Research Article

Patterns and prevalence of cognitive dysfunction in systemic lupus erythematosus

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Abstract

Objective: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, in which cognitive dysfunction is common, but poorly understood. This study aims to characterize the prevalence and patterns of cognitive dysfunction in SLE. **Method:** SLE patients ($n = 95$) and demographically matched healthy controls ($n = 48$) underwent cross-sectional cognitive testing using the 1-hr conventional neuropsychological test battery recommended by the American College of Rheumatology for use in SLE. We used standard deviations (*SD*) from the healthy control group to define impairment. For each cognitive test we compared SLE and control groups using independent samples *t*-tests (or alternatives when needed). We performed cluster analysis using a machine learning algorithm to look for patterns of cognitive dysfunction. **Results:** The SLE group performed significantly worse than healthy controls on every cognitive test. The largest differences were in the domains of verbal fluency, working memory and attention, while fine motor and psychomotor speed were the least affected domains. As expected, the prevalence of cognitive dysfunction varied depending on the *SD* cut-off used, with 49% of participants being >1.5 *SD* below the healthy control mean in at least two cognitive domains. Heat mapping showed variability in the pattern of dysfunction between individual patients and cluster analysis confirmed the presence of two clusters of patients, which were those significantly impaired *versus* those having preserved cognition. **Conclusions:** Cognitive dysfunction is common in SLE but markedly heterogeneous across both cognitive domains and across the SLE group. Cluster analysis supports the use of a binary definition of cognitive dysfunction in SLE.

Keywords: cognition; prevalence; attention; verbal fluency; working memory; cluster analysis

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease associated with significant morbidity and reduced life expectancy (Smith & Gordon, 2010). SLE is nine times more common in women than men and most commonly presents in women of reproductive age. SLE patients present with variable clinical features ranging from mild rash and arthritis to severe, even life-threatening renal, hematologic, or central nervous system manifestations. The disease course is relapsing and remitting and the clinical picture is often complicated by the simultaneous presence of inflammation due to lupus disease activity, chronic multiorgan damage, medication side effects, infection and other co-morbidities including anxiety and depression (Smith & Gordon, 2010).

Cognitive dysfunction is common in SLE with reported prevalence varying from 20 to 81%. The broad range of these estimates is due, at least in part, to methodological differences in test selection, how impairments were defined and comparator groups (Al Rayes et al., 2018; Hanly & Fisk, 2011; Raghunath et al., 2022). Cognitive dysfunction is reported by many SLE patients to be one of the most distressing symptoms of their disease (Al Rayes et al., 2018;

Arntsen et al., 2018), affecting their quality of life and employment (Appenzeller et al., 2009; Panopalis et al., 2007; Raghunath et al., 2022). Despite this high reported prevalence, screening for cognitive dysfunction and formal testing of cognition is rarely performed as part of clinical assessment of SLE patients, resulting in significant under-detection. Consequently, most patients who experience cognitive decline in the context of SLE are not assisted with the psychoeducational and other nonpharmacological strategies that may help them deal with cognitive changes. Furthermore, unlike many other manifestations of SLE, for which we have treatments with substantiated benefits, no evidence-based options yet exist for pharmacological management of cognitive dysfunction in SLE (Kello et al., 2019).

Previous studies examining cognition in SLE have pinpointed some of the cognitive domains involved (Glanz et al., 2005; Kozora et al., 2008; Kozora et al., 2004; Kozora et al., 2015; Olazarán et al., 2009). The most commonly affected cognitive domains are attention, episodic memory, working memory, and executive function, whereas performance on tests of language, reasoning, and motor speed is less often affected. The relative severity

of the domains affected in SLE has not been characterized in detail and is one of the aims of our study. At the level of individual studies, however, results from a given cognitive test are often inconsistent. In addition, varied definitions of cognitive dysfunction have been applied, both in terms of cut-offs used and application of normative data, with many studies not adjusting for education level or premorbid IQ (Hanly & Fisk, 2011). Therefore, a better understanding of cognitive dysfunction in SLE is needed to improve screening and assessment protocols for both clinical and research purposes. Further, characterization of the cognitive deficits enables comparisons to cognitive dysfunction in other conditions, which may provide insights into pathogenesis.

This study aims to characterize patterns of cognitive deficits in SLE patients and to measure the prevalence of cognitive dysfunction in a well-characterised SLE cohort. Specifically, our aim was to extend the understanding of cognitive domains affected in SLE, by assessing a broad range of cognitive domains, using a well-matched healthy control group, and comparing several quantitative definitions of cognitive dysfunction. We hypothesized that patients with SLE had deficits in tests of attention, working memory, executive function, and episodic memory, consistent with published reports. Further, by comparing the SLE group to a well-matched healthy control group, we aimed to extend the literature, to describe which cognitive tests highlight areas of weakness, relative to strengths in performance.

Methods

Participants

We prospectively studied 95 SLE participants consecutively recruited from the Monash Lupus clinic (Melbourne, Australia), a hospital based tertiary service, between October 2018 and February 2020. All were enrolled in the Australian Lupus Registry and Biobank (ALRB), a national multi-centre registry in which longitudinal clinical data is prospectively collected (O'Neill et al., 2017). All patients fulfilled classification criteria for SLE; either the 1997 American College of Rheumatology (ACR) revised criteria (Hochberg, 1997) or the 2012 Lupus International Collaborating Clinics (SLICC) criteria (Petri et al., 2012). We restricted inclusion to adults under the age of 65 to avoid comorbid cognitive disorders associated with ageing. Patients with neurological conditions not definitively related to SLE (such as traumatic brain injury) were also excluded.

We also recruited a demographically matched healthy control (HC) group ($N = 48$), who were matched on age, gender and premorbid IQ to the SLE group. Exclusion criteria included a personal history of autoimmune disease (except stable thyroid disease), presence of a central nervous system neurological condition, any organ failure, or use of immunosuppressive therapy. Control participants were recruited from friends and family of the SLE group participants as well as via advertisement in the local community, university and hospital staff.

