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Longitudinal relationships between cognitive domains and depression and anxiety symptoms in systemic lupus erythematosus

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ABSTRACT

Objectives: To examine i) the relationship between neuropsychological performance and depression and anxiety over time, and ii) the overlap between classification of cognitive dysfunction, anxiety, and depression in SLE.

Methods: 301 patients with SLE were included. Cognition was measured using a modified version of the ACR neuropsychological battery; cognitive dysfunction was defined as z-scores ≤-1.5 on ≥2 domains. Depression and anxiety were measured using the Beck Depression Inventory-II and the Beck Anxiety Inventory, respectively. All measures were assessed at baseline, 6, and 12 months. Their relationships were analyzed using Multiple Factor Analysis (MFA).

Results: Anxiety and depression and neuropsychological performance were stable across time. Factor analysis identified two dimensions explaining 42.2% of the variance in neuropsychological performance. The first dimension (33.1% of the variance) included primarily complex cognitive tests measuring executive function; verbal, visual, and working memory; and complex processing speed. The second dimension (9.1% of the variance) included primarily measures of simple information processing speed or motor dexterity. Anxiety and depression scores were consistently related to the first cognitive dimension. There was substantial overlap in participants classified with cognitive dysfunction and anxiety and depression.

Conclusions: Depression and anxiety symptoms in SLE patients are related to a cognitive dimension incorporating memory, executive function and complex processing speed in a stable manner across one year. Many patients with cognitive dysfunction exhibit clinically significant anxiety and depression. Further research should examine whether cognition improves when anxiety and depression are treated and mechanistic links between anxiety and depression and cognitive dysfunction in SLE.

Introduction

There is a clear and consistent relationship between cognitive dysfunction (CD) and depression and anxiety in systemic lupus

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erythematosus (SLE) [1]. Together, depression, anxiety and CD represent among the most common and disabling neuropsychiatric symptoms associated with SLE [2,3]. SLE patients with CD are more likely to be unemployed and to report being unable to work than SLE patients without CD, and CD is associated with reduced quality of life in SLE [4,5].

SLE patients experience CD in a variety of cognitive domains, including memory, attention, executive function, and visuospatial processing[1,6], and CD in SLE frequently persists over time [7]. The overlap between mood and anxiety and cognitive symptoms in SLE is likely complex and multi-determined. Depression is commonly associated with CD generally outside of SLE [8], and clinical variables specific to SLE such as inflammation and medication side effects may contribute further to both symptom clusters in this patient group [9–11].

While the relationship between CD and depression symptoms in SLE is well established, less is known about which specific cognitive domains are related to depression and anxiety symptoms. One prospective study indicated that, in SLE patients followed for at least three years, higher depressive symptom score was associated with decline in overall cognitive score [12]. This study did not separate cognition into different domains. Although data are limited, higher levels of depressive symptoms have been found to be associated with lower performance on the cognitive domains of attention, processing speed, visuospatial abilities, reaction time and memory in cross-sectional studies [1,13]. A two-year prospective study comparing change in a depressive or anxiety disorder with cognitive scores found that resolution of psychiatric disorder was associated with improvement in memory and verbal fluency [14]. This study was, however, limited by small sample size.

Although the relationship between anxiety and CD in SLE is less well known, depressive and anxiety symptoms are generally highly comorbid, with about 85% of individuals with depression experiencing anxiety symptoms, and 90% of individuals with anxiety disorders experiencing comorbid depression [15]. In SLE specifically, our group previously found that about 51% of SLE patients with depression or anxiety had co-existing anxiety and depression rather than only one or the other [16]. Therefore, both depression and anxiety symptoms should be considered when investigating the relationship between psychiatric symptoms and cognition in SLE.

