndrome. These authors concluded that advances in neuroimaging technology and neuropsychological testing have been contributing to NPSLE diagnostic improvements and have allowed more effective interventions.

**METHOD**

This systematic review was based on a search in the PubMed, EMBASE and SCOPUS databases with the following search terms: (“neuropsychiatric syndromes”) and (“systemic lupus erythematosus”) and (“magnetic resonance imaging” or “MRI” or “magnetization transfer imaging” or “MTI” or “diffusion-weighted imaging” or “DWI” or “diffusion tensor imaging” or “DTI” or “magnetic resonance spectroscopy” or “MRS” or “susceptibility weighted imaging” or “SWI” or “voxel-based morphometry” or “VBM” or “magnetoencephalography” or “MEG” or “electroencephalography” or “EEG” or “optical imaging” or “fNIRS” or “positron emission tomography” or “PET” or “single-photon emission computed tomography” or “SPECT” or “functional neuroimaging” or “fMRI” or “neuroimaging cortical thickness” or “default network” or “resting state” or “default mode network” or “volumetry”). Some filters were applied, only articles with adults, humans and adolescents or children (n=3), year of publication (n=17), review studies (n=10), case studies (n=7), other languages (n=5).

![Fluxogram of reviewed NPSLE studies](https://www.cambridge.org/core/terms).
Table 1: Characterization of criteria used and procedures for assessment of the samples

<table>
<thead>
<tr>
<th>Reference</th>
<th>Criteria of characterization</th>
<th>Procedures for criteria assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Layndajl et al. (2011)†</td>
<td>ACR (1999) case definitions for NPSLE syndromes assessed and classified by 2 rheumatologists: NP symptoms were considered for NPSLE if one or more criteria was accomplished</td>
<td>Described. Not described.</td>
</tr>
<tr>
<td>Konra et al. (2011)†</td>
<td>Judgment by the patient’s rheumatologist to ensure no current or prior important neuropsychiatric disorder other than cognitive impairment</td>
<td>10–15 minute interview to ensure inclusion/ exclusion criteria and a structured psychiatric interview to rule out current depression. Assessment by specialist for exclusion of secondary causes of NP syndromes. Review of medical records. Described. Not described.</td>
</tr>
<tr>
<td>Emmer et al. (2010)†</td>
<td>ACR (1999) case definitions for NPSLE syndromes assessed and classified by one expert rheumatologist</td>
<td>Described. Not described.</td>
</tr>
<tr>
<td>Azarpazhooh et al. (2011)†</td>
<td>ACR (1999) case definitions for NPSLE syndromes</td>
<td>Not described.</td>
</tr>
<tr>
<td>Wilker et al. (2005)†</td>
<td>ACR (1999) case definitions for NPSLE syndromes</td>
<td>Not described.</td>
</tr>
<tr>
<td>Whitehead &amp; Spangenberg (2009)†</td>
<td>Exclusion of all criteria for NPSLE except for headache.</td>
<td>Not described.</td>
</tr>
<tr>
<td>Emmer et al. (2008)†</td>
<td>ACR (1999) case definitions for NPSLE syndromes</td>
<td>Not described.</td>
</tr>
<tr>
<td>Reilin et al. (2006)†</td>
<td>Detailed prospectively collected NPSLE and SLE histories were available</td>
<td>Clinical evaluation for assessment of medical records. Described.</td>
</tr>
<tr>
<td>Tanikawa et al. (2005)†</td>
<td>The CNS involvement was previously assessed by clinical symptoms such as organic brain syndrome seizure, altered micturition and psychiatric disorders.</td>
<td>Clinical assessment of CNS involvement. Described. Not described.</td>
</tr>
<tr>
<td>Langorgulas et al. (2005)†</td>
<td>Not utilized</td>
<td>Clinical interview. Described. Not described.</td>
</tr>
<tr>
<td>Podunkevva et al. (2008)†</td>
<td>Review of medical records.</td>
<td>Not described.</td>
</tr>
</tbody>
</table>

