Cognitive dysfunction in antiphospholipid antibody (aPL)-negative systemic lupus erythematosus (SLE) versus aPL-positive non-SLE patients

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Abstract

Objective

The aim of this study was to compare the cognitive function of antiphospholipid antibody (aPL)-negative systemic lupus erythematosus (SLE) and aPL-positive non-SLE patients.

Methods

Twenty aPL-negative SLE and 20 aPL-positive non-SLE female patients with no history of overt neuropsychiatric manifestations took standardised cognitive tests of learning and memory, attention and working memory, executive functions, verbal fluency, visuoconstruction, and motor function. The primary outcome measure was an established global cognitive impairment index (CII). Cranial magnetic resonance imaging (MRI) was also obtained on all patients.

Results

Twelve of 20 (60%) of the SLE and 8/20 (40%) of the aPL-positive patients had global cognitive impairment on CII; there were no group differences on CII or on individual measures. Cognitive impairment was not associated with duration of disease, level of disease activity, or prednisone use. No correlations were found between clinical disease factors and cognitive impairment, and neither group showed an association between incidental or major MRI abnormalities and cognitive dysfunction.

Conclusion

Both aPL-negative SLE and aPL-positive non-SLE patients, without other overt neuropsychiatric disease, demonstrated high levels of cognitive impairment. No clinical, serologic, or radiologic characteristics were associated with cognitive impairment. Cognitive dysfunction is common in APS and in SLE, but its mechanisms remain unknown.

Key words

systemic lupus erythematosus, antiphospholipid antibodies, cognitive dysfunction, neuropsychology

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Introduction

Cognitive dysfunction occurs in autoimmune disorders such as systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) (1). Studies comparing the prevalence and pattern of cognitive deficits in these illnesses are limited. Cognitive dysfunction has been identified as one of 19 neuropsychiatric (NP) syndromes in SLE by the American College Rheumatology, and is defined as "significant deficits in any or all of the following cognitive functions: complex attention, executive skills (*i.e.* planning, organising, sequencing), memory (*i.e.* learning, recall), visual-spatial processing, language (*i.e.* verbal fluency), and psychomotor speed" (2). Cognitive dysfunction occurs in over 50% of SLE patients with active NP symptoms. Even in the absence of overt NP symptoms, mild cognitive dysfunction occurs in 25–50% of SLE patients (3) and has been identified as one of the most common neurobehavioral disorders in SLE (4). Deficits in attention, learning and recall, verbal and non-verbal fluency, complex psychomotor functions, visuospatial skills, and motor dexterity are relatively consistent; patients with overt NP symptoms (seizures and strokes) have higher levels of cognitive dysfunction. SLE disease duration and activity, use of prednisone, and coexisting depression have not had consistent associations with cognitive dysfunction in SLE.

Antiphospholipid syndrome (APS) is defined by arterial or venous thromboses and/or pregnancy morbidity in association with antiphospholipid antibodies (aPL) (5) measured by anticardiolipin, anti-β_2-glycoprotein-I (aβ_2GPI) ELISA (aCL), or lupus anticoagulant (LA) test. Major Overt NP syndromes that occur in aPL-positive patients include stroke, transient ischaemic attack, seizures, and chorea (6-8). Early studies reported an association between aPL and dementia/cognitive issues in an aging population (9, 10), yet only two peer-reviewed studies have examined the cognitive function of aPL-positive or primary APS patients, independent of lupus, in comparison to controls or other patient groups. Jacobson *et al.* (11) reported cognitive impairment in 26% of 27 non-elderly patients with elevated levels of aCL IgG without autoimmune disease or history of neurological events compared to 4% in controls. Tektonidou *et al.* (12) reported cognitive impairment in 42% of 39 patients with primary APS compared to 18% in controls. Neither of these studies reported consistent associations between cognitive impairment and disease characteristics or depression.

