Spatial Working Memory Impairment in Patients with Non-neuropsychiatric Systemic Lupus Erythematosus: A Blood-oxygen-level Dependent Functional Magnetic Resonance Imaging Study

Chun-Min Zhu, Ye Ma, Lei Xie, Jin-Zhuang Huang, Zong-Bo Sun, Shou-Xing Duan, Zhi-Rong Lin, Jing-Jing Yin, Hong-Bo Le, Dan-Miao Sun, Wen-Can Xu, and Shu-Hua Ma

ABSTRACT. ***Objective.*** Using ethology and functional magnetic resonance imaging (fMRI) to explore mild cognitive dysfunction and spatial working memory (WM) impairment in patients with systemic lupus erythematosus (SLE) without overt neuropsychiatric symptoms (non-NPSLE) and to study whether any clinical biomarkers could serve as predictors of brain dysfunction in this disease.

Methods. Eighteen non-NPSLE patients and 18 matched subjects were all tested using the Montreal cognitive assessment scale test and scanned using blood-oxygen-level dependent fMRI while performing the n-back task to investigate the activation intensity of some cognition-related areas.

Results. Ethology results showed that non-NPSLE patients had mild cognitive dysfunction and memory dysfunction ($p < 0.05$). The fMRI scan confirmed a neural network consisting of bilateral dorsolateral prefrontal cortex (DLPFC), premotor area, parietal lobe, and supplementary motor area (SMA)/anterior cingulate cortex (ACC) that was activated during the n-back task, with right hemisphere dominance. However, only the right SMA/ACC showed a load effect in the non-NPSLE group; the activation intensity of most WM-related brain areas for the non-NPSLE group was lower than for the control group under 3 memory loads. Further, we found that the activation intensity of some cognition-related areas, including the bilateral caudate nucleus/insula and hippocampus/parahippocampal gyrus were lower than the control group under the memory loads. An inverse correlation existed between individual activation intensity and disease duration.

Conclusion. Non-NPSLE–related brain damage with right DLPFC-posterior parietal lobe and parahippocampal gyrus default network causes impairment of spatial WM and mild cognitive dysfunction. Patients with longer disease duration would be expected to exhibit increased central nervous system damage. (First Release January 15 2017; J Rheumatol 2017;44:201–8; doi:10.3899/jrheum.160290)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS SPATIAL WORKING MEMORY
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From the Department of Radiology, First Affiliated Hospital, Medical College of Shantou University; Guangdong Key Laboratory of Medical Molecular Imaging, Shantou, Guangdong; Graduate School of Beijing Normal University, Zhuhai, China.

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C.M. Zhu, MD, Department of Radiology, First Affiliated Hospital, Medical College of Shantou University, and Guangdong Key Laboratory of Medical Molecular Imaging; L. Xie, MD, Department of Radiology, First Affiliated Hospital, Medical College of Shantou University, and Guangdong Key Laboratory of Medical Molecular Imaging; J.Z. Huang, MD, Department of Radiology, First Affiliated Hospital, Medical College of Shantou University, and Guangdong Key Laboratory of Medical Molecular Imaging, and Department of Radiology, Chaonan Minsheng Hospital of Shantou; Z.B. Sun, MD, Department of Radiology, First Affiliated Hospital, Medical College of Shantou University, and Guangdong Key Laboratory of Medical Molecular Imaging, and Department of Radiology, Chaonan Minsheng Hospital of Shantou; S.X. Duan, MD, Department of Radiology, First Affiliated Hospital, Medical College of Shantou University, and Guangdong Key Laboratory of Medical Molecular Imaging; Z.R. Lin, MD, Department of Radiology, First Affiliated Hospital, Medical College of Shantou University, and Guangdong Key Laboratory of Medical Molecular Imaging; J.J. Yin, MD, Department of Radiology, First Affiliated Hospital, Medical College of Shantou University, and Guangdong Key Laboratory of Medical Molecular Imaging; H.B. Le, MD, Department of Radiology, First Affiliated Hospital, Medical College of Shantou University, and Guangdong Key Laboratory of Medical Molecular Imaging; D.M. Sun, MD, Department of Radiology, First Affiliated Hospital, Medical College of Shantou University, and Guangdong Key Laboratory of Medical Molecular Imaging; S.H. Ma, PhD, Professor, Department of Radiology, First Affiliated Hospital, Medical College of Shantou University, and Guangdong Key Laboratory of Medical Molecular Imaging, and Chaonan Minsheng Hospital of Shantou; Y. Ma, MD, Graduate School of Beijing Normal University; W.C. Xu, PhD, Department of Radiology, First Affiliated Hospital, Medical College of Shantou University.