In these multicultural cohorts, in order to be inclusive but ensure sufficient English language proficiency to complete the cognitive assessments, inclusion criteria for both groups required participants to have completed at least part of their high school years in English. This study was completed in accordance with Helsinki Declaration research standards (Association, 2001). All participants provided informed written consent and the study protocol was approved by the Monash Health Human Ethics Committee. Participants received no monetary compensation for this study.

Cognitive testing

We performed cross-sectional cognitive assessment of all participants using the 1-hr conventional neuropsychological test battery recommended by the American College of Rheumatology for use in SLE patients (Liang et al., 1999). This battery has been validated against a longer 4 hr neuropsychological test battery (Kozora et al., 1996) in SLE patients with 90% agreement (Kozora et al., 2004) in classifying patients as having cognitive impairment. Cognitive tests were administered by a trained examiner (SR) under the guidance of a clinical neuropsychologist (YGJ).

The *California Verbal Learning Test (CVLT, version III)* was used to measure verbal learning and memory (Delis, 2017). In this word-list learning test, the examiner read a list of 16 words and asked participants to immediately recall as many words as possible. The same word list and recall attempt is then repeated five times, followed by a distracter word list trial. Participants were then asked to recall the initial list again (known as the short delay recall) and subsequently 20 min later are again asked to recall the list (long delay recall). Finally, participants were asked to identify words from the list with yes or no responses when read a longer list including distracters (48 words total). The outcome measures used were the sum of correct items from the immediate recall trials one to five (maximum score of 80), both the short and long delay recall scores (maximum score 16) and the recognition discriminability index (RDI) calculated from the list word identification task which reflects the ability of the participant to identify target items and reject distractor items as a percentage (Delis et al., 2017).

The *Rey-Ostrrieth Complex Figure Test (ROCF, Form A)* was used to assess visuospatial construction and memory (Rey, 1941). In this paper and pencil task, participants were required to copy a complex figure, and 30 min later were asked to recall this figure on a blank piece of paper. The outcome measures were the copy and 30-min recall scores, which were each marked using a detailed rubric (score range 0–36).

The *Coding test* from the Wechsler Adult Intelligence Scale fourth edition (WAIS-IV), was used to assess processing speed and attention (Wechsler, 2008). In this pencil and paper test participants must fill in as many empty boxes as they can within 2 min with the correct symbols corresponding to numbers using the provided key. The outcome measure is the number of correct symbols entered (raw score).

The *Letter Number Sequencing test* from the WAIS-IV was used to assess verbal working memory and attention (Wechsler, 2008). In this test, the examiner reads sequences of mixed numbers and letters and participants are required to repeat them back with numbers and letters in sequential numerical and alphabetical order. If participants are able to order sequences correctly, they progress to attempt longer sequences up to a maximum of 30 sequences. The outcome measure is the number of sequences recalled correctly (raw score).

The *Controlled Oral Word Association Test* was used to assess verbal fluency (Benton, 1969). We tested categorical fluency by asking participants to name as many animals as they could in 1 min, with the outcome measure being the number of unique responses. Phonemic fluency was measured by three 1-min trials in which participants were asked to name as many words as they could beginning with the letters F, A and S with the outcome measure being the summation of correct responses over these three trials.

The *Trail Making Tests A and B* were used to assess psychomotor speed, complex attention and cognitive sequencing (Bowie & Harvey, 2006). In the Trail Making Test A participants were

required to join a jumbled group of numbers in consecutive order as quickly as possible using pen and paper. In the Trail Making Test B participants were given a mixed group of numbers and letters and were required to join these in consecutive order alternating between number and letter (i.e., 1A-2B-3C) as quickly as possible. The outcome measure for both parts A and B was time in seconds.

The *Stroop Colour-Word test* (Victorian version) was used to assess cognitive flexibility and high-level attention (Strauss et al., 2006). In this task, participants are shown three cards and for each card are asked to name the colour of the consecutive items as quickly as possible. The first card depicts six rows of alternating red, blue, yellow and green dots and the second card shows six rows of random words in these four colors. The third card has six rows of the words red, blue, yellow and green in multiple orders in alternating colors. The outcome measure for this test is the time taken to read the third card in seconds.

A *Finger Tap Test* was used to measure fine motor speed (Strauss et al., 2006). Participants tapped a counter as many times as possible in 25 s performing four trials with each hand. The outcome measures were the average number of taps for both the dominant and non-dominant hands.

The *Test of Premorbid Functioning (TOPF)* was used to assess premorbid IQ to match the academic ability of the two groups (Wechsler, 2011). This is a reading test where participants are asked to read a list of 70 words with atypical pronunciations. The outcome measure is a scaled IQ score, which is determined using the correct number of pronounced words and an age-based reference table.

We first looked at complete American College of Rheumatology battery of 15 test scores which can be split into the following seven domains; visual memory, verbal memory and learning, verbal fluency, working memory, processing speed, complex attention and psychomotor speed. For the purpose of defining cognitive dysfunction, we then selected one test to represent each domain. Where there was more than one test for a specific domain, we selected the test with the best distribution (most normally distributed, or able to be transformed to a normal distribution to allow comparison to the HC group mean) and largest effect size (comparing SLE and HC groups). Using this method, the seven tests included when defining cognitive dysfunction were the Rey-Ostrrieth Complex Figure Test delayed recall score (visual memory), California Verbal Learning Test trials 1–5 sum (verbal memory and learning), Controlled Oral Word Association Test FAS sum (verbal fluency), Letter Number Sequencing raw score (working memory), Coding raw score (processing speed), Trail Making Test part B time (complex attention), and finger tap dominant hand average score (psychomotor speed). We considered whether a cognitive composite measure would have been more useful in describing these data, but elected to present the individual cognitive tests instead to preserve a more detailed account of the performance of individual tests within this cohort.

