Original article

Fibromyalgia, mood disorders, cognitive test results, cognitive symptoms and quality of life in systemic lupus erythematosus

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Abstract

Objectives. Cognitive dysfunction, and comorbidities such as mood disorder and fibromyalgia, are common in SLE. This study aims to explore the associations between fibromyalgia, mood disorders, cognitive symptoms and cognitive dysfunction in SLE patients, and their impact on quality of life.

Methods. We tested cognition in SLE patients and healthy controls, and evaluated cognitive symptoms, mood disorder, fibromyalgia, fatigue and quality of life using patient-reported outcome measures. We examined associations of these comorbidities with both patient-reported cognitive symptoms and cognitive test performance.

Results. High fibromyalgia symptom score and history of depression or anxiety were associated with cognitive dysfunction. There were no significant associations between current depression, anxiety symptoms or fatigue score and objective cognitive dysfunction. In contrast, mood disorder symptoms, history of mood disorder, fibromyalgia symptoms and fatigue all had significant associations with patient-reported cognitive symptoms. There were no significant associations between patient-reported cognitive symptoms and objective cognitive dysfunction. Objective cognitive dysfunction, patient-reported cognitive symptoms, history of mood disorder and fibromyalgia symptoms all had significant associations with poorer quality of life; fibromyalgia had the biggest impact.

Conclusions. Cognitive symptoms are common in SLE, but there were no associations between cognitive symptoms and objective cognitive dysfunction. Depression, anxiety and fibromyalgia were more consistently associated with patient-reported cognitive symptoms than with objective cognitive dysfunction. These factors all have a significant impact on quality of life. Understanding the discrepancy between patient-reported cognitive symptoms and cognitive test performance is essential to advance care in this area of unmet need.

Key words: SLE, cognitive dysfunction, depression, fibromyalgia, quality of life

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Rheumatology key messages

- Fibromyalgia and mood disorder affect cognitive performance but are more consistently associated with cognitive symptoms.
- Patient-reported cognitive symptoms are not associated with cognitive test performance.
- Cognitive impairment, cognitive symptoms, mood disorder and fibromyalgia are associated with poorer quality of life.

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Submitted 7 November 2021; accepted 30 March 2022

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Introduction

SLE is a chronic multisystem autoimmune disease associated with significant morbidity and reduced life expectancy [1]. Cognitive dysfunction is common in SLE at any age, with significant impairment present on cognitive testing in 40–50% of SLE patients [2]. The presence of

cognitive dysfunction in SLE can adversely impact on daily function and employment [3, 4]. Many SLE patients report cognitive symptoms as one of most distressing parts of their disease experience [2, 5]. Despite the high prevalence and clinical significance of cognitive dysfunction in SLE, it is poorly understood [6].

Fibromyalgia, depression and anxiety are associated with both cognitive symptoms and objective cognitive deficits [7–11]. These comorbidities are common in SLE, with a prevalence of fibromyalgia of ∼20% and depression or anxiety in 30–50% [12, 13]. The fundamental process in fibromyalgia has been described as central sensitization, referring to a central excitability or reduced inhibition in the somatosensory nervous system that results in pain amplification [10]. Cognitive symptoms are particularly common in patients with fibromyalgia, and can include a subjective sense of memory loss, language problems, interference with attention and/or executive function. These symptoms feature prominently in fibromyalgia diagnostic criteria and impact measures [10]. They can be measured by the Cognitive Symptoms Inventory (CSI) designed to measure perceived cognitive deficits [14]. Furthermore, deficits in objective cognitive testing also occur in patients with fibromyalgia, across a broad array of cognitive domains [11]. It is also well recognized that depression can affect multiple cognitive domains and be associated with long term cognitive impairment in some patients [15]. Anxiety affects cognitive performance particularly around working memory [16].

Despite the frequent cognitive complaints by patients with fibromyalgia and mood disorders, studies on the impact of these comorbidities on cognitive symptoms and function in SLE cohorts have been limited [7–9]. In this paper we describe the first study to comprehensively examine the associations of fibromyalgia and mood disorders with both patient-reported cognitive symptoms and cognitive test performance, and determine the impact of these factors on quality of life in SLE. In addition, we explore the relationship between patient reported cognitive symptoms and objective cognitive test performance in SLE.

Methods

Participants

Study participants with SLE ($n = 87$) were recruited consecutively from the Monash Lupus Clinic site of the Australian Lupus Registry and Biobank (ALRB), a national registry of SLE patients [17]. All enrolled patients fulfilled either the 1997 ACR [18] or the 2012 Lupus International Collaborating Clinics (SLICC) classification criteria [19]. For this study, we excluded patients with neurological conditions definitively not related to SLE (such as traumatic brain injury), and adults over the age of 65 to avoid potential comorbid cognitive disorders associated with ageing. Disease activity and damage were measured with the SLEDAI-2K and SLICC-ACR Damage Index (SDI), respectively, as previously described [20].

A healthy control (HC) group was recruited as a comparator ($n = 48$) instead of using population norms results, because normative data from women and subjects with a broad spectrum of premorbid IQ is limited. The mean and range of age and premorbid IQ of the HC group were matched to the SLE group. 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. We recruited HCs from family and friends of the SLE participants and via advertisement in the local community. All participants in both SLE and HC groups were English-speaking and had completed at least part of their secondary schooling in English, which was necessary to ensure sufficient English language proficiency for the cognitive assessments. Participants provided written informed consent and received no monetary compensation. The study complies with the Declaration of Helsinki and the research protocol was approved by the Monash Health Human Research Ethics Committee (reference number: LNR/18/MonH/440).

