

# Association of Lipoprotein and Thyroid Hormones With Cognitive Dysfunction in Patients With Systemic Lupus Erythematosus

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## Research Article

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# Abstract

**Background:** Neuropsychiatric systemic lupus erythematosus (NPSLE) occurs up to 75% of adult SLE patients, and is one of the major causes of death in SLE patients. Cognitive dysfunction is a typical clinical feature of NPSLE, which seriously affects the quality of life of patients. Dyslipidemia and thyroid disease, which were prevalent in SLE patients, both related to the neuropsychiatric disturbances, including significant psychiatric and cognitive disturbance. This study aimed to investigate whether cognitive dysfunction in patients with systemic lupus erythematosus (SLE) was related to the expression of serum thyroid hormone and lipoproteins.

**Methods:** A total of 121 patients with SLE and 65 healthy controls (HCs) at Nanjing Drum Tower Hospital completed a cognitive function test, then 81 SLE patients were divided into high cognition (n=33) group and low cognition group (n=48). The differences in clinical and laboratory tests and the correlations between IgG, IgM, albumin, T3, and T4 levels and cognitive function were analyzed. The enzyme-linked immunosorbent assay was used to determine the serum levels of 4 lipoproteins (APOE, APOA1, IGF-1, and IGFBP7) in 81 patients.

**Results:** Patients with SLE were less educated with abnormal cognitive function compared with HCs. The levels of albumin, T3 ( $P < 0.05$ ), and T4 decreased in low-cognition patients, while D-dimer, anti-dsDNA antibody, and IgM levels increased. The serum IgG and IgM levels showed a significant negative correlation with partial cognitive function. The serum T3 and T4 levels positively correlated with cognition. The expression of APOE, APOA1, IGF-1, and IGFBP7 showed no difference between the high- and low-cognition groups. However, the serum APOE level negatively correlated with Line Orientation, APOA1 positively correlated with Coding, and IGFBP7 negatively correlated with Graphic copy ( $P < 0.05$ ), and IGF-1 had no correlation with any cognitive functions.

**Conclusions:** Thyroid hormones (T3 and T4) and lipoproteins (APOE, APOA1, and IGFBP7) were associated with cognitive dysfunction in SLE. Whether T3 and T4 can be used in clinical practice as the biomarkers of cognitive dysfunction in SLE needs further exploration.

## Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by autoantibody production and immune complex deposition, culminating in destructive tissue injury to multiple organ systems including the central nervous system (CNS) [1-2]. Neuropsychiatric SLE (NPSLE) is a form of SLE associated with severe neuropsychiatric (NP) syndromes, including various neurological and psychiatric features [3]. Several studies estimated that up to 75% of patients with SLE experienced NPSLE [4-5]. The symptoms of NPSLE include mood disorders, confusion, headache, and cognitive dysfunction, which significantly degrades the quality of life and affects the survival of patients [6]. However, the underlying disease mechanisms remain largely unknown, as neuropsychiatric symptoms are nonspecific, clinically validated biomarkers for diagnosis are nonexistent, and NPSLE diagnosis is

difficult, often leading to palliative rather than therapeutic protocols [7-8]. Cognitive function assessment is one of the valuable clinical skills used to screen for cognitive impairment and assess the severity of the disease [9]. Many cognitive function assessment tools are available, including Taiwan Mental State Examination [10], Montreal Cognitive Assessment [11], AD8 Dementia Screening Interview [12], and so forth. However, the assessment of cognitive function is incomplete and insensitive to mild cognitive impairment due to the relative simplicity of these scales. Although a complete set of neuropsychological tests can comprehensively assess the level of cognitive function and the severity of the cognitive impairment, it generally takes a long time, is prone to subject fatigue, and is especially not suitable for the clinical evaluation of the elderly [13]. Therefore, tools that are simple to implement and can relatively comprehensively evaluate cognitive function have a great application value. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) overcomes the aforementioned shortcomings. It was originally used to identify the pathological decline of cognitive function in the elderly and also could screen the neuropsychological function status of the general population [14]. Later studies applied it to bipolar disorder [15], multiple sclerosis [16], cerebrovascular disease [17], epilepsy [18], and other diseases with cognitive impairment in different fields. The results showed that RBANS could be used as an effective neuropsychological function screening tool, with good internal consistency, test-retest reliability, structural validity, and parallel validity, and sex has no significant effect on the evaluation results of RBANS. These findings showed that RBANS could be a favorable means of assessing cognitive function in patients with SLE.

Dyslipidemia is prevalent in patients with SLE with an incidence ranging up to 75%. It is characterized as disordered low-density lipoprotein (LDL) and/or decreased high-density lipoprotein (HDL) levels in the serum [19]. Dyslipidemia is associated with disease activity, such as kidney damage and cardiovascular disease, which are the most common complications in patients with SLE and closely related to the long-term prognosis [20-21]. In addition, dyslipidemia is believed to be closely associated with the occurrence of cognitive dysfunction and Alzheimer's disease (AD). The hippocampus is critically important for learning and memory. Researchers found that high-fat diet-induced rats had impaired neurogenesis in the dentate gyrus of the hippocampus [22], decreased hippocampal production of brain-derived neurotrophic factor [23], increased apoptosis of hippocampal neurons, and an associated decrease in the weight of the hippocampus [24], which likely plays a key role in neuronal loss, leading to learning and memory deficits. Nonthyroidal illness syndrome is also prevalent in SLE and characterized by decreased serum triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone levels [25-27]. Thyroid hormones can influence all aspects of lipid metabolism including synthesis, mobilization, and degradation, thus resulting in dyslipidemia [28]. Earliest descriptions of thyroid disease showed a link with neuropsychiatric disturbances, including significant psychiatric and cognitive disturbance, classical slowness of thought, and increased depressive symptoms [29]. Treatment with T4 helps improve the disturbance in mood [30], but not neurocognitive function, especially complex attention tasks and verbal memory tests [31]. Inextricable links exist between SLE, dyslipidemia, and abnormal thyroid hormone levels. However, whether dyslipidemia and thyroid hormone abnormalities in patients with lupus are related to cognitive dysfunction remains unknown.

In this study, the correlation between cognitive function and the levels of serum thyroid hormones (T3 and T4) and lipoproteins (APOE, APOA1, and IGFBP7) in SLE were evaluated. This study aimed to discover the changes in the levels of serum biomarkers and proteins possibly related to the cognitive function in SLE, thus prompting diagnosis or predicting prognosis of SLE.

## Materials And Methods

### 2.1 Patients and study design

A total of 121 patients with SLE who visited the Department of Rheumatology, Nanjing Drum Tower Hospital, Nanjing, China, from May 2019 to May 2020 were prospectively enrolled. All patients were diagnosed according to the SLE criteria of the American College of Rheumatology [32]. The disease activity of these patients was measured using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [33-34]. Patients who had other autoimmune diseases; had a history of familial hyperlipidemia and/or thyroid disease, diabetes mellitus, and/or other rheumatic diseases; and took lipid-lowering agents or thyroid medications were excluded. Active patients were classified into two groups: low-cognition group ( $n = 33$ ; RBANS score: 51–90) and high-cognition group ( $n = 48$ ; RBANS score: 91–130), based on the RBANS score. Patients who developed neuropsychiatric syndromes not attributable to SLE (electrolyte imbalances, infections, or medications) were excluded. Meanwhile, 65 age- and gender-matched healthy controls (HCs) were recruited from the Physical Examination Center of Nanjing Drum Tower Hospital. This study was approved by the ethics committee at The Affiliated Drum Tower Hospital of Nanjing University Medical School (ID: SC201700201) and undertaken according to the guidelines of the Declaration of Helsinki. At entry, patients completed a standardized medical history, laboratory tests, and analyses. All the detections were carried out at the clinical laboratory of Nanjing Drum Tower Hospital. The demographic features of the patients and HC samples are shown in Table 1.

