Lifting the fog of neuropsychiatric lupus

Monahan, R.C.

High prevalence but low impact of cognitive dysfunction on quality of life in patients with lupus and neuropsychiatric symptoms

RC Monahan, HAM Middelkoop, LJJ Beaart- van de Voorde, R Fronczek, RHH Groenwold, M Kloppenburg, TWJ Huizinga, GM Steup-Beekman

Arthritis Care Res. 2022 Apr 26. doi: 10.1002/acr.24904

ABSTRACT

Objective: To evaluate the prevalence and impact of cognitive impairment on health-related quality of life (HRQoL) in patients with systemic lupus erythematosus (SLE) and neuropsychiatric (NP) symptoms.

Methods: Patients with SLE and NP symptoms referred to the Leiden NPSLE clinic (2007-2019) were included. In a multidisciplinary evaluation, NP symptoms were attributed to SLE (NPSLE: inflammatory/ischemic/both (combined)) or other causes. Four cognitive domains were determined: global cognitive function (GCF, score 0-30), learning and memory (L&M), executive function and complex attention (EF&CA), psychomotor speed (PS) (all T-scores). HRQoL was determined using mental/physical component scores (MCS/PCS) of the SF-36. The associations between cognition and NPSLE phenotype and cognition and HRQoL were assessed with multiple regression analyses and linear mixed models corrected for confounding variables and expressed in standard deviations (SDs).

Results: 357 patients (86% female, mean age 44 years) were included. 169/357 patients had a follow-up visit (median FU: 11 months). Impairment in GCF was present in 8% of patients, and in all other cognitive domains in ±50%. Most severe impairment (all domains) was seen in patients with a combined NPSLE phenotype. Diffuse cognitive impairment (L&M, EF&CA and PS) was most common and present more often in patients with an inflammatory phenotype.

A weak association between cognition and HRQoL was found both cross-sectionally and longitudinally. In general, 1 SD lower scores on the cognitive domains were associated with at most 1/5 SD lower HRQoL.

Conclusion: Objective cognitive impairment is common in SLE patients with NP symptoms, but may have a limited influence on HRQoL.

INTRODUCTION

Cognitive dysfunction is a common diffuse central nervous system (CNS) manifestation of systemic lupus erythematosus (SLE). Due to the lack of uniform screening tools and heterogenous study populations, the reported prevalence of cognitive dysfunction in patients with SLE varies greatly, most estimates ranging from 15-80%.[1-4] Cognitive dysfunction is defined by the American College of Rheumatology (ACR) nomenclature as "*significant deficits in any or all of the following main cognitive functions: memory (learning and recall), complex attention, simple attention, executive skills (planning, organizing, and sequencing), visual-spatial processing, language (e.g. verbal, fluency), reasoning/problem solving and psychomotor speed*". It has been demonstrated that specific domains, such as attention and memory, are particularly affected in patients with SLE.[4]

Different mechanisms may be involved in the development of cognitive dysfunction in patients with SLE. SLE-activity itself may lead to CNS inflammation, which may result in cognitive dysfunction.[5,6] In addition, it may be the consequence of vascular injury, for example due to presence of antiphospholipid antibodies.[7] Other factors, such as anxiety, depression, stress, fatigue and medication have also been implied as important.[8,9] Whether the underlying etiology influences the type and severity of cognitive dysfunction, is insufficiently known. In general, cognitive dysfunction attributed to SLE activity (neuropsychiatric lupus; NPSLE) is associated with more severe impairment.[10,11]

It is known that factors associated with cognitive dysfunction, such as anxiety and depression, negatively affect quality of life (QoL).[12,13] However, to date only a limited number of studies have investigated the direct influence of cognition on QoL in patients with SLE.[14-16] Different measurements of cognition (subjective and objective) were used and mostly in models to predict QoL, rather than look at causal associations. Therefore, the impact of cognition on QoL in patients with SLE remains unascertained.

The aim of this study was twofold. First, to identify type and severity of objective cognitive dysfunction in patients with SLE and neuropsychiatric (NP) symptoms of different origins. Second, to study the association between objective cognitive functioning and QoL.

PATIENTS AND METHODS

Study design and population

All patients visiting the Leiden University Medical Center (LUMC) NPSLE tertiary referral center between 2007-2019 with written informed consent and the clinical diagnosis of SLE were included in this study. The NPSLE clinic has been described in detail previously.[17] In summary, patients with a (suspected diagnosis of) SLE that present with NP symptoms are referred to the LUMC NPSLE clinic and are evaluated by a multidisciplinary team, including a rheumatologist, neurologist, clinical neuropsychologist, psychiatrist, neuroradiologist and vascular internist. A broad definition of NP symptoms is used, in which NP symptoms are defined as neurological,

psychiatric or true *neuropsychiatric* symptoms (as in existing literature).[18] A consensus meeting takes place, in which symptoms are attributed to SLE (major NPSLE) or to other causes and/or NP symptoms for which symptomatic treatment suffices (minor/non-NPSLE). In case of major NPSLE, NPSLE phenotypes are determined based on clinical, serological and radiological assessment: inflammatory, ischemic or a combination thereof.[19] Therefore, four phenotypes are present in this study: minor/non-NPSLE and three subtypes of major NPSLE: inflammatory NPSLE, ischemic NPSLE and combined NPSLE. NPSLE syndromes are assigned according to the 1999 ACR case definitions for NPSLE.[18] 371 patients were eligible for this study, of which 357 patients underwent neuropsychological assessment and were included in this study (*Supplementary Figure 1*). Permission for this study was obtained from the Leiden-The Hague-Delft medical ethical committee (P07.177).