Cognitive testing and definition of cognitive dysfunction

A single trained assessor (S.R.) administered the cognitive tests using the 1-hour conventional neuropsychological test battery recommended by the ACR for use in SLE [21]. The ACR battery has been validated in SLE against a more comprehensive 4-hour neuropsychological test battery [22] with 90% agreement [23]. The cognitive assessments were conducted under the guidance of a clinical neuropsychologist (Y.G.J.); see Supplementary methods (available at *Rheumatology* online) for further details on the cognitive tests used.

We defined cognitive dysfunction in SLE patients using s.D. from the HC group. The ACR 2007 response criteria for neurocognitive impairment in SLE clinical trials proposed the use of s.D. thresholds below normative data to determine cognitive dysfunction, with >2 s.D. below normative data (the bottom 2.5th percentile) defined as 'cognitive impairment', and >1.5 s.D. below normative data as a lesser level of cognitive dysfunction [24]. We defined cognitive dysfunction as meeting any of the following three thresholds: (i) two cognitive domains with ≥1.5 s.D. below the HC group mean, (ii) one cognitive domain with ≥2 s.D. below the HC group mean, or (iii) two cognitive domains with ≥2 s.D. below the HC group mean. To capture the spectrum of *cognitive dysfunction* in SLE, we pooled these definitions to categorize each participant as either cognitively impaired or unimpaired. In addition, patients meeting threshold (iii) (at least two cognitive domains each ≥2 s.D. below the HC group mean) were also classified as having *severe cognitive dysfunction*.

Patient-reported outcome measures

We measured cognitive symptoms using the Cognitive Symptoms Inventory (CSI), as a surrogate measure of

perceived cognitive deficits [14]. The CSI is a 21-item patient-reported outcome measure with good construct validity and utility in SLE cohort studies [25], and is recommended by the ACR to assess cognitive symptoms in SLE [24]. We assessed fibromyalgia symptoms using the 2016 ACR fibromyalgia diagnostic criteria questionnaire, which has been validated as a patient-reported outcome tool [10]. This questionnaire is used to derive the central sensitivity score, which is a continuous scale measuring the degree of fibromyalgia symptoms with a maximum score of 31 [10]. The central sensitivity score cut-off of $\geq$12 can be used as a threshold for fibromyalgia diagnosis and was used to define presence of fibromyalgia in this study population [10]. We determined whether patients had a history of anxiety or depression by questioning patients at the time of cognitive testing, and then verified according to medical notes. To measure current anxiety or depression symptoms we used the Hospital Anxiety and Depression Scale (HADS) [12, 26]. Fatigue symptoms were measured using the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale [27, 28]. FACIT scores were inversed by subtracting from the total score of 52 so that higher scores indicated worse fatigue to enable comparison with the other patient-reported outcomes. We measured health-related quality of life using the Medical Outcomes Study 36-item short form health survey (SF-36v2) [29], a generic tool validated in a number of SLE cohorts and clinical trials [30, 31]. The SF-36 comprises eight domains, including physical function, role physical, bodily pain, general health, vitality, social function, role emotional and mental health, which can be aggregated into two summary scores defined as the physical component score and mental component score.

Statistical analysis

For continuous variables we compared the SLE and HC groups using the Mann–Whitney test or Student's *t*-test, depending on the data distribution. Categorical variables were compared using Pearson's χ^2 test.

For regression analysis the variables of interest were central sensitivity score, depression and anxiety symptoms, history of depression or anxiety, fatigue score, and cognitive symptoms. These variables were highly collinear (Pearson correlation coefficients 0.6–0.8 and tetrachoric correlation $P > 0.05$) and hence could not be included as covariates in a single multivariate regression model. We used univariate logistic regression to examine associations between these variables of interest and cognitive dysfunction as the outcome, using the two categories of cognitive dysfunction: cognitive dysfunction (all thresholds pooled) and severe cognitive dysfunction. We then used separate multivariate logistic regression models to examine the relationships between each of these variables of interest and the two cognitive dysfunction categories after adjusting for age, premorbid IQ and past cerebrovascular disease to determine regression adjusted odds ratios. We used the same univariate and adjusted logistic regression methods to examine associations between the variables of interest

and the outcome of patient-reported cognitive symptoms, measured by the CSI score dichotomized into high and low symptoms according to above- or below-median score. In a secondary analysis, we also examined associations with each of the three cognitive dysfunction definitions included in the pooled cognitive dysfunction category as separate endpoints, which did not change our findings; see Supplementary Table S1, available at *Rheumatology* online.

We compared cognitive symptoms scores in impaired *vs* not impaired SLE patients using an unpaired *t*-test. Cognitive impairment rates in SLE patients with high and low cognitive symptom scores were compared using Pearson's χ^2 test.

To compare quality of life as measured by the SF-36, we plotted median scores in the eight SF-36 domains on line charts. We used four line charts to separately compare quality of life between SLE patients with impaired *vs* preserved cognition on testing (using the pooled cognitive impairment definition), high *vs* low cognitive symptom scores (above- *vs* below-median), history of anxiety or depression *vs* no history of mood disorders, and fibromyalgia (central sensitivity score $\geq$12) *vs* no fibromyalgia. We used the Mann–Whitney *U*-test to compare median SF-36 domain scores and summary scores between these groups. *P*-values <0.05 were considered significant and *P*-values <0.005 were considered highly significant. Analyses were performed using STATA software version 15 (StataCorp LLC, College Station, TX, USA).