### 2.2 Cognitive dysfunction study

The cognitive dysfunction in SLE is characterized by deficits in attention, learning and recall, verbal and nonverbal fluency, language, visuospatial skills, executive functions, and motor dexterity [35-37]. A total of 121 patients with NPSLE and 65 normal volunteers were invited to participate in this study. All participants provided additional medical information using an ad-hoc questionnaire and had a physical examination.

The RBANS consisted of five indexes: immediate memory, visuospatial/constructional, attention, language, and delayed memory [38]. Stimuli were contained in a wire-bound, easel-type booklet, making the test easily portable and allowing for bedside administration. The total administration time was 20–30 min. The battery indexes were assessed using the following tests [38]:

- a. **List Learning:** The examiner read aloud a list of 10 words, which were semantically unrelated, early acquired, relatively high-imagery, and as phonetically unique as possible. The participants were asked to recall (without regard for order) as many of these items as possible. After four trials, the

number of words correctly recalled on the fourth trial was used as a measure of verbal learning and memory; the total score was 40 points.

- b. **Immediate Story Memory:** The examiner read a short story including 12 keywords aloud twice, and then the participants were asked to recall this story as possible. The number of keywords correctly recalled was used as a measure of immediate story memory to avoid complicated scoring rules; the total score was 24 points.
- c. **Figure Copy:** The participants were asked to remember a geometric figure comprising 10 parts and then copy this figure in 4 min. Each part received a 2-point score (accuracy and placement); the total score was 20 points.
- d. **Line Orientation:** Two lines were presented at an angle, and the participants needed to select the corresponding lines on a simultaneously presented array. The subject's task on each item was to identify the matching lines. One point was given for each correctly matched line; the total score was 20 points.
- e. **Picture Naming:** The participants were shown 10 pictures and asked to name the objects of the pictures. Semantic cues were given if the object was obviously misperceived (e.g., "umbrella" for mushroom). Naming correctly (including the correct answer according to the prompts) was used as a measure of picture naming; the total score was 10 points.
- f. **Semantic Fluency:** The participants should generate the words as much as possible for a given semantic category (e.g., fruits and vegetables) within 60 s. The semantic categories aimed to minimize retrieval demands and thereby more specifically tap semantic stores rather than retrieval strategies. One point was given for each correct word; the total score was 20 points.
- g. **Digit Span:** The Digit Span was analogous to digits forward on the Wechsler Adult Intelligence Scale (WAIS). There were two string of digits in each item, increasing from 2 to 9 digits. The second given length string was read when the first string was failed. The failure of attempts of two same items was given 0 points; the total score was 16 points.
- h. **Coding:** First, the participants were provided with a row of graphics, each of which corresponded to a number. Later, they were provided with some figures without numbers. They were asked to fill in the number under each figure provided for the second time as fast as possible, according to the corresponding relationship between the figure and the number provided for the first time. Numbers rather than symbols were chosen for the response to avoid the possible detrimental effect of constructional apraxia on performance. The score was the total number of items completed in 90 s.
- i. **List Recall:** In this test, the participants were asked to recall the words provided in the "List Learning" test as many as possible. One point was given for each correctly recalled words, and the total score was 16 points.
- j. **List Recognition:** In this test, the examiner read 20 words aloud, including 10 words provided in the "List Learning" test. The participants were asked to answer whether the words were read before. One point was given for each correct recognition, and the total score was 20 points.

- k. **Delay Story Recall:** In this test, the participants were asked to recall the story provided in the “Story Memory” test. The number of keywords correctly recalled was used as a measure of delay story memory to avoid complicated scoring rules. One point was given for each correctly recalled keywords, and the total score was 12 points.
- l. **Figure Recall:** In this test, the participants were asked to recall and draw the figure provided in the “Figure Copy” test as accurate as possible. Each part received a 2-point score (accuracy and placement) for 20 possible points.

SCALING: For the purpose of the present study, a single reference sample was used to provide the scaling metrics. The norm was established based on the test results of 540 people aged 20–89 years. Raw scores were converted into scaled scores for all participants in the present study using the same scaling metric, regardless of age [38-39].

### 2.3 Measurement of serum autoantibodies

The levels of autoantibodies and lipoproteins of patients in the serum were measured within 1 month of the cognitive function testing. In this phase of the study, participants had a blood sample drawn. A venous puncture was done, and 2 mL of blood was collected in a serum separator tube. The serum from the patients was prepared by centrifugation at 3000 rpm for 10 min in a clinical centrifuge. The autoantibodies, including anti-ds-DNA antibody, anti-Sm antibody, anti-Ribonucleoprotein antibody (anti-RNP), anti-Sjögren’s syndrome A antibody (anti-SSA), anti-Sjögren’s syndrome B antibody (anti-SSB), anti-ribosomal-P antibody, and anti- $\beta$ 2-glycoprotein-I antibody, and immunoglobulins including Immunoglobulin G (IgG), Immunoglobulin M (IgM), Immunoglobulin A (IgA), and Immunoglobulin E (IgE), were analyzed.

### 2.4 Enzyme-linked immunosorbent assay

The expression of apolipoprotein E (APOE, RayBio, USA), apolipoprotein A1 (APOA1, R&D system, USA), insulin-like growth factor-1 (IGF-1, Fcmacs, China), and insulin-like growth factor binding protein 7 (IGFBP7, Arigobio, China) were detected using an enzyme-linked immunosorbent assay (ELISA) kit following the manufacturer’s protocols. In short, a 96-well plate was coated with the antibody (100  $\mu$ L/well) in duplicate and incubated at 4°C overnight. The plate was then washed five times with wash buffer and dried gently on a lint-free paper towel. After the sample was diluted, 100  $\mu$ L of the detection samples was added to each well, and the plate was incubated for 2 h at room temperature. An equal volume (100  $\mu$ L/well) of the substrate solution was added, incubated at room temperature for 30 min, and then protected from light. The reaction was stopped by adding 100  $\mu$ L/well of 1M H<sub>2</sub>SO<sub>4</sub>, and the optical density was determined at a wavelength of 450 nm 5 min later [40]. The results were fitted to the standard curve, and the detection ranges were as follows: APOE (1.5–400 ng/mL), APOA1 (6.3–200 ng/mL), IGF-1 (62.5–4000 pg/mL), and IGFBP7 (625–40000 pg/mL).

### 2.5 Statistical analysis

Data were expressed as means  $\pm$  standard deviation. Differences between two groups were determined using the unpaired-sample Student *t* test if the variance was normally distributed, and the Mann–Whitney *U* test was used for non-normally distributed data. Differences among observed frequencies were tested using the chi-square test, while Pearson’s correlation coefficient was used to calculate the correlation between variables [40]. The correlations were analyzed using Spearman’s correlation test. Data were analyzed and visualized using SPSS16.0 software or GraphPad Prism 7.0 (GraphPad Software, CA, USA), and a two-tailed *P* value  $< 0.05$  was considered statistically significant.

