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Clinical associations of cognitive dysfunction in systemic lupus erythematosus

Sudha Raghunath ,[1,2] Yifat Glikmann-Johnston,[3] Vera Golder,[1,2] Rangi Kandane-Rathnayake,[1] Eric F Morand ,[1,2] Julie C Stout,[3] Alberta Hoi [1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Sudha Raghunath; sudha.raghunath@monash.edu

ABSTRACT

Objective Cognitive dysfunction in SLE is common, but clinical risk factors are poorly understood. This study aims to explore the associations of cognitive dysfunction in SLE with disease activity, organ damage, biomarkers and medications.

Methods We performed cross-sectional cognitive assessment using a conventional neuropsychological test battery, with normative values derived from demographically matched healthy subjects. Endpoints included two binary definitions of cognitive dysfunction and seven individual cognitive domain scores. Clinical parameters included disease activity (SLEDAI-2K) and organ damage (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index). We performed regression analyses to determine associations between clinical parameters and cognitive endpoints.

Results 89 patients with SLE were studied, with median age of 45 and disease duration of 15 years. Organ damage was significantly associated with severe cognitive dysfunction (OR 1.49, CI 1.01–2.22) and worse cognitive test performance in three of the seven individual cognitive domains. In contrast, no significant associations were found between SLEDAI-2K at the time of cognitive assessment and any cognitive endpoints on multivariate analysis. Higher time-adjusted mean SLEDAI-2K was associated with better verbal memory scores but had no significant associations with other cognitive endpoints. The presence of anti-dsDNA antibodies and high IFN gene signature were negatively associated with severe cognitive dysfunction; there were no significant associations with the other autoantibodies studied or any medications. Substance use was significantly associated with lower psychomotor speed. Only 8% of patients who had cognitive dysfunction on testing had been recognised by clinicians on their SDI score.

Conclusions In SLE, cognitive dysfunction was positively associated with organ damage, but not associated with disease activity, and serological activity and high IFN signature were negatively associated. Cognitive dysfunction was poorly captured by clinicians. These findings have implications for preventative strategies addressing cognitive dysfunction in SLE.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

⇒ Cognitive dysfunction in SLE is common, but previous studies have reported mixed findings in relation to associations with disease activity, organ damage, biomarkers and medications.

WHAT DOES THIS STUDY ADD

⇒ We found that organ damage was significantly associated with cognitive dysfunction in a real-world SLE cohort, studied using a comprehensive battery of cognitive testing with normative values derived from demographically matched healthy subjects.

⇒ However, cognitive dysfunction was vastly underdetected in clinical practice, reflected by poor recognition on SDI scoring.

⇒ Clinical and serological activity or high interferon-gene signature were negatively associated with cognitive dysfunction.

HOW THIS STUDY MIGHT AFFECT RESEARCH, POLICY OR PRACTICE

⇒ Clinicians should be aware that cognitive dysfunction is under-recognised in SLE, and patients with high damage accrual are at the greatest risk.

INTRODUCTION

SLE is a chronic multisystem autoimmune disease associated with serious morbidity and reduced life expectancy.[1] Cognitive dysfunction is common in SLE, with measurable impairment present on formal cognitive testing in 40–50% of patients with SLE.[2] The presence of cognitive dysfunction in patients with SLE can adversely impact employment and quality of life,[3 4] and many patients with SLE report cognitive symptoms as one of most distressing parts of their disease experience.[5] Despite the high prevalence and clinical significance of cognitive dysfunction in SLE, clinical associations that might point to potential pathways for preventive intervention are not well understood, with interpretation of many studies limited by methodological variation.[6]

Discrete neurological events as a result of SLE such as seizure, psychosis, acute delirium, stroke or demyelinating syndrome occur much less frequently than cognitive dysfunction. A higher frequency of cognitive

dysfunction has been observed in patients with SLE with prior clinically overt neuropsychiatric lupus including strokes or seizures,[7 8] but cognitive dysfunction was also seen in patients without these discrete neurological events.[9–12] Proposed mechanisms for cognitive dysfunction in SLE include leakage of the blood–brain barrier, permitting direct neurological effects of pathological autoantibodies and pro-inflammatory cytokines. This is supported by recent studies showing abnormalities on dynamic contrast-enhanced MRI scanning.[13–15]

Knowledge about the associations between cognitive dysfunction and disease activity, organ damage, biomarkers and medications may provide insights into the pathophysiology of cognitive dysfunction in SLE and provide opportunities for preventive intervention. Here, we explored the clinical associations of cognitive dysfunction in a well-characterised SLE patient cohort. We defined cognitive dysfunction in terms of objective cognitive impairment at varying thresholds and sought to compare the rate of clinician detection as part of their routine monitoring of patients with SLE.

