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Clinical science

Systemic lupus erythematosus phenotypes formed from machine learning with a specific focus on cognitive impairment

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Abstract

Objective: To phenotype SLE based on symptom burden (disease damage, system involvement and patient reported outcomes), with a specific focus on objective and subjective cognitive function.

Methods: SLE patients ages 18–65 years underwent objective cognitive assessment using the ACR Neuropsychological Battery (ACR-NB) and data were collected on demographic and clinical variables, disease burden/activity, health-related quality of life (HRQoL), depression, anxiety, fatigue and perceived cognitive deficits. Similarity network fusion (SNF) was used to identify patient subtypes. Differences between the subtypes were evaluated using Kruskal–Wallis and χ^2 tests.

Results: Of the 238 patients, 90% were female, with a mean age of 41 years (S.D. 12) and a disease duration of 14 years (S.D. 10) at the study visit. The SNF analysis defined two subtypes (A and B) with distinct patterns in objective and subjective cognitive function, disease burden/damage, HRQoL, anxiety and depression. Subtype A performed worst on all significantly different tests of objective cognitive function ($P < 0.03$) compared with subtype B. Subtype A also had greater levels of subjective cognitive function ($P < 0.001$), disease burden/damage ($P < 0.04$), HRQoL ($P < 0.001$) and psychiatric measures ($P < 0.001$) compared with subtype B.

Conclusion: This study demonstrates the complexity of cognitive impairment (CI) in SLE and that individual, multifactorial phenotypes exist. Those with greater disease burden, from SLE-specific factors or other factors associated with chronic conditions, report poorer cognitive functioning and perform worse on objective cognitive measures. By exploring different ways of phenotyping SLE we may better define CI in SLE. Ultimately this will aid our understanding of personalized CI trajectories and identification of appropriate treatments.

Keywords: SLE phenotypes, cognition, machine learning

Introduction

SLE is a complex autoimmune disease that affects multiple organs, including the brain. The ACR defines central or peripheral nervous system involvement in SLE as neuropsychiatric SLE (NPSLE). NPSLE includes 19 focal or diffuse syndromes and cognitive impairment (CI) is one of the most common diffuse conditions [1]. CI is a significant problem in SLE. The prevalence of CI in SLE has been reported to range between

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Rheumatology key messages

- Using machine learning, this study identified two distinct phenotypes of SLE.
- Phenotype variations included differences in objective and subjective cognitive function, psychiatric measures, HRQoL and disease burden.
- The identification of different SLE phenotypes will aid future cognitive impairment clinical trials.

20 and 80% of patients [2]. The discrepancy among estimates is likely due to different measures being used or different cohorts being studied [3]. Self-reported measures of subjective CI in SLE lead to higher prevalence rates [4] compared with objective measures of CI, where the prevalence is closer to 38% [5].

CI significantly affects health-related quality of life (HRQoL) [6], yet to date there are limited treatment options. In part, this is due to uncertainty regarding the cause, which is likely multifaceted [3]. Many of the factors that can cause CI are not specific to SLE. Non-specific SLE factors affecting cognitive function include mood disorders, anxiety, sleep disturbance, fatigue, pain, CNS-acting medication, cerebral small vessel disease and stroke [7–12], all of which are more prevalent in SLE compared with the general population. SLE-specific factors shown to be associated with CI in SLE include disease activity, duration of disease and disease damage, including changes within the brain [2, 6, 13–15]. These specific and non-specific factors may vary from individual to individual with SLE. In addition, many of the factors that affect CI are interlinked and patients can have multiple combinations of these at any given point [3]. The variability in CI causes and presentations makes it difficult to build cognitive profiles, and ultimately difficult to choose appropriate treatments.

In order to try to better understand the potentially individualized concept/construct and causes of CI in SLE, more specific phenotypes are required. Clinical phenotypes of SLE, such as renal *vs* cutaneous involvement, have long been established, and new research to create more homogeneous SLE subgroups based on features such as molecular mechanisms are ongoing [16]. However, problems with CI may not be addressed by these studies. Interestingly, Pisetsky *et al.* [17] recently proposed the idea of phenotyping SLE patients into two symptomology groups: those with 'classic active autoimmune-driven manifestations' and those with other symptoms such as depression, widespread pain, fatigue and CI. In our study, we take this further and phenotyped SLE patients based on symptom burden [disease damage, system involvement and patient-reported outcomes (PROs)], specifically focusing on cognitive function (objective and subjective). The purpose of this is to understand which factors are associated with CI in SLE. If different phenotypes can be determined, then treatments for CI in SLE can be better tailored to each individual. We used machine learning techniques to look for SLE disease burden phenotypes and then examined the contributing factors associated specifically with CI in SLE.

Patients and methods

Participants

Consecutive SLE patients meeting 2019 EULAR/ACR classification criteria for SLE [18] were approached from the Toronto Lupus Clinic at the University Health Network (UHN) Toronto Western Hospital and asked if they wished to participate. Patients provided written informed consent in accordance with the Helsinki Declaration and the study was reviewed and approved by the UHN Research Ethics Board (CAPCR ID: 15-9582). Inclusion criteria required all participants to be 18–65 years old and to have an adequate level of English to enable completion of the cognitive tasks.

Materials

Demographic, clinical and serological data and PRO measures were collected.