## Results

### 3.1 Clinical characteristics and cognitive function of patients with SLE and HCs

The demographic features of 121 patients with SLE and 65 HCs in the study are summarized in Table 1. The mean age of patients and HCs was  $33.88 \pm 11.77$  and  $36.69 \pm 13.88$  years, respectively. The mean level of education was  $11.95 \pm 3.05$  years in the patient group, which was significantly lower than that in the HC group ( $P < 0.01$ ).

Table 1. Demographic features of the 121 SLE patients and 65 healthy controls in the study.

Variables	SLE (n=121)	HC (n=65)	<i>P</i> Value
Age, (years)	33.88 ( $\pm 11.77$ )	36.69 ( $\pm 13.88$ )	0.150
Females, n (%)	106 (87.60%)	50 (76.92%)	0.093
Education, (years)	11.95 ( $\pm 3.05$ )	13.28 ( $\pm 4.58$ )	$< 0.05^*$
SLEDAI	10 (0-47)	NA	/

Data are expressed as median (minimum - maximum, number (percentage), or mean  $\pm$  standard deviation (SD) values. *P* values are based on independent sample *t*-test and Chi-square test for normally distributed variables. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\*  $P < 0.005$ , vs. Low RBANS Score. The Graph Pad Prism 7.0 and SPSS Statistics 16.0 software were used for statistical analysis.

Afterward, an RBANS was performed on 121 patients and 65 HCs. Significant differences were found in List Learning ( $P < 0.0001$ ) between patients with SLE and HCs, while Immediate Story Recall, Picture Naming, Coding, List Recall, List Recognition Test, and Delayed Story Recall (all  $P < 0.01$ ), as well as Judgment of Line Orientation, Digit Span, and Figure Recall (all  $P < 0.05$ ), were lower in patients with SLE. However, Figure Copy and Semantic Fluency showed no differences (Table 2). These tests corresponded to five cognitive domains: immediate memory, visuospatial/construction, attention, language, and delayed memory. After categorizing the aforementioned cognitive function tests according to these five cognitive domains, the difference between patients and normal volunteers was analyzed. The results showed that levels of immediate memory, visuospatial/construction, attention, and delayed memory were significantly lower in patients than in HCs, while language features showed no obvious difference (Fig. 1).

Table 2. The data of commonly cognitive assessment.

RBANS score	SLE (n =121)	HC (n = 65)	P Value
<b>Immediate memory</b>			
List Learning, median (range)	24 (5-39)	29 (15-36)	< 0.005***
Immediate Story Memory, median (range)	13 (1-22)	16 (1-21)	< 0.01**
<b>Visuospatial/constructional</b>			
Figure Copy, median (range)	20 (14-20)	20 (17-20)	0.2963
Line Orientation, median (range)	17 (8-20)	18 (9-20)	< 0.05*
<b>Language</b>			
Picture Naming, median (range)	9 (7-10)	9 (8-10)	< 0.01**
Semantic Fluency, median (range)	21 (7-33)	23 (11-35)	0.0873
<b>Attention</b>			
Digit Span, median (range)	13 (6-16)	14 (8-16)	< 0.05*
Coding, median (range)	46 (4-70)	54 (13-74)	< 0.01**
<b>Delayed memory</b>			
List Recall, median (range)	5 (0-10)	7 (2-10)	< 0.01**
List Recognition, median (range)	20 (16-20)	20 (17-20)	< 0.01**
Delay Story Recall, median (range)	7 (0-12)	9 (0-12)	< 0.01**
Figure Recall, median (range)	15 (5-20)	16 (7-20)	< 0.05*

Data are expressed as mean  $\pm$  standard deviation (SD) values. P values are based on independent sample t-test for normally distributed variables. \*P < 0.05, \*\*P < 0.01, \*\*\* P < 0.005, vs. Low RBANS Score. The Graph Pad Prism 7.0 software were used for statistical analysis.

### 3.2 Demographic features, clinical manifestations, and treatment of patients

Based on the RBANS score, 81 patients were divided into high-cognition group ( $n = 33$ ) and low-cognition group ( $n = 48$ ). As shown in Table 3, no statistically significant differences in age and sex were found between the two groups. The mean level of education was  $10.77 \pm 3.64$  years in the low-cognition group, which was lower than that in the high-cognition group ( $P < 0.01$ ). The levels of SLEDAI ( $13.91 \pm 11.79$  vs  $9.38 \pm 5.79$ ) significantly increased in patients with low cognition compared with those in high cognition (all  $P < 0.05$ ).

Table 3. Demographic features, clinical manifestations, and treatment of SLE patients.

SLE characteristics	Low Cognition (n=48)	High Cognition (n=33)	P Value
<b>Demographic</b>			
Age, (years)	34.67 ( $\pm$ 12.03)	32.23 ( $\pm$ 10.98)	0.3530
Females, n (%)	40 (83.33%)	30 (90.90%)	0.763
Education, (years)	10.77 ( $\pm$ 3.64)	13.26 ( $\pm$ 3.21)	< 0.01**
SLEDAI, mean $\pm$ (SD)	13.91 ( $\pm$ 11.79)	9.38 ( $\pm$ 5.79)	< 0.05*
<b>Clinical chart review (%)</b>			
Rash, (%)	10 (21.28%)	6 (18.18%)	0.768
Mucosal ulcers, (%)	2 (4.26%)	1 (3.03%)	1.000
Hematuria, (%)	22 (46.81%)	13 (39.33%)	0.510
Proteinuria, (%)	22 (46.81%)	13 (39.33%)	0.510
Pyuria, (%)	14 (39.79%)	11 (33.33%)	0.736
Arthritis, (%)	8 (17.02%)	5 (15.15%)	0.823
Vasculitis, (%)	4 (8.51%)	0 (0%)	0.231
Pleurisy, (%)	1 (2.13%)	1 (3.03%)	1.00
Pericarditis, (%)	1 (2.13%)	0 (%)	1.00
Low complement, (%)	36 (76.60%)	27 (81.82%)	0.574
Anemia, (%)	11 (23.40%)	1 (3.03%)	< 0.05*
Thrombocytopenia, (%)	11 (23.40%)	4 (12.12)	0.203
Leukopenia, (%)	11 (23.40%)	7 (21.21%)	0.817
Lupus nephritis, (%)	19 (40.43%)	20 (60.61%)	0.075
Neurological disorder, (%)	6 (12.77%)	5 (15.15%)	1.00
<b>Current medication (%)</b>			
Prednisone (%)	31 (64.58%)	18 (54.54%)	0.425
Hydroxychloroquine (%)	29 (61.70%)	19 (57.58%)	0.711
Cyclophosphamide (%)	5 (10.64%)	3 (9.09%)	1.000
Azathioprine (%)	1 (2.13%)	1 (3.03%)	1.000
Methotrexate (%)	2 (4.26%)	2 (6.06%)	1.000
Cyclosporine (%)	0 (0%)	2 (6.06%)	0.326

Data are expressed as number (percentage). P values are based on Chi-square test for normally distributed variables. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\*  $P < 0.005$ , vs. Low RBANS Score. The SPSS Statistics 16.0 software were used for statistical analysis.

Patients with low cognition had more frequent anemia (23.4% vs 3.03%) compared with patients with high cognition ( $P < 0.05$ ). Meanwhile, the prevalence of rash, mucosal ulcers, hematuria, proteinuria, pyuria, arthritis, vasculitis, pleurisy, pericarditis, low complement, thrombocytopenia, leukopenia, lupus nephritis, and neurological disorder showed no difference between the two groups. In addition, the treatment with prednisone, hydroxychloroquine, cyclophosphamide, azathioprine, methotrexate, and cyclosporine was not different between the two groups (Table 3).