Chun-Min Zhu and Ye Ma contributed equally to this work.

Address correspondence to S.H. Ma, Professor, Department of Radiology, First Affiliated Hospital, Medical College of Shantou University, Shantou, Guangdong, China. E-mail: mshmshu@163.com

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem involvement and diverse clinical manifestations. According to the American College of Rheumatology (ACR), a neuropsychiatric SLE (NPSLE) diagnosis is defined by clinical, multimodal neurological examinations and a neuropsychological assessment. Cognitive impairment is identified as one of the 19 NPSLE manifestations and defined as significant deficits in any or all of the following cognitive functions: complex attention, executive skills, memory, visual–spatial processing, language, and psychomotor speed[1]. Cognitive functioning of patients with NPSLE is inferior to those without overt neuropsychiatric symptoms (non-NPSLE), and over 25% of non-NPSLE patients are cognitively impaired when compared with controls in areas such as learning, memory, attention, reasoning, and fluency[2,3].

Functional magnetic resonance imaging (fMRI) of the brain while subjects were performing cognitive function tasks including working memory, attention, and language processing, was significantly altered in patients with NPSLE compared with healthy subjects[4,5]. However, because these fMRI studies involved patients with NPSLE, the findings failed to explore whether the brain activities in non-NPSLE subjects were altered. Such knowledge is meaningful because it is currently believed that non-NPSLE patients perform worse on neuropsychiatric tests than healthy subjects[6]. This would lead to a better understanding of the pathogenesis of NPSLE, and provide potential direction for the development of early interventions.

A study using the Rey Auditory Verbal Learning Test to assess working memory (WM) in non-NPSLE patients demonstrated significantly increased brain activities in the anterior medial prefrontal cortex during the learning process. Patients also showed significant positive correlations between learning efficiency and hippocampal activity[7]. Another group of investigators using the Paced Visual Serial Addition Test to test non-NPSLE[8] patients for sustained attention, WM, and speed of information processing demonstrated attenuated brain activities in the cerebellum, posterior cingulate, and the adjacent precuneus in the default mode network.

WM is defined as a component of short-term memory and has been widely considered an important cognitive function, consisting of verbal, object, and spatial WM that handle different types of information[9]. It has been closely linked with other cognitive behaviors[10]. In addition, WM is a limited capacity system that temporarily stores and processes information for use in guiding behavior[11]. The WM capacity refers to the number of items of information that can be maintained over a short interval and contributes to performance in a wide variety of cognitive tasks[12]. Because both of the previous studies focused on the verbal WM, which is different from spatial WM in neural pathway processing[13,14], it is necessary to study whether spatial WM is impaired in non-NPSLE patients.

Therefore, the goal of our study was to map the potential functional abnormalities of spatial WM-related brain areas of non-NPSLE patients under a block-designed n-back task and to study whether any clinical biomarkers could serve as a predictor of brain dysfunction in this disease. We hypothesized that patients have poorer behavior and activation intensity during the WM task.

MATERIALS AND METHODS

Study participants. Eighteen right-handed patients with SLE were recruited from the Department of Rheumatology, the First Affiliated Hospital of Shantou University. All patients satisfied the ACR classification criteria for SLE[15] and had no overt neuropsychiatric syndromes in ACR case definition of NPSLE[1] (e.g., cerebrovascular disease, psychosis, seizures, dysautonomia, neuropathies, or myasthenia gravis). The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[16] and the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC/DI)[17] were used to evaluate disease activity of SLE. Four patients had high levels of disease activity, as indicated by SLEDAI scores > 4, while the other 14 patients had SLEDAI scores ≤ 4. Serum levels of complement components (C3, C4) and anti-dsDNA antibodies were measured in the hospital clinical laboratory. At the time of study enrollment, all patients were taking prednisone; 6 were also prescribed immunosuppressants and 4 nonsteroidal antiinflammatory drugs. Eighteen healthy volunteers were matched with the patient group according to sex, age, handedness, and duration of education. Sociodemographic and clinical characteristics of all the subjects are shown in Table 1.