Statistical analysis

SLE and HC groups comparison
Demographic and clinical characteristics were compared between groups using Mann-Whitney, Chi-squared or *t*-tests depending on the data distribution and variable types. To compare cognitive performance between the SLE group and healthy controls we used independent samples *t*-tests or Mann-Whitney U tests for each of the cognitive tests separately, depending on data distribution. Normality was assessed both visually using histograms and with Shapiro-Wilk as well as skewness and kurtosis testing (sktest

STATA function). Four test scores were $\log_{10}$ transformed to ensure normality (CVLT RDI, Trail making Test A and B, and Stroop). Two tests were non-normally distributed due to ceiling effects, CVLT short and long delay, mainly from the HC group, and were unable to be normalized with transformation. Although these variables were included when comparing cogntive performance between groups, we excluded them from the analysis for defining prevalence of cognitive deficits, and from the cluster analysis. To determine the magnitude of effect in group comparison for each cognitive test, effect size was estimated using Cohen's d statistic. All data analyses and visualizations were performed using STATA (version 15) and R (version 4.0.2) software.

Heatmapping and cluster analysis
To visualize individual patient data, we used heat mapping of cognitive test results ordered by *Z*-scored mean (average across all tests) generated using the *Heatmap()* function from the [ComplexHeatmap] R package. Ten cognitive tests were chosen for inclusion in the cluster analysis, because our sample size limited us to a maximum of ten covariates to form a robust model. This included the same seven tests that were used when defining cognitive dysfunction (as described above) as well as three additional tests (COWAT Animals, Trail making test A, and Stroop interference condition) which had good distribution and effect size. The clustering tendency of the data set was evaluated using Hopkins statistics (using *get_clust_tendency()* function from the [factoextra] R package), in combination with the visual assessment of cluster tendency algorithm which is based on the assessment of the ordered pairwise dissimilarity matrix using Euclidean distance (*fviz_dist()* function from the R [factoextra] package). Additional details regarding the cluster analysis method are provided in supplementary information.

Prevalence of cognitive impairment
To determine the prevalence of cognitive dysfunction within the SLE cohort, we first computed standard deviations (*SD*) for each score for each patient using the health control group mean and *SD* as the comparison. We then classified participants as having significant or lesser impairment on a given task using two different thresholds of impairment. These classifications were based on American College of Rheumatology 2007 response criteria for neurocognitive impairment in SLE clinical trials, which proposed a threshold of >2 *SD* below normative data (the bottom 2.5th percentile) as significant, and a threshold of >1.5 *SD* as a lesser level of impairment (Mikdashi, 2007). Once we classified the impairment levels for each test for each participant, we determined the percentage of SLE patients with cognitive impairment specifying the number of domains affected.

Results

Group comparisons on sample demographics
In the SLE cohort, median (range) age was 45 years (21–64), with 66% having completed tertiary education (Table 1). 62% of SLE participants were Caucasian and the rest predominantly of Asian ethnicity. The SLE and HC groups were well matched demographically with no significant differences between the two groups in age, gender, ethnicity, premorbid IQ or education level (Table 1). There were significantly higher rates of unemployment, depression and anxiety in the SLE group compared to HC. The SLE group had median (range) disease duration of 12.5 years (0.2–38.7 years), disease activity score (SLEDAI-2K (Touma et al., 2010)) of 3

Table 1. Demographic and clinical characteristics of study groups

	SLE group N = 95	HC group N = 48	p-value
Age, median (range)	45 years (22–64)	46 years (23–62)	0.77
Gender, female	93%	92%	0.84
Ethnicity			0.27
Caucasian	62%	58%	
Asian	34%	42%	
Other	4%	0%	
Premorbid IQ[a], mean ± SD	108.6 ± 7.3	110.8 ± 8.3	0.12
(range)	(92–126)	(94–123)	
Education			0.14
Less than secondary	12%	6%	
Secondary	23%	13%	
Tertiary	54%	58%	
Postgraduate	12%	23%	
Paid employment	66%	92%	0.001
Any history of psychiatric illness	48%	8%	<0.0001
History of depression	37%	6%	<0.0001
History of anxiety	27%	6%	0.003

P-values derived from Mann-Whitney, Chi-squared and *t*-test tests.
[a]Premorbid IQ measured by Test of Premorbid Functioning scaled score.
Acronyms: SLE – Systemic Lupus Erythematosus, HC – Healthy Controls.

Table 2. Clinical characteristics of SLE patients (*n* = 95)

Disease duration: median (range)	12.5 years (0.2–38.7)	
ANA positive, *n* (%)	94	99%
dsDNA positive (ever)	77	81%
Anti-Smith positive	14	15%
APLS antibodies (any)	55	58%
APLS antibody triple positive	5	5%
History of cerebrovascular disease	8	8%
History of seizures	6	6%
History of cranial neuropathy	5	5%
Disease Activity score (SLEDAI-2K): median (range)	3 (0–12)	
Organ Damage score (SDI): median (range)	1 (0–7)	
Medications (ever exposed), *n* (%)		
Hydroxychloroquine	89	94%
Prednisolone	75	79%
Mycophenolate	45	47%
Azathioprine	37	39%
Methotrexate	23	24%
Leflunomide	5	5%
Rituximab	5	5%
Cyclophosphamide	3	3%

ANA: anti-nuclear antibodies, dsDNA: anti-double stranded DNA antibodies, APLS: anti-phospholipid syndrome antibodies (Anti-cardiolipin, Beta2glycoprotein and lupus anticoagulant), SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, SDI: Systemic Lupus International Collaborating Clinics-American College of Rheumatology Damage Index.

(0–12), and damage index (SLICC-SDI) score of 1 (0–7) (Table 2). A history of cerebrovascular disease was present in 8%, seizures in 6% and cranial neuropathy in 5% of the SLE group (Table 2).