METHODS

Participants

Study participants for the SLE group (N=89) were recruited consecutively between October 2018 and February 2020 from the Monash Lupus Clinic site of the Australian Lupus Registry and Biobank (ALRB). The ALRB is a national registry of patients with SLE, prospectively collecting longitudinal clinical data, blood and tissue samples since 2007.[16] All enrolled patients fulfil either the 1997 American College of Rheumatology (ACR)[17] or the 2012 Lupus International Collaborating Clinics (SLICC) classification criteria.[18] Adults over the age of 65 were excluded to avoid potential comorbid cognitive disorders associated with ageing. Patients with neurological conditions definitively not related to SLE (such as traumatic brain injury) were also excluded, but those with a history of neuropsychiatric lupus were included.

A healthy control (HC) group was recruited from family and friends of the SLE participants and via advertisement in the local community to provide normative data for the cognitive test result interpretation (N=48). The mean and range of age and premorbid IQ of the HC group was matched to the SLE group; there were no significant differences in age, gender, ethnicity, premorbid IQ or education level between the groups (see online supplemental tables). HC participants were excluded if they had a history of autoimmune disease (except stable thyroid disease), any organ failure, central nervous system neurological condition or were on immunosuppressive therapy.

Study participants underwent cross-sectional cognitive testing during the recruitment period between October 2018 and February 2020. All participants were required to be English-speaking and to have completed at least part of their secondary schooling in English in order to have sufficient English language proficiency for the cognitive assessments. Participants provided informed consent and received no monetary compensation. Patients and the public were not involved in developing the study design. The STROBE guidelines for reporting cohort studies were used to ensure completeness and transparency.[19]

Cognitive testing

A single trained assessor (SR) administered the cognitive assessment using the 1-hour conventional neuropsychological test battery recommended by the ACR for use in SLE.[20] The ACR battery has been validated in SLE against a more comprehensive 4-hour neuropsychological test battery[21] with 90% agreement.[22] The cognitive assessment component of this study was conducted under the guidance of a clinical neuropsychologist (YG-J).

Within the 15 subtest scores obtained from ACR test battery, there is some overlap in the domains tested. Therefore, for the purpose of defining cognitive dysfunction, seven subtest scores with significant magnitude of effect in the SLE group were chosen as outcome measures to represent seven domain groups. The subtests selected are as follows: the Rey-Osterrieth 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) as previously described in further detail.[23]

Defining cognitive dysfunction

Cognitive dysfunction was defined using SDs from the HC group as proposed by the ACR 2007 response criteria for neurocognitive impairment in SLE clinical trials, with >2 SD below normative data (the bottom 2.5th percentile) defined as clear dysfunction and >1.5 SD below normative data as a lesser level of cognitive dysfunction.[24] We defined cognitive dysfunction as meeting any of the following three classification thresholds: (1) two cognitive domains with >1.5 SD below the HC group mean, (2) one cognitive domain with >2 SD below the HC group mean or (3) two cognitive domains with >2 SD below the HC group mean. To capture the spectrum of cognitive dysfunction in SLE, we pooled these definitions to categorise each participant as either cognitively impaired or unimpaired. Patients meeting threshold three (at least two cognitive domains each >2 SD below the HC group mean) were also classified as having severe cognitive dysfunction.

Clinical parameters

Disease activity was assessed at each clinical visit using the Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K)[25] modified as per Thanou *et al*[26] allowing both cross-sectional disease activity measurement at time of cognitive testing and time-adjusted mean SLEDAI-2K calculated using all assessments since registry enrolment. Organ damage was measured annually using the

SLICC-ACR Damage Index (SDI).[27] The SDI includes an item that captures whether cognitive dysfunction is present according to clinician assessment; we examined the concordance of this assessment with formal diagnosis of cognitive dysfunction on neuropsychological test battery.

Current medications, substance use (cannabis, cocaine and other recreational drugs) and alcohol use (weekly drinks) at the time of cognitive assessment were recorded. All medications were analysed in a binary fashion (present or absent at time of cognitive testing) except prednisolone for which time-adjusted mean dose was also calculated using all data since registry enrolment. Antiphospholipid antibodies were defined as the presence of either anti-cardiolipin antibodies, anti-beta-2-glycoprotein antibodies or lupus anticoagulant while antiphospholipid syndrome was defined as persistently elevated antiphospholipid antibodies and a clinical event.[28] Metabolic indices including BMI, elevated triglycerides, reduced HDL cholesterol, elevated arterial blood pressure (or drug therapy for hypertension) and elevated fasting glucose (or drug therapy for hyperglycaemia) were collected using methodology as previously described[29]; the presence of metabolic syndrome was defined as having at least three out of these five criteria.[30]