Participants were ineligible for our study if they had organic brain disorders; alcohol or drug abuse; pregnancy; any physical illness such as hepatitis, brain tumors, or epilepsy; a history of a psychiatric disorder or

Table 1. Demographic and clinical characteristics and MOCA performance of the study participants. Data are expressed as mean ± SD, except where indicated.

Characteristics/ MOCA Performance	SLE Patients, n = 18	Controls, n = 18	p*
Sex, female/male	16/2	16/2	
Mean age, yrs	27.50 ± 4.20	26.22 ± 2.29	0.265
Education, yrs	13.22 ± 1.26	12.89 ± 1.71	0.511
Disease duration, yrs	3.22 ± 1.86		
SLEDAI	3.55 ± 2.12		
SLICC/DI	0.44 ± 0.62		
C3, mg/dl, normal range 79–152	84.00 ± 37.91		
C4, mg/dl, normal range 16–38	16.11 ± 9.21		
Anti-dsDNA antibody titer	9.00 ± 15.88		
Prednisolone, mg/day	9.58 ± 5.64		
Visuospatial/executive	5.00 ± 0.00	3.55 ± 0.86	< 0.001
Naming	3.00 ± 0.00	3.00 ± 0.00	
Attention	5.94 ± 0.24	4.72 ± 0.96	< 0.001
Language	2.56 ± 0.51	1.22 ± 0.43	< 0.001
Abstraction	2.00 ± 0.00	1.72 ± 0.46	0.015
Memory	4.78 ± 0.43	4.28 ± 0.57	0.006
Orientation	5.94 ± 0.24	5.72 ± 0.46	0.07
Total	29.28 ± 0.75	25.00 ± 1.78	< 0.001

* P values are based on t tests. MOCA: Montreal Cognitive Assessment; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index; SLICC/DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

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treatment with psychotropic medications; MRI scan contraindications; or if they were illiterate or uncooperative. The brain MR images (T1- and T2-weighted) were inspected by 2 experienced neuroradiologists to exclude any gross structural abnormalities of the brain.

The study was approved by the Medical Ethics Committee of Shantou University with the following reference number: SUMC 2012XM-0021, and conformed to the Declaration of Helsinki. All subjects provided informed consent and signed formal permission for all procedures.

Behavior assessment. The Montreal Cognitive Assessment (MOCA)[18] is designed to assess cognitive function, including visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation. The standard for evaluation is according to Wang, *et al*[19]: calculating overall scores and correcting for the degree of cultural bias (such as the number of years of education for a 12-year-old or younger, add 1 point; the total score is out of 30). Those scoring 26 points or greater are considered as having normal cognitive function, < 26 points is mild cognitive dysfunction, and ≤ 19 points indicates dementia. Behavioral tests were completed by 2 certified teachers from the Medical College of Shantou University who were blind to the study.

WM task paradigm. The block-designed spatial n-back task was used to evaluate spatial WM (Figure 1A)[20]. It started with a 2-s cue that instructed the subjects how to perform the task. After a 1-s delay, 10 stimuli were presented to the subjects serially. Each stimulus was displayed for 2 s, then a fixation cross appeared for 1 s. During this 3-s period, the subjects used their thumbs to press the right or the left key of the response box, and their performance accuracy and reaction time were automatically recorded by the computer. A baseline control block was also adopted, during which the fixation cross was displayed and the subjects were asked to look at it while taking a rest.

There were 4 epochs in an fMRI scan. Each epoch comprised a 0-, 1-, and 2-back task block, and was followed by a baseline control block (Figure 1B). All the subjects underwent 2 fMRI scans. The sequence of the task blocks was 0-, 1-, and 2-back in 1 scan, and 2-, 1-, and 0-back in the other. These 2 task sequences were counterbalanced across all the subjects in each group. In addition to functional scans, each subject also underwent high-resolution 2-dimensional and 3-D anatomical scans for functional overlay and stereotaxic transformation. Before MRI scanning, all subjects were trained outside the scanner room to guarantee they had understood the instructions correctly.

The E-prime psychological experimental software system was used to display the stimuli. The software was run on a Windows XP computer system equipped with a 640 × 480 resolution display.

Image acquisition. Scans of fMRI were obtained using a General Electric 1.5 Tesla MR scanner and quadrature coil-acquired signal. Headphones and earplugs were provided to shield background noise. Cross-sectional images were acquired to correct for the localization of axial anatomical images.