PRO measures

PRO measures were collected using the 36-item Short Form Health Survey (SF-36) version 2, general time frame (4 weeks) [19], LupusQoL [20], 20-item Perceived Deficits Questionnaire (PDQ-20) [21], Beck Depression Inventory-II (BDI-II) [22], Beck Anxiety Inventory (BAI) [23] and Fatigue Severity Scale (FSS) [24].

Clinical outcomes

SLE disease activity was assessed using the SLEDAI 2000 (SLEDAI-2K) [25] and disease damage using the SLICC/ACR Damage Index (SDI) [26].

Cognitive assessments

The comprehensive 1 hour ACR Neuropsychological Battery (ACR-NB) [27] was undertaken, using the Hopkins Verbal Learning Test-Revised (HVLT-R) [28] instead of the California Verbal Learning Test (CVLT) [29] and with the addition of Trail Making Test A. The HVLT-R is shorter and an easier test compared with the CVLT, which could have rendered our battery less sensitive than the original ACR-NB. However, the addition of Trail A to our battery helps to offset that, as it adds overall sensitivity to the battery. In addition, the Montreal Cognitive Assessment (MoCA) was administered and the Revised North American Adult Reading Test can assess for estimated premorbid IQ.

The 19 cognitive tests administered represented six cognitive domains: manual motor speed, simple attention and processing speed, visual–spatial construction, language processing, learning and memory and executive functioning (Table 1). Performance on the cognitive tests examining dexterity (finger tapping) can be affected by SLE damage or current pain status. As such, during the administration of the task the psychometrist assessed the participant's physical capability and recorded any limitations. This was then accounted for at the analysis stage.

Design and procedures

Data collected for this study are part of a longitudinal project involving multiple visits. However, this article will only discuss data from the baseline visit, collected 12 January 2016–24

Table 1. ACR-NB domains and cognitive test scores

Domains	Test scores	Domains	Test scores
Manual motor speed	Finger tapping test: dominant hand Finger tapping test: non-dominant hand	Language processing	COWAT Animal fluency test
Simple attention and processing speed	Trail A Stroop colour naming Stroop word reading	Learning and memory	Visual–spatial: RCFT recall, RCFT delay recall, RCFT recognition Verbal [28]: HVLT-R delayed recall, HVLT-R recognition, HVLT-R total recall
Visual–spatial construction	RCFT copy	Executive functioning	Stroop (interference score) WAIS letter-number WAIS-III digit Symbol/SDMT Trail B Auditory consonant Trigrams test

Our battery is identical to the ACR-recommended cognitive battery for adults with SLE except that the HVLT-R was substituted for the CVLT and the Trail Making Test A was added. The HVLT-R is shorter and an easier test compared with CVLT, which could have rendered our battery less sensitive than the original ACR-NB. However, the addition of Trails A to our battery helps to offset that, as it adds overall sensitivity to the battery. In addition, the MoCA was administered and the Revised North American Adult Reading Test can assess for estimated premorbid IQ.
RCFT: Rey–Osterrieth Complex Figure Test; COWAT: Controlled Oral Word Association Test; SDMT: Symbol Digit Modalities Test.
References for all tests can be found in the supplementary material, available at *Rheumatology* online.

September 2019. The majority of participants completed all outcome measures on the same day; the remaining participants completed all the assessments within 1 month. Cognitive testing was performed by six psychometrists, all of whom received significant training and supervision from the study psychologist. Before a new psychometrist started working with participants their testing was checked for high agreement on administration and scoring; no differences were observed.

Analyses

Algorithm to determine CI status

Participants were categorized as having CI based on the following algorithm: participants must have impaired performance in two or more domains (domains defined in Table 1), domains 1–4 were considered impaired if one or more tests within the domains had a *z*-score ≤ -1.5 and domains 5 and 6 required two or more tests to have a *z*-score ≤ -1.5 [30].

The definition of CI in SLE has yet to be formally established and researchers have used varying definitions [5, 31]. Our algorithm is based on ACR guidance and results from previous studies that suggest an SD of 2 or a *z*-score cut-off of 1.5 is indicative of impairment on cognitive tests [32, 33]. This study had multiple tests within cognitive domains, so to avoid overestimation of CI in a specific domain, the above algorithm was devised.

SNF

The demographic and clinical data, PROs and cognitive test results were used in the SNF analysis. Where data were missing, imputation using the median values from the whole sample was used [34]. All variables used within the SNF analysis were first assigned to one of seven key themed groups: patient baseline characteristics, anxiety and depression, health-related quality of life (HRQoL), disease burden, clinical blood work and medication and objective and subjective measures of cognitive function. The group assignation of each variable can be seen in Table 2. These grouped variables, 'data sets' hereafter, were then transformed into patient similarity networks and fused using SNF to create an integrated network [35]. The eigengaps algorithm was used to identify the best number of clusters based on the fused network. Spectral clustering, a type of clustering that uses a combination of principal component analysis (PCA) and *k*-means clustering, was then used to generate participant subtypes [36].

PCA

Using PCA, the ACR-NB tests were reduced to generate a factor score (CI factor score). PCA was used to obtain lower-dimensional data while preserving as much of the data's variation as possible.

Differences between the SNF subtypes

We then assessed the associations of the SNF subtypes with all the variables in our dataset using χ^2 tests for categorical data and Kruskal–Wallis tests for continuous data. Significance was set at $P < 0.05$ and Bonferroni corrected significance was set at $P < 0.0008$.