Patient characteristics

Patient information was collected during patient interview and later retrieved from electronical medical files. The following patient characteristics were collected: age, gender, smoking status, presence of diabetes and the antiphospholipid syndrome[20], SLE duration, SLE disease activity index-2000 (SLEDAI-2K)[21], Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI)[22], 1997 ACR classification criteria for SLE[23], education level (low: 0-6 years, middle: 7-12 years, high: >12 years), presence or absence of major NPSLE, NPSLE phenotype, NPSLE syndrome[18] and the presence of depressive and/or anxiety disorder according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[24]

Cognitive assessment

All patients received an extensive neuropsychological assessment on the day of visit to the NPSLE clinic, adapted from the neuropsychological test battery as suggested by the 1999 ACR NPSLE nomenclature and case definition system.[18] For this study, the following neuropsychological tests were included: minimal mental state exam (MMSE)[25], Wechsler memory scale (WMS)[26], STROOP colour and word test (STROOP)[27] and trail-making test (TMT).[28] As described in detail previously[29], these tests are categorized in four cognitive domains, as suggested by the DSM-5[24]:

1. Global cognitive functioning: MMSE (total score);
2. Learning and memory: Wechsler Memory Scale (T-score);
3. Executive function and complex attention: STROOP3 (T-score) and TMT-B (T-score);
4. Psychomotor speed: STROOP1 + 2 (time), TMT-A (T-score)

For the domain global cognitive functioning, moderate cognitive impairment was defined as a score of ≤25/30 and severe impairment as a score of ≤20/30. For the three other cognitive domains, moderate impairment was defined as a score of ≥1 standard deviation lower than the Dutch general population (i.e., T-score ≤40)[30] and severe impairment as a score of ≥2 standard deviation lower than the Dutch general population (i.e., T-score ≤30). In cognitive domains consisting of multiple tests (3. and 4.), scores were averaged. If individual test scores were missing, the domain T-score was based only on the available tests.

Health-related QoL

All patients received the Dutch version of the Short Form-36 (SF-36) at visit to the NPSLE clinic. The SF-36 is a self-administered validated questionnaire to assess health-related QoL (HRQoL).[31] The SF-36 consists of eight domains of health status: physical functioning; physical role limitations; bodily pain; general health perceptions; energy/vitality; social functioning; emotional role limitations and mental health. Individual test scores are transformed to range from zero (worst possible health) to hundred (best possible health.[32] A scoring algorithm is used to convert these transformed scores into the eight domains listed above. For this study, summary mental component score (MCS) and physical component score (PCS) were calculated using norm-based scoring, which employs linear transformation to achieve standardized scores with a mean (standard deviation; SD) of 50 (10) for each dimension by using the Dutch general population as a reference group.[31] Higher PCS and MCS indicate a better HRQoL.

Follow-up assessment

Follow-up visits take place on indication, such as initiation of immunosuppressive treatment in patients with inflammatory/combined NPSLE or uncertainty about attribution of NP symptoms to SLE (2007-2019). A number of patients (~25%) received follow-up for research purposes between 2013-2014. The follow-up visit is identical to the baseline visit and also includes amongst others questionnaires and neuropsychological assessment.

Statistical analysis

Distributions of continuous variables were visually inspected using histograms. Baseline characteristics were presented as mean (SD) for normally distributed continuous variables, as median with interquartile range [IQR] for non-normally distributed continuous variables and percentages for categorical variables.

Cognition was compared at baseline between different NPSLE phenotypes (minor/non-NPSLE, inflammatory, ischemic and combined) using multivariable regression analyses, corrected for age, sex, education level and psychiatric morbidity. An additional analysis was performed comparing frequency and type of cognitive impairment in patients with and without a depressive disorder. Cognition was compared in individuals with a baseline and follow-up within two years using the Wilcoxon signed-rank test (global cognitive function, non-normal distribution) and paired T-test (all other cognitive domains, normal distribution) in all patients and per NPSLE phenotype. Median difference (95% CI) for global cognitive function and mean differences (95% CI) for all other cognitive domains were calculated.

The main analyses to assess associations between cognition and HRQoL (MCS/PCS) were multivariable regression analyses corrected for the potential confounding variables age, sex, education, smoking, diabetes and psychiatric morbidity per cognitive domain. Cognition and HRQoL were both evaluated at baseline (cross-sectionally). As additional analyses, associations between cognitive function and HRQoL (MCS/PCS) were assessed after a median of 11 months of follow-up (longitudinally) in all patients with a follow-up visit using a linear mixed model. Time

and confounding variables (age, sex, education, smoking, diabetes and psychiatric morbidity) were modeled using fixed effects. All models included random intercept and slope to account for the longitudinal aspect of the data, and an unstructured correlation matrix was used.

Missing data

Cognitive assessment was unavailable for 14 patients (4%). Reasons for lack of cognitive assessment were missing documentation (n = 6), severe disease (e.g. coma or catatonic state, n = 4), language barrier (n = 2), recent full cognitive assessment elsewhere (n = 1) and severe visual disturbance (n = 1). In addition, elements of the cognitive assessment were missing in some of the remaining patients (n = 357): global cognitive function: n = 5 (1%), learning & memory: n = 3 (1%), executive function and complex attention in 26 patients (7%) and psychomotor speed in 14 patients (4%). QoL assessment (SF-36) was missing in 25 patients (7%). Complete case analyses were performed as main analyses and several imputation methods were used as sensitivity analyses.

Sensitivity analyses

Multiple sensitivity analyses were performed. To ascertain the quality of our data as well as the validity of our methodology, known clinical phenotypes, namely the associations between depression and HRQoL (MCS) and anxiety and HRQoL were assessed using multivariable regression analyses corrected for age, sex and education. Furthermore, two analyses were performed to assess the influence of missing data. First, the association between cognition and HRQoL was studied after multiple imputation using chained equation (MICE) of missing HRQoL data. Second, analyses were repeated after imputation of missing cognitive data with the value of the 25th, 10th and 5th percentile from the available data of the missing cognitive domain. In addition, an alternative statistical method to assess the association between cognition and HRQoL was performed: linear regression analyses for the longitudinal analysis instead of linear mixed models. All sensitivity analyses are reported in *Supplementary Materials part II*.
All statistical analyses were performed using STATA statistical software version 16. Figures were created using R version 4.1.2. (package: UpSet) and Graphpad Prism version 9.0.1..