The following measures were used for T1 anatomical imaging of conventional SE sequences: TR = 505 ms, TE = 14 ms, 20 slices, flip angle = 90°, field of view (FOV) = 230 × 230 mm, matrix = 256 × 256, 6-mm section thickness, and 1-mm gap. Functional images were then acquired at the same locations as the anatomical slices by using a gradient-recalled echo, echo-planar imaging sequence with the following measures: TR = 2000 ms, TE = 45 ms, 20 slices, flip angle = 90°, FOV = 230 × 230 mm, matrix = 64 × 64, 6-mm section thickness, and 1-mm gap. Finally, fast low-angle radio frequency pulse sequence was used to acquire 3-D data of the whole brain as follows: TR = 30 ms, TE = 3.0 ms, flip angle = 30°, FOV = 250 × 250 mm, matrix = 256 × 256, slice thickness = 1.3 mm, 1.3-mm section thickness, no gap, and 120 slices.

Image processing. First, the original data were converted using MRI Convert software. Functional image preprocessing and statistical analysis were then analyzed using Analysis of Functional NeuroImages, including data preprocessing, statistical analysis, and result display. In data preprocessing, all functional datasets were processed to remove any linear drift, correct motion, be normalized to the stereotaxic coordinates of Talairach and Tournoux, and

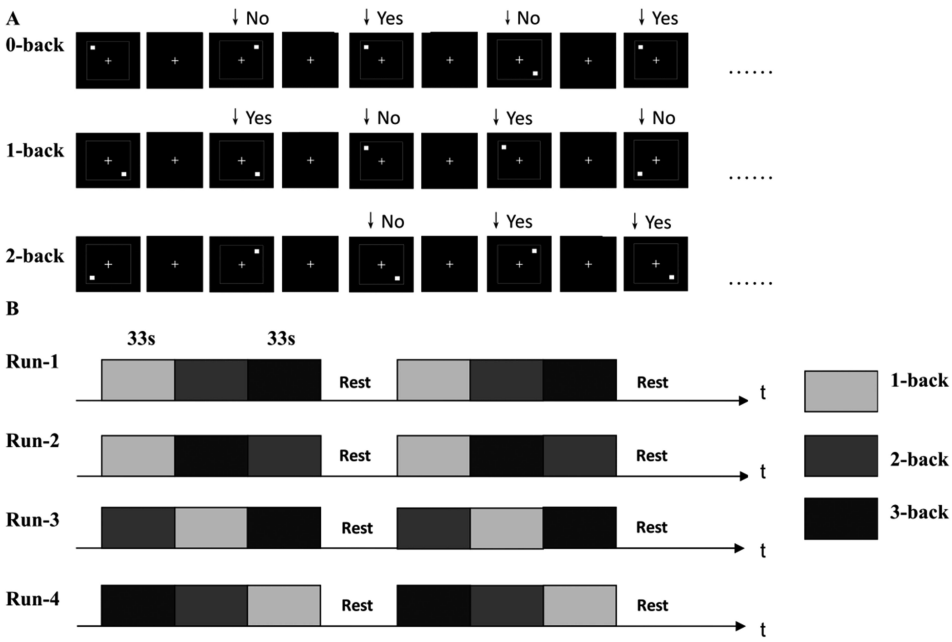

Figure 1. N-back task and fMRI experimental design. A. Sample trials of n-back tasks. 0-back: "judge the current position of the white box whether or not the same as the first position"; 1-back: "judge the current position of the white box whether or not the same as the first position before the current one"; 2-back: "judge the current position of the white box whether or not the same as the second position before the current one". "Yes" means the 2 compared stimuli are the same, "No" means the 2 compared stimuli are different. B. Two scans were done for each subject. The task blocks contained 0-, 1-, and 2-back; each lasted 33 s. The baseline control block (Rest) also lasted 33 s, and only a fixation cross was displayed. fMRI: functional magnetic resonance imaging.

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be spatially smoothed with a Gaussian filter (full-width half-maximum = 6 mm). Any scan in which the head motion was larger than 2 mm or rotation larger than 10° was excluded from further analysis.