Characterizing the relationship between mood and anxiety symptoms and cognitive dysfunction in SLE would be valuable for several reasons. First, gaining a more detailed understanding of the overlapping clusters of mood and neurocognitive symptoms will allow researchers to map the underlying neuroanatomy and neurobiology of these deficits in more detail, to characterize patients according to the symptom clusters that they demonstrate, and ultimately to develop tailored interventions. Relatedly, understanding which cognitive domains have the potential to change with management of depression and anxiety symptoms (or vice versa) provides important clinical information for patients and clinicians. For example, if research were to identify that patients with SLE and depressive symptoms are likely to experience improvement in attention, but not episodic memory, with depression treatment, we will know that treatment of memory impairment in SLE requires a different strategy than simply treating depression.

Thus, the aim of this study was to examine the relationship between cognitive performance across domains and anxiety and depressive symptoms over time in a well-characterized cohort of patients with SLE.

Patients and methods

Participants

This study included 301 consecutive patients from a well-characterized SLE cohort attending the Toronto Lupus Clinic between August 2017 – January 2019.

Inclusion criteria were women and men aged 18 years and older, with a diagnosis of SLE fulfilling ≥4 of the American College of Rheumatology (ACR) criteria or three ACR criteria with a typical biopsy lesion of SLE (skin or kidney) [17]. Patients were excluded if they were mentally or physically unable to participate as determined by the Toronto Lupus Clinic healthcare team; this includes presence of aggressive behaviour or known diagnosis of intellectual disorder, or if they were non-English speaking and unable to understand or complete the questionnaires. This project was reviewed and approved by the University Health Network Research Ethics Board, and all patients provided informed written consent for this study collection.

Measures

We collected sociodemographic and clinical information on all participants.

Cognition was measured by a neuropsychological battery recommended by the American College of Rheumatology (ACR) for use in SLE with minor adaptations, which demonstrates good psychometric properties in this population [6,18]. The battery consists of the following neuropsychological tests: Finger Tapping test, dominant and non-dominant hand; Trails A and B [19]; Rey Complex Figure Test (RCFT) [20]; Controlled Oral Word Association Test (COWAT) [21]; Hopkins Verbal Learning Test-Revised (HVLT-R) [22]; Stroop test, color score, word score and interference score [23]; Wechsler Adult Intelligence Scale (WAIS) letter-number task [24]; WAIS-III digit-symbol substitution task [24]; and Consonant Trigrams [25]. The neuropsychological subtests grouped according to representative cognitive domain are shown in Table 1. Our battery is identical to the ACR battery except that the HVLT-R was used in place of the California Verbal Learning Test and Trails A was added.

Raw scores were converted to z-scores using age- and gender-adjusted normative data for the analyses. A domain was defined as impaired if a z-score of ≤-1.5 was reached in at least one test in the following domains: manual motor speed, simple attention and

Table 1
Neuropsychological subtests included in each cognitive domain.

Cognitive Domain	Representative Subtests
Manual motor speed	Finger Tapping Test (dominant and non-dominant hands)
Simple attention and processing speed	Trails A Stroop Color Naming Stroop Word Reading
Visual-spatial construction	RCFT Copy
Language processing	COWAT (category and language fluency)
Learning and memory	
Visuospatial	RCFT Delayed Recall RCFT Delayed Recognition
Verbal	HVLT-R Delayed Recall HVLT-R Recognition HVLT-R Total Recall
Executive Function and working memory	Stroop Interference WAIS Letter-Number Consonant Trigrams (lower value from 18 or 36 second trial used) WAIS-III Digit Symbol Trails B

COWAT = Controlled Oral Word Association Test; HVLT-R = Hopkins Verbal Learning Test-Revised;
RCFT = Rey Complex Figure Test; WAIS-III = Wechsler Adult Intelligence Scale, 3rd ed.

processing speed, visual-spatial construction and language processing or z-score of ≤-1.5 in two or more tests in the following domains: learning and memory and executive functioning. Participants were classified as CD if they received a z-score of ≤1.5 on two or more domains.