### 3.3 Comparison of clinical and laboratory characteristics of patients

The study investigated the laboratory parameters of patients enrolled in this study (Table 4). Patients with low cognition had substantially lower albumin ( $31.76 \pm 5.79$  mg/dL vs  $34.91 \pm 4.13$  mg/dL;  $P < 0.01$ ), T3 ( $3.20 \pm 1.03$  ng/dL vs  $3.71 \pm 1.06$  ng/dL;  $P < 0.05$ ), and T4 levels ( $12.51 \pm 3.43$   $\mu$ g/dL vs  $14.97 \pm 2.14$   $\mu$ g/dL;  $P < 0.05$ ). The levels of anti-dsDNA antibody ( $P < 0.05$ ) and IgM ( $P < 0.01$ ) and the number of B cells ( $P < 0.05$ ) were higher and the D-dimer levels were considerably higher in patients with low cognition ( $P < 0.001$ ). The incidence of other clinical indexes, including globulin, 24-h urine protein (24-h UP), C3, C4, C-reactive protein, and creatinine (Cr), displayed no difference between the two groups.

In addition, the difference in the proportion of various blood cells in the peripheral blood between the two groups was detected. The results showed that the number of B cells was higher in the low-cognition group ( $0.15 \pm 0.16$  % vs  $0.10 \pm 0.13$  %;  $P < 0.05$ ), but no difference was found in the numbers of erythrocytes, WBCs, CD3<sup>+</sup> cells, CD3<sup>+</sup>CD4<sup>+</sup> cells, CD3<sup>+</sup>CD8<sup>+</sup> cells, and natural killer cells between the groups (Table 4). As shown in Table 4, the serum levels of anti-dsDNA antibodies ( $P < 0.05$ ) and IgM ( $P < 0.01$ ) were both higher in patients with low cognition. However, no statistically significant differences in positive rates of anti-Sm antibodies, anti-RNP antibodies, anti-SSA antibodies, anti-SSB antibodies, anti-Rib P antibodies, and anti- $\beta_2$ GPI antibodies, as well as the levels of IgG, IgA, and IgE, were found between the two groups.

Table 4. Comparison of clinical and laboratory characteristics of SLE patients.

SLE characteristics	Low Cognition (n=48)	High Cognition (n=33)	P Value
<b>Clinical characteristics</b>			
Globulin, mg/dL	28.18 (±7.97)	27.94 (±6.59)	0.764
Albumin, mg/dL	31.76 (±5.79)	34.91 (±4.13)	< 0.01**
24-h urine protein, (g/24 h)	1.97 (±2.59)	1.88 (±3.11)	0.433
C3 Levels, mg/dL	0.66 (±0.32)	0.77 (±0.29)	0.143
C4 Levels, mg/dL	0.12 (±0.08)	0.14 (±0.06)	0.323
CRP (mg/dL)	12.36 (±14.00)	11.95 (±16.98)	0.869
D-dimer (mg/dL)	1.74 (±1.28)	0.75 (±0.82)	< 0.001***
Cr (µmol/L)	86.95 (±80.42)	66.07 (±36.13)	0.200
BUN (mmol/L)	8.04 (±5.66)	7.07 (±4.69)	0.491
UA (µmol/L)	362.20 (±129.73)	339.38 (±142.41)	0.523
GFR (mL/min/1.73 m <sup>2</sup> )	117.37 (±56.97)	140.31 (±83.36)	0.223
ESR (mm/hour)	50.53 (±32.03)	42.59 (±28.74)	0.271
PLT (10 <sup>9</sup> /L)	149.32 (±79.69)	176.09 (±90.84)	0.099
TSH (mIU/L)	2.78 (±2.31)	2.69 (±2.21)	0.830
T3 Levels (ng/dL)	3.20 (±1.03)	3.71 (±1.06)	< 0.05*
T4 Levels (µg/dL)	12.51 (±3.43)	14.97 (±2.14)	< 0.05*
<b>Blood Cells</b>			
Erythrocyte, (%)	68.66 (±118.01)	40.23 (±66.60)	0.419
WBC, (10 <sup>9</sup> /L)	4.73 (±2.42)	5.43 (±3.62)	0.255
CD3+ cells, (%)	0.73 (±0.50)	0.67 (±0.40)	0.605
CD3+CD4+ cells, (%)	0.33 (±0.22)	0.30 (±0.23)	0.591
CD3+CD8+ cells, (%)	0.39 (±0.29)	0.36 (±0.19)	0.563
B cells, (%)	0.15 (±0.16)	0.10 (±0.13)	<0.05*
NK cells, (%)	0.06 (±0.06)	0.06 (±0.04)	0.929
<b>Autoantibodies</b>			
Anti-dsDNA antibodies, U/mL	746.12 (±441.82)	314.56 (±223.99)	<0.05*
Anti-Sm antibodies, n (%)	10 (21.28%)	8 (24.24%)	0.754

Anti-RNP antibodies, n (%)	16 (34.04%)	13 (39.39%)	0.624
Anti-SSA antibodies, n (%)	19 (40.43%)	14 (42.42%)	0.858
Anti-SSB antibodies, n (%)	4 (8.51%)	2 (6.06%)	1.000
Anti-Rib-P, n (%)	10 (21.28%)	11 (33.33%)	0.228
Anti- $\beta$ 2-GPI, n (%)	1 (2.13%)	0 (0%)	1.000
IgM (mg/dL)	1.13 ( $\pm$ 0.72)	0.76 ( $\pm$ 0.41)	<0.01**
IgG (mg/dL)	14.52 ( $\pm$ 6.79)	12.56 ( $\pm$ 5.34)	0.172
IgA (mg/dL)	2.49 ( $\pm$ 1.60)	2.56 ( $\pm$ 1.19)	0.857
IgE (mg/dL)	0.26 ( $\pm$ 0.44)	0.23 ( $\pm$ 0.41)	0.620

Data are expressed as number (percentage), or mean  $\pm$  standard deviation (SD) values. P values are based on independent sample t-test and Chi-square test for normally distributed variables. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\*  $P < 0.005$ , vs. Low RBANS Score. The Graph Pad Prism 7.0 and SPSS Statistics 16.0 software were used for statistical analysis.

### 3.4 Correlation analysis between cognitive function and IgG, IgM dsDNA, and albumin levels

The characteristics of SLE are high levels of autoantibodies and damages to multiple organs [41]. The serum anti-dsDNA antibodies are considered a diagnostic marker and one of the classification criteria for SLE [42-44]. Moreover, abnormal immunoglobulin levels were observed in many of the patients. The results showed that the IgG level was inversely associated with neuropsychological tests of immediate memory (List Learning:  $r = -0.344$ ,  $P < 0.01$ ; Immediate Story Recall:  $r = -0.264$ ,  $P < 0.05$ ; Fig. 2A and 2B). Besides, attention (Digit Span:  $r = -0.288$ ,  $P < 0.01$ ; Coding:  $r = -0.294$ ,  $P < 0.05$ ; Fig. 2C and 2D) and delayed memory (Delayed Story Recall:  $r = -0.289$ ,  $P < 0.01$ ; Figure Recall:  $r = -0.275$ ,  $P < 0.05$ ; Fig. 2E and 2F) showed a similar correlation, while no significant correlation was found with the other six cognitive functions (Supplementary Fig. 1). The serum IgM level showed a significant negative correlation with Immediate Story Recall ( $r = -0.267$ ,  $P < 0.05$ ; Fig. 2G), Picture Naming ( $r = -0.299$ ,  $P < 0.01$ ; Fig. 2H), Digit Span ( $r = -0.243$ ,  $P < 0.05$ ; Fig. 2I), Delayed Story Recall ( $r = -0.299$ ,  $P < 0.01$ ; Fig. 2J), and Figure Recall ( $r = -0.254$ ,  $P < 0.05$ ; Fig. 2K). Nevertheless, no correlation was found with other cognitive functions (Supplementary Fig. 2). However, dsDNA did not have a significant correlation with any cognitive function (Supplementary Fig. 3).