Data analysis included group and individual analysis. For group analysis, correlation analysis based on the direct contrast between the tasks and baseline control was carried out to generate the activation map for each group ($p < 0.05$, cluster size > 20 voxels). These activation maps were used to locate the regions of interest (ROI). Repeated measures of ANOVA were used for interclass and intragroup analysis. For each subject, correlation analysis was performed on the functional data to generate 3 activation maps ($p < 0.05$, cluster size > 20 voxels). The amplitudes of the average blood oxygen level–dependent (BOLD) responses at the 3 n-back levels were calculated for each ROI of individual subjects, and then these data were analyzed to judge whether there were load effects for each ROI.

Data analysis. A 2-sample t test was applied to compare MOCA-Chinese revised (CR) performance, reaction time of n-back task, age, sex, and level of education between the 2 subject groups. Performance accuracy was compared using Fisher's exact test. The load effects of ROI and performance of n-back task within groups were evaluated using the general linear model for repeated measurements. Also calculated were linear correlation between the activation intensity of individual patients and C3, C4, anti-dsDNA, disease activity, SLICC/DI, disease duration, age, and daily prednisone dose. Results were considered statistically significant when $p < 0.05$. Results were expressed as the mean ± SD except where indicated otherwise. Statistical analysis was performed with the Statistical Package for Social Science for Windows (v. 19.0; IBM).

RESULTS

Behavior assessment. MOCA-CR scores for all subjects (Table 1) showed there were no significant differences in either naming or orientation subtests. By contrast, there were significant differences between groups for the abstraction and memory subtests ($p < 0.05$), and for visuospatial/executive, attention, language subsets, and total scores ($p < 0.01$). Six patients scored < 26 (one 22, four 23, one 24) and none scored < 19. All of the control subjects scored > 26.

Performance accuracy and reaction time of n-back task. Performance accuracy means the percentage of correctly reported stimuli in the total number of stimuli to be recalled in certain n-back conditions. Reaction time refers to the time it takes to press the button when the stimuli are shown. Accuracy and reaction time were significantly different among the 3 tasks within groups ($p < 0.001$). In other words, as memory load increased from 0-back to 2-back, accuracy of the groups gradually decreased and mean reaction time gradually lengthened. This suggested that there was a memory-related load effect in both groups. Accuracy was significantly different between groups in the 2-back task ($p = 0.002$) but not in 0-back ($p = 0.505$) or 1-back tasks ($p = 0.319$). Reaction times of the 3 n-back tasks were significantly different between groups ($F = 169.26$, $p < 0.0001$). It was longer in patients with SLE, especially in the 2-back task. Interclass analysis of the 3 tasks demonstrated that the reaction times in the 0-back and 1-back tasks were not significantly different between groups ($p > 0.05$), while in the 2-back task there was a significant difference between SLE and the control group ($p < 0.001$). These results are shown in Table 2.

Results of fMRI. BOLD responses from the network of brain regions involved in performing the n-back tasks of both groups were combined. The findings showed that a common cortical network consisting of bilateral dorsolateral prefrontal cortex (DLPFC), bilateral premotor areas (PreMA), the supplementary motor area (SMA), and bilateral parietal areas (PA) were activated, with a right hemispheric dominance (Figure 2). Moreover, all subjects also showed the same cortex and subcortical areas being activated, including the bilateral caudate nucleus/insula and bilateral parahippocampal gyrus/hippocampal, all of which may be correlated with cognitive function. The BOLD responses of these areas changed as the n-back level changed and were identified as ROI.

BOLD signal changes of n-back task load. It is widely known that BOLD signal changes are correlated with the n-back level in WM- related brain areas, which means they should increase as memory load increases; this is referred to as the load effect. In the control group, the load effect appeared in DLPFC, PreMA, SMA, and PA as expected ($F = 57.15$, $p < 0.001$; $F = 26.28$, $p < 0.001$; $F = 19.36$, $p < 0.001$; $F = 44.88$, $p < 0.001$, respectively), which indicated that the load effect in these ROI can be used as an index to analyze the data of the SLE group. For the SLE group, the load effect only appears in SMA/ACC ($F = 54.69$, $p < 0.001$), and this did not vary in the right (R)-DLPFC, R-PA, and PreMA ($F = 1.00$, $p = 0.374$; $F = 1.50$, $p = 0.232$; $F = 1.33$, $p = 0.275$). The BOLD signal changes of the R-DLPFC, R-PA, and SMA/ACC of the 2 groups under 3 different task loads are shown in Figure 3.