Results

We recruited 360 participants; 331 declined to participate. Those who declined were slightly older (41 *vs* 45 years), were diagnosed with SLE at an older age (27 *vs* 29 years) and had a longer disease duration (14 *vs* 16 years). No differences were seen in sex or education level. Of those recruited, 38 withdrew and 21 were withdrawn by the principal investigator (PI). Reasons for withdrawals included language barriers, visual problems, inability to dedicate time to the study or no longer wished to participate. A further 63 were removed due to missing data that could not be imputed. Comparisons between those who withdrew/were excluded and those who were included showed differences in education (excluded had a greater number who attended college but a lesser number who attended university) and disease activity levels (excluded had a higher score, 4 *vs* 3). No differences were seen in age, sex, age at diagnosis, disease duration, disease damage or medication use. The following results represent data from 238 SLE participants. All participants completed all cognitive tests on the same day. Table 3 shows the baseline characteristics and that this cohort is a representative sample of SLE patients.

The SNF analysis revealed two participant subtypes based on the seven data sets listed in Table 2. Subtype A was

Table 2. Grouped variables (data sets)

Data set	Variables
Baseline[a] characteristics	Age at SLE diagnosis Age at baseline visit Disease duration at baseline visit Sex Employment status up to baseline visit Education level up to baseline visit Income quintile
Anxiety and depression	Beck Depression Inventory-II score Beck Anxiety Inventory score
HRQoL	SF-36: Bodily Pain, General Health, Mental Health, Physical Functioning, Role Emotional Role Physical, Social Functioning, Vitality, Physical Score, Mental Score LupusQoL: Physical, Emotional, Body Image, Pain, Planning, Fatigue, Intimate, Burden
Disease burden	SLEDAI-2K score SDI total score and SDI by organs: SDI Ocular, SDI Neurologic, SDI Renal, SDI Pulmonary, SDI Cardiologic, SDI Vascular, SDI Gastrointestinal, SDI MSK, SDI Skin, SDI Gonad, SDI Diabetes, SDI Malignancy SLE involvement in the following systems within the last 10 years based on the nine organ systems of the SLEDAI-2K: CNS, Vasculitis, Skin, MSK, Serositis, Renal, Immunology, Haematology, Constitutional FSS Fibromyalgia
Clinical blood work and medication	Treated within 3 months of study visit with: • Glucocorticoids • Antimalarials • Immunosuppressives Average prednisone dose within 3 months of baseline visit Blood test results for (results within 3 months of baseline visit or closest possible result): • Anti-Ro • Anti-La • Anti-Smith • Anti-RNP • Anti-phospholipid (anti-cardiolipins IgG and IgM and lupus anticoagulant) • Anti-dsDNA • Anti-smRNP • Anti-Scl-70 • Anti-Jo-1 • Anti-centromere • Anti-chromatin • Anti-ribosomal P • C3 • C4
Objective cognitive measures	All ACR-NB cognitive tests as seen in Table 1
Subjective cognitive measures	PDQ-20: individual question results, total score and the four subscores (attention and concentration, retrospective memory, prospective memory and planning and organisation)

The research team identified seven key themes/data sets. Variables collected as part of the study were then assigned to the most relevant data set. The assignation of all variables can be seen in this table.
[a] Baseline refers to the first visit when all measures were collected, including patient characteristics, PROs and cognitive assessment.
References for all tests can be found in the supplementary material, available at *Rheumatology* online.

composed of 119 participants and subtype B of 119 (Fig. 1), the groups were of equal size by chance.

Age, sex and age at diagnosis were statistically different between the two subtypes (Table 4) but disease duration and current immunosuppressant, glucocorticoid and biologic use were not. Subtype A was older at the study visit and at age of diagnosis compared with subtype B, but had a comparable disease duration. Subtype B had more participants with positive anti-dsDNA, low C3 and low C4 results. Significant differences between the subtypes for the PROs were found from the HRQoL measures, fatigue score and depression and anxiety measures. Significant differences in disease measures were found for comorbid fibromyalgia, disease activity, disease damage [specifically in the following organs: musculoskeletal (MSK), cardiovascular and gonadal] and disease manifestations in the last 10 years (specifically MSK, CNS and skin disease involvement; Table 4). Subtype A had greater levels of fatigue, depression, anxiety, fibromyalgia and disease burden/damage and poorer HRQoL compared with subtype B.

Cognitive measures

The two subtypes were significantly different on all subjective measures of cognition from the PDQ-20 and 11 of the 19 objective cognitive test scores from the ACR-NB. Subtype A experienced the worst cognitive impairment on all subjective and objective measures (Table 4). Although more participants in subtype A [$n = 66$ (55%)] had CI, as defined by our algorithm, compared with subtype B [$n = 55$ (44%)], this was not statistically significant ($P = 0.19$).

From the PCA, the first two dimensions (components) explained 40.1% of the variance in neuropsychological performance. The first dimension (subsequently referred to as the CI factor score), explained 29.7% of the variance and primarily included tests such as complex processing speed [Wechsler Adult Intelligence Scale, 3rd ed. (WAIS-III) digit symbol], executive function–task switching (Trail B) and verbal memory (HVLT-R total recall). A subtype comparison with the CI factor score showed again that subtype A had lower scores, indicating greater CI compared with subtype B ($P < 0.001$; Fig. 2).