Studies suggest that both SLE and aPL can result in cognitive dysfunction; however, direct comparison of cognition across these disorders is difficult due to methodological issues. Many prior studies of SLE have not specifically screened out or identified those patients with positive aPL. The prevalence of positive aPL in patients with SLE is approximately 30–40% (13). In SLE studies of cognition, the prevalence of aPL has ranged from 6% to 38% (6, 14-17) and the presence of aPL in SLE patients has been associated with greater impairment in memory, visuomotor speed, and visuoconstruction (16, 18-20).

The aim of this study was to compare the cognitive function of aPL-negative SLE patients and aPL-positive non-SLE patients without prior neuropsychiatric histories; our goal was also to determine the association between aPL and cognitive dysfunction independent of lupus diagnosis. In addition, in both groups we compared the clinical characteristics of patients who had normal and abnormal cognitive function.

Methods

Study Cohort

Twenty aPL-negative SLE ("SLE") and 20 persistently aPL-positive non-SLE ("aPL") adult (>18 years of age) female patients participated in this cross sectional study. All SLE patients had a diagnosis based on the ACR Classification Criteria (21); SLE patients with positive aPL (LA test, aCL IgG/M/A, or aβ_2GPI IgG/M/A) within 6 months of the study entry were excluded (patients had been tested for all three aPL tests as part of the standard of care). Antiphospholipid antibody-positive patients had a positive LA test as defined by the International Society on Thrombosis and Haemostasis (5); aCL

IgG/M/A isotype, present in ≥40U; and/or aβ_2GPI IgG/M/A isotype, present in ≥40U, on two or more occasions, at least 12 weeks apart (within one year prior to screening).

Subjects in either group were excluded if they had a history of other systemic autoimmune diseases, stroke, transient ischaemic attack, vascular dementia, epilepsy, multiple sclerosis, prior traumatic brain injury, central nervous system (CNS) infection or tumour, major psychiatric disorder (depression, schizophrenia, bipolar disorder), learning disability, substance abuse as defined by DSM-IV standards (22) and/or via diagnosis by health professional, neuropsychological testing within the past year, diabetes, hepatitis C, human immunodeficiency infection, uncontrolled hypertension, or cardiovascular compromise.

Study procedures

Patients were recruited from the Hospital for Special Surgery (HSS) rheumatology clinic and local private practices between October 2008 and December 2011. The HSS Institutional Review Board approved the study. All eligible patients had a 30-minute prescreening visit with the study physician, which included the informed consent process, a lupus or aPL-specific medical history and physical examination, SLE ACR Classification Criteria, Updated Sapporo APS Classification Criteria, and SLE disease activity indices (Systemic Lupus Disease Activity Index [SLEDAI] (23), and the Systemic Lupus International Collaborating Clinics Damage Index for SLE [SLICC] (24); measures that have been useful in evaluating disease activity in SLE as well as APS patients (25, 26).

After the screening visit and eligibility determination was completed, the subjects were scheduled for neuropsychological testing and cranial magnetic resonance imaging (MRI). The testing consisted of a brief interview, utilising our previously published form (27), regarding subject demographics and additional neuromedical information as well as the administration of the extended ACR neuropsychological battery. A brief measure of depression, The Beck Depression Inventory-Second Edition (BDI-II) (28) was also administered. The MRI appointment was scheduled within two weeks of the cognitive testing appointment.