Depression was measured using the Beck Depression Inventory-II (BDI-II) [26], a self-report rating scale with widespread use in psychiatric and medical populations, including SLE [27,28]. Anxiety was measured using the Beck Anxiety Inventory (BAI) [29], another self-report rating scale with psychometric evidence in SLE [30]. In keeping with psychometric evidence in patients with medical illness generally and with SLE, participants were classified as having clinically significant depression if they scored ≥ 18 on the BDI-II [31,32] and clinically significant anxiety if they scored ≥ to 19 on the BAI [30].

Participant data are taken from three time points: baseline, 6 months, and 12 months.

Statistical analysis

Multiple factor analysis (MFA) is a generalization of principal component analysis (PCA) [33]. Its goal is to analyze several data sets of variables collected on the same set of observations, or—as in its dual version—several sets of observations measured on the same set of variables. Given that the neuropsychological battery was collected over time, MFA aims to summarize all variables from the battery into different dimensions (same way) taking into account the longitudinal structure of the data.

MFA provides classical outputs of general factor analysis as follows:

1. Produces coordinates for each observation, meaning that patients with similar coordinates imply similar responses in the battery test.
2. Correlation coefficient between dimensions and variables, meaning that we determine how strongly each test from the battery influences each dimension.

All analyses were done in R using the library FactoMineR [33]. This library has the advantage of dealing with missing values by imputing them in such a way that the imputed values have no weight on the MFA results.

Furthermore, we used Pearson's correlations to explore the relationship between each individual neuropsychological subtest with anxiety (BAI) and depression (BDI-II) scores at each timepoint.

Results

The sociodemographic data and descriptive clinical and neuropsychological data of the participants are shown in Table 2. Participants were 89% women and 55.3% Caucasian. Mean (SD) disease duration was 14 (10.1) years and adjusted mean (SD) SLEDAI in the five years prior to study entry was 3.8 (3.5). Participants' mean (SD) BDI-II and BAI scores at baseline were 15.3 (12.5) and 16.6 (13). The mean score is below the clinical cut-offs for depression and anxiety (higher scores indicate more severe symptoms), but as demonstrated by the wide standard deviations, scores were variable among participants. At baseline, 33.2% of participants scored within the clinical range for depression (BDI-II ≥ 18) and 36.2% scored in the clinical range for anxiety (BAI ≥ 19).

As shown in Fig. 1, participants' anxiety and depression scores were stable across the three timepoints. Mean (SD) BDI-II scores were 15.3 (12.5) at baseline, 13.6 (11.6) at 6 months, and 15.3 (12.0) at 12 months and mean BAI scores were 16.6 (13.0) at baseline, 14.4 (12.2) at 6 months, and 15.2 (12.3) at 12 months. Neuropsychological scores were similarly stable across timepoints (data not shown).

Table 2
Baseline sociodemographic and clinical data for study participants (N = 301).

Variable	Value
Age at study entry, mean ± SD	41.0 ± 12.1
Gender, N (%)	
Female	268 (89)
Male	33 (11)
Ethnicity, N (%)	
Asian	33 (11)
Black	61 (20.3)
Caucasian	166 (55.3)
Others	40 (13.4)
Highest education level attained, N (%)	
Less than high school	9 (3.4)
High school	48 (16.1)
Community college	110 (36.9)
University	130 (43.6)
Age at SLE diagnosis, mean ± SD years	27.0 ± 10.5
Disease duration at study entry, mean ± SD years	14.0 ± 10.1
Adjusted mean SLEDAI in five years before study entry, mean ± SD	3.8 ± 3.5
SDI, mean ± SD	1.1 ± 1.5
Corticosteroid medication, N(%)	132 (48.4)
Anti-malarial medication, N(%)	225 (82.4)
Immunosuppressive medication, N(%)	157 (57.5)
Baseline BDI-II, mean ± SD	15.3 ± 12.5
Baseline BAI, mean ± SD	16.6 ± 13.0
NPSLE*, N (%)	76 (25.3)