Biomarkers

Serological status in relation to anti-dsDNA, anti-Smith, anti-Ro, any of the antiphospholipid antibodies and complement was collected as part of the ALRB protocol using commercially available assays. Interferon-gene signature status was determined using the interferon module from Modular Immune Profile Test (DxTerity Diagnostics, Rancho Dominguez, CA, USA), which provides either a high, borderline or low result, using whole blood mRNA samples processed and analysed as described.[31]

Statistical analysis

We examined seven cognitive endpoints separately including cognitive dysfunction using two binary definitions (a pooled definition and severe dysfunction as explained previously) and seven individual cognitive domains expressed as z scores (in comparison with the healthy control group mean). We used logistic regression for the two binary endpoints and linear regression for the continuous cognitive domain endpoints. Variables with p value <0.1 on univariate regression were included in the multivariate model; likelihood ratio tests were used to select for inclusion from collinear pairs.

We compared SDI domain scores in cognitively impaired versus not impaired patients with SLE using Fisher's exact tests. SDI domain scores were recorded in a binary fashion, and we included any item scored within that category. We also performed univariate regression analyses for associations between metabolic indices and cognitive dysfunction.

In a subgroup analysis, we focused on 69 patients with SLE for whom interferon-gene signature results were available, and examined associations between interferon-gene signature and cognitive dysfunction. Univariate regression was performed in addition to χ^2 tests to compare interferon-gene signature testing between cognitively impaired versus not impaired patients with SLE. P values <0.05 were considered statistically significant. All analyses were performed using STATA software V.15.

RESULTS

Participant characteristics

Patients from the Monash Lupus Clinic (n=286) were recruited during October 2018 to February 2020, and 89 patients with SLE agreed to take part in the study. The median (range, IQR) age of the patients was 45 (22–64, 20), 62% were of European and the rest predominantly Asian ancestry, and 66% had completed some form of tertiary education; see table 1. The patients with SLE had a median (range, IQR) disease duration of 15.3 (0.2–38.7, 17) years, disease activity (SLEDAI-2K) of 3 (0–12, 4) and damage score (SDI) of 1 (0–7, 2) at the time of cognitive testing. A history of cerebrovascular disease was present in 13%, seizures in 8% and cranial neuropathy in 5%. The prevalence of any level of cognitive dysfunction in the SLE group was 52% with 19% having severe dysfunction, and both were significantly more frequent in the SLE group than in the HC group (p=<0.001 and 0.001, respectively).

Clinical associations of cognitive dysfunction

On univariate analysis, increased age, disease duration, SDI and substance use were all associated with reduced performance on cognitive testing; see table 2. Increased premorbid IQ, disease activity according to either time adjusted mean SLEDAI-2K or SLEDAI-2K at the date of assessment, azathioprine use and hypocomplementemia were associated with improved performance on cognitive testing. There were no significant associations of other medications, including glucocorticoids and antimalarials, with any of the cognitive endpoints studied. Anti-dsDNA antibodies and anti-Ro antibodies had negative univariate associations with severe cognitive dysfunction, which were significant enough to meet the threshold for inclusion in multivariate analysis (p values 0.092 and 0.087, respectively). There were no significant associations of other autoantibodies, such as anti-Smith antibodies or anti-phospholipid antibodies, or presence of anti-phospholipid syndrome, with any of the cognitive endpoints studied.

Using a significance threshold of p value <0.1 for inclusion, we further analysed these findings using multivariate analysis (table 3). Disease duration was highly collinear with both age and SDI and hence was not included in the multivariate models based on likelihood-ratio testing. Higher premorbid IQ was associated with improved cognitive test performance, whereas increased age was

Table 1 Demographic and clinical characteristics of SLE group

Age, median (IQR) (range)	45 years (20) (22–64)
Sex, female n (%)	82 (92%)
Ethnicity, n (%)	
White	56 (63%)
Asian	31 (35%)
Other	2 (2%)
Disease duration: median (IQR) (range)	15.0 years (17) (0.2–38.7)
Observation period: median (IQR) (range)	5.5 years (7.6) (0–11.8)
ANA positive, n (%)	94 (99%)
dsDNA positive, n (%)	77 (81%)
Anti-Smith positive, n (%)	14 (15%)
APLS antibodies (any), n (%)	55 (58%)
APLS antibody triple positive, n (%)	5 (5%)
APLS (syndrome), n (%)	13 (14%)
History of cerebrovascular disease, n (%)	12 (13%)
History of seizures, n (%)	8 (8%)
History of cranial neuropathy, n (%)	5 (5%)
History of substance use, n (%)	13 (15%)
SLEDAI-2K at assessment: median (IQR) (range)	3 (4) (0–12)
Time-adjusted mean SLEDAI-2K: median (IQR) (range)	4 (3) (0–13)
SDI: median (IQR) (range)	1 (2) (0–7)
Immunosuppressants, n (%)	
Hydroxychloroquine	84 (88%)
Prednisolone	34 (36%)
Mycophenolate	33 (35%)
Azathioprine	15 (16%)
Methotrexate	14 (15%)
Leflunomide	2 (2%)
Rituximab	1 (1%)
Belimumab	1 (1%)
Cyclophosphamide	0 (0%)
Cognitive dysfunction (all thresholds pooled)*, n (%)	49 (52%)
Severe cognitive dysfunction†, n (%)	18 (19%)