Measures

- Neuropsychological tests

A battery of tests was administered which are recommended by the ACR and for which the reliability as well as the validity has been established in SLE (2, 29). The tests and test scores used in this battery included: the *Wechsler Test of Adult Reading* (30) – a vocabulary-based test that measures pre-morbid full scale intelligence quotient (FSIQ); WAIS-*III Digit Symbol Subtest-total score* (Dig Sym) (31) which requires psychomotor speed, concentration and graphomotor abilities; *Trail Making Test-Part B – total time* (Trails B) (32) which measures psychomotor speed, attention and cognitive sequencing; *Stroop Colour and Word Test-Colour-Word – total score* (Stroop) (33) which measures complex attention and "shifting" of sets by naming color print for words written in different colors. The learning trials (summation of trials 1-5) and long delay free recall measures from the *California Verbal Learning Test-Form II* (CVLT-II) (34) were selected to measure learning and recall of verbal material. The immediate and 30-minute delayed recall of the *Rey-Osterrieth Complex Figure Test* (Rey-O Immediate, Rey-O Recall) (35, 36) was selected to assess visual learning and memory. *WAIS-III Letter Number Sequencing – total score* (LNST) (31) was selected as a measure of auditory working memory. *Controlled Oral Word Association Test – total score* (FAS) *and Animal Naming Test – total score* (Animals) (37) were selected as measures of letter and category verbal fluency. *Finger Tapping Test – Dominant* (Tapping Dom) *and Non-dominant hands* (Tapping NDom) (32) was used as a test of simple fine motor speed bilaterally. Additionally, four tests were identified as sensitive to SLE patients in our prior study (29) and were included for analysis. *WAIS-III Block Design – total score* (Blocks) (38) was obtained as a measure of visuoconstruction. *Paced Auditory Serial Addition Test – total score* (PASAT) (39) was obtained as a measure of rapid auditory information processing; *Digit Vigilance Test – total time* (Dig Vig) (40) was used to measure sustained visual attention; and the *Category Test – total score* (Category) (32) was used a measure of general abstracting ability and analytic skills.

A cognitive impairment index (CII) was calculated using 12 selected test scores from the ACR-SLE battery identified above (29). Each score was converted to t-scores using demographically corrected normative data (34, 41, 42). T-scores below 40 were considered impaired. The CII has a range of 0 to 12, with a higher number representing greater cognitive impairment.

- Neuroimaging measures

MRI images of the brain were also acquired with a 3T GE MR scanner at the Citigroup Biomedical Imaging Center in New York, NY. The MR imaging protocol included a 3-plane localiser and a T1-weighted 3D SPGR volume imaging scan (about 124 coronal slices, 1 mm slice thickness, TR/TE/TI/FA = 9ms/1.9ms/500ms/8°, 256 x 192 image matrix over a field-of-view of 240x180 mm^2, with an in-plane resolution of 0.94 x 0.94 mm^2, imaging time = 9:12min), A T2 weighted TR=4000, Te 100ms imaging sequence will be followed by a FLAIR TR/TE/TI= 10000/162/2200 matrix size 256x256. FLAIR has used for better tissue contrast for cortical lesions and white matter lesions in SLE (43). A neuroradiologist (RZ) blind to subject group clinically evaluated the scans and characterised scans as normal, incidental or mild clinical findings, or major clinical findings requiring additional assessment. Incidental or mild categories included minimal white matter hyperintensities or very mild volume loss within the expected range for aPL and SLE subjects. Clinical findings requiring additional assessment included potential evidence of stroke, tumours or extensive white matter hyperintensities or volume loss suggesting significant atrophy.

Statistical analysis

All statistical analyses were conducted using the SAS statistical analysis

package (version 9.2; SAS Institute Inc., Cary, NC). We compared the two groups in terms of demographics (age, education, gender, and ethnicity) and health characteristics (duration of disease, disease activity/severity, and medication use). All continuous variables were compared using a non-parametric Wilcoxon rank sum test. All categorical variables were compared using a Fisher's exact test. Correlations were analysed between clinical measures and cognitive scores using Spearman correlation. For all analyses, two-tailed tests were used. *p*-values less than 0.05 were designated statistically significant.

Results

Demographic and clinical characteristics

SLE patients had disease duration mean of 153.8±118.7 months; lupus manifestations included: malar rash (80%), discoid rash (5%), photosensitivity (65%), oral ulcers (30%), renal disorder (50%), haematologic disorder (20%), arthritis (90%), antinuclear antibody (100%), and immunologic disorder (90%). Lupus-related medications at the time of enrolment included hydroxychloroquine (75%), mycophenolate mofetil (25%), methotrexate (5%), rituximab (5%), azathioprine (5%), warfarin (5%), prednisone (50%), and non-steroidal anti-inflammatory drugs (NSAIDs; 15%) (Table I).