Patterns of cognitive dysfunction

The SLE group performed significantly worse than the HC group on every cognitive test. Table 3 shows the comparisons between the raw score means for each group. Using conventional qualitative descriptors for effect sizes, the effect sizes are considered large or very large for verbal fluency, Letter-Number Sequencing, ROCF recall, Coding, CVLT list learning, and the interference condition of the Stroop Test (Figure 1). The two Trail-making conditions had medium effects, and the finger tapping test had a small effect.

Visual inspection of cognitive test performance at the individual SLE participant level using heat mapping revealed substantial variability between patients in both the severity and patterns of cognitive deficits (Figure 2). We utilized cluster analysis techniques to identify underlying structures in the data set, to determine whether there were specific patterns among SLE patients with varying performance on cognitive testing. The data set was considered clusterable based on Hopkins statistics value of 0.64 and the ordered pairwise dissimilarity matrix shown in Supplementary Figure 1. Compared to hierarchical clustering, *k*-means appeared to be the optimal clustering approach (see Supplement). Poor performance of hierarchical clustering was further confirmed with a coefficient of correlation between cophenetic distances and the Euclidean distances lower than 0.75 for all tested linkage methods. The optimal number of clusters (*k* = 2) for *k*-means clustering was confirmed by the elbow method, the silhouette method and the NbClust function, albeit not by the gap statistics (average silhouette width: 0.26; Dunn index: 0.22, Supplementary Figures 2A–D).

We identified that two clusters of patients optimally fitted the data set (Figure 3a). Visual inspection via heat mapping, with SLE participants grouped according to their cluster number, did not reveal any specific pattern of affected cognitive domains within the more impaired cluster 1 (Figure 3b), but rather segregated participants on the magnitude of their cognitive performances, along with demographic characteristics (Table 4). Cluster 1 SLE patients were significantly younger, had higher premorbid IQ, and better performance on cognitive tests compared to Cluster 2. Performance on individual cognitive tests was consistently better in Cluster 1 with all mean cognitive test Z-scores being within 1 *SD* of the HC mean (mean Z-scores range −0.14 to −0.7) compared to Cluster 2 patients who demonstrated significant impairment across all tests (mean Z-scores range −0.9 to −2.3). Following the identification of these two clusters and the high rate of cognitive impairment in Cluster 2, we conducted an post hoc exploratory analysis to determine whether rates of psychiatric illness were also higher in this group. There were significantly higher rates of psychiatric illness in Cluster 2 compared to Cluster 1 (62% *vs.* 28%) (Table 4).

Prevalence of cognitive dysfunction in SLE

In terms of the prevalence of cognitive dysfunction, using the threshold of ≥ 2 tests 1.5 *SD* below the HC mean 49% of SLE patients were considered impaired (Table 5). Utilising a more conservative definition of cognitive dysfunction of ≥ 2 tests 2 *SD* below the HC mean, 19% of SLE patients were considered impaired.

Discussion

Our study results provide unequivocal evidence that cognitive dysfunction is common in SLE, with SLE patients, as a group, performing worse on every cognitive test when compared to the HC group. In terms of the cognitive domains most often affected in SLE, attention and working memory had qualitatively larger effect sizes and motor speed was relatively less affected, findings generally consistent with previous studies in SLE (Coin et al., 2015; Glanz et al., 2005; Kozora et al., 2008; Kozora et al., 2004). We also found that verbal fluency was one of the most significantly affected domains, but previous studies have had inconsistent findings on this test, with some studies suggesting a similar prevalence of impairment to our findings (Coin et al., 2015; Olazarán et al., 2009), while others reporting it to be relatively preserved (Glanz et al., 2005; Kozora et al., 2015; Loukkola et al., 2003). Similarly, reports on psychomotor speed impairment in SLE have revealed

Table 3. Summary of cognitive performance of SLE and healthy control groups

Cognitive domain	Cognitive test	SLE group[a] n = 95	HC group[a] n = 48	p-value	Effect size[b]	% affected (SLE group) ≥2 SD[c]
Verbal learning & memory	CVLT trials 1–5 sum	50.9 ± 8.9 (19–70)	58.9 ± 9.1 (45–71)	25.5 p < 0.0001	0.90	13.7%
Verbal memory – recall	CVLT short delay	12[d] (2–16)	13[d] (7–16)	p 0.0005[d]	0.65[d]	21%
Verbal memory – recall	CVLT long delay	11[d] (3–16)	14[d] (7–16)	p < 0.0001[d]	0.81[d]	26%
Verbal memory – retrieval	CVLT RDI	93.3 ± 8.1 (64–100)	96.1 ± 5.3 (79–100)	5.48 p 0.03	0.41	8.4%
Visuospatial construction	ROCF copy score	33.1 ± 3.6 (16–36)	35.1 ± 1.34 (29–36)	21.47 p 0.0002	0.82	29.5%
Visual memory	ROCF recall score	19.1 ± 6.6 (3–32)	24.6 ± 4.7 (12–33)	26.1 p < 0.0001	0.90	24.2%
Working memory and attention	LNS raw score	18.1 ± 2.7 (9–26)	21.1 ± 3.4 (16–28)	33.7 p < 0.0001	1.03	7.4%
Verbal fluency (phonemic)	COWAT FAS sum	40.7 ± 12.4 (16–80)	53.2 ± 12.2 (33–84)	32.6 p < 0.0001	1.01	15.8%
Verbal fluency (semantic)	COWAT animals	21.4 ± 5.2 (8–32)	28.1 ± 6.3 (18–43)	46.8 p < 0.0001	1.21	11.6%
Processing speed	Coding raw score	69.4 ± 15.2 (33–114)	84.0 ± 18.0 (44–134)	26.3 p < 0.0001	0.91	5.3%
Psychomotor speed	Trail making test A[e]	28.3 ± 10.5 (13–81)	23.6 ± 7.6 (14–48)	9.58 p 0.002	0.55	10.5%
Complex attention and cognitive sequencing	Trail making test B[e]	80.2 ± 40.8 (29–267)	56.9 ± 21.1 (30–153)	18.5 p < 0.0001	0.76	16.8%
Cognitive flexibility and high-level attention	Stroop Int[e]	26.5 ± 7.1 (13–42)	21.1 ± 6.3 (12–44)	22.3 p < 0.0001	0.84	13.7%
Fine motor speed	Finger tap dominant mean[f]	146 ± 20.9 (89–193)	155.9 ± 20.7 (116–204.5)	7.15 p 0.008	0.47	5.3%
Fine motor speed	Finger tap non-dominant mean[f]	127.4 ± 19.8 (78–177)	135.1 ± 17.6 (99–177)	5.16 p 0.02	0.40	5.4%