*Cognitive dysfunction defined by comparing to HC group data and meeting any of the three definition thresholds used.
†Severe cognitive dysfunction defined by meeting the most severe definition threshold used (at least two cognitive domains each >2 SD below the HC group mean).
APLS, anti-phospholipid syndrome (antibodies tested were anti-cardiolipin, Beta2glycoprotein and lupus anticoagulant); dsDNA, anti-double stranded DNA antibodies; HC, healthy control; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

associated with lower cognitive performance, on multiple cognitive endpoints.

A significant association was observed between higher SDI and severe cognitive dysfunction (OR 1.49, CI 1.01–2.22) as well as worsened cognitive test performance in three out of the seven individual cognitive domains assessed, specifically working memory, processing speed and complex attention (table 3). No significant associations were found between SLEDAI-2K at the time of cognitive assessment and any of the cognitive test endpoints. Higher time-adjusted mean SLEDAI-2K was associated with better verbal memory scores, but had no significant associations with other cognitive endpoints. The presence of anti-dsDNA antibodies was associated with significantly reduced frequency of severe cognitive dysfunction (OR 0.14, CI 0.02–0.92), but there were no significant associations between hypocomplementemia and any cognitive endpoints on multivariate analysis. Substance use was significantly associated with reduced psychomotor speed. There were no significant associations between any medication at the time of assessment or time-adjusted mean prednisolone dose and cognitive test performance. In addition, subsequent post hoc analysis did not find significant associations between any historic medication exposures and cognitive test results.

Subgroup analysis of association between interferon-gene signature and cognitive dysfunction

Among 43 patients with SLE with high IFN gene signature, 18 (42%) had cognitive dysfunction using the pooled definition compared with 14/20 (70%) in the low IFN gene signature group (p=0.042). On univariate regression analysis, high IFN gene signature status was significantly associated with reduced likelihood of cognitive dysfunction by the pooled definition (OR 0.21, CI 0.08–0.79), but no association with severe cognitive dysfunction was found.

Analysis of damage categories

Of all the clinical parameters, increased SDI was most consistently associated with reduced cognitive test performance. We therefore examined the distribution of the SDI domain categories in more detail (table 4). Damage in the ocular and neuropsychiatric domains were both significantly associated with higher proportions of cognitive dysfunction using both the pooled and severe cognitive dysfunction and damage in the cardiovascular category was associated with increased severe cognitive dysfunction (see table 4). On analysis of the individual disorders within the neuropsychiatric SDI domain, seizures were associated with an increased prevalence of cognitive dysfunction using the pooled definition. Past malignancy was associated with reduced incidence of cognitive dysfunction by the pooled definition only.

The association between cardiovascular domain damage and cognitive dysfunction was seen only with severe cognitive dysfunction. Univariate regression analysis was performed to assess specific associations with features of

Table 2 Univariate analysis of clinical associations of cognitive dysfunction in SLE