The cerebrospinal fluid (CSF)/serum quotient of albumin, known as quotient albumin (Q albumin), is widely accepted as a biomarker for estimating blood–brain barrier (BBB) function [45]; BBB plays a critical role in the pathogenesis of NPSLE [46]. The potential relationship between the serum albumin levels in SLE and cognitive dysfunction was analyzed. The results showed that the albumin levels correlated positively with List Learning, Immediate Story Recall, and Figure Copy (all  $P < 0.05$ ; Fig. 2L, M,

and 2N), as well as List Recognition Test and Delayed Story Recall (both  $P < 0.01$ ; Fig. 2O and 2P), but had no relationship with other cognitions (Supplementary Fig. 4).

### 3.5 Correlation analysis between cognitive function and C3, C4, and lipoprotein levels

Studies indicated that a significant higher prevalence of thyroid autoantibodies was observed in patients with SLE compared with HCs [47-48]. Many studies tried to associate thyroid abnormalities with clinical findings of SLE, but with no unified conclusion [49-51]. This study explored the relationship between the serum T3 and T4 levels and cognitive functions in patients with SLE. A regression analysis revealed that the serum T3 levels positively correlated with Immediate Memory, including List Learning ( $r = 0.293$ ,  $P < 0.05$ ; Fig. 3A) and Immediate Story Recall ( $r = 0.269$ ,  $P < 0.05$ ; Fig. 3B). Moreover, Figure Copy ( $r = 0.321$ ,  $P < 0.05$ ; Fig. 3C), Digit Span ( $r = 0.285$ ,  $P < 0.05$ ; Fig. 3D), List Recall ( $r = 0.187$ ,  $P < 0.05$ ; Fig. 3E), List Recognition test ( $r = 0.245$ ,  $P < 0.01$ ; Fig. 3F), and Delayed Story Recall ( $r = 0.258$ ,  $P < 0.05$ ; Fig. 3G) also correlated positively with the T3 level. The serum T4 level positively correlated with up to nine items ( $0.275 \leq r \leq 0.417$ ; all  $P < 0.05$ ; Fig. 3H–3P), including List Learning, Immediate Story Recall, Figure Copy, Digit Span, Coding, List Recall, List Recognition test, Delayed Story Recall, and Figure Recall.

The results indicated that T3 and T4 levels positively correlated with most cognitive functions. Increasing evidence shows that thyroid hormones (mainly T3 and T4) were involved in all aspects of lipid metabolism [52-54]. The relationship between thyroid hormones and lipid metabolism is evident in patients with thyroid dysfunction [55-56]. Moreover, lipid metabolism was markedly altered in patients with SLE [57]. The serum of 81 patients was collected for ELISA, and the expression of four lipoproteins (APOE, APOA1, IGF-1, and IGFBP7) was analyzed to explore any correlation between lipid metabolism and cognitive dysfunction in patients with SLE. The results showed no significant difference in the expression of these four proteins between the two groups (Fig. 4A, 4B, 4C, and 4D). Then, the correlations between the levels of these four lipoproteins and cognitive function were analyzed. The serum APOE levels significantly negatively correlated with Line Orientation ( $r = -0.206$ ,  $P < 0.05$ ; Fig. 4E), and IGFBP7 and Figure Recall ( $r = -0.223$ ,  $P < 0.05$ ; Fig. 4F), whereas APOA1 showed a positive correlation with Coding ( $r = -0.207$ ,  $P < 0.05$ ; Fig. 4G). Apart from this, no other correlations were found.

## Discussion

In the present study, the cognitive function was lower in patients with SLE compared with HCs. Lower education; higher SLEDAI score; lower albumin, T3, and T4 levels; and higher D-dimer, anti-dsDNA antibodies, and IgM levels were found in patients with low cognition compared with those with high cognition. Besides, cognitive function was closely associated with the IgG, IgM, albumin, T3, and T4 levels in patients. Apart from this, four lipoproteins (APOE, APOA1, IGF-1, and IGFBP7) were detected by ELISA. Although these four lipoproteins showed no difference between the two groups, APOE, APOA1, and IGFBP7 expression correlated with cognition. An important finding of the present study was that the abnormal levels of serum T3, T4, and lipoproteins might be associated with cognitive dysfunction in SLE.

NPSLE is a severe complication of SLE, which results in severe neurodegenerative changes and threatens life [58]. NPSLE is characterized by a variety of neurological manifestations, making the diagnosis of NPSLE a formidable challenge for rheumatologists [59-60]. Patients with NPSLE had multiple NP events, of which 91.2% affected the CNS, including cognitive dysfunction, headache, mood disorder, seizures, anxiety, and psychoses. The most common clinical manifestations were cognitive dysfunction, which occurred in 42.1% of patients [61]. In addition, this study showed that nervous system involvement was the initial presentation of SLE, while more than 50% of NPSLE occurred within the first 5 years after the onset of SLE [61]. This finding indicated that patients with SLE were likely to undergo cognitive dysfunction before the diagnosis of NPSLE. Therefore, 121 patients with SLE and 65 HCs were recruited for the cognitive assessment using RBANS. The results showed that the cognitive functions of patients with SLE, including immediate memory, visuospatial/constructional, attention, and delayed memory, were significantly lower than the cognitive functions of HCs before the diagnosis of NPSLE. Patients with SLE had a worse response in the lingual gyrus compared with the HCs; this region was associated with visual attention, visual encoding/processing, and working memory [62-63]. This opinion might explain why patients with SLE performed worse on attention, memory task, and visuospatial/constructional memory.

SLE is a prototypic autoimmune disease caused by the loss of B cell tolerance and subsequent recognition of self-antigens and becoming autoreactive [64-65]. In this study, the proportion of B cells obviously increased in patients. Also, the B cell hyper-reactivity could induce an accumulation of autoreactive plasma cells [66], which secreted a variety of autoantibodies, including anti-dsDNA, anti-Sm, anti-Ro, anti-SSA, anti-SSB, anti-Rib-P, and anti- $\beta$ 2-GPI, to mediate the occurrence of SLE [67]. The levels of anti-dsDNA and IgM increased in the low-cognition group compared with the high-cognition group, but anti-Sm, anti-RNP, anti-SSA, anti-SSB, anti-Rib-P, anti- $\beta$ 2-GPI, IgG, IgA, and IgE levels all showed no difference. The serum levels of anti-dsDNA antibodies fluctuated with disease activity, whereas others were not altered (anti-Sm, anti-Ro, anti-La, anti-cardiolipin) [68] owing to the different origins of antibody-secreting cells, which partially explained the results. However, in a cohort of 100 randomly selected patients, the higher positive rate of IgG anti-cardiolipin antibodies was found in patients with moderate/severe cognitive impairment, but no difference was found in the incidence of other autoantibodies [67]. Besides, in the present study, the plasma albumin level, as a biomarker of disease activity in SLE [69], decreased in the low-cognition group. The results indicated that the changes in serum IgM, dsDNA, and albumin levels might be associated with cognitive dysfunction in patients with SLE. As expected, IgM showed negative correlations with cognitive function, albumin correlated positively with cognitive function, but dsDNA showed no correlation.