[a]Values are given as mean ± SD and range; a higher score indicates better performance except for the Trail Making Test and Stroop Test.
[b]As measured by Cohen's d.
[c]Percentage of SLE patients performing ≥2 SD below the HC group mean in the corresponding task (bottom 2.5th percentile).
[d]Non-normally distributed hence reported as median and comparison using Mann-Whitney U tests; Cohen's d has still been performed which we acknowledge is not methodologically robust for non-normally distributed data but has been included here for the purpose of comparison.
[e]Time in Seconds.
[f]Dominant finger tap n = 94 and non-dominant side n = 92 as patients with hand weakness or severe deformity were excluded.
SLE: Systemic Lupus Erythematosus, HC: Healthy Control, CVLT: California Verbal Learning Test, RDI: Recognition Discriminability Index, ROCF: Rey-Ostrrieth Complex Figure Test, LNS: Letter Number Sequencing subset of the Wechsler Adult Intelligence Scale IV, COWAT: Controlled Oral Word Association Test, Stroop Int: Stroop test interference condition.

inconsistent results (Emori et al., 2005; Glanz et al., 2005; Loukkola et al., 2003; Monastero et al., 2001; Montero-Lopez et al., 2016; Nishimura et al., 2015; Skeel et al., 2000); our findings place it among the least severely affected domains, although still significantly affected. The rationale of looking for consistent abnormality in specific functional domains is based on the possibility that these observations can give us further insight into which specific brain systems are most subject to the impact of SLE, which could then be further investigated with imaging studies.

Factors that are likely contributors to the inconsistent results in previous studies of cognitive dysfunction in SLE include diverse demographic and disease characteristics of the groups studied, and methods of defining cognitive dysfunction. Inclusion criteria for SLE patients in cognitive studies have ranged from only including SLE patients with prior psychiatric or neurological history (Cesar et al., 2015; Covey et al., 2012), to studies that specifically exclude these patients (Coin et al., 2015; Glanz et al., 2005; Kozora et al., 2008; Mak et al., 2012; Montero-Lopez et al., 2016; Olazarán et al., 2009; Shucard et al., 2004; Skeel et al., 2000). Other inclusion criteria which have been applied inconsistently include high disease activity (Nishimura et al., 2015), medication use (Nishimura et al., 2015), neuroimaging changes (Emori et al., 2005), and combinations of these factors (Kozora et al., 2015). Given the likely effects of these factors on cognition, selection criteria for study participation would be expected to influence

rates and even types of cognitive impairments found. For example, glucocorticoids may affect language abilities (Prado & Crowe, 2019) and SLE patients with past neurological history may have more deficits in psychomotor speed compared those with no neurological history (Loukkola et al., 2003). Finally, methods used to define cognitive dysfunction vary greatly regarding the data used for comparison, the cut-off definition thresholds used and whether individual tasks or composite measures were utilised. Some studies use comparison groups of healthy controls (Glanz et al., 2005; Kozora et al., 2004) while others use published normative data (Skeel et al., 2000), both with varying degrees of demographic matching. We used a HC group that was well-matched to the SLE group for age, gender, premorbid IQ and educational level, which are known to influence cognitive test abilities (Lezak et al., 2012).

The finding of high inter-individual variability in the pattern of cognitive dysfunction, as demonstrated by heat mapping, has also been noted in prior studies (Monastero et al., 2001; Olazarán et al., 2009). This variability is potentially attributable at least in part to comorbidities and the diverse and variable clinical manifestations of SLE itself. Comorbidities such as mood disorders, fibromyalgia and discrete neurological events are common in SLE and may affect cognition. Mood disorders have been found to correlate with both cognitive symptoms and objective cognitive deficits in SLE (Hanly et al., 2012; Petri et al., 2010; Vogel et al., 2011).
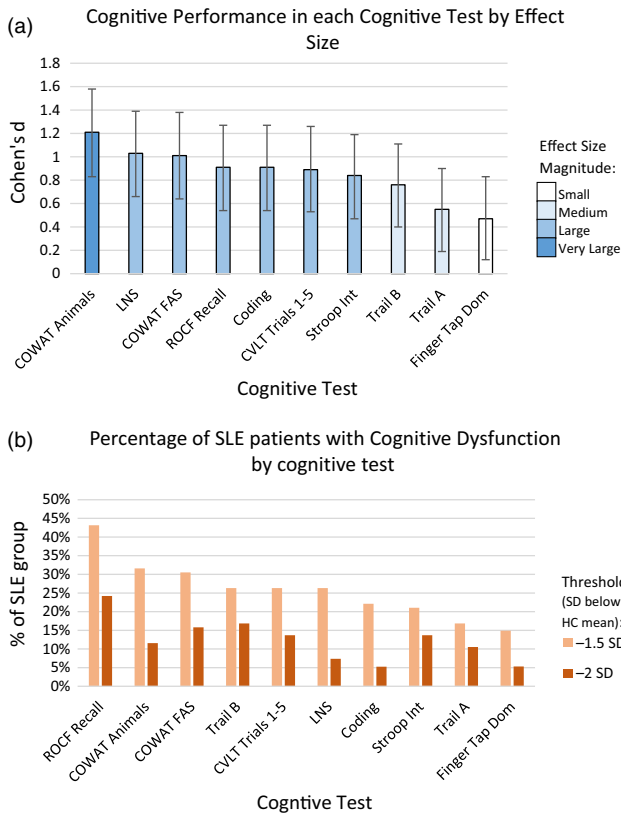
Figure 1. Cognitive performance of SLE group by cognitive test. a. Cognitive Performance in each Cognitive Test by Effect Size. Magnitude of effect as measured by Cohen's d in SLE ($N = 95$) compared to HC group of each cognitive test. Bars indicate 95% confidence intervals. b. Percentage of SLE patients with Cognitive Dysfunction by cognitive test. Percentage of SLE patients ($N = 95$) with impairment in each cognitive test using a threshold of 1.5 or 2 SD below the HC group mean. SLE: Systemic Lupus Erythematosus, HC: Healthy Control, SD – Standard Deviations, ROCF Recall: Rey-Ostrrieth Complex Figure Test Recall Score, COWAT: Controlled Oral Word Association Test. Trail A & B: Trail making test subsets A and B, CVLT Trails 1–5: California Verbal Learning Test trials 1–5 sum, LNS: Letter Number Sequencing subset of the Wechsler Adult Intelligence Scale IV raw score, Coding: Coding subset of the Wechsler Adult Intelligence Scale IV raw score, Stroop Int: Stroop test interference condition, Finger tap dominant – Finger tapping speed dominant hand.