			Individual cognitive domains (tests)§						
	Cognitive dysfunction (all thresholds pooled)†	Severe cognitive dysfunction‡	Visual memory	Verbal memory	Verbal fluency	Working memory	Processing speed	Complex attention	Psychomotor speed
	OR using logistic regression		Coefficient using linear regression						
Age (years)	**1.06****	**1.07**	**−0.04****	**−0.02**	0.00	−0.01	**−0.03****	**−0.04****	**−0.03****
Premorbid IQ (points)	**0.87****	**0.82****	**0.07****	**0.05****	**0.07****	**0.04****	**0.04**	**0.07****	0.03¶
Disease duration (years)	**1.04**	**1.05**	**−0.05****	−0.01	0.01	−0.01	**−0.02**	**−0.03**	**−0.02**
SDI	**1.40**	**1.50**	**−0.35****	−0.06	−0.05	−0.10¶	**−0.20****	**−0.28****	−0.02
SLEDAI-2K	**0.83**	0.94	0.03	**0.09****	0.04	0.02	0.02	0.05	0.04
Time-adjusted mean SLEDAI-2K††	**0.81**	0.93	0.04	**0.16****	0.05	0.01	0.01	0.05	**0.09**
Prednisolone	0.63	0.88	0.04	0.19	0.09	0.19	0.33¶	0.29	0.30
Time-adjusted mean prednisolone dose	0.97	1.00	−0.02	0.05	−0.01	0.01	0.00	0.00	0.04
Hydroxychloroquine	0.57	0.58	−0.02	0.26	0.38	−0.23	0.04	0.41	−0.24
Mycophenolate	0.82	0.67	0.21	0.38¶	−0.02	0.72	−0.15	−0.06	0.36
Azathioprine	0.41	0.26	0.50	0.19	−0.05	0.29	**0.48**	**0.93**	0.34
Methotrexate	1.30	1.91	−0.42	−0.29	0.22	0.11	−0.42¶	−0.04	0.07
Leflunomide	0.94	4.47	−1.25	−1.00	−1.40¶	0.29	−0.13	−0.75	−0.21
Anti-dsDNA	0.46	0.37¶	0.24	0.28	0.14	0.12	0.22	0.36	0.34
Anti-Sm	0.66	0.28	0.03	0.42	−0.08	0.03	0.36	0.07	−0.07
Anti-Ro	0.98	0.37¶	0.37	0.26	−0.10	0.22	0.05	0.15	0.10
Any APLS abs	1.06	0.37	0.24	0.14	0.15	0.13	0.16	0.06	0.20
Triple-positive APLS abs	1.54	1.05	−0.26	0.02	−0.59	0.16	−0.01	−0.30	−0.28
APLS	2.37	1.34	−0.33	−0.19	0.33	−0.10	−0.35	−0.44	−0.05
Complement	0.31¶	0.66	0.23	**0.69**	−0.09	0.13	0.35	0.29	**0.86****
Substance use (ever)	2.36	3.32¶	−0.16	−0.26	−0.38	−0.20	**−0.63**	−0.60	**−0.76**
Alcohol use (weekly drinks)	0.96	0.91	−0.04	0.02	0.03	0.03	−0.03	0.01	−0.01

Covariates are collected at the time of cognitive test assessment, unless otherwise stated.
*p<0.05, **p<0.005.
†Cognitive dysfunction defined by comparing to HC group data and meeting any of the three definition thresholds used.
‡Severe cognitive dysfunction defined by meeting the most severe definition threshold used (at least two cognitive domains each ≥2 SD below the HC group mean).
§Specific cognitive tests used for each domain are as follows: visual memory—Rey-Osterrieth Complex Figure Test Recall Score; verbal memory—California Verbal Learning Test trials 1–5; verbal fluency—Controlled Oral Word Association Test FAS Sum; working memory—Letter Number Sequencing score; processing speed—Coding score; complex attention—Trail making test B time in seconds (longer indicates worse performance); psychomotor speed—finger tap test dominant hand score.
¶p=0.05–0.1 hence also meets inclusion for multivariate analysis.
††Time-adjusted mean SLEDAI-2K calculated for the entire duration of observation since enrolment to the Australian Lupus Registry and Biobank. Significant results bolded.
APLS, anti-phospholipid syndrome (antibodies tested were anti-cardiolipin, Beta2glycoprotein and lupus anticoagulant); dsDNA, anti-double stranded DNA antibodies; HC, healthy control; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC-SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Table 3 Multivariate analysis of clinical associations of cognitive dysfunction in SLE

			Individual cognitive domains (tests)§						
	Cognitive dysfunction (all thresholds pooled)†	**Severe cognitive dysfunction‡**	**Visual memory**	**Verbal memory**	**Verbal fluency**	**Working memory**	**Processing speed**	**Complex attention**	**Psychomotor speed**
	OR (CIs) using logistic regression		**Coefficient (CIs) using linear regression**						
Age (years)	**1.06*** (1.01, 1.11)	1.05 (0.99, 1.12)	**−0.03*** (−0.05 to −0.01)	−0.01 (−0.03 to −0.00)			−0.01 (−0.03, 0.00)	**−0.02*** (−0.04 to −0.00)	**−0.03**** (−0.05 to −0.01)
Premorbid IQ (points)	**0.87**** (0.79, 0.94)	**0.81**** (0.70, 0.94)	**0.06**** (0.22, 0.09)	**0.05**** (0.02, 0.07)	**0.07**** (0.05, 0.10)	**0.04**** (0.02, 0.06)	**0.02*** (0.00, 0.05)	**0.06**** (−0.02 to −0.09)	0.01 (−0.01, 0.04)
SDI at assessment	1.26 (0.87, 1.82)	**1.49*** (1.01, 2.22)	**−0.25**** (−0.41 to −0.09)			−0.07 (−0.17, 0.03)	**−0.15**** (−0.25 to −0.06)	**−0.18*** (−0.32 to −0.03)	
SLEDAI-2K at assessment	0.89 (0.75, 1.07)								
Time-adjusted mean SLEDAI				**0.13**** (0.05, 0.21)					0.024 (−0.09, 0.08)
Prednisolone							0.17 (−0.16, 0.50)		
Azathioprine							0.18 (−0.26, 0.62)	0.64 (0.00, 1.27)	
Methotrexate							−0.31 (−0.76, 0.15)		
Leflunomide					−1.20 (−2.86, 0.46)				
Anti-dsDNA		**0.14*** (0.02, 0.92)							
Anti-Ro		0.53 (0.12, 2.46)							
Complement	0.49 (0.08, 3.03)			0.11 (−0.45, 0.69)					0.62 (−0.01, 1.25)
Substance use		1.04 (0.52, 17.92)					−0.38 (−0.83, 0.07)		**−0.64*** (−0.01, 1.25)