The association between thyroid disease and SLE has been reported for more than 50 years [70]. Both hypothyroidism and thyroid nodules are found more frequently in patients with SLE than in the general population [71]. The rate of thyroid cancer is twice as prevalent in patients with SLE as in those without SLE [72]. In recent years, the impact of serum thyroxine levels on cognitive function has attracted widespread attention gradually, but no consistent conclusions have been drawn. A study on mild cognitive impairment and dementia showed that patients with relatively high T3 levels showed impairment in memory and visuospatial and executive functions [73]. However, patients with acute

coronary syndrome having low T3 levels had a poorer health-related quality of life (including general health, social functioning, and role emotional) than those with normal levels at a 1-year follow-up [74]. A study on subjective cognitive decline showed that higher T3 levels were associated with better verbal memory performance (immediate and delayed recall tasks) in APOE  $\epsilon$ 4 carriers [75]. The results showed that T3 and T4 levels decreased in patients with low cognition, and a significant positive correlation was found between T3 and T4 levels and cognitive function, which was consistent with the aforementioned view and supported that T3 and T4 had protective cognitive functions.

Dyslipidemia is one of the major risk factors for SLE, leading to a high prevalence of premature atherosclerosis and coronary artery disease in patients with SLE [76-77]. In addition, impaired renal function is also associated with dyslipidemia [78-79]. Thyroid hormones influence all aspects of lipid metabolism; especially T3 induces LDL receptor gene expression, enhancing LDL clearance [80]. A report revealed that low free T3 was an independent risk factor for dyslipidemia in patients with SLE [81]. The present study did not show the difference in the expression of serum lipoproteins (APOE, APOA1, IGF-1, and IGFBP7) between the two groups, but three of the aforementioned parameters showed a correlation with the cognitive function: APOE negatively correlated with Line Orientation, APOA1 positively correlated with Coding, and IGFBP7 negatively correlated with Figure Recall. Four years ago, an interesting result was reported: APOE knock-out (KO) mice had synaptic loss and cognitive dysfunction. Although these mice had synaptic loss and dysfunction similar to that in APOE KO mice, they did not have the learning and memory impairment observed in APOE KO mice; also, the memory deficit in the APOE KO mice was specific to female mice [82]. These results indicated that the cognitive impairment in mice was specifically caused by abnormal peripheral blood lipids but not by the expression of APOE in the brain. In AD, accelerated cognitive decline and abnormal internal environment, structure, and function of the brain were also found in APOE  $\epsilon$ 4 carriers [83]. Leon et al. compiled "The Role of APOE in Cerebrovascular Dysfunction" and pointed out multiple mechanisms of APOE involvement in cognitive dysfunction [84], which could be used to explain the results of the present study. ApoA1 is responsible for transporting cholesterol to the liver. It is a critical component in the formation of HDL. The overexpression of ApoA1 might effectively inhibit the age-related decline in memory and learning ability [85-86]. Moreover, Kawano et al. found that the levels of ApoA1 were strikingly lower in a group of late-onset nonfamilial AD [87]. These studies and the results of the present study both proved a positive correlation between APOA1 and cognitive functions. IGF-1 is an essential neurotrophic factor produced both peripherally and in the brain; adequate levels of serum IGF-1 may be necessary for normal cognitive functioning [88-89]. The serum IGF-1 levels were significantly elevated in patients with SLE and inversely correlated with age [90]. Shankar et al. supported that both high and low levels of IGF-1 might induce poor cognitive function and that optimum levels of IGF-1 might be associated with better cognitive function [91]. Therefore, this explained why the correlation between IGF and cognitive function was not observed in patients with high and low cognitive function.

## Conclusion

In conclusion, the findings indicated that T3 and T4 levels frequently decreased in patients with low cognition, and the cognitive function was associated with T3, T4, APOE, APOA1, and IGFBP7 levels in patients with SLE. The results suggested that T3 and T4 could be used in clinical practice as biomarkers for cognitive dysfunction in SLE.

## Abbreviations

SLE: Systemic lupus erythematosus; NPSLE: Neuropsychiatric SLE; CNS: systemic lupus erythematosus; central nervous system; LDL: low-density lipoprotein; HDL: high-density lipoprotein; NTIS: No thyroidal illness syndrome; T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone; ACR: American College of Rheumatology; SLEDAI: SLE disease activity index; RBANS: Repeatable battery for the assessment of neuropsychological status; MMPI: Minnesota multiphasic personality inventory; CRP: C-reactive protein; Cr: Creatine; BUN: blood urea nitrogen; UA: uric acid; GFR: glomerular filtration rate; ESR: erythrocyte sedimentation rate; PLT: platelets; TSH: thyroid stimulating hormone; CSF: cerebrospinal fluid; BBB: Blood–brain barrier; APOE: Apolipoprotein E; APOA1: apolipoprotein A1; IGF-1: insulin-Like growth factor-1; IGFBP7: insulin-like growth factor binding protein 7; AD: Alzheimer’s disease.

## Declarations

### Ethics approval and consent to participate

This research was approved by the Ethics Committee at The Affiliated Drum Tower Hospital of Nanjing University Medical School (ID: SC201700201) and was undertaken according to the guidelines of the Declaration of Helsinki. All recruited patients and healthy controls signed informed consent forms.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets generated during and analyzed during the current study are not publicly available due to respect participants’ rights to privacy and to protect their identity, but are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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### Authors' contributions

Huan Dou, Yayi Hou and Jun Liang conceived and designed the project. Li Lu, Jinglei Chen and Wei Kong performed the experiments, analyzed the data. Huan Dou, Kangxing Zhou and Jun Liang interpreted the patient data. Li Lu, wrote the manuscript, and Huan Dou and Jun Liang revised the manuscript. All authors read and approved the final manuscript.