Results

Participant characteristics

The median age of the SLE group was 45 (range 22–64) years, 62% were Caucasian and the rest predominantly Asian, with 68% having completed some form of tertiary education (Table 1). The SLE group had a median disease duration of 15.3 (range 0.2–38.7) years, disease activity (SLEDAI-2K) of 3 (range 0–12), and damage index (SDI) of 1 (range 0–7). A history of cerebrovascular disease was present in 11%, seizures in 8% and cranial neuropathy in 6%.

The SLE and HC groups were well matched demographically with no significant differences between the groups in age, gender, ethnicity, premorbid IQ or education level. The prevalence of any level of cognitive dysfunction in the SLE group was 51%, with 16% having severe dysfunction, both significantly more frequent than in the HC group. Fibromyalgia symptoms were frequent in SLE patients with a median central sensitivity score of 8 (range 0–27) and 26% meeting the threshold for a diagnosis of fibromyalgia. A history of depression or anxiety was present in 49% of SLE patients. Among SLE patients who reported a history of depression and/ or anxiety ($n = 43$), 35% ($n = 15$) were currently taking anti-depressants or anxiolytics. All fibromyalgia,

TABLE 1 Demographic and clinical characteristics of study groups

	SLE group (n = 87)	HC group (n = 48)	P-value[a]
Age, median [IQR] (range), years	45 [20] (22–64)	46 [24] (23–62)	0.88
Gender, female, n (%)	80 (92)	44 (92)	0.95
Ethnicity, n (%)			0.34
Caucasian	54 (62)	28 (58)	
Asian	30 (34)	20 (42)	
Other	3 (4)	0	
Premorbid IQ[b], mean (S.D.)	108.7 (7.2)	110.8 (8.3)	0.12
Education, n (%)			0.25
Less than secondary	10 (11)	3 (6)	
Secondary	18 (21)	6 (13)	
Tertiary	48 (55)	28 (58)	
Postgraduate	11 (13)	11 (23)	
Paid Employment, n (%)	53 (61)	44 (92)	0.001
Central Sensitivity Score[c], median [IQR] (range)	8 [8] (0–27)	3 [2] (0–9)	<0.00001
Fibromyalgia[c], n (%)	23 (26)	0 (0)	<0.0001
History of depression or anxiety, n (%)	43 (49)	4 (8)	<0.0001
History of depression, n (%)	33 (38)	3 (6)	<0.0001
History of anxiety, n (%)	23 (26)	3 (6)	0.004
Depression symptoms[d], median [IQR] (range)	5 [7] (0–15)	1 [3] (0–9)	<0.00001
Anxiety symptoms[d], median [IQR] (range)	6 [6] (0–20)	4.5 [4] (0–13)	0.0005
Depression or anxiety symptoms[c], median [IQR] (range)	12 [11] (0–29)	6 [6] (1–19)	<0.00001
Fatigue score[e], median [IQR] (range)	21 [15] (8–44)	12 [6] (4.3–23)	<0.00001
Cognitive dysfunction (all thresholds pooled)[f], n (%)	44 (51)	8 (16)	<0.001
Severe cognitive dysfunction[g], n (%)	14 (16)	0 (0)	0.001
Cognitive Symptoms[h], median [IQR] (range)	31 [13] (19–52)	26 [4] (21–35)	<0.0001

[a]Compared using Mann–Whitney, χ^2 and t-tests. [b]Test of Premorbid Functioning scaled score. [c]Central Sensitivity Score derived from 2016 Fibromyalgia Diagnostic Criteria, ≥ 12 = diagnosis of fibromyalgia. [d]Using Hospital Anxiety and Depression Scale. [e]Functional Assessment of Chronic Illness Therapy Fatigue Scale (reversed). [f]Cognitive dysfunction defined by comparing with HC group data and meeting any of the three definition thresholds used. [g]Severe cognitive dysfunction defined by meeting the most severe definition threshold (≥ 2 cognitive domains >2 S.D. below HC group mean). [h]Cognitive Symptoms Inventory score. HC: healthy control; IQR: interquartile range.

depression, anxiety and fatigue measures were significantly higher in SLE patients than in the HC group.

Associations with cognitive test results

Older age, low premorbid IQ and a history of cerebrovascular disease were significantly associated with cognitive dysfunction on univariate analysis; see Supplementary Table S2, available at *Rheumatology* online. On univariate analysis central sensitivity score was significantly associated with cognitive dysfunction (using the pooled definition), and history of depression or anxiety symptoms was associated with both categories of cognitive dysfunction (Table 2). After adjustment for age, premorbid IQ and history of cerebrovascular disease, the association between central sensitivity score and cognitive dysfunction by the pooled definition remained, and history of anxiety and depression was strongly associated with severe cognitive dysfunction. There were no significant associations between current symptoms of depression, anxiety or fatigue score and any category of cognitive dysfunction.

Associations with cognitive symptoms

On univariate analysis, high central sensitivity scores, increased depression and anxiety symptoms, history of

depression or anxiety, and fatigue score all had significant associations with cognitive symptoms (Table 2). These associations remained significant after adjusting for age, premorbid IQ and history of cerebrovascular disease.