Note. †studies that characterize the participants according to the 19 ACR neuropsychiatric syndromes; - studies that do not characterize the sample according to the neuropsychiatric syndromes; NP= Neuropsychiatric; WAIS-Rs = Wechsler Adult Intelligence Scale-Revised; SLEDAI = Disease Activity Index; SLICC = The Systemic Lupus International Collaborating Clinics; DMS = Diagnostic and Statistical Manual of Mental Disorders; EEG= electroencephalogram; MRI=magnetic resonance imaging; TEE=Transesophageal echocardiography; VHD=Valvular heart disease.
Table 2: Characterization of neuroimaging studies: aim and methods

<table>
<thead>
<tr>
<th>Reference</th>
<th>Aim</th>
<th>Study design</th>
<th>Sample</th>
<th>Neuroimaging methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumral et al. (2011)</td>
<td>To provide an inventory of brain abnormalities on conventional MRI in NPSLE and to interpret pathogenetic mechanisms.</td>
<td>Observational retrospective</td>
<td>Active NPSLE patients (n=74)</td>
<td>MRI (T1- and T2-weighted images and either proton density-weighted or FLAIR in the axial plane)</td>
</tr>
<tr>
<td>Kurosu et al. (2011)</td>
<td>To examine hippocampal volumes and neuroimaging alterations in relation to memory in non-NPSLE.</td>
<td>Comparative prospective</td>
<td>Non-NPSLE patients (n=81)</td>
<td>MRI and MRS of the right and left hippocampal areas (right and left)</td>
</tr>
<tr>
<td>Emmere et al. (2010)</td>
<td>To quantify any perfusion abnormalities and to determine their contribution to NPSLE.</td>
<td>Comparative</td>
<td>Active NPSLE patients (n=15)</td>
<td>Volumetric MRI and MRS of the right and left hippocampal areas (right and left)</td>
</tr>
<tr>
<td>Arapazuddin et al. (2010)</td>
<td>To clarify the pathophysiology of the CNS involvement in SLE.</td>
<td>Comparative</td>
<td>Patients with SLE (n=68), NPSLE (n=24) and non-NPSLE (n=44)</td>
<td>Transcranial Doppler (middle cerebral arteries)</td>
</tr>
<tr>
<td>Davey et al. (2010)</td>
<td>To investigate the role of CED in SLE and in NPSLE.</td>
<td>Comparative</td>
<td>Patients with SLE (n=61)</td>
<td>Transcranial Doppler Ultrasonography (middle cerebral artery)</td>
</tr>
<tr>
<td>Whittall and Spangenberg (2009)</td>
<td>To investigate the possible association between impaired cognitive function and chronic headache in SLE.</td>
<td>Comparative</td>
<td>Patients with SLE but without the antiphospholipid (n=61), no headaches group (n=21), migrainous headaches (n=10), aura (n=1), other headaches (n=11), tension type headaches (n=7)</td>
<td>MRI using gadolinium (Ventriculo-brain ratios was calculated)</td>
</tr>
<tr>
<td>Harboe et al. (2008)</td>
<td>To compare the prevalence and pattern of NPSLE to Primary Sjögren syndrome using the ACR criteria.</td>
<td>Comparative</td>
<td>Patients with SLE (n=68)</td>
<td>MRI</td>
</tr>
<tr>
<td>Emmere et al. (2008)</td>
<td>To investigate if, in NPSLE patients, MRI histogram parameters are related to neuropsychological findings from proton MR imaging and to determine whether MTR changes are specific to NPSLE.</td>
<td>Comparative</td>
<td>SLE patients (n=15)</td>
<td>MRI (Axial T1-weighted spin-echo, axial slices)</td>
</tr>
<tr>
<td>Podrasky et al. (2008)</td>
<td>To determine the volume of pathological foci in the brain tissue of NPSLE and non-NPSLE patients and to find out if that volume depends on clinical records.</td>
<td>Comparative</td>
<td>Patients with NPSLE (n=29)</td>
<td>Volumetric MRI in FLAIR</td>
</tr>
<tr>
<td>Cio et al. (2007)</td>
<td>To compare clinical manifestations, brain MRI findings and prognosis of NPSLE and NBD.</td>
<td>Comparative</td>
<td>Patients with NPSLE (n=25)</td>
<td>MRI (T1-weighted images, T2-weighted images and FLAIR)</td>