The finger tapping dexterity test was found to be invalid for four participants due to physical or pain difficulties caused by SLE, as reported by the psychometrist. The analysis was run with these four results removed.

Table 3. Baseline characteristics of the study cohort ($N = 238$)

Variables	Values
Age at assessment, years, mean (S.D.)	41 (12)
Female, *n* (%)	214 (90)
Education level (data missing for 4 patients), *n* (%)	Grade 8: 9 (3.8) High school graduate: 44 (18.5) College: 80 (33.6) University: 105 (44.1)
Age at diagnosis, years, mean (S.D.)	26 (11)
Disease duration at assessment, years, mean (S.D.)	14 (10)
SLEDAI-2K score, mean (S.D.)	3.0 (3.4)
SDI score, mean (S.D.)	1.1 (1.5)
Immunosuppressant use, *n* (%)	131 (55)
Current antimalarial use, *n* (%)	195 (82)
Glucocorticoid use, *n* (%)	115 (48)
Biologic medication use, *n* (%)	15 (6.3)

Secondary SNF analysis

A total of 63 participants had to be removed from the analysis due to large amounts of missing baseline data from PROs and psychiatric measures. In order to include these participants in a repetition of our analyses, for sensitivity purposes, we checked their subsequent study visits for a more complete data set. If a more complete visit was found, this was used in our secondary analyses. A total of 21 participants were added to the second SNF analysis (Supplementary Fig. S1, available at *Rheumatology* online).

Using 259 participants in the second SNF analysis revealed no differences (Supplementary Table S1, available at *Rheumatology* online) except the subtype numbers: subtype A = 135, subtype B = 124. All participants remained in the same subtype for both SNF analyses, except two, who were originally in subtype B but moved to subtype A in the second SNF.

Discussion

In this analysis using machine learning, we identified two distinct SLE participant subtypes. These subtypes had important differences in a range of features, including objective and subjective cognitive function measures, HRQoL, disease burden, psychiatric measures, age, age at diagnosis and gender. Subtype A had the most objective and subjective cognitive impairment, as well as scoring more poorly on all PROs and clinical measures mentioned compared with subtype B.

Subtype differences were seen across all cognitive domains except manual motor speed and simple attention. Subtype A performed worse on all statistically significant different cognitive tests (11 of 19) compared with subtype B. However, the percentage of people with CI (as defined by our algorithm) did not differ statistically between the two subtypes. This is of

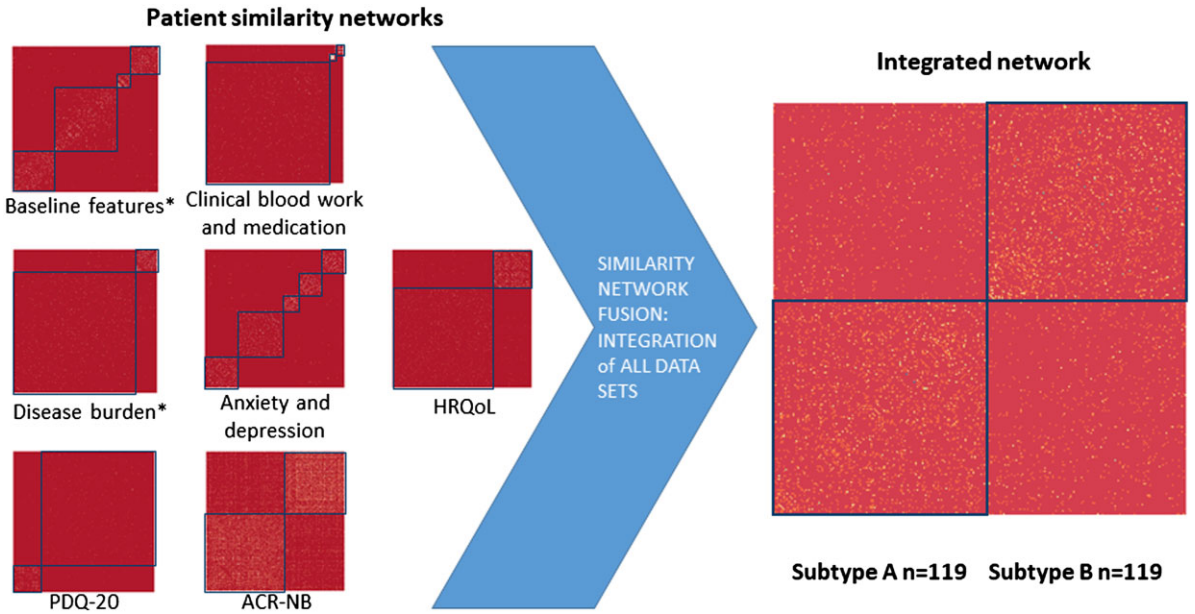

Figure 1. SNF for baseline visit data. Prior to our SNF analysis we created seven data sets: patient baseline features, clinical blood work and medication, disease burden, anxiety and depression, HRQoL, subjective (PDQ-20) and objective (ACR-NB) measures of cognitive function (Table 2). These data sets were transformed into patient similarity networks. The patient similarity networks were then fused using SNF to create an integrated network. The above diagram shows the seven patient similarity networks on the left and the integrated network on the right. Clusters for the networks are outlined in blue. The integrated network revealed two significant cluster subtypes. These subtypes were defined by patterns from the seven patient similarity networks and each subtype has 119 participants. *Demographic and clinical variables used within the patient baseline and disease burden information included age, sex, marital and employment status, education and income level, age at diagnosis, disease damage, disease activity, fatigue and fibromyalgia status