Significant results bolded.
*p<0.05, **p<0.005.
†Cognitive dysfunction defined by comparing to HC group data and meeting any of the three definition thresholds used.
‡Severe cognitive dysfunction defined by meeting the most severe definition threshold used (at least two cognitive domains each ≥2 SD below the HC group mean).
§Specific cognitive tests used for each domain are as follows: visual memory—Rey-Osterrieth Complex Figure Test Recall Score; verbal memory—California Verbal Learning Test trials 1–5; verbal fluency—Controlled Oral Word Association Test FAS Sum; working memory—Letter Number Sequencing score; processing speed—Coding score; complex attention—Trail making test B time in seconds (longer indicates worse performance); psychomotor speed—finger tap test dominant hand score.
dsDNA, anti-double stranded DNA antibodies; HC, healthy control; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Table 4 Comparison of SDI categories in cognitively impaired vs not impaired patients with SLE

	Cognitive dysfunction categories					
	Cognitive dysfunction (all thresholds pooled)†			Severe cognitive dysfunction‡		
	Impaired n (%), total n=49	Not impaired n (%), total n=46	Comparison§	Impaired n (%), total n=18	Not impaired n (%), total n=77	Comparison
SDI domain categories¶						
Ocular	**8 (16%)**	**0 (0%)**	**0.006****	**5 (28%)**	**3 (4%)**	**0.006****
Neuropsychiatric	**13 (27%)**	**2 (4%)**	**0.004****	**7 (39%)**	**8 (10%)**	**0.007****
Renal	3 (6%)	4 (9%)	0.71	3 (17%)	4 (5%)	0.12
Pulmonary	4 (8%)	1 (2%)	0.36	2 (11%)	3 (4%)	0.24
Cardiovascular	9 (18%)	5 (11%)	0.39	**6 (33%)**	**8 (10%)**	**0.023***
Peripheral vascular	6 (12%)	3 (7%)	0.49	2 (11%)	7 (9%)	0.68
Gastrointestinal	1 (2%)	0 (0%)	1.00	0 (0%)	1 (1%)	1.00
Musculoskeletal	13 (27%)	5 (11%)	0.52	5 (28%)	13 (17%)	0.32
Skin	8 (16%)	5 (11%)	0.55	2 (11%)	11 (14%)	0.72
Premature gonadal failure	2 (4%)	3 (7%)	0.67	1 (6%)	4 (5%)	0.95
Diabetes	0 (0%)	1 (2%)	0.48	0 (0%)	1 (1%)	1.00
Malignancy	**0% (0)**	**6 (13%)**	**0.011***	0 (0%)	6 (8%)	0.59
SDI neuropsychiatric category in detail						
Cognitive impairment	3 (6%)	1 (2%)	0.62	2 (11%)	2 (3%)	0.16
Seizures	**5 (10%)**	**0 (0%)**	**0.033***	1 (6%)	4 (5%)	1.00
Cerebrovascular accident (any)	6 (12%)	2 (4%)	0.17	3 (17%)	5 (6%)	0.16
Cranial or peripheral neuropathy	4 (8%)	1 (2%)	0.36	2 (11%)	3 (4%)	0.17
Transverse myelitis	0% (0)	0 (0%)		0 (0%)	0 (0%)	

Significant results bolded.
*p<0.05, **p<0.005.
†Cognitive dysfunction defined by comparing to HC group data and meeting any of the three definition thresholds used.
‡Severe cognitive dysfunction defined by meeting the most severe definition threshold used (at least two cognitive domains each ≥2 SD below the HC group mean).
§Comparsion between rate of each SLICC-SDI category in impaired vs non-impaired patients with SLE made using Fisher's exact tests.
¶Disease categories within SLICC-SDI score, for each patient a category was recorded as affected if at least one point had been recorded in that category.
HC, healthy control; SLICC-SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

metabolic syndrome, such as BMI, triglycerides, HDL, blood glucose, hypertension, aspirin use, ACE-inhibitor therapy, statin therapy or a pooled definition of metabolic syndrome and cognitive dysfunction; no significant associations were found.