RESULTS

Study population

Three hundred fifty-seven patients were included in this study (see *Supplementary Figure 1*). The majority of patients was female (86%) and mean age was 44 (SD: 14) years. Median SLE disease duration was four years [IQR: 1-13] and median disease activity as measured by SLEDAI-2K was four [IQR: 2 – 8] (*Table 1*). Most patients (64%) received education for 7-12 years. A depressive disorder according to the DSM-5 was present in 80 patients (22%) at study visit. After multidisciplinary assessment, NP symptoms were attributed to SLE (major NPSLE) in 103 patients (29%) and an inflammatory phenotype was the most common subtype of NPSLE (49/103). The type of NPSLE syndromes present according to the 1999 ACR case definitions is provided in *Supplementary Table 1*. In total, 169 patients (47%) had a follow-up visit, with a median follow-up time of eleven months [IQR: 6 – 28].

Table 1 Baseline characteristics of 357 patients referred to the LUMC NPSLE clinic (2007-2019)

	NPSLE clinic 2007-2019 (n = 357)
Demographics	
Female	308 (86)
Age	44 ± 14
Education	
Low	15 (4)
Middle	230 (64)
High	112 (32)
Current Smoking	101 (28)
SLE characteristics	
Duration of SLE, years	4 [1-13]
SLEDAI-2K	4 [2-8]
SDI	1 [0-2]
Comorbidities	
Diabetes	15 (4)
Antiphospholipid syndrome	67 (19)
Depressive disorder	80 (22)
Anxiety disorder	17 (5)
Attribution of NP symptoms	
Major NPSLE	
Inflammatory	49 (14)
Ischemic	29 (8)
Combined	25 (7)
Minor/non-NPSLE	254 (71)

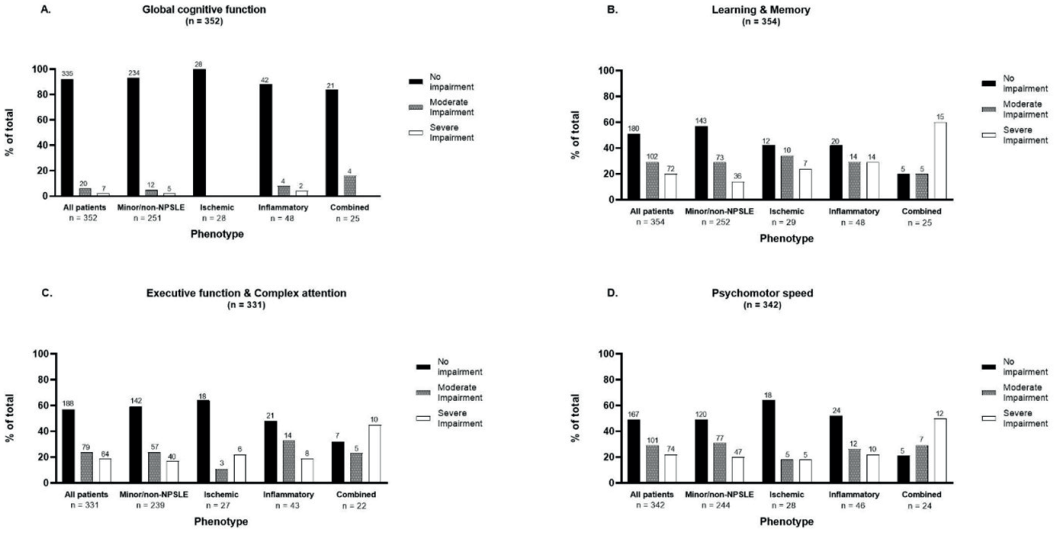
Results are presented as n (%), mean ± sd or median [IQR]
NP = neuropsychiatric; SLE = systemic lupus erythematosus; SLEDAI = SLE disease activity index; SDI = SLICC/ACR damage index

Cognitive impairment

In the entire study population (n = 357), cognitive impairment was common (*Figure 1 and Supplementary Table 2*). The cognitive domain global cognitive function (GCF) was the least affected, with moderate impairment present in 6% and severe impairment in 2% of the 352 patients in whom GCF was assessed. All other cognitive domains were impaired in approximately half of the patients: moderate and severe impairment occurred in the domain learning and memory (L&M) in 29% and 20% of the 354 patients respectively; in executive function and complex attention (EF&CA) this was 24 and 19% of the 331 patients respectively and in the domain psychomotor speed (PS) this was 29% and 22% of the 342 patients respectively. This high level of cognitive impairment was seen in all NPSLE phenotypes and was most pronounced in major NPSLE with a combined phenotype (*Figure 1*). This finding was confirmed using multivariable regression analyses: after correction for age, sex, education and psychiatric morbidity, patients without major NPSLE generally performed better than patients