The aPL patients had a mean disease duration of 58.8±80.1 months (defined as the duration since the first positive aPL determination); 17 fulfilled the Updated Sapporo Classification Criteria for APS (5): vascular event [VE] only 9; pregnancy morbidity [PM] only 4; and VE+PM 4. Sixteen of 20 (80%) patients had a positive LA test, 16 (80%) aCL IgG/M/A, and 16 (80%) aβ_2GPI; the number of patients with single, double, and triple aPL-positivity was 3 (15%), 6 (30%), and 11 (55%), respectively. Antiphospholipid antibody-related medications at the time of enrolment included aspirin (25%), hydroxychloroquine (30%), warfarin (40%), prednisone (5%), and NSAIDs (10%).

Table I demonstrates additional demographic and clinical characteristics of SLE and aPL patients. There were no differences in terms of age, education, or BDI-II scores. More Caucasians and higher estimated premorbid Full Scale IQ were reported in the aPL group. SLE patients had a significantly greater length of disease duration and a higher percent of subjects on prednisone. There were no other clinical differences between the groups.

Clinical interpretation of the cranial

Table I. Comparison of demographic and health characteristics of SLE and aPL+ subjects.

Variable	SLE (n: 20)	aPL (n: 20)	*p*-value
Ethnicity, A / AA / C / H (%)	10/ 35/ 40 /15	10/ 0/ 80/ 10	***0.013***
Mean age (years) and SD	36.5 ± 11.7	37.6 ± 8.6	0.555
Mean education (years) and SD	15.6 ± 2.4	16.4 ± 2.3	0.273
Mean diagnosis duration (months) and SD	153.8 ± 118.7	58.8 ± 80.1	***0.001***
Mean SLEDAI score and SD	2.5 ± 2.2	1.3 ± 1.5	0.096
Mean SLICC score and SD	0.6 ± 0.9	0.6 ± 0.8	0.891
Mean prednisone dose (mg/day) and SD	4.6 ± 5.8	0.8 ± 3.4	***0.006***
% on prednisone	50.0	5.0	***0.003***
Mean BDI-II Score	10.8 ± 8.9	8.4 ± 5.3	*0.490*
% BDI-II Non to Minimal	70 (14/20)	90 (18/20)	
% BDI-II Mild	15 (3/20)	5 (1/20)	*0.200*
% BDI-II Moderate	10 (2/20)	5 (1/20	
% BDI-II Severe	5 (1/20)	0	
Estimated Full Scale IQ	102.9 ± 11.1	109.9 ± 8	***0.032***

Ethnicity: A: Asian; AA: African American; C: Caucasian; H: Hispanic.
SLEDAI: SLE disease activity index.
BDI-II: Beck Depression Inventory-Form II (none to minimal=0-13, mild=14-19, moderate=20-29, severe>30).
SLICC: the Systemic Lupus International Collaborating Clinics Damage Index for SLE.
**p*-values from Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables.

Table II. Composite scores and individual test t-scores on neuropsychological measures by group.

Variable	SLE (n:20)		aPL (n:20)		*p*-value**
	Mean	SD	Mean	SD	
Cognitive Impairment Index					
No. of ACR impaired cognitive test scores (range 0-12)	4.4	2.7	3.4	2.6	0.172
Individual Cognitive Test t-scores					
*WAIS-III Digit Symbol	40.1	12.3	43.6	9.4	0.336
*WAIS-III Letter-Number Sequencing Test	48.6	10.4	51.0	9.8	0.304
*STROOP Color-Word Test	48.9	10.9	48.3	9.5	0.957
*Trail Making Test B	41.0	11.2	40.7	8.7	1.000
*FAS (Verbal Fluency)	44.0	10.6	47.3	10.9	0.363
*Animals (Semantic Fluency)	44.2	13.6	48.8	13.0	0.342
*CVLT-II Immediate (Learning)	50.5	14.2	48.7	11.2	0.851
*CVLT-II Recall	46.0	16.3	47.3	12.4	1.000
*REY-O Immediate Recall	37.9	16.5	40.6	13.3	0.436
*REY-O Delayed Recall	36.9	16.1	39.1	13.1	0.428
*Tapping: Dominant hand	51.2	12.2	51.5	12.9	0.823
*Tapping: Non-dominant hand	49.4	10.5	53.9	12.9	0.521
WAIS-III Block Design	48.7	12.3	51.1	9.5	0.342
PASAT	43.2	12.3	47.1	12.6	0.331
Digit Vigilance Test	42.3	10.1	46.2	11.0	0.280
Category Test	48.2	9.4	47.4	8.1	0.851