Associations between cognitive symptoms and cognitive test results

Cognitive symptom scores were significantly higher in SLE patients than in HCs (Table 1). However, patient-reported cognitive symptom score was not associated with performance on cognitive tests using logistic regression (Table 2). To expand on this observation, we examined the mean and range of cognitive symptom scores in SLE patients with or without cognitive dysfunction, as shown in Table 3. Regardless of the threshold for cognitive dysfunction, the mean and range of cognitive symptoms were comparable to those who were not impaired. Consistent with this observation, the proportions of patients meeting the definition for cognitive dysfunction were similar in the group with high cognitive symptom scores compared to the group with low cognitive symptoms scores (44% *vs* 47%). SLE patients who reported more cognitive symptoms did not have higher rates of cognitive dysfunction (Table 4). Interestingly, in patients with lower cognitive symptom scores, there was a

TABLE 2 Regression Analysis of Mood Disorders, Fibromyalgia and Cognitive Test Results and Cognitive Symptoms in SLE

	Cognitive dysfunction (all thresholds pooled)[a]	Severe cognitive dysfunction[b]	Cognitive symptoms
Unadjusted odds ratio (95% CI)			
Central Sensitivity Score	**1.10*** (1.02, 1.18)	1.08 (1.00, 1.18)	**1.17**** (1.07, 1.27)
Depression and anxiety symptoms	1.05 (0.99, 1,11)	1.04 (0.97, 1.12)	**1.15**** (1.08, 1.24)
History of depression or anxiety	**2.47*** (1.08, 5.65)	**4.92***(1.48, 16.34)	**3.19*** (1.36, 7.49)
Fatigue score	1.02 (0.98, 1.06)	1.00 (0.95, 1.06)	**1.16**** (1.10, 1.22)
Cognitive symptoms	1.30 (0.57, 2.96)	0.43 (0.14, 1.36)	n/a
Regression-adjusted[c] odds ratio (95% CI)			
Central Sensitivity Score	**1.10*** (1.02, 1.12)	1.05 (0.94, 1.17)	**1.17**** (1.07, 1.28)
Depression and anxiety symptoms	1.05 (0.98, 1.13)	1.00 (0.90, 1.10)	**1.17**** (1.08, 1.26)
History of depression or anxiety	1.89 (0.70, 5.09)	**8.15*** (1.55, 42.96)	**3.17*** (1.30, 7.72)
Fatigue score	1.02 (0.97, 1.08)	0.98 (0.91, 1.06)	**1.16**** (1.08, 1.23)
Cognitive symptoms	1.50 (0.54, 4.15)	0.27 (0.06, 1.22)	n/a

[a]Cognitive dysfunction defined by comparing to HC group data and meeting any of the three definition thresholds used. [b]Severe cognitive dysfunction defined by meeting the most severe definition threshold ($\geq$2 cognitive domains >2 s.d. below HC group mean). [c]All adjusted for age, premorbid IQ and past cerebrovascular disease. Measures used: Central Sensitivity Score derived from 2016 Fibromyalgia Diagnostic Criteria; depression and anxiety symptoms—Hospital Anxiety and Depression Scale; Fatigue Score—Functional Assessment of Chronic Illness Therapy Fatigue Scale (reversed); Cognitive Symptoms Score—Cognitive Symptoms Inventory score dichotomized by median. Significant results shown in bold: *$P < 0.05$, **$P < 0.005$. HC: healthy control. n/a: Not applicable.

TABLE 3 Comparison of cognitive symptoms scores in cognitively impaired *vs* not impaired SLE patients.

	SLE—impaired	SLE—not impaired	*P*-value[a]
Cognitive dysfunction (all thresholds pooled)[b] (*n* impaired = 44/87)	34 (20–52)	33 (19–52)	0.26
Severe cognitive dysfunction[c] (*n* impaired = 14/87)	31 (22–45)	34 (19–52)	0.22

Values are mean (range). Cognitive symptoms as measures by Cognitive Symptoms Inventory (CSI) score. [a]Unpaired *t*-test used. [b]Cognitive dysfunction defined by comparing with HC group data and meeting any of the three definition thresholds used. [c]Severe cognitive dysfunction defined by meeting the most severe definition threshold used (at least two cognitive domains each >2 s.d. below the HC group mean). HC: healthy control.

TABLE 4 Comparison of rates of cognitive dysfunction in SLE patients with high *vs* low cognitive symptom scores

	High cognitive symptoms group (*n* = 49)	Low cognitive symptoms group (*n* = 38)	*P*-value[c]
Patients with cognitive dysfunction (all thresholds pooled)[a]	44%	47%	0.60
Patients with severe cognitive dysfunction[b]	10%	27%	**0.032**

Percentages represent proportion of SLE patients with cognitive dysfunction (according to each definition) within high and low cognitive symptom groups. Cognitive symptoms as measures by Cognitive Symptoms Inventory (CSI) score—high *vs* low score dichotomized around median. [a]Cognitive dysfunction defined by comparing to HC group data and meeting any of the three definition thresholds used. [b]Severe cognitive dysfunction defined by meeting the most severe definition threshold used (at least two cognitive domains each >2 s.d. below the HC group mean). [c]Pearson's χ^2 test used to compare groups. HC: healthy control. Significant results bolded.

notably higher rate of severe cognitive dysfunction, compared with the rate observed in patients with higher cognitive symptom scores (27% *vs* 10%, $P = 0.032$).