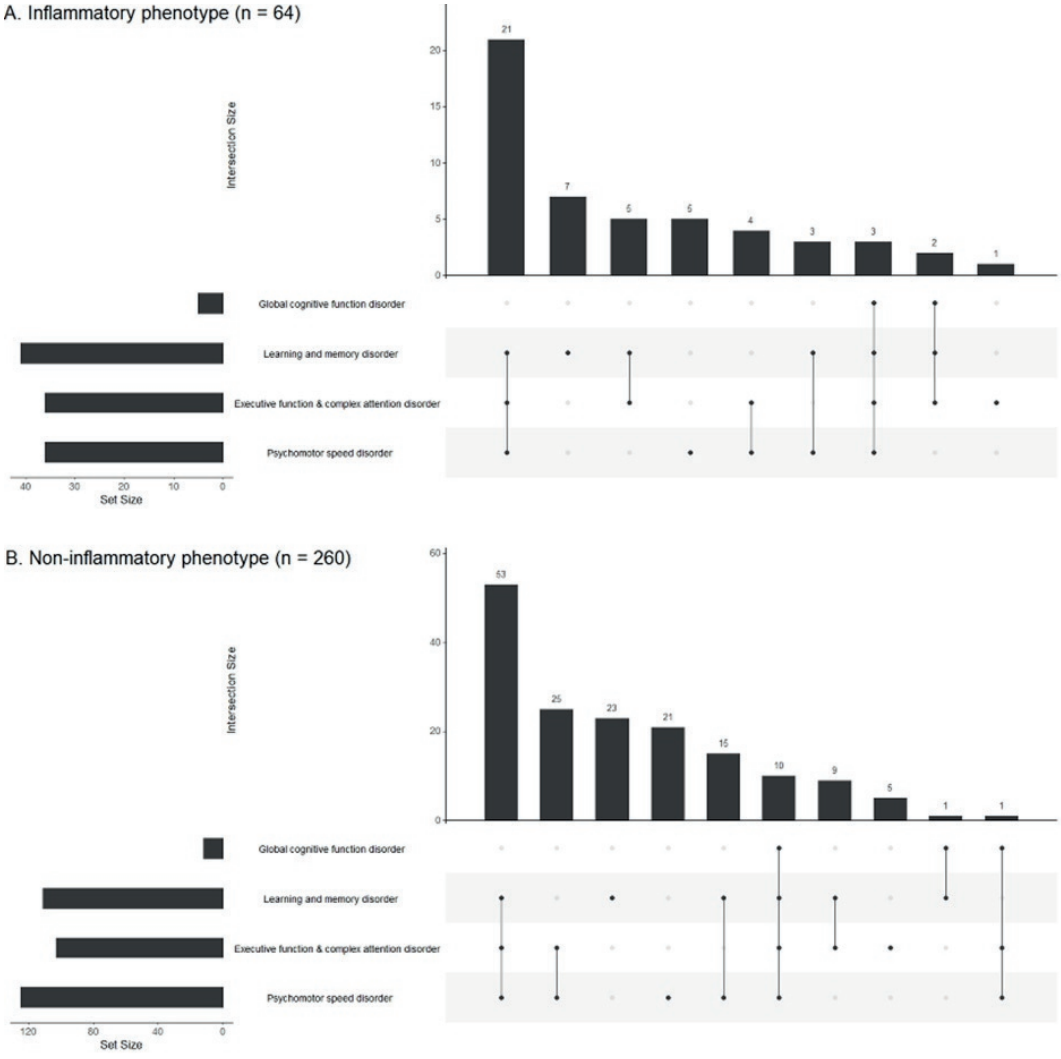
with major NPSLE. This difference was only statistically significant in patients with a combined NPSLE phenotype (*Supplementary Table 3*). Patients with a combined phenotype had a T-score of approximately 10 points lower (1 SD of the normal Dutch population) than patients with minor/non-NPSLE on 3 out of 4 cognitive domains. Furthermore, the pattern of cognitive impairment was evaluated in patients that had information on all four cognitive domains (n = 324). The most common pattern was a combination of impairment in L&M, EF&CA and PS. This pattern was observed more frequently in patients with an inflammatory origin of NP symptoms (inflammatory/combined phenotype) than NP symptoms of other origin (21/64, 33% vs 53/260, 20%) (*Figure 2*).

Figure 1A-D. Prevalence of impairment in different cognitive domains in patients with SLE and neuropsychiatric symptoms of different origins visiting the LUMC clinic between 2007-2019.



The y-axis represents the % of patients within different categories, whereas the numbers above the bars represent the number of patients.

Figure 2A-B. Pattern of cognitive impairment in patients with SLE and neuropsychiatric symptoms with an A. inflammatory origin (inflammatory or combined NPSLE, n = 64) or B. other origin (ischemic NPSLE or other causes, n = 260)



* *Connected dots show which domains are impaired simultaneously. *Only patients that had complete assessment of all four cognitive domains (n = 324) were included in this figure*

As depression was frequently present (22%) and as it is known to influence cognitive performance, a comparison of cognitive impairment was made between patients with (n = 80) and without (n = 277) a depressive disorder. Severe cognitive impairment was more frequent in patients with depression than without in the domains EF&CA and PS. The other domains were similar (*Supplementary Table 4*).

Cognition was also evaluated over time in 122 patients with a follow-up visit within two years. In all cognitive domains, an improvement was seen over time (*Table 2*). Median change (95% CI) of GCF score was 1 (0.5; 1.5) and mean change (95% CI) was 3.7 (1.9; 5.5) for L&M, 4.4 (2.6; 6.3) for EF&CA and 2.6 (0.9; 4.5) for PS. Additional analyses revealed that patients with an inflammatory and combined phenotype showed the most improvement at follow-up in all cognitive domains (*Supplementary Table 5*).

Table 2 Cognitive function at baseline and follow-up visit within two years in patients with SLE and neuropsychiatric symptoms

	Total study population n = 357	**All patients with FU ≤ 2 years** n = 122		
	Baseline	Baseline	Follow-up	Difference* (95% CI)
Global cognitive function	28 [27-30]	28 [27-29]	29 [27-30]	0.7 (0.6; 0.7)
T-score				
Learning & Memory	37.8 ± 13.8	35.1 ± 16.8	38.8 ± 17.1	3.7 (1.9; 5.5)
Executive function & complex attention	40.5 ± 13.2	38.4 ± 14.4	42.8 ± 13.0	4.4 (2.6; 6.3)
Psychomotor speed	38.5± 12.2	36.2 ± 12.7	38.9 ± 12.4	2.6 (0.9; 4.5)