ACR: American College of Rheumatology systemic lupus erythematosus (SLE) recommended neuropsychological battery; CVLT: California Verbal Learning Test-II; Rey-O: Rey-Osterrieth Complex Figure Test; Tapping: Finger Tapping Test; PASAT: Paced Auditory Serial Addition Test.
*Indicates test scores included in the American College of Rheumatology systemic lupus erythematosus (SLE) recommended neuropsychological battery
***p*-values from Wilcoxon rank sum test.

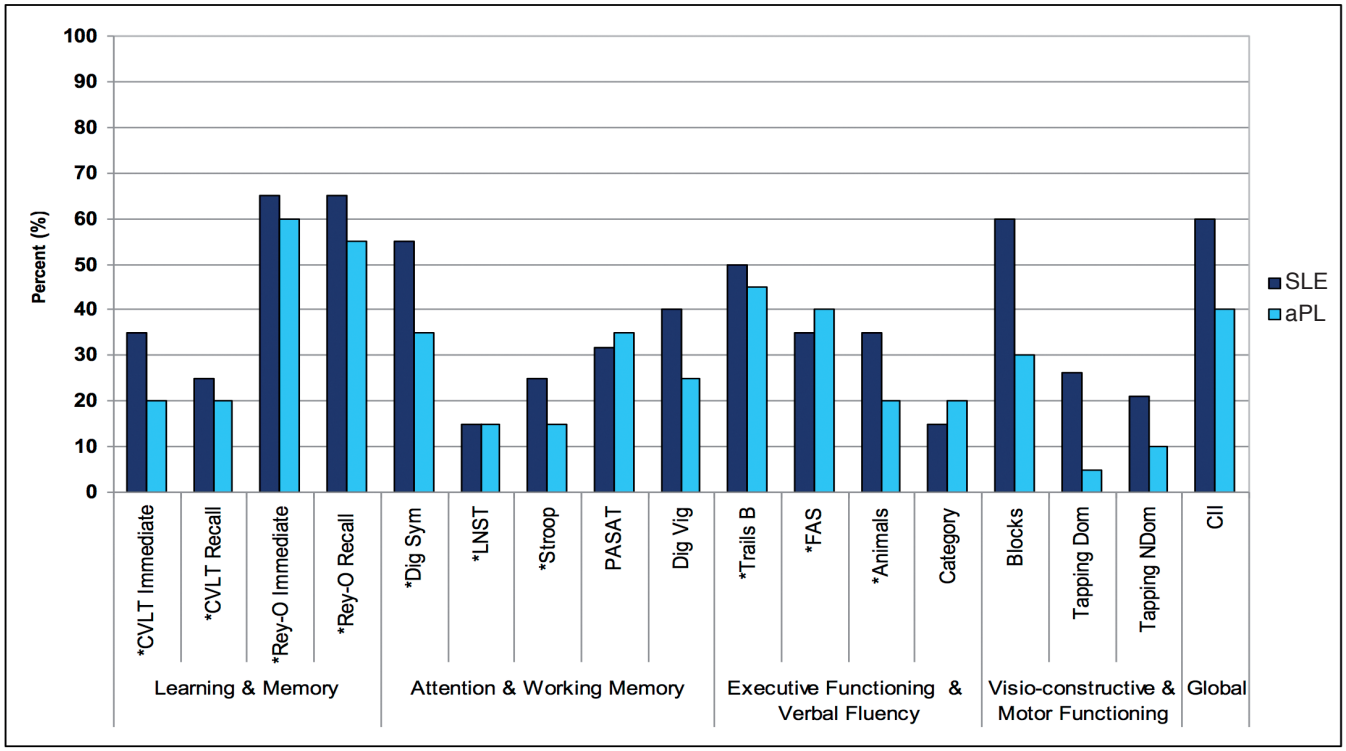

Fig. 1. Percent Impairment on Individual and Global Neuropsychological Measures.
CVLT: California Verbal Learning Test-II; Rey-O: Rey-Osterrieth Complex Figure Test; Dig Sym: WAIS-III Digit Symbol Test; LNST: WAIS-III Letter-Number Sequencing Test; Stroop: Stroop Colour and Word Test; PASAT: Paced Auditory Serial Addition Test; Dig Vig: Digit Vigilance Test; Trails B: Trail Making Test Part B; FAS: Verbal Fluency; Animals: Category Fluency; Category: Category Test; Blocks: WAIS-III Block Design Test; Tapping: Finger Tapping Test (dominant hand and non-dominant hand); CII: Cognitive Impairment Index.

MRIs showed that 10/20 (50%) in the SLE group were normal and 2/20 (10%) were clinically abnormal, both having extensive white matter hyperintensities and atrophy. Eight of 20 (40%) showed findings that were judged to be incidental/clinically insignificant, including 8 with white matter hyperintensities, 5 with mild atrophy and 2 with both. In the aPL group, 9/20 (45%) were normal and 2/20 (10%) were clinically abnormal with each having extensive WM damage. Nine of 20 (45%) showed incidental/clinically insignificant findings, all white matter hyperintensities, 3 had mild cortical atrophy and one had both white matter hyperintensities and atrophy.

Neuropsychological test results

There were no differences between the SLE and aPL subjects on the CII or the individual cognitive tests as noted in Table II. Figure 1 demonstrates the percent impairment across the individual tests as well as percent of patients with four or more of the 12 tests from the CII impaired. Using the CII impairment level (four or more of 12 tests below a T-score of 40), 12/20 (60%) of the SLE patients and 8/20 (40%) of aPL patients were cognitively impaired (p=0.206). For both SLE and aPL patients the highest frequency of impairment occurred in visual learning and memory (Rey-O Intermediate and Delayed recall), visuomotor speed and flexibility (Trails B and Dig Sym), verbal fluency (FAS), visuoconstruction (Blocks) and rapid auditory information processing (PASAT).