Fibromyalgia is a common comorbidity in SLE (Torrente-Segarra et al., 2010), known to be associated with deficits on cognitive testing but especially impacts patient-reported cognitive symptoms (Raghunath et al., 2022). Discrete neurological events such as seizures or stroke are common in SLE and have been found to increase the prevalence of cognitive dysfunction (Kozora et al., 2004; Loukkola et al., 2003). However, it should be noted that cognitive dysfunction is found in the absence of overt neurological insult in SLE patients (Monastero et al., 2001; Nishimura et al., 2015), which is consistent with our data in that less than 10% of patients had a history of stroke, seizure, or cranial neuropathy. Finally, cognitive function in SLE can be adversely affected by medications used in its treatment, many of which, including glucocorticoids and methotrexate, may negatively affect cognition (McLaurin et al., 2005; Meade et al., 2018). The interplay between comorbidities, medication, and cognition within our SLE cohort will be the subject of separate study.

Our cluster analysis has confirmed the merit of a dichotomous approach in classifying SLE patients with cognitive dysfunction. Using an unbiased machine learning approach, we showed that the data forms two clusters with one being significantly cognitively impaired. The fact that both cognitive deficits and psychiatric illness are more common in this group suggests more brain involvement; the extent and structural impact of this warrants further research. The other cluster appears to have relatively preserved cognition, although across this cluster, many participants display abnormalities in one or more cognitive tests. Cluster analysis has previously been applied in IgG4 disease, another chronic multisystem autoimmune disease, delineating three to five groups of patients with specific clinical and serological associations (Li et al., 2020; Niwamoto et al., 2021). To the best of our knowledge, this is the first application of cluster analysis to cognitive dysfunction in SLE. Given the heterogeneity of SLE cognitive dysfunction and the multiple etiological factors and comorbidities involved, we hypothesized that this approach would reveal subgroups that shared cognitive test performance characteristics, but instead we found the optimal cluster number was two, allowing us to dichotomise more severe patients from less severely affected patients. A cluster analysis only including impaired patients may be able
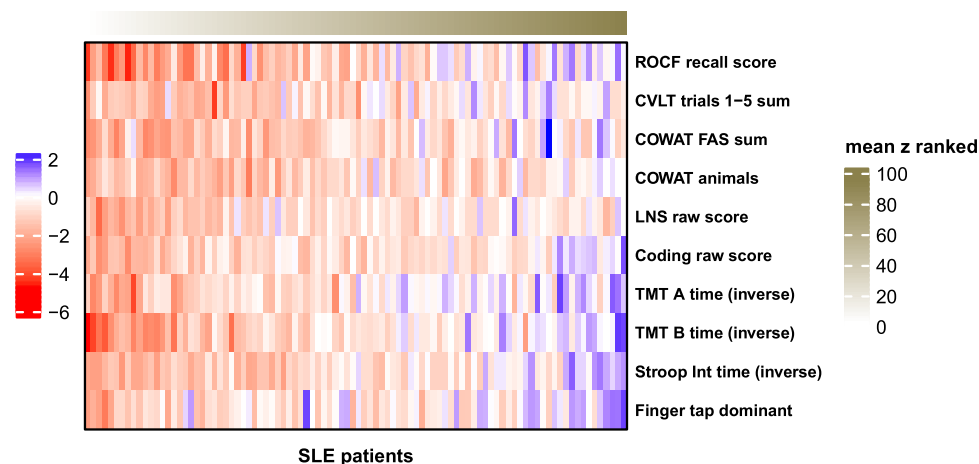
Figure 2. Heat map of individual SLE patients ordered from lowest to highest mean cognitive test score. Each row represents a cognitive test and each column an individual SLE patient ($n = 95$). The brown gradient colour bar on the row above the heatmap represent the ordering of SLE patients from lowest to highest mean cognitive test score (average across all 10 select tests – see Methods). The timed tests Stroop test, Trail A and Trail B tests were inversed so that higher Z scores indicate better performance (i.e. lower times), as all other tests are scored as higher Z scores indicating better performance. The highest and lowest values are displayed as pure blue or red, respectively. SLE: Systemic Lupus Erythematosus, ROCF: Rey-Osterrieth Complex Figure Test, CVLT: California Verbal Learning Test, COWAT: Controlled Oral Word Association Test. LNS: Letter Number Sequencing subset of the Wechsler Adult Intelligence Scale IV, Coding: Coding subset of the Wechsler Adult Intelligence Scale IV, TMT A & B: Trail making test subsets A and B, Stroop Int: Stroop test interference condition, Finger tap dominant – Finger tapping speed dominant hand.