</tr>
<tr>
<td>Rölden et al. (2006)</td>
<td>To determine whether VHD and brain injury are associated with nonfocal NPSLE.</td>
<td>Comparative</td>
<td>Patients with monocular NPSLE (n=18)</td>
<td>MRI (T1-weighted volume, T2-weighted axial, DWI series and a FLAIR)</td>
</tr>
<tr>
<td>Tonkonow et al. (2005)</td>
<td>To evaluate the usefulness of the average amount of CBF for NPSLE.</td>
<td>Correlational</td>
<td>Patients NPSLE (n=16)</td>
<td>SPECT (CBF and BPS values were evaluated)</td>
</tr>
<tr>
<td>Lampopoulos et al. (2005)</td>
<td>To describe the prevalence and clinical manifestations of abnormalities on EEG in patients with APS and/or NPSLE.</td>
<td>Comparative, descriptive and correlational</td>
<td>Patients non-NPSLE (n=57)</td>
<td>EEG (electrodes were positioned according to the international 10-20 system, and standard recordings were performed for 15-20 minutes during relaxed wakefulness, with sessions of overbreathing and photic stimulation)</td>
</tr>
<tr>
<td>Cotton et al. (2004)</td>
<td>To evaluate with high-field MRI the CNS involvement in a series of SLE patients with or without NPSLE and to detect a possible relationship between MRI and clinical parameters.</td>
<td>Comparative</td>
<td>Patients with a SLE (n=58)</td>
<td>MRI (including diffusion weighted-images, high-resolution 3D T1 weighted-images)</td>
</tr>
<tr>
<td>Ammako et al. (2004)</td>
<td>To evaluate whether serum matrix metalloproteinase-9 levels are associated with NPSLE, particularly cognitive dysfunction, evaluated by neuropsychological tests and MRI.</td>
<td>Comparative prospective</td>
<td>Patients with SLE (n=50)</td>
<td>MRI (T1-weighted T1-weighted, T2-weighted, and coronal FLAIR sequences; axonal 3-dimensional T2 fast spin-echo and gadolinium-enhanced 3-D T1 spoiled gradient-echo images)</td>
</tr>
<tr>
<td>Shmii et al. (2003)</td>
<td>To compare FLAIR imaging with proton density-T2 weighted (PD-T2) imaging in NPSLE.</td>
<td>Comparative</td>
<td>Patients with NPSLE (n=28)</td>
<td>MRI (T1, T2, and FLAIR)</td>
</tr>
<tr>
<td>Samra et al. (2003)</td>
<td>To apply the new ACR nomenclature for NPSLE, to determine the prevalence of the different NPSLE and to evaluate which of these manifestations correlate with APL.</td>
<td>Descriptive, correlational</td>
<td>523 patients with SLE</td>
<td>MRI (standard spin-echo technique)</td>
</tr>
<tr>
<td>Walecki et al. (2002)</td>
<td>To determine the value of modern imaging techniques (MR sequences - FLAIR, DWI) in the diagnosis of cerebral changes in NPSLE.</td>
<td>Observational</td>
<td>Patients with neurological symptoms of SLE (n=50)</td>
<td>MRI (SE, FSE, FAST, FLAIR sequences and in 12 cases also in EPI DWI sequences; T1 and T2-weighted images in sagittal and transverse planes were analyzed)</td>
</tr>
<tr>
<td>Kamra et al. (2002)</td>
<td>To investigate the association of metabolite signals with NPSLE manifestations and to compare the results with those from patients non-NPSLE and normal controls.</td>
<td>Comparative</td>
<td>Patients with SLE (n=35)</td>
<td>MRI and/or MRA Extravascular Doppler Transcranial Doppler Sonography, Doppler sonography Electrocardiography Transforaminal/transesophageal Echocardiography</td>
</tr>
<tr>
<td>Karaski et al. (2000)</td>
<td>To identify variables that are associated with the evolution of cerebral changes on sequential MRI scans as well as with clinical outcomes in NPSLE.</td>
<td>Observational prospective, follow-up</td>
<td>Patients with SLE (including 14 with the APS) who had been hospitalized with primary NP disease (n=32)</td>
<td>MRI (T1-weighted density T2-weighted 2,500/30/20 ms, and coronal scans).</td>
</tr>
</tbody>
</table>