Table 4. Significant differences between the subtypes for variables inputted into the original SNF analysis ($N = 238$)

Variables	Subtype A ($n = 119$)	Subtype B ($n = 119$)	*P*-value
Baseline demographic and clinical variables			
Age at assessment, years, median (IQR)	46 (31–54)	37 (30–47)	0.001
Female, *n* (%)	113 (95)	101 (85)	0.016
Age at diagnosis, years, median (IQR)	28 (20–36)	23 (17–30)	0.003
Anti-dsDNA number positive, *n* (%)	37 (31)	61 (51)	0.002
Low C3, *n* (%)	33 (28)	63 (53)	**<0.001**
Low C4, *n* (%)	3 (3)	23 (19)	**<0.001**
Depression, anxiety and fatigue, median (IQR)[a]			
Beck Depression Inventory-II	22 (14–31)	7 (2–11)	**<0.001**
Beck Anxiety Inventory	23 (17–34)	7 (3–11)	**<0.001**
FSS	5.67 (4.56–6.22)	3.22 (1.95–4.44)	**<0.001**
HRQoL, median (IQR)[b]			
SF-36 Mental	36 (29–46)	54 (45–58)	**<0.001**
SF-36 Physical Role	31 (26–37)	50 (43–54)	**<0.001**
LupusQoL Physical Health	53 (36–69)	94 (81–97)	**<0.001**
LupusQoL Burden	50 (17–67)	83 (75–92)	**<0.001**
LupusQoL Pain	50 (33–67)	100 (83–100)	**<0.001**
LupusQoL Emotional	63 (42–77)	92 (79–100)	**<0.001**
LupusQoL Body Image	69 (40–88)	92 (75–100)	**<0.001**
LupusQoL Planning	58 (42–75)	100 (92–100)	**<0.001**
LupusQoL Fatigue	38 (25–53)	81 (66–94)	**<0.001**
LupusQoL Intimate	63 (25–75)	100 (100–100)	**<0.001**
Fibromyalgia, *n* (%)			
Fibromyalgia	25 (21)	3 (3)	**<0.001**
SLICC/ACR Damage Index			
SDI total score, median (IQR)	1 (0–2)	0 (0–1)	**<0.001**
MSK damage, *n* (%)	34 (29)	11 (9)	**<0.001**
Cardiovascular damage, *n* (%)	14 (12)	1 (1)	0.001
Gonadal, *n* (%)	6 (5)	0	0.04
Disease activity			
SLEDAI-2K score, median (IQR)	2 (0–4)	3 (0.5–4)	0.01
SLE system involvement within the last 10 years, *n* (%)			
MSK	108 (91)	88 (74)	0.001
CNS	33 (28)	16 (13)	0.01
Skin	111 (93)	100 (84)	0.04
Subjective measures of cognition—PDQ-20,[c] median (IQR)			
Attention and concentration	12 (10–15)	6 (3–9)	**<0.001**
Retrospective memory	10 (7–13)	5 (2–7)	**<0.001**
Prospective memory	9 (6.5–11)	4 (2–6)	**<0.001**
Planning and organisation	11 (8–14)	5 (2–7)	**<0.001**
Total score	41 (34–51)	21 (11–29)	**<0.001**
Objective measures of cognition—ACR-NB *z*-scores,[d] median (IQR)			
2.1 Trail A	0.51 (−0.32–0.98)	0.76 (0.05–1.25)	0.01
2.2 Stroop colour naming	−0.2 (−0.87–0.67)	0.2 (−0.61–1.08)	0.03
3 RCFT copy	−0.95 (−2.45–0.08)	−0.26 (−1.24–0.43)	0.01
4.1 COWAT	−0.33 (−0.98–0.29)	0.04 (−0.78–0.65)	0.02
5.1 RCFT recall	−1.07 (−1.90 to −0.08)	−0.39 (−1.29–0.37)	**<0.001**
5.2 RCFT delay recall	−0.99 (−2.05 to −0.08)	−0.52 (−1.34–0.41)	0.01
5.4 HVLT-R delayed recall	−1.13 (−2.05 to −0.08)	−0.61 (−1.64–0.28)	**<0.001**
5.6 HVLT-R recognition	−1.06 (−1.75 to −0.52)	−0.67 (−1.39–0.17)	**<0.001**
6.1 Stroop interference score	0.24 (−0.41–0.81)	0.61 (−0.08–1.34)	0.01
6.3 WAIS-III digit symbol	0 (−0.99–0.67)	0.33 (−0.33–0.99)	**<0.001**
6.5 Auditory consonant trigrams test	−1.19 (−1.80–0.23)	0.11 (−1.50–0.82)	**<0.001**

[a] Higher scores indicate greater levels of depression, anxiety and fatigue.
[b] Higher scores indicate better HRQoL.
[c] Higher scores indicate more perceived cognitive impairment.
[d] Higher *z*-scores indicate less cognitive impairment.
Not significant: cognitive impairment based on algorithm ($P = 0.19$), domain 1.1 ($P = 0.54$), domain 1.2 ($P = 0.3$), domain 2.3 ($P = 0.53$), domain 4.2 ($P = 0.05$), domain 5.3 ($P = 0.42$), domain 5.5 ($P = 0.3$), domain 6.2 ($P = 0.11$), domain 6.4 ($P = 0.18$).
Bold text = Bonferroni corrected.
RCFT: Rey–Osterrieth Complex Figure Test; COWAT: Controlled Oral Word Association Test.