Neuropsychological and clinical associations

Correlations between the global cognitive score (CII), demographics, major clinical features such as disease duration (in months), disease activity and severity (SLEDAI and SLICC), prednisone dose, and depression score (BDI-II) can be found in Table III for each group. For SLE only, cognitive impairment was associated with lower education and higher depression.

There was no significant difference between the CII (range 0–12) between those with abnormal/incidental MRI findings and those without (p=0.75). In the SLE patients 5/10 (50%) with abnormal/incidental finding MRI's were cognitively impaired (CII>4), and 8/10 (80%) with normal MRI's were cognitively impaired. In aPL patients, 5/11 (45.5%) with abnormal/incidental finding MRI's were cognitively impaired and only 3/9 (33.3%) patients with normal MRI's had global cognitive impairment.

Discussion

This study demonstrates that aPL-negative SLE patients and aPL patients without SLE who have no history of overt/major NP disorder have high levels of global cognitive impairment. Using a global index score with high reliability and validity, 60% of the SLE patients and 40% of the aPL patients were cognitively impaired. In prior studies utilising the same test battery in control subjects similar in age, education, and gender, overall cognitive impairment was approximately 18-20% (14, 29).

Table III. Correlations between Cognitive Impairment Index (CII) and demographic and clinical characteristics in SLE and aPL groups.

Variable	SLE		aPL	
	Spearman Correlation Coefficient	*p*-value	Spearman Correlation Coefficient	*p*-value
Age	-0.039	0.871	0.022	0.928
Education (years)	-0.508	0.022	-0.223	0.345
Disease duration (months)	-0.226	0.338	0.159	0.503
Prednisone dose (mg/day)	0.015	0.950	-0.161	0.498
SLEDAI score	0.262	0.264	0.280	0.232
SLICC score	-0.188	0.428	0.157	0.508
BDI-II score	0.525	0.018	0.156	0.511

SLEDAI: SLE disease activity index; SLICC: the Systemic Lupus International Collaborating Clinics Damage Index for SLE; BDI-II: Beck Depression Inventory-Form II.