Missing data, variable (N): Ethnicity (1); Education (3); SDI (8); Corticosteroid (28); Anti-malarial (28); Immunosuppressive (28); Baseline BDI (60); Baseline BAI (60); NPSLE (1)
BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II; NPSLE = Neuropsychiatric Systemic Lupus Erythematosus; SDI = Systemic Lupus Erythematosus International Collaborating Clinics/ACR Damage Index; SLE = Systemic Lupus Erythematosus; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index
*NPSLE defined as the presence of any of the following from the SLEDAI: seizures, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache or cerebrovascular accident

Given the limited mean and intra-individual variability in measures of neuropsychological performance, depression and anxiety over one year, we were not able to analyze a model examining the relationship between change in neuropsychological performance and change in affective symptoms. Instead, we combined the measures over time using MFA, as described above.

PCA identified two dimensions that explained 42.2% of the variance in neuropsychological performance at baseline (Fig. 2). The first dimension, explaining 33.1% of the variance, primarily included more complex cognitive tests, including those measuring executive function-task switching (Trails B), verbal and visual memory (HVLT and RCFT recall scores), complex processing speed (WAIS digit-symbol), and working memory (Consonant Trigrams). Trails A (a measure of motor speed) also contributed to this dimension. The second dimension, explaining 9.1% of the variance, was primarily explained by measures of simple information processing speed or motor dexterity, including the Stroop color and word reading scores and hand tapping. HVLT-R, recognition score, also contributed to this dimension, as did HVLT-R delayed recall. Language tests (COWAT language and category fluency) contributed a relatively small amount (less than 5%) to both dimensions.

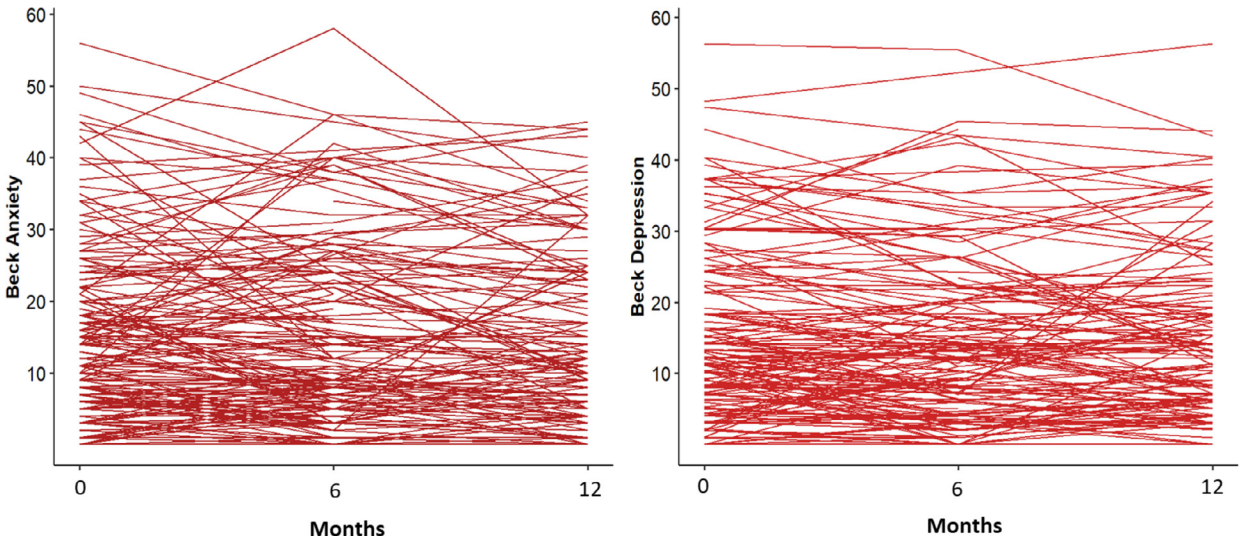

Fig. 1. Participants' scores on Beck Anxiety Inventory and Beck Depression Inventory across the three timepoints. Each line represents an individual patient's trajectory.