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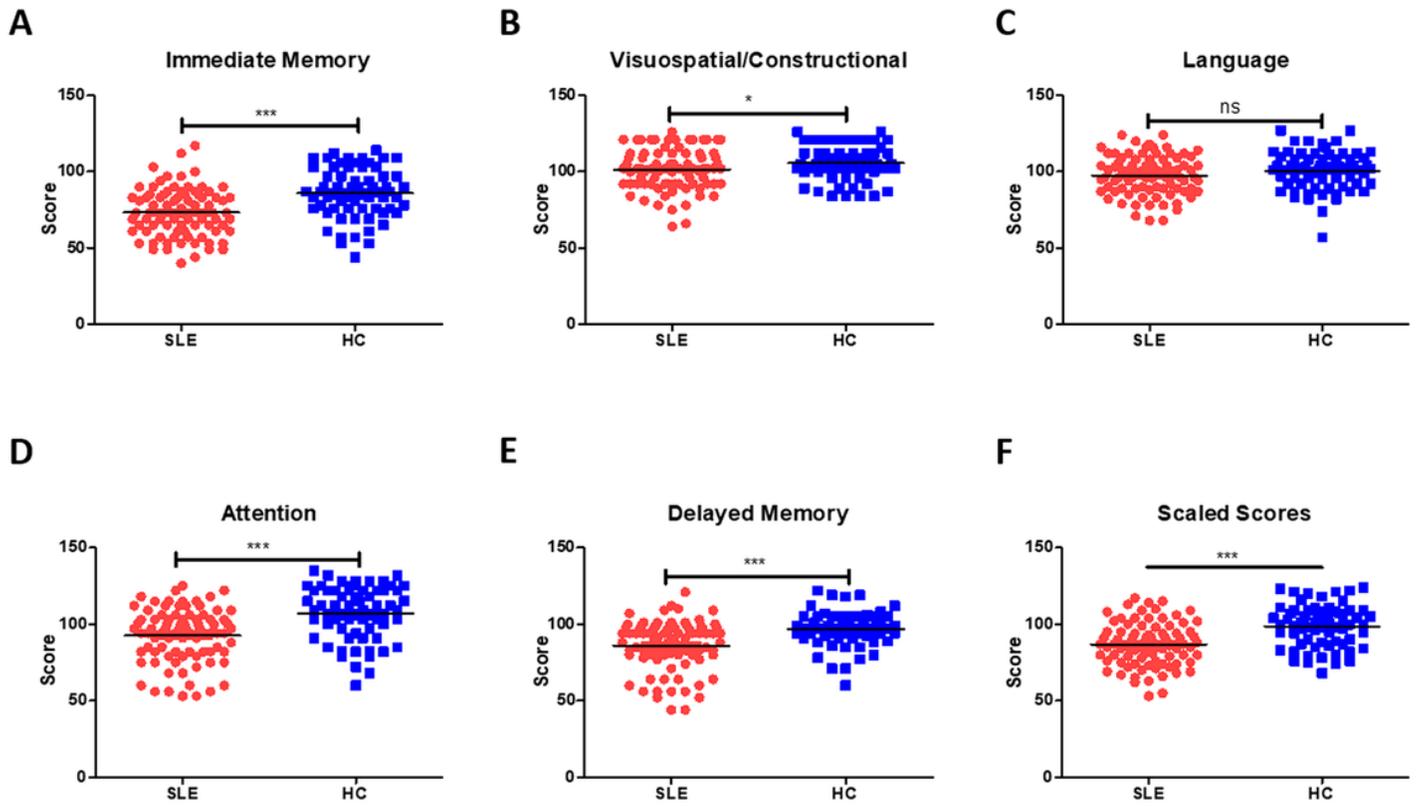
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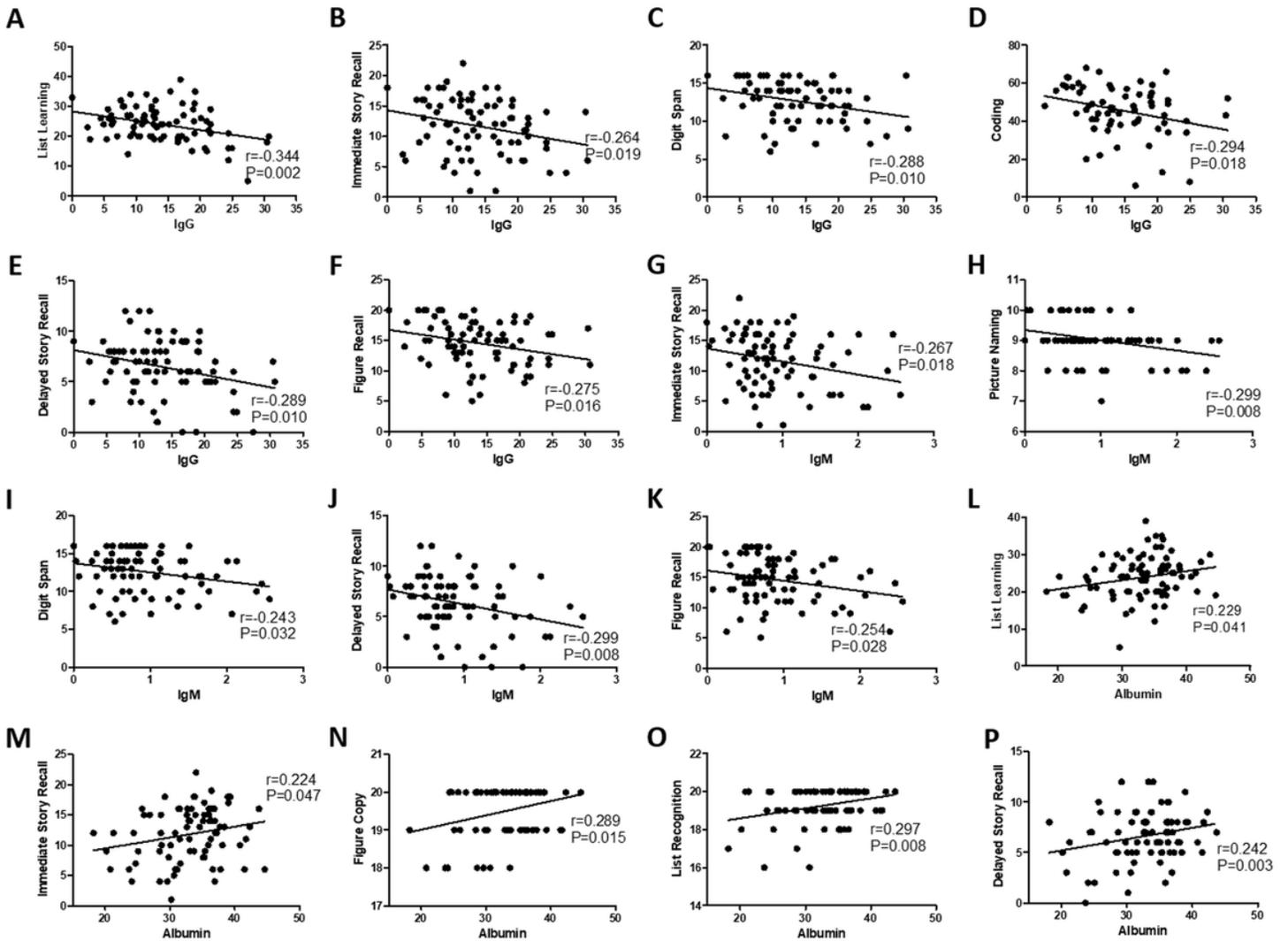
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## Figures