Of the 49 patients who had cognitive dysfunction on objective cognitive testing, 18 of whom had severe cognitive dysfunction, only 4 had their cognitive dysfunction recognised by clinicians on their SDI score.

DISCUSSION

Cognitive dysfunction is common in SLE and causes significant disability, but interpretation of the current literature has been limited by methodological issues. We sought to clarify the clinical associations in SLE with cognitive endpoints and found that among disease and treatment-related clinical factors, organ damage was the most consistent clinical variable associated with cognitive dysfunction. We used matched healthy controls for comparison, unlike previous studies that have used published normative data that did not take into account education or premorbid IQ, which can have a large impact on cognitive test results.[32] In our study, we also examined for the presence of cognitive dysfunction using a variety of cognitive tests to evaluate different cognitive domains and used two thresholds of cognitive dysfunction to provide a thorough assessment. This study was performed on a real-world cohort, and unlike previous studies did not have exclusions such as patients with previous anxiety or depression or past discrete neurological events. We also found that cognitive dysfunction was vastly underdetected in clinical practice, being under-recognised by clinician assessment on SDI scoring.

While the correlation between organ damage and cognitive dysfunction has been reported in previous studies,[33 34] findings regarding associations with disease activity measures have been conflicting. In our study, the association of organ damage and cognitive dysfunction was consistent across all cognitive test domains, and remained after adjustment for age, premorbid IQ or education. Despite our comprehensive cognitive testing, we did not observe an association between current or prior disease activity and cognitive dysfunction. Some previous studies shown a relationship between disease activity and cognitive dysfunction, but these were generally limited by narrow patient inclusion criteria,[12] limited cognitive testing[35] or small sample size.[33] A lack of association between disease activity and cognitive dysfunction

was observed in other studies.[36–40] In our study, using matched controls and a larger sample size, we found that increased time-adjusted SLEDAI-2K correlated with improved verbal memory, and no other association with the other cognitive endpoints was found.

The effects of disease activity on cognition are complex. Although patients with severe acute neuropsychiatric manifestations can experience delirium and can present with acute cognitive dysfunction, the more common scenario is exemplified by what we studied, which is the presence of cognitive dysfunction in patients who were recruited from ambulatory care. At the time of recruitment, no patient was experiencing acute neuropsychiatric manifestations. Our cohort reflects real-world cross-sectional clinical experience, and thus participating patients had a range of disease activity, with median SLEDAI-2K of 3 (IQR 4, range 0 to 12), at the time of cognitive assessment. We also included an additional covariate of time-adjusted mean SLEDAI that captures information about disease activity across a period of observation. The range of disease activity both at the time of testing and over the duration of observation allows us to comment on relevant associations. Our findings suggest that pathogenic mechanisms that mediate contemporary disease activity in SLE may not be the same as those causing cumulative cognitive dysfunction.

High interferon-gene signature is known to be associated with serological and clinical activity in SLE.[41] In our study, we found univariate associations between high interferon-gene signature and better cognitive performance. Anti-dsDNA positivity and hypocomplementemia also had a negative association with severe cognitive dysfunction. In murine lupus models, type 1 interferons stimulate microglia activation,[42] suggesting a possible pathogenetic basis for interferon-driven central nervous system injury that is not supported by our clinical findings. Previous studies have found no correlation between both serum and cerebrospinal fluid interferon alpha levels and cognitive test performance in SLE.[12 38] Ethnicity may play a role in this finding, as Asian ethnicity has been associated with better cognitive performance particularly on IQ testing[43] and higher disease activity in SLE as previously demonstrated in our multiethnic lupus cohort.[44]

We explored relationships between cognitive dysfunction and medication use, as some previous studies have suggested that prednisolone use is associated with declining cognitive function,[36] although a small randomised controlled trial (n=10) suggested some benefit from glucocorticoid therapy for cognitive performance in SLE.[45] We did not observe any associations between glucocorticoid use or immunosuppressant use (both at the time of cognitive assessment and past exposure) and cognitive endpoints. Not unexpectedly, substance use correlated with worse cognitive test performance specifically in psychomotor speed. This finding is consistent with previous literature on the effect of substance abuse on cognition,[46] although this is the first study reporting these effects in patients with SLE.