importance, as it suggests a dichotomous definition of CI in SLE may fail to identify the more subtle CI differences that are common in SLE [3] and a better way to define CI in SLE may be required. The current gold standard to assess CI in SLE proposes administering multiple cognitive tests covering six cognitive domains [32]. Using results from multiple tests is difficult for hypothesis testing and, as such, many SLE researchers have tried to simplify this into a dichotomous variable [31], as we did. However, a better approach may involve using continuous variables, such as those derived from factor

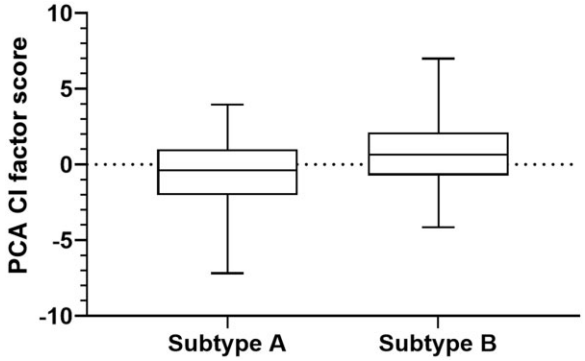

Figure 2. Subtype comparison with the CI factor score. Differences between the two subtypes for the PCA determined the CI factor score (generated from all ACR-NB tests; $P < 0.001$. The CI factor score accounted for 29.7% of the variance and was associated predominantly with tests of executive function and verbal memory

analysis. In our study we also used PCA as a method to combine multiple cognitive test scores. Our PCA-generated factor score was found to be significantly different between our subtypes, again showing subtype A to be more impaired.

The disease damage and system involvement variables revealed significant differences between the subtypes in multiple systems. For disease damage, these included differences in cardiovascular, MSK and gonadal systems, and for system involvement these included MSK, CNS and skin. Subtype A had higher levels of burden in all of these systems compared with subtype B. Although a direct association between CI and levels of disease burden are beyond the scope of this article, it is interesting to see that the subtype with greater levels of disease burden also performed worse on cognitive testing. Many of the systems that have been shown to be more affected in subtype A have been found to be associated with CI in previous research and these systems are discussed below.

Both CNS involvement and cardiovascular damage in SLE are associated with alterations to brain structures and cognitive decline [2, 37]. Studies have repeatedly shown connections between cardiovascular disease and cognitive impairment [37]. Also, risk factors associated with cardiovascular disease are often associated with cerebrovascular disease [38]. Cerebral small vessel disease (SVD), a marker of cerebrovascular disease, has been shown to affect cognitive function in SLE patients [11, 39]. SLE patients with evidence of SVD, such as white matter hyperintensities, had a greater association with CI and stroke [12].

MSK involvement may be linked to deficits in cognition through pain. It is well known that MSK involvement can cause pain in SLE [40], and pain is associated with impaired cognition [41, 42]. This relationship is bidirectional, with both cognition and pain sharing neuronal pathways [43]. Distraction from cognitive tasks can help to reduce feelings of pain [43, 44], but more frequently pain negatively impacts cognition. The limited processing capacity of the brain means that the experience of pain can divert attention away from cognitive tasks, leading to CI. A worry or fear of pain can also cause hypervigilance, meaning an increased focus on pain and a reduction in cognitive abilities [44, 45]. Indirectly pain can also impact cognition by its associations with mood disorders and poor sleep quality [9, 45]. Further research examining direct associations between CI, CNS and MSK involvement and cardiovascular damage, while exploring different phenotypes of SLE is needed.

Diagnosis of fibromyalgia was found to be different between our subtypes, with a greater number of those in subtype A having this comorbidity. Also, subtype A scored worst on all HRQoL subscores compared with subtype B. Previous work has found HRQoL to be negatively impacted by CI [46]. This has also been shown to affect employment status and social interactions [46], indicating that understanding the links between CI and HRQoL is vital to improve patients' lives.

Fatigue levels were also found to be different between the subtypes. Fatigue is a complex construct and can be separated into multiple subdomains, such as cognitive and physical [47]. Cognitive fatigue has been associated with altered brain processes during cognitive tasks and may be linked to patient-reported 'brain fog' or subjective measures of cognitive function [48]. One theory suggests that overuse of compensatory brain mechanisms can lead to cognitive fatigue and potentially overt CI [48, 49]. However, others have failed to find associations between subjective and objective measures of cognition, stating subjective CI is more closely associated with depression and anxiety than objective CI [4]. Depression and anxiety are important factors when assessing cognitive function, and we did find differences between the subtypes for these factors, but they may not be the main driving factor [48]. What was interesting about this work was that we found the subtype with poorer performance in objective cognitive measures also had higher self-reported subjective CI. Subtype A had the highest levels of impairment for both measures. Clearer definitions and understandings of the relationships are needed for the terms cognitive fatigue, brain fog and subjective and objective measures of CI in SLE.