Fig. 2 shows the results of the MFA demonstrating neuropsychological tests at each timepoint in relation to the two cognitive dimensions with depression and anxiety scores at each timepoint shown as supplementary variables. Individual neuropsychological subtest scores and depression and anxiety scores were highly correlated with each other across all three timepoints. Depression and anxiety were most strongly related to the first neuropsychological dimension, particularly to sub-tests representing verbal and visual memory

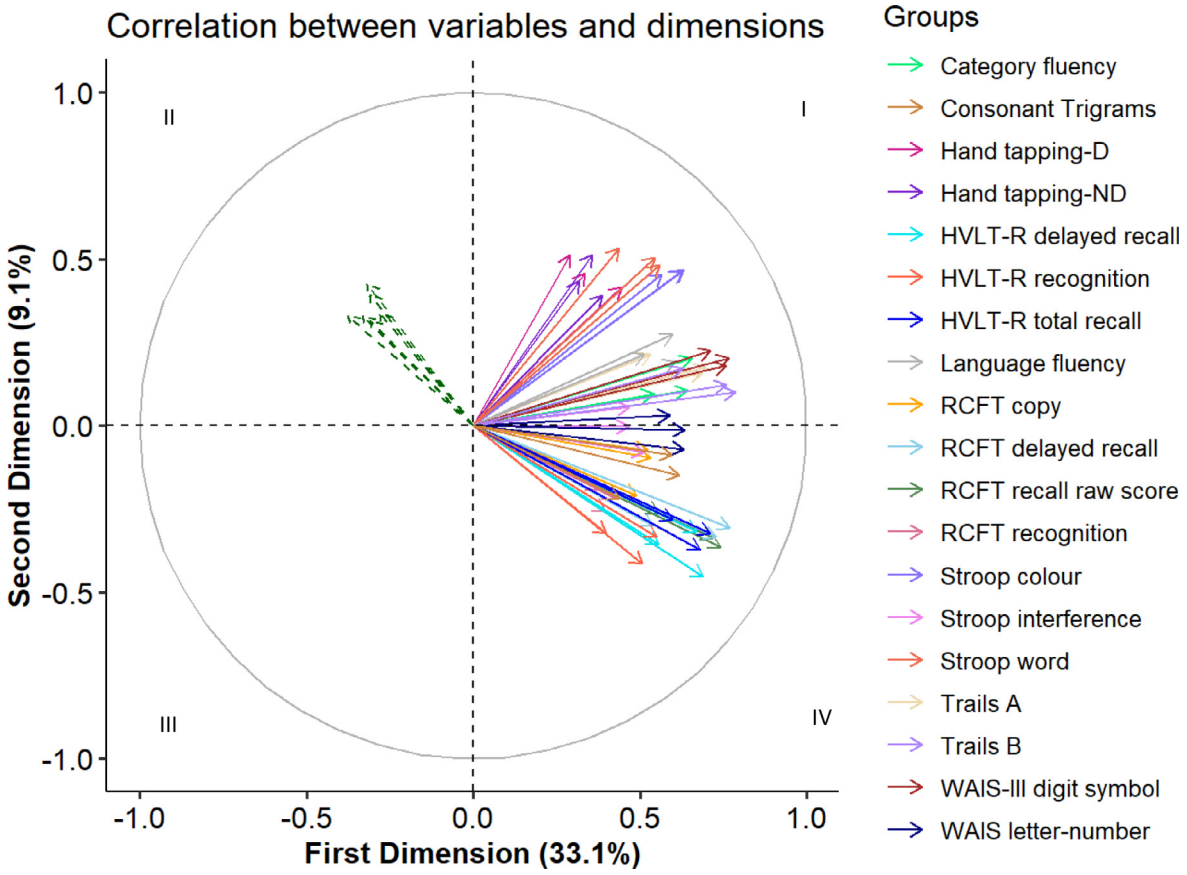

Fig. 2. Results of MFA showing representative neuropsychological tests at each timepoint in relation to the two cognitive dimensions. Axis x represents the first dimension explaining 33.1% of the variance in cognition and axis y represents the second dimension. Affective symptoms at each time point are shown as supplementary variables (six dark green, dotted arrows in quadrant II). The length of each arrow represents the strength of the relationship between the variable it represents and the cognitive dimensions. Variables whose representative arrows are close in proximity are more strongly related (e.g. depression and anxiety are highly correlated and the cognitive tests are highly correlated to each other across timepoints). The closer to 180 degrees the angle between the arrows representing anxiety and depression and those representing the cognitive tests, the stronger the relationship between the variables they represent. For example, depression/anxiety symptoms are most strongly related to HVLT-R recall and recognition and RCFT delayed recall (verbal and visual memory). If the angle between two arrows is 90 degrees, the two variables are independent. Hence, anxiety and depression have no relationship with hand tapping and Stroop color scores (motor dexterity and simple information processing speed).

(HVLT-R recall and recognition and RCFT delayed recall) and working memory (Consonant Trigrams), with higher depression and anxiety scores associated with poorer test performance. There was a much weaker relationship between depression and anxiety and the second cognitive dimension.