(a) **Cluster plot**

(b)
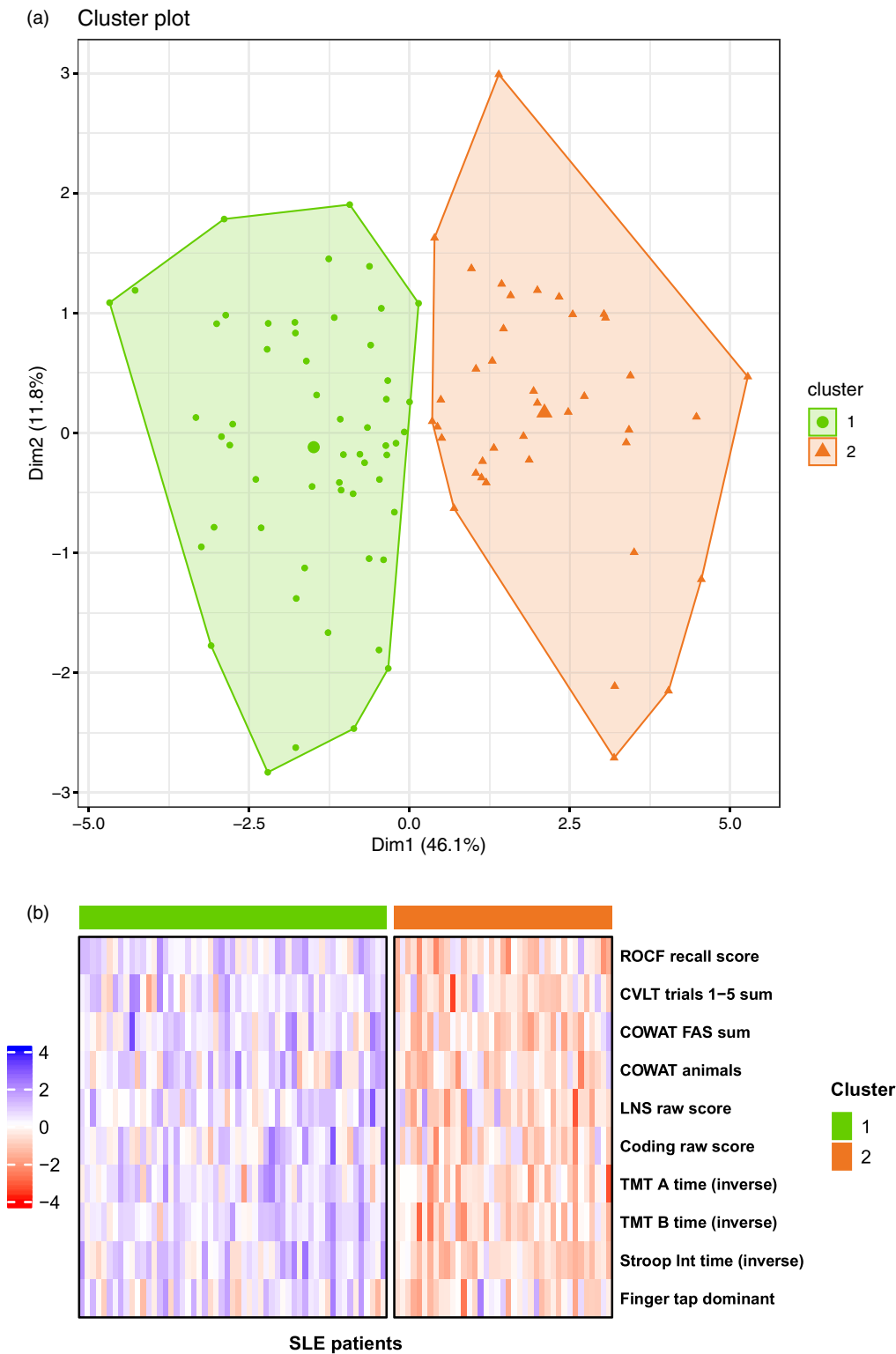
SLE patients

Figure 3. Cluster analysis of SLE patients using k-means algorithm. a: Metric multidimensional scaling plot of k-means cluster analysis of SLE patient. b: Heat map of cognitive test performance organised by cluster number. Unsupervised clustering of 94 SLE patients performed using k-means algorithm with $K = 2$. (a) Metric multidimensional scaling (MDS) plot of clusters of SLE patients; the green dots and orange triangles represent the two clusters of patients with SLE, namely Cluster 1 and Cluster 2. (b) Heatmap of the clusters of SLE patients; the green and orange colours on the row above the heatmap represent the two clusters of patients with SLE, where the highest and lowest values are displayed as pure blue and pure red, respectively. Each row represents a cognitive test and each column one individual SLE patient. Patients are grouped by cluster. The timed tests Stroop test, Trail A and Trail B tests were inversed so that higher Z scores indicate better performance (i.e. lower times), as all other tests are scored as higher Z scores indicating better performance. Z-scores were standardised (Z-score) across the 10 tests in order to perform cluster analysis. The highest and lowest values are displayed as pure blue and pure red, respectively. SLE: Systemic Lupus Erythematosus, ROCF: Rey-Ostrrieth Complex Figure Test, CVLT: California Verbal Learning Test, COWAT: Controlled Oral Word Association Test. LNS: Letter Number Sequencing subset of the Wechsler Adult Intelligence Scale IV, Coding: Coding subset of the Wechsler Adult Intelligence Scale IV, TMT A & B: Trail making test subsets A and B, Stroop Int: Stroop test interference condition, Finger tap dominant – Finger tapping speed dominant hand.

to better delineate patterns among SLE patients with cognitive dysfunction. Larger cohorts would be required for such analysis, or multi-centre studies, again highlighting the importance of consistent methodologies.