Comparison of activated brain areas between groups. Between-group analysis of activation intensity under the 3 levels of memory load were evaluated by subtracting the values for the SLE group from the control group (Table 3), indicating that more brain areas were activated in the control group, and activation intensity of most memory-related brain areas was greater in the control group, especially in the 2-back task load. Bilateral DLPFC and PA were activated in the 0-back task load when we defined the contrast as the control group versus SLE group, and bilateral DLPFC, PA, and SMA in the 1-back task load, and the bilateral DLPFC, PA, PreMA, and SMA in the 2-back task load.

Correlation analysis. We found a significant inverse correlation between activation intensity of patients with SLE during the WM tasks and disease duration in the DLPFC ($r = -0.766$, $p < 0.001$), PA ($r = -0.711$, $p = 0.001$), PreMA ($r = -0.688$, $p = 0.002$), and SMA ($r = -0.634$, $p = 0.005$). Further, no other correlation for the activation intensity was observed for the serum biomarkers and clinical indices.

DISCUSSION

In our study we aimed to explore whether non-NPSLE patients exhibit poorer ethology and cerebrovascular response to a challenging cognitive task. We found that the patients with SLE have lower MOCA-CR subitem scores and

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Table 2. Performance accuracy and reaction time of the n-back task in patients with systemic lupus erythematosus (SLE) and healthy controls (mean ± SD). Intragroup analysis of both groups used a general linear model for repeated measures, and p < 0.001. Interclass analysis of the n-back task between the SLE group and control group used 2 independent-sample t tests (RT) and Fisher's exact test (accuracy).

n-back	Group				p	
	Control Group, n = 18		SLE Group, n = 18		Fisher's Exact Test	T test
	Accuracy, %	RT, ms	Accuracy, %	RT, ms	Accuracy, %	RT, ms
0-back	99.24	655.79 ± 45.43	98.48	674.09 ± 58.51	0.505	0.302
1-back	97.47	821.63 ± 55.09	96.00	845.23 ± 129.14	0.319	0.483
2-back	90.00	965.57 ± 51.15	81.67	1103.22 ± 167.59	0.002	0.003

RT: reaction time.

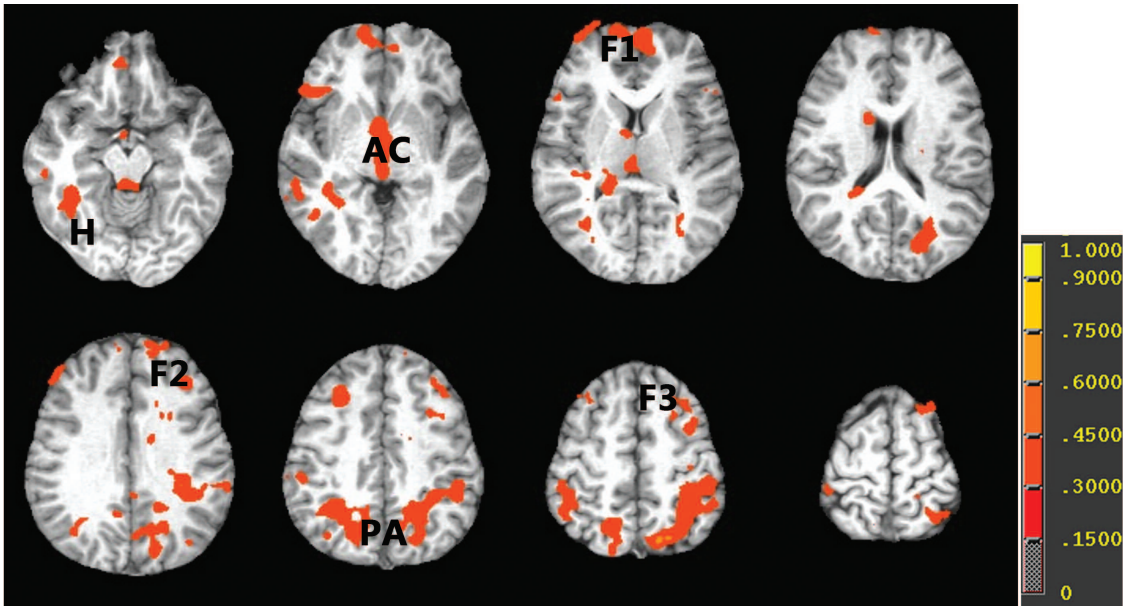

Figure 2. Regions of interest of both groups. Red/yellow areas denote areas of activation. R: right hemisphere; L: left hemisphere; F1: dorsolateral prefrontal cortex; F2: bilateral premotor areas; F3: supplementary motor area/anterior cingulate cortex; PA: parietal lobe, AC: anterior cingulate; H: hippocampal/parahippocampal gyrus.