In order to further explore the relationship between anxiety and depression at each timepoint and individual neuropsychological domains, we calculated Pearson's correlation coefficients between each neuropsychological test and the BDI-II and BAI. In the supplementary material (**Table S1**) we present the correlation matrix demonstrating relationships between depression and anxiety scores and each individual neuropsychological test at each timepoint. Again, tests of verbal and visual memory (HVLT and RCFT recall and recognition scores), as well as working memory (Consonant Trigrams), were correlated to anxiety and depressive symptoms, though with weak correlation strengths in the range of 0.3 to 0.4. Other neuropsychological tests did not demonstrate a clinically relevant correlation with anxiety or depression.

The distribution of participants with CD, depression and anxiety is shown in Fig. 3. 38.2% of participants were categorized CD at baseline, 36.2% were anxious and 33.2% were depressed. There is substantial overlap among these classifications (see quadrant II on Fig. 3), though there is a group of participants classified as having CD without anxiety or depression (quadrant III, Fig. 3). These participants were more likely to exhibit impairment in neuropsychological tests that load onto dimension 2.

Discussion

In our cohort of SLE patients, anxiety and depression scores, which were generally stable over the course of a year, were correlated with a cognitive dimension explained primarily by neuropsychological tests of memory, executive function and complex processing speed. Subtests of verbal and visual memory, as well as working memory, were most strongly related to anxiety and depression in our patient group. Further, there was substantial overlap between SLE patients categorized as having CD and clinically significant levels anxiety and depression, demonstrating the clinical relevance of these results.

Our findings are generally in keeping with previous cross-sectional studies examining the relationship between neuropsychological performance and depression, in which depression was found to be related to a variety of domains in SLE patients [1,13], including attention, processing speed, visuospatial abilities, reaction time and memory. However, our exploratory correlation analysis examining the relationship between anxiety and depression with individual neuropsychological subtests suggests that visual and verbal memory domains may be of particular relevance. Further research should examine whether treatment of depression in SLE results in improvement in memory and other cognitive domains, and, if so, via which potential mechanisms. If cognitive dysfunction does not improve with depression treatment (or with lupus treatment) then, ultimately, other management strategies may be needed. For example,