Results are presented as mean ± sd or median [IQR]
*median difference (95% CI) for global cognitive function and mean difference (95% CI) for all other domains

Cognition and HRQoL

HRQoL assessment was available for 332 patients. Mean MCS was 37.8 (SD: 12.8) and mean PCS was 36.6 (SD: 10.0). The association between cognition and HRQoL was assessed cross-sectionally (*Table 3*). An association was found between cognition and MCS in nearly all cognitive domains. For GCF, the association (B (95% CI)) after adjustment was 0.56 (0.07; 1.22) (score: 0-30); for L&M: 0.19 (0.07; 0.31); for EF&CA 0.12 (0.02; 0.22) and for PS: 0.07 (-0.04; 0.18) (T-scores). This means that for example a ten point higher T-score (= 1 SD of the general Dutch population) on the L&M domain was associated with a 1.9 point higher (approximately 1/5 SD of the general Dutch population) MCS in our study. An association was also found between cognition and PCS in nearly all cognitive domains: GCF: 0.37 (-0.14; 0.87), for L&M: 0.14 (0.04; 0.25); for EF&CA 0.16 (0.07; 0.25) and for PS: 0.21 (0.12; 0.31). Additional analyses assessing the association between cognition and the eight domains of HRQoL separately were unremarkable (*Supplementary Table 6*). The longitudinal analyses with the patients that had a follow-up visit (n = 169) showed nearly identical results to the cross-sectional analyses (*Table 4*).

Table 3 Association between baseline cognition and baseline quality of life in patients with SLE and neuropsychiatric symptoms (n = 332)

	Mental component score		
	B	**Adj B***	**95% CI**
Global cognitive function±	0.56	0.64	0.07; 1.22
Learning & Memory *(T-score)*	0.20	00.19	0.07; 0.31
Executive function & complex attention *(T-score)*	0.16	0.12	0.02; 0.22
Psychomotor speed *(T-score)*	0.12	0.07	-0.04; 0.18
	Physical component score		
Global cognitive function±	0.49	0.37	-0.14; 0.87
Learning & Memory *(T-score)*	0.15	0.14	0.04; 0.25
Executive function & complex attention *(T-score)*	0.16	0.16	0.07; 0.25
Psychomotor speed *(T-score)*	0.21	0.21	0.12; 0.31

*These data represent B's and 95% CI's resulting from multiple regression analyses corrected for age, sex, education, psychiatric morbidity, diabetes and smoking

±Global cognitive function: MMSE score (raw score, range: 0-30)

For all T-scores and the MCS + PCS, 10 points = 1 SD of the Dutch general population. *Example interpretation: 10 points higher learning & memory score (=1 SD) is associated with a 1.9 point higher on the MCS (=1/5 SD)*

Table 4 Association between cognition and quality of life over time in patients with SLE and neuropsychiatric symptoms (n = 169)

	Mental component score		
	B	**Adj B***	**95% CI**
Global cognitive function±	0.56	0.68	0.19; 1.16
Learning & Memory *(T-score)*	0.18	0.18	0.09; 0.27
Executive function & complex attention *(T-score)*	0.18	0.14	0.05; 0.23
Psychomotor speed *(T-score)*	0.14	0.10	0.01; 0.19
	Physical component score		
Global cognitive function±	0.59	0.44	0.03; 0.85
Learning & Memory *(T-score)*	0.16	0.15	0.08; 0.22
Executive function & complex attention *(T-score)*	0.14	0.13	0.06; 0.21
Psychomotor speed *(T-score)*	0.17	0.17	0.09; 0.24

*These data represent B' s and 95% CI's resulting from linear mixed model corrected for age, sex, education, psychiatric morbidity, diabetes and smoking

±Global cognitive function: MMSE score (raw score, range: 0-30)

For all T-scores and the MCS + PCS, 10 points = 1 SD of the Dutch general population. *Example interpretation: 10 points higher learning & memory score (=1 SD) is associated with a 1.9 point higher over time on the MCS (=1/5 SD)*

Sensitivity analyses

As quality assurance, the association between depression and HRQoL and anxiety and HRQoL was assessed. As expected, a strong association (B (95% CI)) was found between depression and MCS (-13.6 (-16.6; -10.6)), implying that the presence of a depressive disorder decreased the MCS with more than one standard deviation. A strong association was also found between anxiety and MCS (-8.0 (-14.4; -1.5)). The PCS was not clearly affected by the presence of depression (0.8 (-1.8; 3.4)) or anxiety (-0.1 (-5.2; 4.9)). After multiple imputation using chained equation, similar results for the association between cognition and HRQoL cross-sectionally were found (*Supplementary Table 7*). Different multiple imputations for missing data on cognitive function also yielded similar results to the main analyses (*Supplementary Table 7*). In addition, the association between cognition and HRQoL was assessed longitudinally using linear regression analyses instead of using mixed models, which also revealed similar results (*Supplementary Table 8*).

DISCUSSION

The first aim of our study was to identify the type and severity of cognitive impairment in patients with SLE and NP symptoms of different origins. We demonstrate that objective cognitive impairment is present in around half of patients that are referred for NP symptoms in SLE and is most pronounced in NPSLE patients with both signs of inflammation and ischemia (combined phenotype). Most patients showed a diffuse pattern of cognitive impairment (multiple domains involved) and this pattern was more frequently seen in patients with NP symptoms of an inflammatory origin. In general, some improvement of cognition was seen over time. The second aim was to identify the association between objective cognitive function and HRQoL. We demonstrate that an association is present, but weak.