In prior studies of SLE patients without overt NP involvement the rates of cognitive dysfunction were generally lower than the 60% reported in this study. In our two prior studies in which SLE patients were similarly screened and administered the same test battery, global cognitive impairment was 23% in 22 SLE patients (29) and 24% 84 SLE patients (14). The reason for higher rates of cognitive impairment in this sample of SLE subjects is unclear and may in part be related to longer disease duration or additional health, environment, and socioeconomic differences that were not measured. Forty percent of the aPL patients screened to be negative for pre-existing NP disorders were cognitively impaired in this study. This is consistent with one prior study of patients specifically diagnosed with aPL (12) but higher than the subjects classified as asymptomatic but aPA positive (11).

In both the SLE and aPL groups, the pattern of cognitive difficulties was similar with impaired performance in visual and verbal learning and memory, visuomotor speed, attention and information processing, verbal fluency, and problem solving. These areas of impairment are consistent with many prior studies in SLE studies assessing a wide range of cognitive functions (3). This study suggests that aPL patients also have a wide range of cognitive impairments consistent with one prior study (11) and greater than the attention and fluency deficits noted in another study (12). This diffuse pattern of cognitive impairment in the groups suggests both have global *versus* focal cerebral changes. The careful selection and characterisation of the two samples further suggests that unique mechanisms underlying cogntive deficits in these autoimmune diseases exist.

Given our goal of determining the association between aPL and cognitive dysfunction independent of lupus diagnosis, we did not include SLE patients with aPL in our study. Tektonidou *et al*. (12) did not find a difference in cognitive performance between patients with primary APS and those with SLE-associated APS. In contrast, aPL positivity was statistically more frequent (15.7%) in SLE patients classified as having a cognitive disorder compared to the SLE patients without cognitive impairment (7.6%) in another study (6). A relationship between persistently elevated aPL and cognitive impairment/decline has also been reported in SLE (44, 45). Future studies that include a third control aPL-positive SLE group at baseline, and evaluate all groups over time, may be necessary to identify the most important risks and mechanisms associated with cognitive impairment in these patients.

In our study, clinical characteristics were not associated with cognitive dysfunction in either SLE or aPL patients. SLE patients with higher self-reported symptoms of depression and lower education had greater cognitive dysfunction, but overall disease characteristics, including medications, were not related to cognitive impairment. Symptoms of depression are common in SLE (46) and despite a statistical lack of group difference, SLE subjects in this study had higher scores and this has correlated with cognitive dysfunction in some prior studies (3). At least half of subjects in the SLE or aPL groups had either abnormal MRI or incidental MRI findings of white matter change or cortical atrophy. However, we found no associations between cognitive impairment or number of cognitive tests abnormal and the MRI findings in either group. In a different cohort of SLE patients without overt NP, the first author found few abnormal MRI's yet did find associations between learning and memory and neurometabolic functions of the hippocampal region (47) and attention/learning and memory deficits with neurometabolic functions of white matter (48). Tektonidou reported a relationship between cognitive dysfunction and white matter lesions in APS (12) and many other studies suggest that WM abnormalities are common in APS. Continued studies are warranted in this area.

Our study has some limitations. Firstly, the sample size is small and we do not have a healthy matched control group as well as aPL-positive SLE patients. Secondly, we included a heterogeneous group of aPL-positive patients with or without APS; however we believe aPL-associated cognitive dysfunction is independent of the history of thrombosis (excluding stoke). Thirdly, we do not have information about the recent average and cumulative steroid dose of our patients. Despite these limitations, this study is the first to compare cognition in persistently aPL-positive patients and SLE patients without aPL.

In summary, the 40–60% cognitive impairment rate in these two autoimmune patient groups is relatively high considering subjects with overt NP activity were excluded. Although the current study suggests similar domains of cognitive impairment in both groups, larger studies will be necessary to evaluate if cognitive impairment domain differences exist between the two diagnoses. Continued studies that assess and compare bio behavioral characteristics of patients with SLE, aPL and SLE with aPL who experience cognitive decline over time may be the next useful step in understanding and subsequently treating cognitive dysfunction.

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