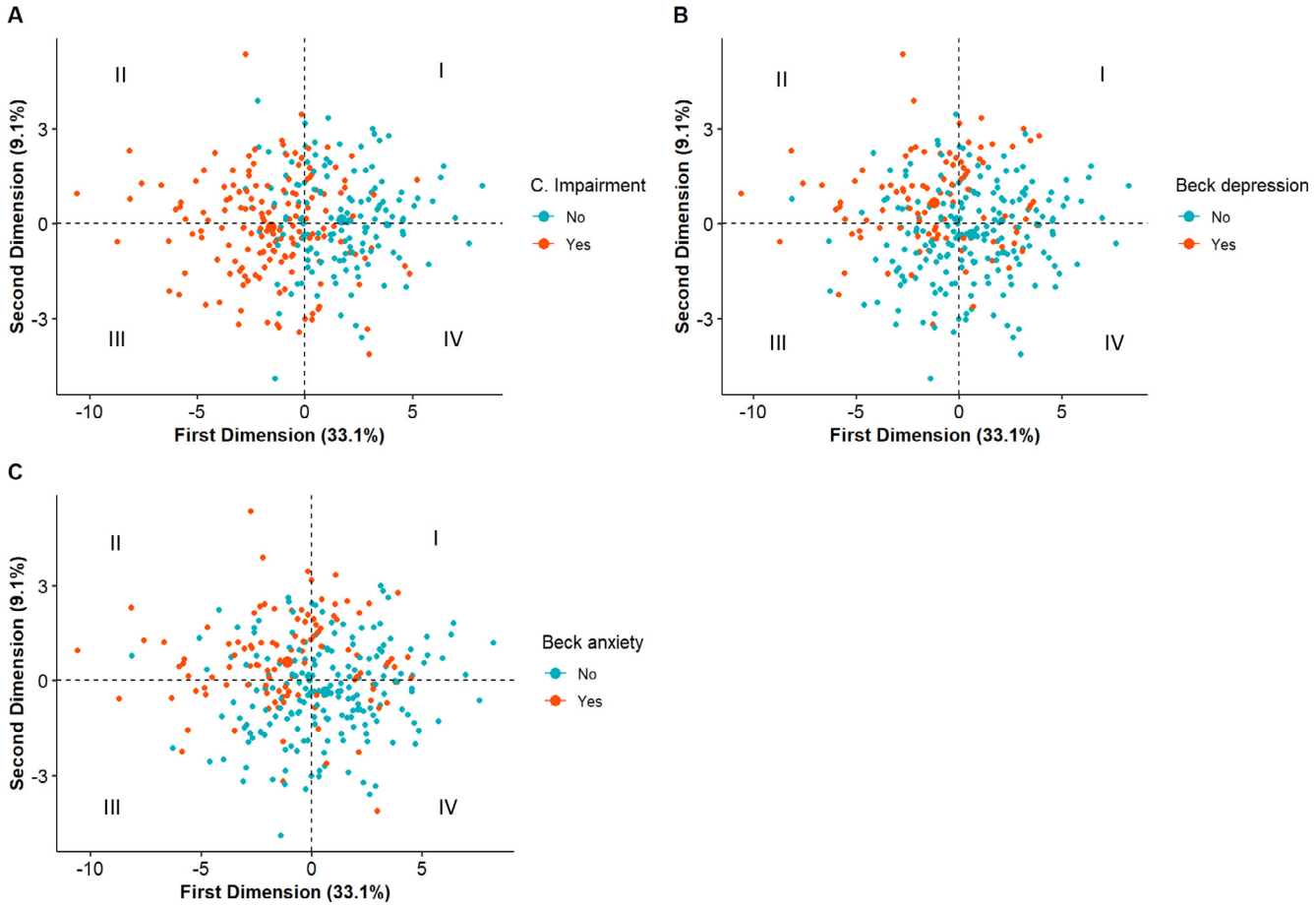

Fig. 3. Axis x represents the first cognitive dimension (explaining 33.1% of the variance) and axis y represents the second dimension. Distribution of individual participants in the cohort classified by presence or absence of cognitive dysfunction (A), depression (B), or anxiety (C). There is substantial overlap in participants classified as having cognitive dysfunction (CD), depression and anxiety. For example, many participants quadrant II of the graphs demonstrate CD plus anxiety and depression. However, there is a subset of participants with CD (shown in quadrant III of the graphs) who are classified as having cognitive dysfunction without anxiety and depression. These participants are more likely to do poorly on cognitive tests that load onto dimension 2.

repetitive transcranial magnetic stimulation (rTMS), a non-invasive neurostimulation technique, has been shown to improve cognitive dysfunction in other populations, and could conceivably be used in SLE if researchers were able to determine appropriate neuroanatomical targets [34]. For example, in a double-blind sham-controlled trial, rTMS, delivered to the left dorsolateral prefrontal cortex of patients with schizophrenia (another clinical group with cognitive dysfunction), was shown to improve immediate memory [35]. Another potential management strategy used in other populations to target specific cognitive deficits is cognitive training, a rehabilitative strategy that uses interventions such as education, adaptive strategies, cognitive skills training, and mindfulness-type activities to improve specific cognitive and functional deficits [1,36].