Note. Neuro Behçet's disease (NBD); Cerebral Blood Flow (CBF); antiphospholipid syndrome (APS); cerebrovascular endotelial dysfunction (CED); antiphospholipid antibodies (aPL); Magnetic resonance imaging (MRI); Non-neuropsychiatric systemic lupus erythematosus (non-NPSLE); neuropsychiatric systemic lupus erythematosus (NPSLE); Fluid Attenuated Inversion Recovery (FLAIR); systemic lupus erythematosus (SLE); fast spin echo (FSE); diffusion weighted imaging (DWI); magnetization transfer ratio (MTR); fast spin echo (FAST); valvular heart disease (VHD); antiphospholipid syndrome (APS).

those published in English, French, Spanish, or Portuguese were reviewed. Repeated articles and papers published before 2000 were excluded because they occurred prior to the ACR classification criteria. Sixty-six articles were reviewed manually, resulting in 21 full text reviewed papers, after exclusion criteria analysis. Abstracts were excluded for not having included at least one group with NPSLE, not using at least one neuroimaging technique as a tool for assessment, not being empirical, and with single or multiple case studies. The systematic review fluxogram can be viewed in the Figure.

**RESULTS**

Table 1 presents the characterization of adopted criteria and procedures for each article. The majority of studies (70%) classified NPSLE according to ACR recommendations. However, a great number of them did not use all ACR methods.
findings to characterize NPSLE2,17,21-32, 25% aimed to structure or function measurement as dependent variables. A review according to their aim, design, sample distribution, main psychiatric/functional evaluations (40%).

findings of this population26,29,31,33,34, 20% investigated cognitive findings to describe SLE in general17,23,30. The majority of samples analyzed included two groups, general SLE patients compared to healthy controls (20%)17,22,30,32 or NPSLE compared to a non-NPSLE (15%)21,28,35. Moreover, two groups continue to be compared, but in these studies NPSLE were compared with other diseases (10%)21,33, NPSLE with healthy controls (10%)19,36, general SLE with other disorders (5%)24. Finally, a few studies had only one group of NPSLE patients (15%)2,23,31,34. In this way, 70% of these studies had a comparative design15,17,22,28,30,33,36. The most common neuroimaging techniques to measure brain structure or function as dependent variables were MRI (75%)2,17,18,23-32,34,37, then transcranial Doppler (15%)21,22,32, MRS (10%)17,25, and the following techniques, MTT, SPECT, EEG and extracranial Doppler, with 5% each.

In Table 3 it can be observed that only 14 of 20 articles, included in this analysis, had cited specifically the 19 neuropsychiatric syndromes. It also shows the ten most prevalent

Table 3: The four neuropsychiatric (NP) manifestations most prevalent in patients with SLE according to ACR case definitions for NPSLE