Impaired cognitive function in multiple cognitive domains, including executive functioning and complex attention, has been demonstrated previously in patients with (NP)SLE.[10,11,33] We have also confirmed this in the past in a specific subset of patients of our NPSLE clinic.[29] Our current study demonstrated that GCF as measured by the MMSE was impaired in <10% of patients, which is lower than most previous reports, with impairment ranging up to 46%.[4] As the MMSE has been developed for severe cognitive dysfunction and dementia, it may be less useful to detect the type of cognitive dysfunction present in patients with SLE. Assessment of the three other cognitive domains enabled the detection of more subtle impairment and revealed that cognitive impairment was present in nearly half of all patients in each cognitive domain, even though median SLE duration was only four years in our study cohort. Apart from the frequency and severity of cognitive impairment, we also sought to study the pattern of impairment, as this could potentially serve as a tool to distinguish NP symptoms due to inflammation (requiring immunosuppressive treatment) from other origins. We found that the most frequent pattern was a diffuse impairment in multiple domains, and that the patterns were very similar in patients with and without an inflammatory origin, but more frequent in the former. As there are more dimensions to cognition than described in our study, future research should investigate whether

there are notable differences in other cognitive domains (e.g. visuospatial processing) between patients with inflammatory and non-inflammatory NP symptoms.

Approximately one third of patients had a follow-up visit at our clinic between six months and two years. In these patients, a stable or even improved cognition was seen over time. Longitudinal data on cognition in SLE is limited changes in all directions have been described (worsening, improvement, no change at all).[34-40] As in clinical practice we encounter many SLE patients that worry about (further) cognitive decline, these data provide some reassurance that cognitive decline is limited over two-years' time. However, only a subset of patients was seen for follow-up, therefore the results should be interpreted with caution. The improvement we have identified in our study may be explained in multiple ways: regression to the mean, as in general more severe patients are seen for follow-up, learning effect, as the same neuropsychological tests were performed at baseline and follow-up, or true improvement over time due to treatment and subsiding of NP symptoms. Further research focusing on the effect of treatment on cognition in patients with SLE is necessary to solve this question.

As cognitive impairment occurs frequently in patients with SLE, we sought to identify its impact on QoL. It is known that several factors related to cognition, such as depression, negatively impact QoL.[12, 13] HRQoL was low in our study, with average component scores more than 1 SD lower than that of the general population. This is in line with our previous work.[41, 42] In our current study, we indeed found a strong negative impact of anxiety and depressive disorders on (mental components of) HRQoL. However, contrary to our expectations and previous research[43], only a weak association appeared to be present between cognition and HRQoL. The few other studies performed to date on this topic showed a clear association between cognition and HRQoL, but their different designs may explain these seemingly contradicting findings. First, the exposure (cognition) was assessed in different ways in all studies and the outcome (HRQoL) was assessed either with the SF-36 or SF-12 (one study).[16] Second, different methodological approaches to calculate the effect of cognition on HRQoL were used: correlation coefficients without correction for confounders[14 15] and an ANCOVA model to predict HRQoL, which also included multiple variables unrelated to cognition.[16] Lastly, one study looked at subjective cognitive impairment rather than objective cognitive impairment.[14] It seems likely that an individuals' perceived limitations in cognition associate (more) strongly with self-assessed HRQoL, and experienced cognitive dysfunction is known to differ strongly from objective cognitive dysfunction in patients with SLE.[44] Hence, we hypothesize that HRQoL is influenced by subjective rather than objective cognitive impairment, and patient reported outcome measures for cognition are perhaps a more useful tool for e.g. future intervention trials with QoL as main outcome.

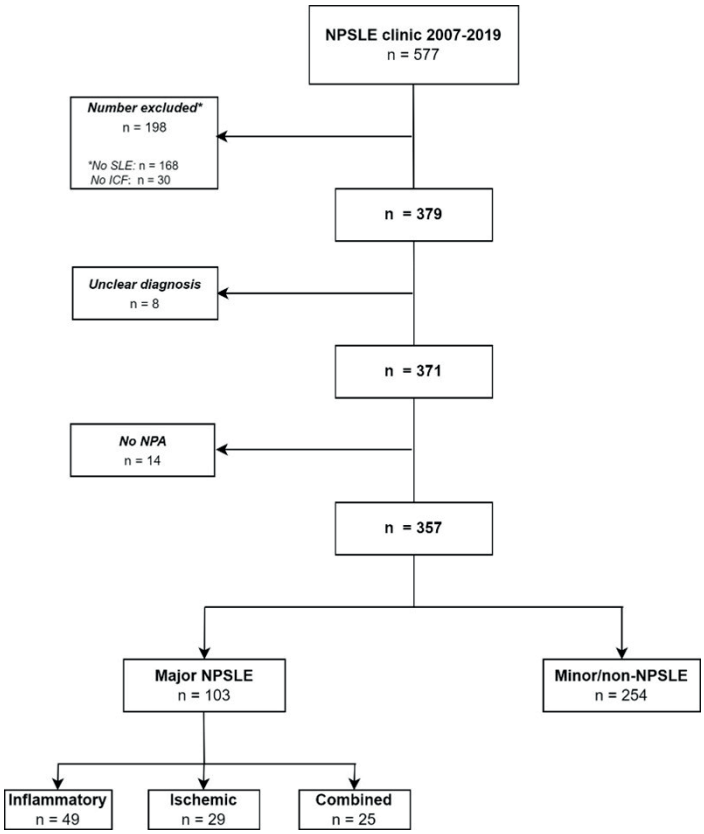
Our study has several strengths. We present a relatively large, well-defined cohort of patients with SLE and NP symptoms of different origins and all patients underwent standardized assessment including neuropsychological assessment. Furthermore, we are the first to study the association between cognition and HRQoL in depth in patients with SLE and using different analysis techniques, we confirm the robustness of our findings.