Associations with quality of life

In SLE patients, six of the eight quality-of-life domain scores were significantly lower in patients with cognitive dysfunction (Fig. 1A). Given that the analysis above revealed a disconnection between patient-reported cognitive symptoms and objectively measured cognitive function, we separately examined quality-of-life in relation to cognitive symptoms. As shown in Fig. 1B, seven of eight quality-of-life domains were significantly lower in the SLE group with high cognitive symptoms. All eight

FIG. 1 Impact of cognitive dysfunction, symptoms, mood disorders and fibromyalgia on quality of life in SLE
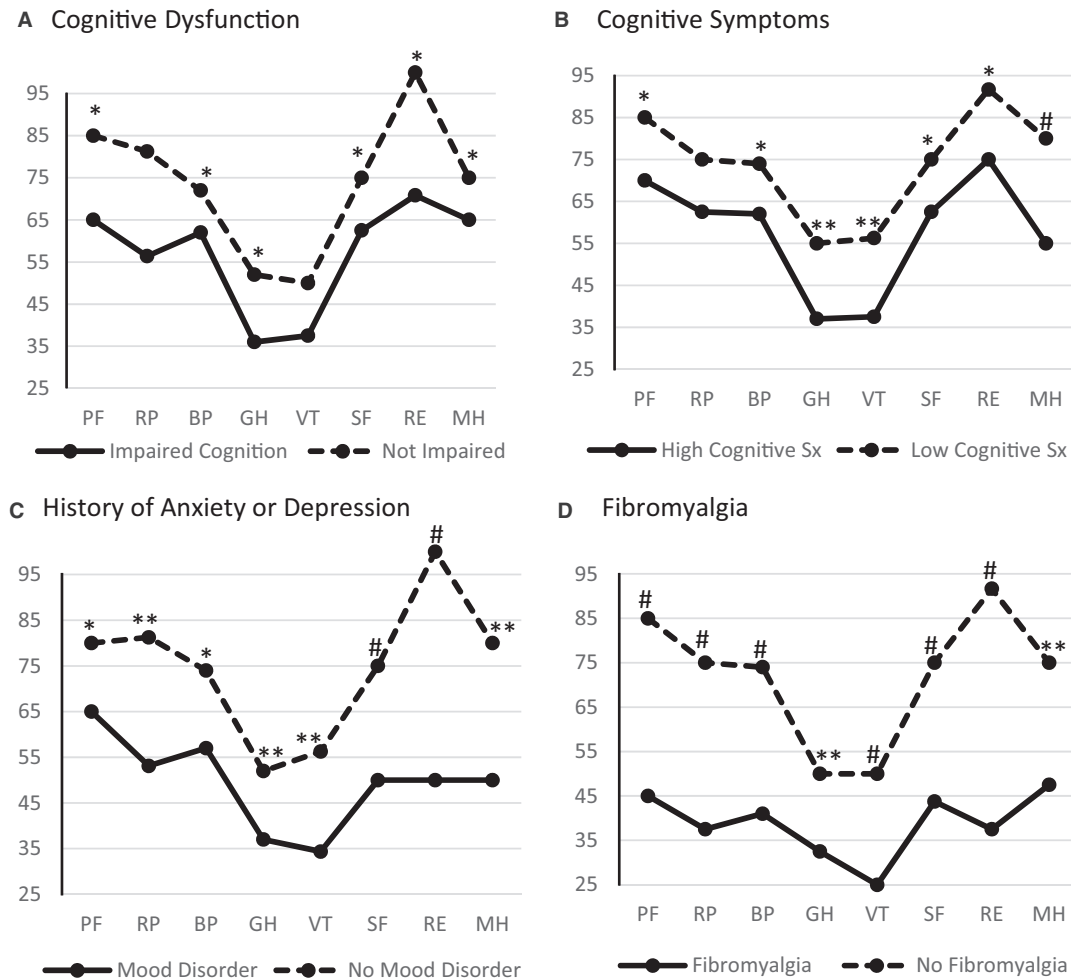
Line charts comparing median scores in each of the eight short form 36 (SF-36) domains between SLE patients with impaired and preserved cognition on testing using the pooled definition (**A**), high *vs* low cognitive symptom scores on the Cognitive Symptoms Inventory (**B**), past history of anxiety or depression *vs* no history of mood disorders (**C**), and fibromyalgia *vs* no fibromyalgia (**D**). *$P < 0.05$, **$P < 0.005$, #$P < 0.0005$. SF-36 domains: PF: physical functioning, RP: role physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role emotional, MH: mental health. Sx: symptoms.

quality of life domains were significantly lower in SLE patients with a history of anxiety or depression and in those with fibromyalgia (Fig. 1C and D). The median scores in every quality-of-life domain were lowest in SLE patients with fibromyalgia.

On further analysis of quality of life using the SF-36 summary scores, SLE patients with cognitive dysfunction had lower physical component score (median 42.4 in impaired *vs* 48.5 in not impaired, $P = 0.03$), as did SLE patients who met the threshold for fibromyalgia diagnosis (median 35.1 *vs* 48.5, $P < 0.0001$). Mental component scores were consistently lower in all four subgroups studied. The largest difference in mental component scores was seen in those with or without fibromyalgia (median 33.7 *vs* 50.5, respectively, $P = 0.0004$), followed by the comparison between those

with or without history of anxiety and depression (median 36.8 *vs* 52.8, respectively, $P < 0.0001$), cognitive symptoms (median 42.9 *vs* 51.7, respectively, $P = 0.0005$) and cognitive dysfunction (median 42.6 *vs* 50.66.11, respectively, $P = 0.02$).