An important finding of this study is that cognitive dysfunction was vastly under-detected in clinical practice, even in a centre where annual SDI assessment in the clinic is routine. Of the 49 patients who had cognitive dysfunction on objective cognitive testing, only 4 (8%) had cognitive dysfunction recognised in the SDI domain which captures either cognitive dysfunction or psychosis that persists for longer than 6 months. Screening is not performed in the usual clinic setting, and formal neuropsychological assessment is not part of routine care and is only done in patients who present to their treating physician with cognitive complaints.

In terms of SDI domains, some appear to be more prominent in patients with cognitive dysfunction. The presence of damage in the ocular and neuropsychiatric domains were both significantly associated with cognitive dysfunction. Previous studies have similarly found higher incidence of cognitive dysfunction in patients with SLE with some of the neuropsychiatric domain conditions such as seizures and strokes.[7] In our study, cardiovascular domain damage was also associated with severe cognitive dysfunction. The relationship of metabolic syndrome and cognitive function in SLE has been explored in other studies, with some risk association with type 2 diabetes[36] and increased BMI,[38] whereas hypertension was not associated with cognitive dysfunction[36 38] and aspirin may in fact be protective.[36] Findings on the relationship between hypercholesterolemia and cognition in SLE have been inconsistent.[36–38] In our study, we found no associations between metabolic syndrome and cognitive performance.

Surprisingly, history of malignancy appeared to be associated with reduced cognitive dysfunction in our cohort. The effect of malignancy on cognition in lupus has not been previously studied. However, given that patients with cancer are known to have increased risk of both short-term and long-term cognitive dysfunction,[47] this finding was unexpected. However, a previous study from our centre noted a possible association between malignancy and low interferon signature in SLE.[31] It should also be noted that the cancer type, stage and treatments experienced by patients varied substantially, so a more detailed investigation of this in a larger cohort would be of interest.

There are some limitations to this study. Although the sample size is reasonable for a study that uses formal cognitive testing in the evaluation of cognitive dysfunction in patients with SLE, it is still relatively small when considering all the potential confounding covariates. Analysis of the SDI domain categories was limited by sample size and low frequency of individual organ domain damage events. Further exploration of the relationship between specific SDI domain categories and cognitive function would be of interest. As a cross-sectional observational study, we studied association of exposures of interest and the outcome of cognitive dysfunction, and causal inference should be interpreted carefully. Longitudinal analysis of the relationship between cognitive dysfunction and disease activity

and organ damage would be of interest; a previous study suggests that cognitive dysfunction improves over time in the majority of patients.[37]

The relationship between mood disorders and cognitive performance is important to consider, as they may contribute to cognitive impairment seen in patients with SLE. The aim of this study was to focus on the relationship between cognitive function and clinical factors such as disease activity, damage, biomarkers and commonly used medications in SLE. We specifically chose not to exclude patients with common comorbidities in order to assess a 'real world' SLE cohort, in which there is high prevalence of depression and anxiety.[48 49] In a separate study focusing on comorbidities, the results of which we have published,[4] we found that there was a clear relationship between mood disorders and cognitive endpoints, in particular cognitive symptoms, in our SLE cohort.

Lastly, it is possible for some potential selection bias of patients who agreed to have the comprehensive neuropsychological assessment. We are conscious of this but have only excluded patients who do not have adequate proficiency in English to complete the tasks and recruited consecutive consenting patients. Healthy control group participants were recruited predominantly from family and friends of the SLE participants and via advertisement in the local community; their health status was self-reported. We believe that our study is generalisable for our English-speaking patients.

In conclusion, organ damage has a consistent association with worse cognitive performance in patients with SLE, whereas disease activity, serological activity and interferon-gene signature status did not. These findings highlight that cognitive dysfunction can occur in patients with SLE who do not exhibit high disease activity at a given point in time, and patients with more accumulated damage are particularly at risk. Screening is important in this population, as evidenced by the finding that SDI cognitive domain scoring vastly underestimated the prevalence of cognitive dysfunction identified by formal testing. Future studies should explore the potential mechanism of higher rates of cognitive dysfunction in patients without serological activity or high interferon-gene signature, as this may represent a specific subgroup of patients with SLE at higher risk that is currently unexplained.

Author affiliations
[1]Centre for Inflammatory Diseases, School of Clinical Sciences, Monash University, Melbourne, Victoria, Australia
[2]Rheumatology Department, Monash Health, Melbourne, Victoria, Australia
[3]Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University, Melbourne, Victoria, Australia

Twitter Sudha Raghunath @Sudha_Raghunath

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ORCID iDs
Sudha Raghunath http://orcid.org/0000-0002-3062-7328
Eric F Morand http://orcid.org/0000-0002-9507-3338
Alberta Hoi http://orcid.org/0000-0002-9416-7383

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