In terms of prevalence, previous studies have reported on very wide differences in prevalence, but as we see in this study, the prevalence can differ widely based on the definition used. A metanalysis of 35 studies using conventional cognitive test batteries in SLE patients found that prevalence of cognitive dysfunction varied from 15 to 79% with a pooled prevalence of 38% (Al Rayes et al., 2018). We sought here to study a well-characterised cohort of SLE patients using a matched control group and preset thresholds for definition of cognitive dysfunction. The prevalence of cognitive dysfunction in SLE patients was 49%, based

Table 4. Comparison of demographics and cognitive test results by cluster

	Cluster 1	Cluster 2	Comparison[a] (*p*-value)
n	55	39	
Demographics – mean (range)			
Age	40 (22–61)	48 (23–64)	0.0015
Premorbid IQ	111 (99–126)	104 (92–119)	<0.0001
Psychiatric illness – *n* (%)			
History of any psychiatric illness	21 (38%)	24 (62%)	0.026
History of depression	14 (25%)	20 (51%)	0.01
History of anxiety	13 (24%)	13 (33%)	0.3
Percentage with CD by definition			
2 domains 1.5 *SD* below HC	16%	95%	<0.001
1 domain 2 *SD* below HC	11%	85%	<0.001
2 domains 2 *SD* below HC	0%	46%	<0.001
Mean scores[b] by test			
ROCF recall score	–0.4	–2.3	<0.0001
CVLT trials 1–5 sum	–0.5	–1.5	<0.0001
COWAT FAS sum	–0.5	–1.7	<0.0001
COWAT animals	–0.7	–1.6	<0.0001
LNS raw score	–0.6	–1.4	<0.0001
Coding raw score	–0.5	–1.29	<0.0001
TMT A time (inverse)	–0.04	–1.3	<0.0001
TMT B time (inverse)	–0.2	–2	<0.0001
Stroop Int time (inverse)	–0.3	–1.6	<0.0001
Finger tap dominant	–0.14	–0.9	0.0001
Number of impaired tests – mean (range)			
-1.5 *SD* below HC	0.6 (0–2)	3.7 (1–6)	<0.0001
-2 *SD* below HC	0.1 (0–1)	2 (0–6)	<0.0001

[a]Comparisons between the SLE and healthy control groups using Mann-Whitney, Chi squared and *t* tests.
[b]*Z*-scores in comparison to HC group mean.
HC: Healthy Control, ROCF: Rey-Ostrrieth Complex Figure Test, CVLT: California Verbal Learning Test, COWAT: Controlled Oral Word Association Test. LNS: Letter Number Sequencing subset of the Wechsler Adult Intelligence Scale IV, Coding: Coding subset of the Wechsler Adult Intelligence Scale IV, TMT A & B: Trail making test subsets A and B, Stroop Int: Stroop test interference condition, Finger tap dominant – Finger tapping speed dominant hand.

Table 5. Percentage of cognitively impaired SLE patients by threshold

	≥1.5 *SD* below HC	≥2 *SD* below HC
≥1 tests/domain	66%	41%
≥2 tests/domains	49%	19%
≥3 tests/domains	26%	13%
≥4 tests/domains	23%	9%

Impairment defined by number of cognitive domains either 1.5 or 2 *SD* below healthy control group mean. Seven subtest scores were included; Rey-Ostrrieth Complex Figure Test (ROCF) Recall score, California Verbal Learning Test (CVLT) trials 1–5 sum, Controlled Oral Word Association Test (COWAT) FAS sum, Letter Number Sequencing raw score, Coding Raw score, Trail Making B test time and Finger tapping speed dominant hand average score. See Table 4 for specific domains of these tests.
SLE – Systemic Lupus Erythematosus, HC – Healthy Control, *SD* – Standard Deviations.

on a threshold of >1.5 *SD* below the mean of the HC group in at least two cognitive domains.

Our study demonstrates that the patterns of cognitive dysfunction in SLE are complex. As many SLE patients have preserved cognition, using whole group comparison to define impairment may result in an under representation of the impairment experienced by individual patients. For example, in the study of Kozora et al. (Kozora et al., 2008), only one of 16 cognitive tests that were used significantly differed between the SLE participants and healthy controls at the group level. However, at least 10% of SLE participants were impaired on 13 of 16 cognitive tests, and 40–50% of

patients had impaired performance on at least two cognitive measures. Hence, while it may seem cumbersome, future study should report both group level comparative data and the proportion of patients impaired, to accurately represent cognition within an SLE cohort.

Our study has certain limitations. The sample size of the sub-group of cognitively impaired SLE patients was insufficient to perform cluster analysis among impaired patients only; the prevalence of cognitive impairment was not known until the study was fully recruited and analyzed. Future research with a larger sample size to allow better exploration of patterns within cognitively impaired patients would be of benefit. Another potential limitation was the high education levels compared to previous studies (Kozora et al., 2004; Olazarán et al., 2009), with 66% having completed tertiary education, however, we accounted for this by the use of a well-matched control group.

In conclusion, our study showed that there is a high prevalence of cognitive dysfunction in patients with SLE. This suggests that screening for cognitive dysfunction should be part of routine assessment of SLE, therefore we have evaluated a screening tool in a subsequent study (Raghunath et al., 2021). Importantly, despite the clear separation between impaired and unimpaired patients, substantial variability in the pattern of cognitive dysfunction was seen, indicating that patients in whom screening leads to formal neuropsychological testing should be tested over a broad range of domains. Despite significant variability in performance of cognitive tests among individual patients, our unbiased mathematical approach has shown that on a group level patients cluster into impaired and unimpaired groups, supporting the use of a binary definition of cognitive dysfunction that could be applied in future studies.

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