Discussion

In this study, we aimed to explore the associations between fibromyalgia, mood disorders, cognitive symptoms and cognitive dysfunction in SLE patients, and their impact on quality of life. These factors have been explored to some extent in SLE cohorts, but no previous study has comprehensively compared all of these factors in relation to both cognitive test performance and

cognitive symptoms. We found that comorbidities such as fibromyalgia, depression and anxiety have some associations with cognitive dysfunction, but stronger associations with increased cognitive symptoms. Importantly, we also found that patient-reported cognitive symptoms are not associated with cognitive dysfunction, but that both increased cognitive symptoms and reduced cognitive function are associated with poorer quality of life.

Central sensitivity scores were significantly associated with objective cognitive dysfunction but had a slightly stronger association with cognitive symptoms. The pathophysiology of fibromyalgia is characterized by central sensitization and disordered pain regulation, which includes changes in neural networking and neurotransmitter function, proposed as mechanisms for the associated cognitive changes [32]. In addition, pain may contribute to cognitive changes in fibromyalgia because central pain processing results in possible competition for brain resources [33]. Other features of fibromyalgia such as poor sleep and fatigue, as well as medications, can also adversely influence cognitive performance [32]. There has been minimal research on the impact of fibromyalgia on cognition in SLE cohorts. One study suggested, contrary to our findings, that cognitive dysfunction was not associated with fibromyalgia [34]; this was in a cohort of inactive lupus patients with the method of assessing for fibromyalgia not specified. No previous studies have explored the effect of fibromyalgia on patient-reported cognitive symptoms in SLE.

We found that a history of anxiety and depression was strongly associated with severe cognitive dysfunction. The effect of depression on objective cognitive test performance has been well established in SLE [9]. Limited longitudinal studies also suggest depression may worsen the trajectory of SLE patients with cognitive dysfunction; while cognition improves in some patients over time, a history of depression has been associated with persistently poorer cognitive function [35]. Separate studies have found that patient-reported cognitive symptoms in SLE patients correlate more with mood disorders than with objective cognitive deficits [7, 8]. In our study, current active symptoms of depression (as measured by the Hospital Anxiety and Depression Scale) did not correlate with objective cognitive dysfunction but were associated with increased cognitive symptoms. The effect of history of anxiety and depression *vs* current depressive symptoms has not been previously compared in an SLE cohort. However, studies in the elderly have shown that cognitive disorders, such as early dementia, are more common in patients with a long-standing history of depression and the cognitive changes can persist long-term even in patients who respond to antidepressant therapy [15].

We found that fatigue score correlated with cognitive symptoms but not with objective cognitive function. Past qualitative studies have suggested that fatigue is related to cognitive symptoms in SLE [36]. One study found a correlation between fatigue and poorer cognitive

test performance in SLE patients with previous neuropsychiatric lupus, but not in those with no prior neuropsychiatric manifestations [37]. Another study in a cohort of patients with inactive lupus suggested that, contrary to the majority of the literature, cognitive function was not associated with previous depression [34]. These studies suggest that patient selection plays a large role in the variability of findings and that factors such as disease activity and past neuropsychiatric manifestations may modify the effect of mood disorder and fatigue on cognition in SLE.

We found no positive correlation between patient-reported cognitive symptoms and objective cognitive test results, a finding which had previously been described in SLE [7, 8]. It was particularly notable that the absence of cognitive symptoms did not exclude the presence of severe cognitive impairment. Such discrepancies between cognitive symptoms and cognitive test performance have been reported in other conditions including post-chemotherapy, depression and fibromyalgia alone [38–40]. One potential explanation for the discordance between symptoms and cognitive test results, as well as the greater effect of mood disorders, fibromyalgia and fatigue on cognitive symptoms than on objective cognitive tests, is the presence of complex distractors or competing interests. Standardized neuropsychological test batteries tend to test attention to focal stimuli rather than the ability to allocate attention to competing stimulus sources such as the distractors involved in cognitive tasks in real life [41]. The most consistent cognitive deficits in fibromyalgia cohorts have been found in attention, working memory and executive function, with deficits being more profound in the presence of distracting stimuli [32]. Similar studies in multiple sclerosis patients with comorbid depression found that patients with at least mild depression had significantly worse multitasking, while standard mono-tasking cognitive assessments appeared less sensitive to depression-related cognition changes [42]. Alternatively, it is possible that lack of insight plays a role in patients with severe cognitive dysfunction reporting fewer symptoms.

We found that cognitive dysfunction, cognitive symptoms, history of depression or anxiety, and fibromyalgia symptoms all have significant associations with poorer quality of life. Of these comorbidities, fibromyalgia symptoms as measured by higher central sensitivity score had the greatest negative effect on quality of life. In our study, the differences in median SF-36 domains and summary scores for patients with and without these variables of interest were not only statistically significant but also well above published minimal clinically important differences in SLE cohorts, or the smallest difference in score that patients perceive as beneficial [43]. The minimal clinically important difference in SF-36 summary scores is 2.5–5 [43]; in our study, group differences in physical and mental component summary scores, respectively, for cognitive dysfunction were 5.94 and 6.11 and for fibromyalgia were 13.32 and 16.86. Consistent with our findings, a previous study in SLE using an

abbreviated form of the SF-36 found that cognitive dysfunction worsens both physical and mental component scores [44]. A separate study confirms our finding that cognitive symptoms have significant effects on only the mental component score [8]. Previous separate studies have also suggested that both fibromyalgia [30, 45] and depression [46] are related to poorer health-related quality of life in SLE; one study found that depression had a bigger effect than cognitive dysfunction, similar to our results [44]. However, our study was the first to compare the relative effect of all these factors in an SLE cohort.