<table>
<thead>
<tr>
<th>References</th>
<th>NPSLE (n=)</th>
<th>Four most prevalent ACR criteria for NPSLE - Peripheral Nervous System (PNS)</th>
<th>n(%)</th>
<th>Four most prevalent ACR criteria for NPSLE - Central Nervous System (CNS)</th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Lyamidi et al. (2011)</td>
<td>54</td>
<td>Not included as the four most prevalent ACR criteria for NPSLE</td>
<td></td>
<td>Headache disorders</td>
<td>27 (50.4)</td>
</tr>
<tr>
<td>2-Arunanadha et al. (2010)</td>
<td>24</td>
<td>Not described</td>
<td></td>
<td>Seizure disorder</td>
<td>19 (25.6)</td>
</tr>
<tr>
<td>3-Davey et al. (2010)</td>
<td>61</td>
<td>Not included as the four most prevalent ACR criteria for NPSLE</td>
<td></td>
<td>Cognitive dysfunction</td>
<td>16 (21.6)</td>
</tr>
<tr>
<td>4-Emmer et al. (2010)</td>
<td>15</td>
<td>Not included as the four most prevalent ACR criteria for NPSLE</td>
<td></td>
<td>Psychosis</td>
<td>13 (17.5)</td>
</tr>
<tr>
<td>5-Emmer et al. (2008)</td>
<td>34</td>
<td>Not included as the four most prevalent ACR criteria for NPSLE</td>
<td></td>
<td>Headache disorder</td>
<td>55 (90)</td>
</tr>
<tr>
<td>6-Harbec et al. (2008)</td>
<td>68</td>
<td>Cognitive dysfunction</td>
<td>38 (55.8)*</td>
<td>Seizure disorder</td>
<td>26 (38.2)*</td>
</tr>
<tr>
<td>7-Podrazilová et al. (2008)</td>
<td>29</td>
<td>polyneuropathy</td>
<td>18(26.4)*</td>
<td>Headache disorder</td>
<td>18 (26.4)*</td>
</tr>
<tr>
<td>8-Chv et al. (2007)</td>
<td>25</td>
<td>Not included as the four most prevalent ACR criteria for NPSLE</td>
<td></td>
<td>Psychosis</td>
<td>11 (33)</td>
</tr>
<tr>
<td>9-Cotton et al. (2004)</td>
<td>44</td>
<td>Not included as the four most prevalent ACR criteria for NPSLE</td>
<td></td>
<td>Cognitive dysfunction</td>
<td>9 (31)</td>
</tr>
<tr>
<td>10-Sanna et al. (2003)</td>
<td>323</td>
<td>Not included as the four most prevalent ACR criteria for NPSLE</td>
<td></td>
<td>Headache</td>
<td>9 (31)</td>
</tr>
<tr>
<td>11-Wilmer et al. (2003)</td>
<td>28</td>
<td>Not included as the four most prevalent ACR criteria for NPSLE</td>
<td></td>
<td>Cognitive dysfunction</td>
<td>8 (32)</td>
</tr>
<tr>
<td>12-Kumar et al. (2002)</td>
<td>25</td>
<td>Not included as the four most prevalent ACR criteria for NPSLE</td>
<td></td>
<td>Depression</td>
<td>9 (31)</td>
</tr>
<tr>
<td>13-Karuna, et al. (2000)</td>
<td>32</td>
<td>Not included as the four most prevalent ACR criteria for NPSLE</td>
<td></td>
<td>Stroke</td>
<td>14 (46)</td>
</tr>
<tr>
<td>14-Podrazilová et al. (2008)</td>
<td>29</td>
<td>Not included as the four most prevalent ACR criteria for NPSLE</td>
<td></td>
<td>Seizures</td>
<td>11 (33)</td>
</tr>
</tbody>
</table>

Note. + studies that characterize the participants according to the 19 ACR neuropsychiatric syndromes; - studies that did not characterize the sample according to the 19 ACR neuropsychiatric syndromes.
ACR criteria identified by the 14 neuroimaging studies were, seizure/cerebrovascular disease (85.71%), the most prevalent; followed by cognitive dysfunction (78.57%), and headache (78.57%). Then by mood disorder (57.14%), psychosis (28.57%), acute confusional state (21.42%), cranial neuropathies (14.28%), stroke, and demyelinating syndromes (7.14%).

Neuropsychological functions most frequently assessed by the studies were concentrated attention (33.33%), cognitive flexibility (28.57%), visual episodic memory (28.57%), processing speed (28.57%), and verbal episodic memory (23.81%), as can be seen in Table 4. The frequency was calculated considering that each article and instrument could have assessed one or more cognitive function. The most used neuropsychological tests, aiming to assess different cognitive components, were: Rey Complex figure, Stroop Color and Word Test, Mini-Mental State Auditory Verbal Learning Test.

**DISCUSSION**

This systematic review showed some important issues to better understand the main classification criteria and assessment methods used to differentiate NPSLE from non-NPSLE samples in neuroimaging studies. In regard to the criteria and evaluation procedures used to characterize the samples, more than half of the articles from this present review had classified their neuropsychiatric samples according to the recommendations of 1999 ACR NPSLE criteria. However, only three of these articles fully described the ACR recommendations including laboratorial, clinical, neurological/neuroimaging, as well as cognitive and psychiatric/functional evaluations. Among the ones that employed cognitive assessment, less than half used the same or similar instruments to the neuropsychological battery recommended by ACR. Several of these studies did not describe whether they used cognitive measurements. Furthermore, a couple of these studies used only two instruments in which one of them was the Mini Mental State Examination.