This study does have some limitations. First, the data reported are all cross-sectional, so they do not provide answers regarding long-term outcomes. However, we have collected these data for multiple time points and will begin longitudinal analysis as our next step. Second, we had missing data for some tests on the ACR-NB, SF-36 and autoantibody results. To address this, in the SNF analysis, median imputation was used. In addition, a sensitivity analysis with patient data imputed from alternative research visits showed concordant results. Third, due to the complexity of cognitive function in SLE and the many factors associated with this condition, a number of variables were considered and analyses undertaken. In order to control for the multiple comparisons, we also highlighted Bonferroni-corrected significant results within our main results (Table 4). It is also worth noting the high level of education within our study population, which is known to impact cognitive ability [50]. This is representative for our Canadian lupus cohort but may not be in other settings. Fourth, we found significant results for disease damage in the gonadal system, which may be linked to the effects of oestrogen on CI. However, it is a limitation of this study that we do not have further information on oestrogen status, but this should be considered in future studies. Lastly, our results showed significant findings for MSK involvement/damage, HRQoL pain subscore and fibromyalgia, suggesting higher levels of pain was an important factor within subtype A. However, we did not include a stand-alone pain measure in this study and therefore could not explore this further. Given the potential importance of pain on CI in SLE, this will be taken into account in future work.

This study is the first to use machine learning to phenotype symptom burden in SLE with a specific focus on CI. The results demonstrate the complexity of CI in SLE and that individual, multifactorial phenotypes exist. The main characteristics of those with increased impairment on objective cognitive tasks were greater subjective levels of CI, disease burden and damage; poorer psychiatric status; poorer HRQoL; and increased levels of pain and fatigue. Further work investigating cognitive fatigue and brain mechanisms in SLE is needed. Overall, these results may aid in phenotyping CI in SLE. This will then help in our understanding of personalized CI trajectories and identifying appropriate treatment options.

Supplementary data

Supplementary data are available at *Rheumatology* online.

Data availability

All data relevant to this study are included in the article or uploaded as supplementary information.

Authors' contributions

M.B. and C.T. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in the study conception and design, acquisition of data and analysis and interpretation of data.

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References

1. Govoni M, Hanly JG. The management of neuropsychiatric lupus in the 21st century: still so many unmet needs? Rheumatology (Oxford) 2020;59:v52–62.
2. Ho RC, Husain SF, Ho CS. Cognitive dysfunction in patients with systemic lupus erythematosus: the challenge in diagnosis and management. Rheumatol Pract Res 2018;3:205990211879243.
3. Seet D, Allameen NA, Tay SH, Cho J, Mak A. Cognitive dysfunction in systemic lupus erythematosus: immunopathology, clinical manifestations, neuroimaging and management. Rheumatol Ther 2021;8:651–79.
4. Hanly JG, Su L, Omisade A, Farewell VT, Fisk JD. Screening for cognitive impairment in systemic lupus erythematosus. J Rheumatol 2012;39:1371–7.
5. Rayes HA, Tani C, Kwan A *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. Semin Arthritis Rheum 2018;48:240–55.
6. Mackay M. Lupus brain fog: a biologic perspective on cognitive impairment, depression, and fatigue in systemic lupus erythematosus. Immunol Res 2015;63:26–37.
7. McLaurin EY, Holliday SL, Williams P, Brey RL. Predictors of cognitive dysfunction in patients with systemic lupus erythematosus. Neurology 2005;64:297–303.
8. Peralta-Ramirez MI, Coin-Mejias MA, Jimenez-Alonso J *et al*. Stress as a predictor of cognitive functioning in lupus. Lupus 2006;15:858–64.
9. Kozora E, Ellison MC, West S. Depression, fatigue, and pain in systemic lupus erythematosus (SLE): relationship to the American College of Rheumatology SLE neuropsychological battery. Arthritis Rheum 2006;55:628–35.
10. Sweet JJ, Doninger NA, Zee PC, Wagner LI. Factors influencing cognitive function, sleep, and quality of life in individuals with systemic lupus erythematosus: a review of the literature. Clin Neuropsychol 2004;18:132–47.
11. Wiseman SJ, Bastin ME, Jardine CL *et al*. Cerebral small vessel disease burden is increased in systemic lupus erythematosus. Stroke 2016;47:2722–8.
12. Mikdashi JM, Castellani RJ. Cerebral small vessel disease in systemic lupus erythematosus: histopathological study. In: 2014 ACR/ARHP Annual Meeting. http://acrabstracts.org/abstract/cerebral-small-vessel-disease-in-systemic-lupus-erythematosus-histopathological-study/.
13. Mackay M, Tang CC, Vo A. Advanced neuroimaging in neuropsychiatric systemic lupus erythematosus. Curr Opin Neurol 2020;33:353–61.
14. Barraclough M, McKie S, Parker B *et al*. Altered cognitive function in systemic lupus erythematosus and associations with inflammation and functional and structural brain changes. Ann Rheum Dis 2019;78:934–40.
15. Tay SH, Mak A. Anti-NR2A/B antibodies and other major molecular mechanisms in the pathogenesis of cognitive dysfunction in systemic lupus erythematosus. Int J Mol Sci 2015;16:10281–300.
16. Guthridge JM, Lu R, Tran LT-H *et al*. Adults with systemic lupus exhibit distinct molecular phenotypes in a cross-sectional study. eClinicalMedicine 2020;20:100291.
17. Pisetsky DS, Clowse MEB, Criscione-Schreiber LG, Rogers JL. A novel system to categorize the symptoms of systemic lupus erythematosus. Arthritis Care Res 2019;71:735–41.
18. Aringer M, Costenbader K, Daikh D *et al*. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis 2019;78:1151–9.
19. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 1994;32:40–66.
20. McElhone K, Abbott J, Shelmerdine J *et al*. Development and validation of a disease-specific health-related quality of life measure, the LupusQol, for adults with systemic lupus erythematosus. Arthritis Rheum 2007;57:972–9.