One of the limitations of our study was multicollinearity between fibromyalgia, depression and fatigue variables, which prevented comparing them in a single multivariate regression model. This issue has also been noted in previous studies in SLE [8] and generally has been addressed in a similar manner. This multicollinearity is not surprising given that the relationships between fibromyalgia, depression and fatigue are complex. These clinical syndromes overlap and also share some pathophysiological pathways such as the hypothalamic–pituitary–adrenocortical axis, autonomic nervous system and neurotransmitter dysfunction [47]. In addition, the relationships between these comorbidities, SLE and cognitive dysfunction may be multidirectional. The effects of SLE activity including neuroinflammation on central nervous system functioning are known to cause mood disorders and both direct peripheral neurological damage and physiological stress in SLE could also contribute to the development of fibromyalgia [48]. Our sample was highly educated, with 68% having completed some form of tertiary education; education and premorbid IQ have significant effects on cognitive test performance [41]. Therefore, despite our well-matched control group, these findings may not necessarily be able to be extrapolated to populations with lower education. In addition, given our study was cross sectional, we did not explore the effect of the variables of interest on changes in cognitive test performance or cognitive symptoms over time.

Another limitation in our measurement of depression and anxiety relates to our selection of only one instrument, namely the HADS, which is a general measure of anxiety and depressive symptoms in a medical population. There are many other instruments used to assess depression and anxiety in SLE, but HADS performs well with good sensitivity and specificity when evaluated [49].

In summary, mood disorders and fibromyalgia are associated with cognitive dysfunction in SLE patients but are more clearly linked to the cognitive symptoms that patients experience. Given these comorbidities are potentially reversible, identifying their contributions to cognitive dysfunction, patient-reported cognitive symptoms and quality of life is helpful as a potential avenue for treatment. Understanding that there is a discrepancy between cognitive symptoms and objective cognitive dysfunction is important in interpreting cognitive measures and incorporating them into both clinical practice and advancing research in this area of need.

Data availability statement

All data are incorporated into the article and its online supplementary material.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Brey R, Holliday S, Saklad A *et al.* Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. Neurology 2002;58:1214–20.

2 Al Rayes H, 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.

3 Panopalis P, Julian L, Yazdany J *et al.* Impact of memory impairment on employment status in persons with systemic lupus erythematosus. Arthritis Rheum 2007;57:1453–60.

4 Appenzeller S, Cendes F, Costallat LT. Cognitive impairment and employment status in systemic lupus

erythematosus: a prospective longitudinal study. Arthritis Rheum 2009;61:680–7.

5 Arntsen K, Wildman P, Gross D. Lupus: Patient Voices. Joint report by Lupus Research Alliance, Lupus Foundation of America and Lupus and Allied Diseases Association for the CDER and FDA2018. http://www.lupuspfdd.org/LupusPFDDReportwCover.pdf.

6 Raghunath S, Glikmann-Johnston Y, Hanly JG *et al.* Cognitive dysfunction in systemic lupus erythematosus: how do we advance our understanding? Lancet Rheumatol 2022;4:e293–302.

7 Vogel A, Bhattacharya S, Larsen J *et al.* Do subjective cognitive complaints correlate with cognitive impairment in systemic lupus erythematosus? A Danish outpatient study. Lupus 2011;20:35–43.

8 Hanly JG, Su L, Omisade A *et al.* Screening for cognitive impairment in systemic lupus erythematosus. J Rheumatol 2012;39:1371–7.

9 Petri M, Naqibuddin M, Carson KA *et al.* Depression and cognitive impairment in newly diagnosed systemic lupus erythematosus. J Rheumatol 2010;37:2032–8.

10 Wolfe F, Clauw DJ, Fitzcharles M-A *et al.* 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 2016;46:319–29.

11 Bell T, Trost Z, Buelow MT *et al.* Meta-analysis of cognitive performance in fibromyalgia. J Clin Exp Neuropsychol 2018;40:698–714.

12 Kwan A, Marzouk S, Ghanean H *et al.* Assessment of the psychometric properties of patient-reported out-comes of depression and anxiety in systemic lupus erythematosus. Semin Arthritis Rheum 2019;49:260–6.

13 Wolfe F, Petri M, Alarcon GS *et al.* Fibromyalgia, systemic lupus erythematosus (SLE), and evaluation of SLE activity. J Rheumatol 2009;36:82–8.

14 Pincus T, Swearingen C, Callahan L, editors. A self-report cognitive symptoms inventory to assess patients with rheumatic diseases: Results in eosinophilia-myalgia syndrome (EMS), fibromyalgia, rheumatoid arthritis (RA), and other rheumatic diseases. Arthritis Rheum 1996;39:S261.

15 Perini G, Ramusino MC, Sinforiani E *et al.* Cognitive impairment in depression: recent advances and novel treatments. Neuropsychiatr Dis Treat 2019;15:1249–58.

16 Lukasik KM, Waris O, Soveri A *et al.* The relationship of anxiety and stress with working memory performance in a large non-depressed sample. Front Psychol 2019;10:4.

17 O'Neill S, Morand EF, Hoi A. The Australian lupus registry and biobank: a timely initiative. Med J Aust 2017;206:194–5.

18 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.