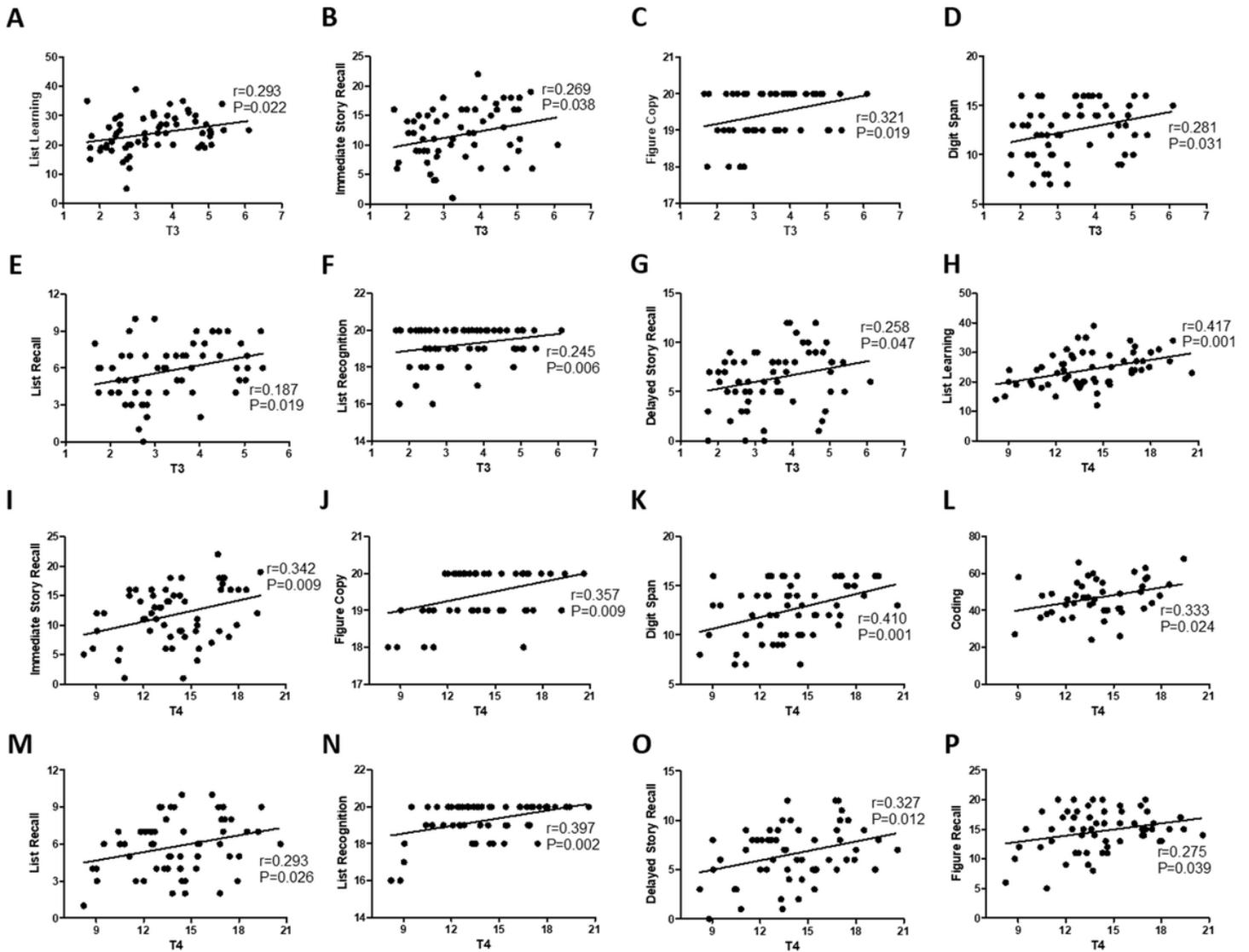
**Figure 1**

Cognitive function of patients with SLE and HCs The difference of Immediate Memory (A), Visuospatial/Constructional (B), Language (C), Attention (D), Delayed memory (E) between patients with SLE and HCs. Then, scores in the above 5 cognitive areas were converted into scaled scores (F).



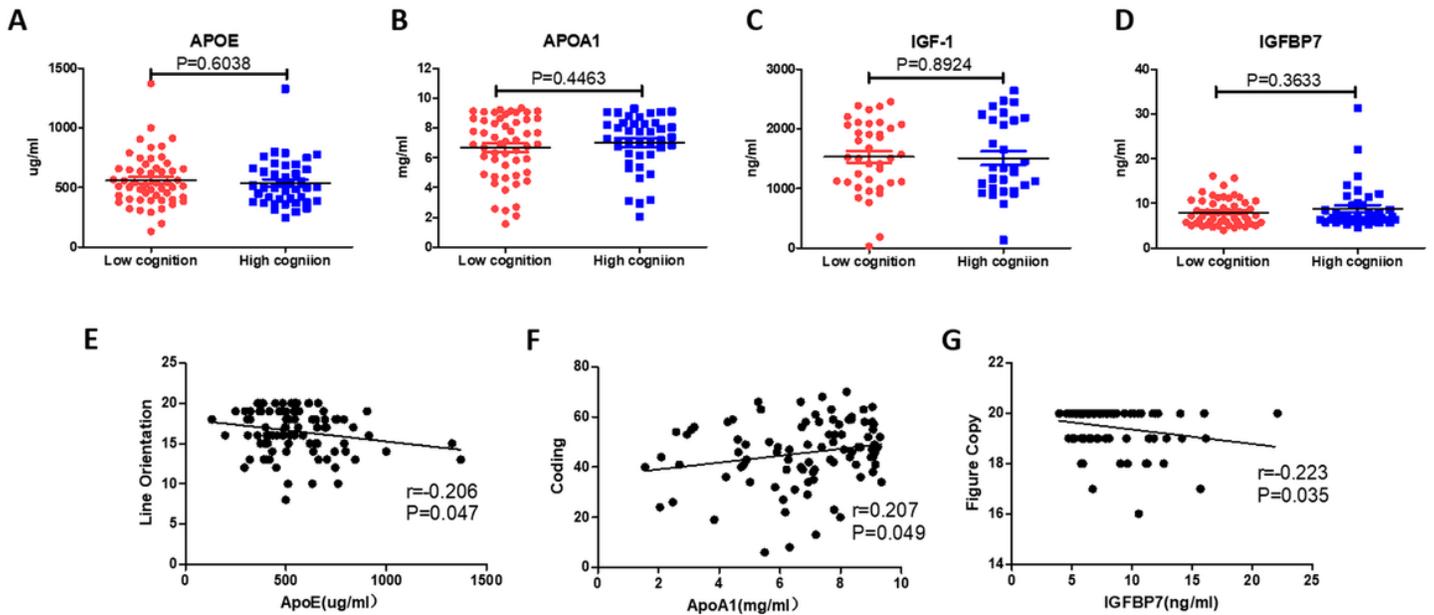
**Figure 2**

Correlation analysis between cognitive function and IgG, IgM, and albumin levels. Correlation between IgG and List learning (A), Immediate Story Recall (B), Digit Span (C), Coding (D), Delayed Story Recall (E), and Figure Recall (F) in patients with SLE. Correlation between IgM and Immediate Story Recall (G), Picture Naming (H), Digit Span (I), Delayed Story Recall (J), and Figure Recall (K) in patients with SLE. Correlation between IgM and List learning (L), Immediate Story Recall (M), Figure Copy (N), List Recognition (O) and Delayed Story Recall (P) in patients with SLE.



**Figure 3**

Correlation analysis between cognitive function and T3, T4 serum levels. Correlation between T3 and List learning (A), Immediate Story Recall (B), Figure Copy (C), Digit Span (D), List Recall (E), List Recognition (F), and Delayed Story Recall (G) in patients with SLE. Correlation between T4 and List learning (H), Immediate Story Recall (I), Figure Copy (J), Digit Span (K), Coding (L), List Recall (M), List Recognition (N), Delayed Story Recall (O), and Figure Recall (P) in patients with SLE.



**Figure 4**

The expression of serum lipoprotein and the correlation between cognitive function. The difference of serum APOE (A), APOA1 (B), IGF-1 (C), and IGFBP7 between different cognitive patients with SLE. Correlation between APOE and List Orientation (E) in patients with SLE. Correlation between APOA1 and Coding (F) in patients with SLE. Correlation between IGFBP7 and Figure Copy (G) in patients with SLE.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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