21. Sullivan J, Edgley K, Dehoux E. SA survey of multiple sclerosis: part 1: perceived cognitive problems and compensatory strategy use. Can J Rehabil 1990;4:99–105.
22. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Personal Assess 1996;67:588–97.
23. Kwan A, Marzouk S, Ghanean H *et al.* Assessment of the psychometric properties of patient-reported outcomes of depression and anxiety in systemic lupus erythematosus. Semin Arthritis Rheum 2019;49:260–6.
24. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The Fatigue Severity Scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121–3.
25. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288–91.
26. Gladman D, Ginzler E, Goldsmith C *et al.* The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363–9.
27. Bertsias GK, Ioannidis JP, Aringer M *et al.* EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. Ann Rheum Dis 2010;69:2074–82.
28. Shapiro AM, Benedict RH, Schretlen D, Brandt J. Construct and concurrent validity of the Hopkins Verbal Learning Test–revised. Clin Neuropsychol 1999;13:348–58.
29. Reitan RM, Wolfson D. The Halstead-Reitan neuropsychological test battery: theory and clinical interpretation. Tucson, Arizona: Neuropsychology Press, 1985.
30. Tayer-Shifman OE, Green R, Beaton DE *et al.* Validity evidence for the use of automated neuropsychologic assessment metrics as a screening tool for cognitive impairment in systemic lupus erythematosus. Arthritis Care Res 2020;72:1809–19.
31. Yuen K, Green R, Bingham K *et al.* Metrics and definitions used in the assessment of cognitive impairment in systemic lupus erythematosus: a systematic review. Semin Arthritis Rheum 2021;51: 819–30.
32. ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599–608.
33. He JW, Diaz Martinez JP, Bingham K *et al.* Insight into intraindividual variability across neuropsychological tests and its association with cognitive dysfunction in patients with lupus. Lupus Sci Med 2021;8:e000511.
34. Berkelmans GFN, Read SH, Gudbjörnsdottir S *et al.* Population median imputation was noninferior to complex approaches for imputing missing values in cardiovascular prediction models in clinical practice. J Clin Epidemiol 2022;145:70–80.
35. Wang B, Mezlini AM, Demir F *et al.* Similarity network fusion for aggregating data types on a genomic scale. Nat Methods 2014;11: 333–7.
36. Von Luxburg U. A tutorial on spectral clustering. Stat Comput 2007;17:395–416.
37. Leritz EC, McGlinchey RE, Kellison I, Rudolph JL, Milberg WP. Cardiovascular disease risk factors and cognition in the elderly. Curr Cardiovasc Risk Rep 2011;5:407–12.
38. Arboix A. Cardiovascular risk factors for acute stroke: risk profiles in the different subtypes of ischemic stroke. World J Clin Cases 2015;3:418–29.
39. Wiseman SJ, Bastin ME, Amft EN *et al.* Cognitive function, disease burden and the structural connectome in systemic lupus erythematosus. Lupus 2018;27:1329–37.
40. Di Franco M, Guzzo MP, Spinelli FR *et al.* Pain and systemic lupus erythematosus. Reumatismo 2014;66:33–8.
41. Beck K, Gao X, Cheng Y, Greco CM. Patient-reported cognitive impairment, pain, and depressive symptoms in patients with systemic lupus erythematosus and comorbid depression. Arthritis Rheumatol 2015;67(Suppl 10):abstract 2476.
42. Reyes Del Paso GA, Pulgar A, Duschek S, Garrido S. Cognitive impairment in fibromyalgia syndrome: the impact of cardiovascular regulation, pain, emotional disorders and medication. Eur J Pain 2012;16:421–9.
43. Khera T, Rangasamy V. Cognition and pain: a review. Front Psychol 2021;12:673962.
44. Seminowicz DA, Davis KA. A re-examination of pain-cognition interactions: implications for neuroimaging. Pain 2007;130:8–13.
45. Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. Prog Neurobiol 2011;93:385–404.
46. Mendelsohn S, Khoja L, Alfred S *et al.* Cognitive impairment in systemic lupus erythematosus is negatively related to social role participation and quality of life: a systematic review. Lupus 2021;30: 1617–30.
47. Kawka L, Schlencker A, Mertz P, Martin T, Arnaud L. Fatigue in systemic lupus erythematosus: an update on its impact, determinants and therapeutic management. J Clin Med 2021;10:3996.
48. Barraclough M, McKie S, Parker B, Elliott R, Bruce IN. The effects of disease activity on neuronal and behavioural cognitive processes in systemic lupus erythematosus. Rheumatology 2021;61:195–204.
49. Paul F. Pathology and MRI: exploring cognitive impairment in MS. Acta Neurol Scand 2016;134:24–33.
50. Lövdén M, Fratiglioni L, Glymour MM, Lindenberger U, Tucker-Drob EM. Education and cognitive functioning across the life span. Psychol Sci Public Interest 2020;21:6–41.