There are also several limitations to acknowledge. First, there were missing data, which could have influenced our study results. Patients with the most severe NP presentations, that were unable to undergo cognitive assessment, were excluded from this study. It is possible that this has influenced the comparison between NPSLE phenotypes, as severe NP illness is more often seen as a result of inflammation. Seeing the limited number of patients excluded due to severe illness in general (n = 4, of which 3 with inflammatory NPSLE), we believe that this has not strongly influenced our findings. In addition, sensitivity analyses with different types of imputation for missing data did not alter our study results. Second, only a limited number of patients had a follow-up visit and follow-up was performed on indication (e.g. initiation of immunosuppressive treatment). Therefore, the improvement of cognition at follow-up should be interpreted with caution and further research is necessary to identify the pattern of cognition over time. Furthermore, subjective cognition was not measured, which could have resulted in missing more subtle impairment not registered with neuropsychological assessment. Lastly, as patients of this study were from a tertiary referral center for NP symptoms, the frequency of cognitive impairment is not generalizable to the entire SLE population. In addition, although correction for important confounders (including anxiety and depression) were made, it cannot be excluded that the associations between cognition and HRQoL are not generalizable to all patients with SLE.

In conclusion, objective cognitive impairment was found in half of patients with SLE and NP symptoms. Patients with an inflammatory origin of NP symptoms generally showed the most severe impairment and more frequently had impairment in multiple domains. Despite cognitive problems being commonly mentioned as burdensome symptom in clinical practice, only a weak association between HRQoL and objective cognitive function was present.

SUPPLEMENTARY MATERIALS

Supplementary Figure 1 Patient inclusion process



IC = informed consent; *NPA** = neuropsychological assessment; *NPSLE* = neuropsychiatric systemic lupus erythematosus

*Of the patients excluded because of lack of NPA, the NPSLE diagnosis was minor/non-NPSLE: n = 8, inflammatory NPSLE: n = 4 combined NPSLE: n = 2

Remaining Supplementary Files are available through *https://onlinelibrary.wiley.com/doi/abs/10.1002/acr.24904* .

REFERENCES

1. Schwartz N, Stock AD, Putterman C. Neuropsychiatric lupus: new mechanistic insights and future treatment directions. Nat Rev Rheumatol. 2019;15(3):137-52.
2. Ho RC, Husain SF, Ho CS. Cognitive dysfunction in patients with systemic lupus erythematosus: The challenge in diagnosis and management. Rheumatology Practice and Research. 2018;3.
3. Kozora E, Arciniegas DB, Filley CM, West SG, Brown M, Miller D, et al. Cognitive and neurologic status in patients with systemic lupus erythematosus without major neuropsychiatric syndromes. Arthritis & Rheumatism. 2008;59(11):1639-46.
4. Rayes HA, Tani C, Kwan A, Marzouk S, Colosimo K, Medina-Rosas J, et al. What is the prevalence of cognitive impairment in lupus and which instruments are used to measure it? A systematic review and meta-analysis. Seminars in Arthritis and Rheumatism. 2018;48(2):240-55.
5. Seet D, Allameen NA, Tay SH, Cho J, Mak A. Cognitive Dysfunction in Systemic Lupus Erythematosus: Immunopathology, Clinical Manifestations, Neuroimaging and Management. Rheumatology and Therapy. 2021;8(2):651-79.
6. Mackay M. Lupus brain fog: a biologic perspective on cognitive impairment, depression, and fatigue in systemic lupus erythematosus. Immunologic Research. 2015;63(1-3):26-37.
7. Donnellan C, Cohen H, Werring DJ. Cognitive dysfunction and associated neuroimaging biomarkers in antiphospholipid syndrome: a systematic review. Rheumatology. 2021.
8. Plantinga L, Lim SS, Bowling CB, Drenkard C. Perceived stress and reported cognitive symptoms among Georgia patients with systemic lupus erythematosus. Lupus. 2017;26(10):1064-71.
9. Petri M, Naqibuddin M, Carson KA, Wallace DJ, Weisman MH, Holliday SL, et al. Depression and Cognitive Impairment in Newly Diagnosed Systemic Lupus Erythematosus. The Journal of Rheumatology. 2010;37(10):2032-8.
10. Leslie B, Crowe SF. Cognitive functioning in systemic lupus erythematosus: a meta-analysis. Lupus. ;27:920-9.
11. Zabala A, Salgueiro M, Sáez-Atxukarro O, Ballesteros J, Ruiz-Irastorza G, Segarra R. Cognitive Impairment in Patients With Neuropsychiatric and Non-neuropsychiatric Systemic Lupus Erythematosus: A Systematic Review and Meta-analysis. Journal of the International Neuropsychological Society. 2018;24(6):629-39.
12. Mok CC, Chan KL, Ho LY. Association of depressive/anxiety symptoms with quality of life and work ability in patients with systemic lupus erythematosus. Clin Exp Rheumatol. 2016;34(3):389-95.
13. Parperis K, Psarelis S, Chatzittofis A, Michaelides M, Nikiforou D, Antoniade E, et al. Association of clinical characteristics, disease activity and health-related quality of life in SLE patients with major depressive disorder. Rheumatology. 2021;60(11):5369-78.
14. Alarcón GS, Cianfrini L, Bradley LA, Sanchez ML, Brooks K, Friedman AW, et al. Systemic lupus erythematosus in three ethnic groups. X. Measuring cognitive impairment with the cognitive symptoms inventory. Arthritis Care & Research. 2002;47(3):310-9.
15. Tam L-S, Wong A, Mok VCT, Zhu Y-E, Kwok L-A, Li TK, et al. The Relationship Between Neuropsychiatric, Clinical, and Laboratory Variables and Quality of Life of Chinese Patients with Systemic Lupus Erythematosus. J Rheum. 2008;35:1038-45.
16. Calderón J, Flores P, Aguirre JM, Valdivia G, Padilla O, Barra I, et al. Impact of cognitive impairment, depression, disease activity, and disease damage on quality of life in women with systemic lupus erythematosus. Scandinavian Journal of Rheumatology. 2016;46(4):273-80.
17. Zirkzee EJ, Steup-Beekman GM, van der Mast RC, Bollen EL, van der Wee NJ, Baptist E, et al. Prospective study of clinical phenotypes in neuropsychiatric systemic lupus erythematosus; multidisciplinary approach to diagnosis and therapy. J Rheumatol. 2012;39(11):2118-26.
18. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum. 1999;42:599-608.
19. Monahan RC, Fronczek R, Eikenboom J, Middelkoop HAM, Beaart-van de Voorde LJJ, Terwindt GM, et al. Mortality in patients with systemic lupus erythematosus and neuropsychiatric involvement: A retrospective analysis from a tertiary referral center in the Netherlands. Lupus. 2020;29(14):1892-901.
20. Miyakis S, Locksin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haem. 2006;4:295-306.
21. Gladman DD, Ibanez D, Urowitz MB. Systemic Lupus Erythematosus Disease Activity Index 2000. J Rheumatol.