Although the ACR criteria developed a system in which researchers could have one name for each of 19 neuropsychiatric syndromes to advance knowledge and investigation of this pathology, there are still a large number of studies, as shown in this review, which do not totally benefit from the ACR nomenclature. Neuroimaging studies have used different definitions of NP syndromes and presented lack of evaluation descriptions, methodological heterogeneity of design, with some of them being based on retrospective chart reviews, and all of these factors have contributed to important limitations in this field. There is still a large discrepancy amongst neuroimaging studies that can be strongly related to not following all of the recommendations for NPSLE of ACR.

Among the 19 neuropsychiatric syndromes from ACR, it was observed that even though the studies included in this review were not necessarily trying to investigate the prevalence of these syndromes, most of them had reported the most frequent NP manifestations. The most prevalent syndrome in this review was seizure/cerebrovascular disease; this result may be related to the neuroimaging exam sensitivity to capture alterations in the white matter. Accordingly with clinical diagnosis, cognitive dysfunctions as well as headache disorder were reported in more than half of these investigations. Unlike the results of this review, several studies have highlighted cognitive dysfunction as one of the most common NP manifestations followed by headaches. Even though these two syndromes were not reported as the most frequent ones in this review, they were still highly classified. The high frequency of cognitive dysfunctions can be related to the fact that most of the neuropsychiatric syndromes classified by the ACR may affect the central nervous system, causing cognitive alterations. In regard to the other syndromes, mood disorders were present in approximately half of the studies and the least prevalent ones were stroke and demyelinating syndromes. Although the ACR criteria for the 19 NPSLE syndromes also include disorders of the peripheral nervous system, they were not added in this review due to the selection of studies that have been in neuroimaging.

Formal neuropsychological assessments have not been used routinely in these neuroimaging studies, possibly for logistical reasons, as there is currently no validated universally accepted screening tool for cognitive dysfunction regarding each probable impaired component in SLE. The Mini-Mental Status Examination that has been used quite often, is not sufficiently sensitive to measure specific cognitive deficits in this population. Moreover, cognitive dysfunction may vary over time in patients with NPSLE, and standardized cognitive instruments may contribute to identification of cognitive status of these patients over time. However, it is crucial that cognitive test results be interpreted based on normative data appropriate for age, education, sex, and ethnic group. Standardized neuropsychological tests are noninvasive tools that can evaluate the effect of SLE on the brain. They can be used as a follow-up

<table>
<thead>
<tr>
<th>Cognitive function</th>
<th>Number of articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention - Concentrated</td>
<td>7</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>6</td>
</tr>
<tr>
<td>Episodic memory - Visual</td>
<td>6</td>
</tr>
<tr>
<td>Processing speed</td>
<td>6</td>
</tr>
<tr>
<td>Episodic memory - Verbal</td>
<td>5</td>
</tr>
<tr>
<td>Inhibition</td>
<td>4</td>
</tr>
<tr>
<td>Praxis</td>
<td>4</td>
</tr>
<tr>
<td>Attention - Altered</td>
<td>3</td>
</tr>
<tr>
<td>General cognitive status</td>
<td>3</td>
</tr>
<tr>
<td>IQ</td>
<td>3</td>
</tr>
<tr>
<td>Visuo-spatial and motor functioning</td>
<td>3</td>
</tr>
<tr>
<td>Working memory</td>
<td>2</td>
</tr>
<tr>
<td>Attention - Not specified</td>
<td>2</td>
</tr>
<tr>
<td>Language</td>
<td>1</td>
</tr>
<tr>
<td>Lexical-semantic access</td>
<td>1</td>
</tr>
<tr>
<td>Naming</td>
<td>1</td>
</tr>
<tr>
<td>Reading</td>
<td>1</td>
</tr>
<tr>
<td>Semantic memory</td>
<td>1</td>
</tr>
<tr>
<td>Verbal planning</td>
<td>1</td>
</tr>
</tbody>
</table>

Note. Most articles investigated more than one cognitive function.