The relationship between depression and cognitive impairment in SLE is likely multifactorial and influenced by both individual factors (genetics, environment) and disease-specific factors (autoantibodies, cytokines, disrupted blood brain barrier, cerebrovascular injury) [37]. In humans generally, a variety of cytokines and chemokines have been associated with both depressive symptoms and cognitive dysfunction [38]. Patients with a clinical diagnosis of major depression have been shown to have increased levels of inflammatory markers TNF-alpha, c-reactive protein, interleukin (IL)-1 and IL-6 [39,40]. In SLE, IL-6 and IL-10 have been found to be associated with depression scores [11], and IL-6 has been shown to be related to learning and attention [10], suggesting a potential common role for IL-6 in both CD and depression in SLE. In SLE, inflammation may contribute to cognitive and psychiatric symptoms via a number of mechanisms, including through excitotoxic damage to pertinent gray matter regions and to white matter microstructure in associated tracts [41,42]. Medication side effects, particularly corticosteroids [9], may also contribute to both psychiatric and cognitive symptoms.

Given the lack of variability in depression and anxiety symptoms and neuropsychological performance over time, we were not able to evaluate the relationship between change in anxiety and depression and differential change in neuropsychological performance in the various domains. However, the stability of the relationship between symptoms of depression and anxiety and neuropsychological performance that we observed over time supports previous cross-sectional findings [1,13] and promotes the need for continued investigation into these relationships using longer, longitudinal study designs.

In our patient cohort, neuropsychological subtests loaded onto two dimensions: “simple speed” (dominant hand tapping, Stroop color naming and word reading) or a more complex dimension that was primarily explained by memory, executive function and complex processing speed. The results of the factor analysis were stable across time, and these two dimensions explained approximately 42% of the total variance in neuropsychological performance. We are not aware of any studies to date that have examined the factor structure of the ACR battery in SLE patients. In this study we used PCA with a goal of reducing multiplicity in our analyses, meaning that our results should not be interpreted as a definitive factor structure of the ACR. However, given that individual neuropsychological subtests may represent variable constructs across populations (e.g. a low score on a “memory” test might represent a true memory deficit in one clinical population, but be secondary to attentional deficits in another) [43,44], future studies with a primary aim of examining the factor structure of the ACR in SLE will assist in understanding the nature of cognitive impairment in this population.

Strengths of our study include the involvement of a well-characterized, large cohort of SLE patients with validated measures obtained across three timepoints. Unlike most previous studies in this area, we examined both anxiety and depression symptoms, rather than depression alone. Limitations include missing BDI-II and BAI scores in some participants. Unlike the neuropsychological testing, the depression and anxiety questionnaires were self-report and some participants did not complete them. These data are potentially not missing completely at random and, while our data analytic technique (MFA) is not affected by missing data, not having these participants’ data in our analysis still has the potential to bias the results. Additional limitations include lack of clinical diagnosis of anxiety or depressive disorders, the lack of systematic recording of psychiatric medication use, and a relatively short follow up period (one year). These limitations would be addressed by larger and longer-term datasets.

Conclusion

In conclusion, depression and anxiety symptoms in SLE patients are related to a cognitive dimension incorporating memory, executive function and complex processing speed in a stable manner across one year, with neuropsychological tests of memory being most strongly related on exploratory analysis. We found a high degree of overlap in participants identified as having CD and demonstrating anxiety and depression. Further clinical research should examine whether and to what extent cognition improves when anxiety and depression are treated, as well as the mechanistic links between anxiety and depression and CD in SLE.

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Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2021.09.008.

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