2002;29:288-91.
22. Gladman D, Ginzler E, Goldsmith C, Fortin PR, Liang M, Urowitz MB, et al. The development and initial validation of the Systemic Lupus International Collabarating Clinic/American College of Rheumatology damage index for systemic lupus erythematosus arthritis & Rheumatism. 1996;39:363-9.
23. Hochberg MC. Updating the American College of Rheumatology Revised Criteria for the Classification of Systemic Lupus Erythematosus. Arthritis & Rheumatism. 1997;40:1725.
24. Association AP. Diagnostic and statistical manual of mental disorders (5th ed.)2013.
25. Folstein MF, Folstein SE, McHugh PR. "Minimal-Mental State" A pracitcal method for grading the cognitive state of patients for the clinician J Psych Res 1975;12:189-98.
26. Wechsler D. A Standardized Memory Scale for Clinical Use. The Journal of Psychology. 1945;19:87-95.
27. Stroop JR. Studies of interference in serial verbal reactions. Journal of Experimental Psychology 1935;18:643-62.
28. Tombaugh T. Trail Making Test A and B: Normative data stratified by age and education. Archives of Clinical Neuropsychology. 2004;19(2):203-14.
29. Monahan RC, Inglese F, Middelkoop H, van Buchem M, Huizinga TWJ, Kloppenburg M, et al. White matter hyperintensities associate with cognitive slowing in patients with systemic lupus erythematosus and neuropsychiatric symptoms. RMD Open. 2021;7(2).
30. Schmand B, Houx P, de Koning I. Normen van psychologische tests voor gebruik in de klinische neuropsychologie. Excelbestand met bijbehorende toelichting 2012 [cited 2020]. Available from: www.psynip.nl.
31. Aaronson NK, Muller M, Cohen PDA, Essink-Bot M-L, Fekkes M, Sanderman R, et al. Translation, Validation, and Norming of the Dutch Language Version of the SF-36 Health Survey in Community and Chronic Disease Populations. J Clin Epidemiol. 1998;51:1055-68.
32. Burholt V, Nash P. Short Form 36 (SF-36) Health Survey Questionnaire: normative data for Wales. Journal of Public Health 2011;33:587-603.
33. Loukkola J, Laine M, Ainiala H, Peltola J, Metsänoja R, Auvinen A, et al. Cognitive Impairment in Systemic Lupus Erythematosus and Neuropsychiatric Systemic Lupus Erythematosus: A Population-Based Neuropsychological Study. Journal of Clinical and Experimental Neuropsychology. 2003;25(1):145-51.
34. Hanly JG, Disk JD, Eastwood B. Clinical course of cognitive dysfunction in systemic lupus erythematosus. J Rheum. 1994;21(10):1825-31.
35. Hay EM, Huddy A, Black D, Mbaya P, Tomenson B, Bernstein RM, et al. A prospective study of psychiatric disorder and cognitive function in systemic lupus erythematosus. Ann Rheum Dis. 1994;53:298-303.
36. Hanly JG, Cassell K, Disk JD. Cognitive function in systemic lupus erythematosus: results of a 5-year prospective study. Arthritis & Rheumatism. 1997;40(8):1542-3.
37. Carlomagno S, Migliaresi S, Sannino M, Sanges G, Di Iorio G. Cognitive impairment in systemic lupus erythematosus: a follow-up study. J Neur. 2000;247:273-9.
38. Waterloo K, Omdal R, Husby G, Mellgren SI. Neuropsychological function in systemic lupus erythematosus: a five-year longitudinal study. Rheumatology. 2002;41:411-5.
39. Appenzeller S, Cendes F, Costallat LTL. Cognitive impairment and employment status in systemic lupus erythematosus: A prospective longitudinal study. Arthritis & Rheumatism. 2009;61(5):680-7.
40. Kozora E, Filley CM, Erkan D, Ulug AM, Vo A, Burleson A, et al. Longitudinal evaluation of diffusion tensor imaging and cognition in systemic lupus erythematosus. Lupus. 2018;27:1810-8.
41. Monahan RC, Beaart- van de Voorde LJJ, Steup-Beekman GM, Magro-Checa C, Huizinga TWJ, Hoekman J, et al. Neuropsychiatric symptoms in systemic lupus erythematosus: impact on quality of life. Lupus. 2017;26:1252-9.
42. Magro-Checa C, Beaart- van de Voorde LJJ, Middelkoop HAM, Dane ML, van der Wee NJA, van Buchem MA, et al. Outcomes of neuropsychiatric events in systemic lupus erythematosus based on clinical phenotypes; prospective data from the Leiden NP SLE cohort. Lupus. 2017;26(5):543-51.
43. Mendelsohn S, Khoja L, Alfred S, He J, Anderson M, DuBois D, et al. Cognitive impairment in systemic lupus erythematosus is negatively related to social role participation and quality of life: A systematic review. Lupus. 2021.
44. Hanly JG, Su LI, Omisade A, Farewell VT, Fisk JD. Screening for Cognitive Impairment in Systemic Lupus Erythematosus. The Journal of Rheumatology. 2012;39(7):1371-7.