19 Petri M, Orbai AM, Alarcon GS *et al.* Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.

20 Koelmeyer R, Nim HT, Nikpour M *et al.* High disease activity status suggests more severe disease and damage accrual in systemic lupus erythematosus. Lupus Sci Med 2020;7:e000372.

21 Liang MH, Corzillius M, Bae SC *et al.* The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599–608.

22 Kozora E, Thompson LL, West SG *et al.* Analysis of cognitive and psychological deficits in systemic lupus erythematosus patients without overt central nervous system disease. Arthritis Rheum 1996;39:2035–45.

23 Kozora E, Ellison MC, West S. Reliability and validity of the proposed American College of Rheumatology neuropsychological battery for systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2004;51:810–8.

24 Mikdashi JA, Esdaile JM, Alarcón GS *et al.*; Ad Hoc Committee on Lupus Response Criteria: Cognition Sub-committee. Proposed response criteria for neurocognitive impairment in systemic lupus erythematosus clinical trials. Lupus 2007;16:418–25.

25 Alarcón GS, Cianfrini L, Bradley LA *et al.*; Lumina Study Group. Systemic lupus erythematosus in three ethnic groups. X. Measuring cognitive impairment with the cognitive symptoms inventory. Arthritis Care Res (Hoboken) 2002;47:310–9.

26 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.

27 Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes 2003;1:79.

28 Kosinski M, Gajria K, Fernandes AW *et al.* Qualitative validation of the FACIT-Fatigue scale in systemic lupus erythematosus. Lupus 2013;22:422–30.

29 Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Med Care 1992;30:473–83.

30 Kiani AN, Strand V, Fang H, Jaranilla J, Petri M. Predictors of self-reported health-related quality of life in systemic lupus erythematosus. Rheumatology (Oxford) 2013;52:1651–7.

31 Alarcón GS, McGwin G, Uribe A *et al.* Systemic lupus erythematosus in a multiethnic lupus cohort (LUMINA). XVII. Predictors of self-reported health-related quality of life early in the disease course. Arthritis Rheum 2004;51:465–74.

32 Kravitz HM, Katz RS. Fibrofog and fibromyalgia: a narrative review and implications for clinical practice. Rheumatol Int 2015;35:1115–25.

33 Torta RGV, Tesio V, Ieraci V *et al.* Fibro-fog. Clin Exp Rheumatol 2016;34:S6–8.

34 Gladman DD, Urowitz MB, Slonim D *et al.* Evaluation of predictive factors for neurocognitive dysfunction in patients with inactive systemic lupus erythematosus. J Rheumatol 2000;27:2367–71.

35 Touma Z, Moghaddam B, Su J, Katz P. Cognitive function trajectories in association with the depressive symptoms trajectories in systemic lupus erythematosus

over time. Arthritis Care Res (Hoboken) 2021;73: 1436–43.

36 Sterling K, Gallop K, Swinburn P et al. Patient-reported fatigue and its impact on patients with systemic lupus erythematosus. Lupus 2014;23:124–32.

37 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.

38 Hutchinson AD, Hosking JR, Kichenadasse G et al. Objective and subjective cognitive impairment following chemotherapy for cancer: a systematic review. Cancer Treat Rev 2012;38:926–34.

39 Elkana O, Falcofsky AK, Shorer R et al. Does the cognitive index of the symptom severity scale evaluate cognition? Data from subjective and objective cognitive measures in fibromyalgia. Clin Exp Rheumatol 2019;37: 51–7.

40 Srisurapanont M, Suttajit S, Eurviriyanukul K et al. Discrepancy between objective and subjective cognition in adults with major depressive disorder. Sci Rep 2017; 7:3901.

41 Lezak MD, Howieson DB, Bigler ED et al. Neuropsychological Assessment. 5th edn. New York: Oxford University Press, 2012.

42 Glukhovsky L, Kurz D, Brandstadter R et al. Depression and cognitive function in early multiple sclerosis: multitasking is more sensitive than traditional assessments. Multiple Sclerosis J 2021;27: 1276–83.

43 Strand V, Chu AD. Measuring outcomes in systemic lupus erythematosus clinical trials. Expert Rev Pharmacoecon Outcomes Res 2011;11:455–68.

44 Flores P, Aguirre JM, Valdivia G et al. Impact of cognitive impairment, depression, disease activity, and disease damage on quality of life in women with systemic lupus erythematosus. Scand J Rheumatol 2017;46:273–80.

45 Moon SJ, Kang KY, Kwok SK et al. Differences in quality of life determinants according to the presence of fibromyalgia in middle-aged female patients with systemic lupus erythematosus: a multicenter, cross-sectional, single-ethnicity cohort. Int J Rheum Dis 2018;21: 1173–84.

46 Schmeding A, Schneider M. Fatigue, health-related quality of life and other patient-reported outcomes in systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2013;27:363–75.

47 Singh L, Kaur A, Bhatti MS et al. Possible molecular mediators involved and mechanistic insight into fibromyalgia and associated co-morbidities. Neurochem Res 2019;44:1517–32.

48 Mackay M. Lupus brain fog: a biologic perspective on cognitive impairment, depression, and fatigue in systemic lupus erythematosus. Immunol Res 2015;63: 26–37.

49 de Almeida Macêdo E, Appenzeller S, Lavras Costallat LT. Assessment of the Hospital Anxiety and Depression Scale (HADS) performance for the diagnosis of anxiety in patients with systemic lupus erythematosus. Rheumatol Int 2017;37:1999–2004.