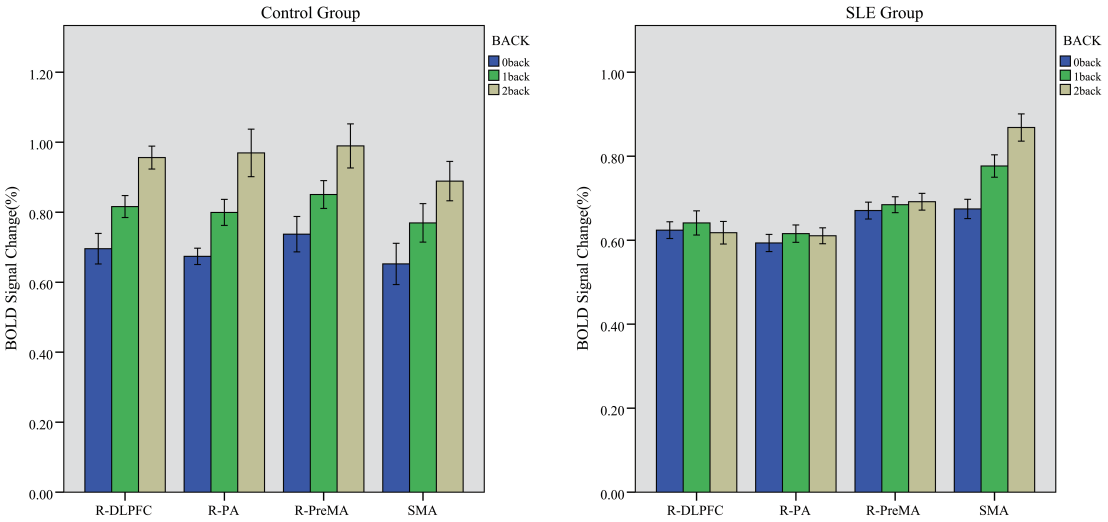

Figure 3. Load effect of BOLD response and BOLD signal changes in regions of interest (R-DLPFC, R-PA, R-PreMA, and R-SMA) of the control group and the systemic lupus erythematosus (SLE) group under 3 different task loads. BOLD: blood-oxygen-level dependent; R-DLPFC: right dorsolateral prefrontal cortex; R-PA: right parietal areas; R-PreMA: premotor areas; R-SMA: supplementary motor area.

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Table 3. Broca's areas (BA) differences between control group and SLE group for 3 different tasks.

N-back Task	Anatomic Site	R/L	Activation Volume, mm^3	Talairach Coordinates, mm X	Y	Z	BA	t value
0-back	Medial frontal gyrus	R	66	8	–26	60	6	13.25
		L	164	–1	40	43	6	24.30
	Inferior frontal gyrus	R	31	47	10	26	9	28.09
	Inferior parietal lobule	R	81	–38	–47	48	40	20.18
		L	233	–40	–28	37	40	31.40
	Cingulate gyrus	R/L	238	2	–9	28	24	25.51
	Insula	L	34	–28	20	20	13	21.97
	Anterior cingulate	R/L	139	0	4	–7	25	17.03
	Parahippocampal gyrus	R	133	20	–38	3	30	27.06
1-back	Middle frontal gyrus	R	71	26	19	39	8	15.31
		L	54	–28	12	58	6	29.98
	Superior frontal gyrus	R	25	14	34	43	8	15.36
		L	53	–22	15	52	8	22.19
	Medial frontal gyrus	L	30	–13	34	46	8	19.25
	Inferior frontal gyrus	L	22	–28	10	29	6	15.13
	Inferior parietal lobule	R	50	35	–46	42	40	15.52
		L	351	–28	–43	26	40	29.37
	Cingulate gyrus	R/L	139	2	–43	39	–	19.66
	Anterior cingulate	R	78	5	6	–8	25	9.88
		L	38	–19	22	26		23.74
	Parahippocampal gyrus	L	30	–28	–32	–3	27	12.45
	Fusiform gyrus	R	80	44	–31	–21	20	16.37
		L	30	–56	–53	–26	37	25.97
	Caudate	R	70	20	7	22	–	15.21
2-back	Middle frontal gyrus	R	161	29	–19	50	4	19.51
		L	44	–28	12	58	6	24.34
	Superior frontal gyrus	R	55	11	27	53	8	22.09
		L	131	–13	31	50	8	28.11
	Inferior parietal lobule	R	50	41	–30	30	40	11.59
		L	122	–46	–37	49	40	14.93
	Cingulate gyrus	R/L	70	–1	–40	33	31	20.41
	Anterior cingulate	R/L	64	–1	7	22	33	13.69
	Hippocampus/parahippocampal gyrus	R	60	23	–38	3	30	26.32
		L	31	–7	–35	4		17.65
	Caudate/insula	L	223	–37	–29	–3		28.82
	Precuneus	R	27	38	–67	35	7	13.28
		L	41	–4	–67	28	31	14.87