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*Table 4: Frequency of cognitive functions assessed*
or to monitor alterations or progress of the disease. In addition, it can be very useful to measure treatment outcomes\(^1\). Usually most studies do not use these guidelines as Kozora et al\(^{19}\) did. Their study found that the ACR-SLE neuropsychological battery is valid and reliable\(^{15}\), even though constant development of new batteries or investigation about accuracy for diagnosis in SLE patients of existing batteries is the focus of several studies\(^{10}\).

Regarding the frequency of test utilization and assessed cognitive processes, sustained attention, cognitive flexibility, verbal and visual episodic memory and processing speed have been more focused. Amongst the main assessment methods, sustained attention was investigated mainly by means of bi and tripartite paradigms (such as Digit Span, Trail Making Test and Stroop Color and Word test), which were developed to measure components of executive function; episodic memory was assessed through classical paradigms of Rey Complex Figure and Auditory Verbal Learning, which are highly sensitive but at the same time do not use verbal complex stimuli, such as discourse; and processing speed was indirectly evaluated through tasks that required mostly focused attention, praxis and executive functions, which requires careful interpretation of results mainly when motor output is required. In general, it is noteworthy to point out assessment methods in these studies are mainly standardized and inherently artificial tools, lacking of ecological approaches.

Characterization of cognitive impairment is still a challenge, when the complexity of the disease in its physical and emotional aspects is considered. However, many studies suggest these cognitive functions are also the most frequent or significantly impaired\(^{38-40}\), and that some deficits are present even when psychological and emotional aspects are controlled\(^{36}\). In Olazarán et al\(^{39}\) language function showed a high rate of impairment, especially in language comprehension, notwithstanding the findings of the present research pointed out that language and communication do not seem to be a priority for most neuroimaging studies investigating SLE. This review has shown that neuroimaging and neuropsychological measurements are mostly used to characterize NPSLE samples, instead of contributing to the diagnosis of this disease.

In regard to brain imaging techniques, our frequency analysis demonstrated that MRI is the most used neuroimaging procedure in the neurological assessment of NP in SLE patients. This technique is able to visualise common lesions found in SLE patients, such as atrophy, hemorrhage, focal and diffuse hyperintensities\(^{34}\). A challenge in the use of this method is that it is not always correlated with clinical symptoms, and might indicate gaps in the diagnostic understanding of the mechanisms of SLE\(^11\). Although this technique may indeed be sensitive, this sensitivity and recent developments by no means makes them a standard of care for NPSLE at the present time.

It has being observed, however, that few studies have utilized more advanced neuroimaging techniques to investigate other aspects than lesion location that might be of interest for the comprehension of functional or structural-related organization of cognitive functioning\(^{41}\). Few studies administered DTI, for example, illustrating that, in spite of recent evidence of the sensitivity of these techniques and the relationship between white matter damage and other clinical variables of the disease, such as medications\(^{42}\), studies still favor traditional techniques instead of advanced ones. This present systematic review will not discuss the peripheral nervous syndromes from the 19 NPSLE ACR classifications, due to our selection of only neuroimaging studies, which was one of our limitations.

Considering the remaining limitations in the field investigating NPSLE, some of these seem to need more specific solutions. The 19 NP syndromes or even others still not officially recognized can be assessed by means of standardized and specifically validated, cognitive assessments and imaging techniques based on discriminating findings that could accurately differentiate NPSLE from non-NPSLE. Among these assessment procedures, in order to solve the confounding variables, one of the possible solutions could be to assess the performance and functional impact of the neuropsychiatric syndromes in SLE, exploring together the neural correlates by means of advanced neuroimaging techniques. However, while some of these techniques may indeed be sensitive, their sensitivity and recent development by no means makes them a standard of care for NPSLE at the present time. In summary, the ACR system seems to be the best way to classify neuropsychiatric syndromes associated with SLE, although the application of neuropsychological and neuroimaging procedures seems still not be frequently present in neuroimaging studies as recommended by ACR, 1999. In this review, we have focused on methodological issues - future studies could explore neuroimaging correlates of NPSLE and include other studies besides neuroimaging to describe how NP syndromes in SLE samples are classified.

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REFERENCES