P = 0.05. Cluster size = 20. SLE: systemic lupus erythematosus; R/L: right/left lobes.

total scores, which is consistent with prior studies[3,21]. Nevertheless, 1 MOCA-CR test does not confirm cognitive impairment. It may be more convincing to determine cognitive impairment through a neuropsychological battery of standardized tests of short-term and longterm verbal and visuospatial memory, visuoconstructional abilities, nonverbal reasoning, language, and attention. A score in the pathological range in 2 or more tests has been considered a criterion for cognitive impairment[3].

We also found that the accuracy gradually decreased and mean reaction time gradually lengthened as memory load increased in patients with SLE. Moreover, while both groups showed a similar accuracy in the 0-back and 1-back tasks, there was a significant difference in the 2-back task. WM had the physical characteristic of "capacity constraints"[22], suggesting the load range was beyond the limit of the WM capacity when performing the 2-back tasks and is consistent with a prior study[23]. Together these provide evidence that memory function was impaired in non-NPSLE patients, indicating they may have WM-related brain area dysfunction.

BOLD fMRI was further used to map the location of injured brain areas and to explore the mechanisms of spatial WM impairment in non-NPSLE patients. The results revealed a common cortical network activated by the n-back task in both groups, which consisted of bilateral DLPFC, PA, PreMA, and SMA/ACC. In our previous study[20,24], we found similar WM-related brain activations, but in the current study we further found that the hippocampal/parahippocampal gyrus were also activated. In addition, we found a partial lateral advantage, consistent with previous studies reporting

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spatial information mostly being processed in the right hemisphere[13,14].

The PFC is responsible for the metaprocessing of spatial location sequence and is considered the consolidation and operation center of neural mechanisms in WM, including attention and inhibition, and the management and integration of memory information[25,26]. In particular, the DLPFC has been associated with manipulation processes of WM[27,28]. The posterior part of the PA is the main location for storage of spatial information[29], and PreMA and SMA are mainly involved in the rehearsal of spatial information[30]. Therefore, not only are the cortical brain regions related to spatial WM, but also the interaction of cortical and subcortical structures may be the neural basis of spatial WM. Further quantitative analysis showed that the load effect of the BOLD response appeared in all ROI in the control group. However, a similar load effect only appears in SMA/ACC in patients, and this did not vary with the n-back load in the right DLPFC, PA, and PreMA, which confirms that there is dysfunction in spatial WM in this group. One report found cooperative activation between DLPFC and PA during kinesis in dynamic spatial WM[31]. In our study the bilateral DLPFC and PA of the SLE group were not as activated as those in the control group, indicating that the dysfunction of spatial WM in non-NPSLE patients was related to the dysfunction of the DLPFC-PA network.

Interestingly, previous studies have reported that patients with SLE show increased BOLD responses in the PFC, PA, and SMA when performing WM tasks as compared with healthy controls, while both performed similarly[4,8]. These findings are consistent with a model that states that intact cognitive performance can be maintained in patients with SLE through compensatory increased neuronal activation. However, in our current study we used a block-designed n-back task to evaluate spatial WM, which is different from others' experiment methods, and it is the first time, to our knowledge, that the spatial WM and the brain activity network in non-NPSLE patients was investigated. The results revealed patients that failed to reach the normal performance level in the 2-back task and showed lower activation than the control group. We tentatively attribute this to the broken compensatory mechanism. As a task becomes more difficult, a point is reached at which a participant is unable to maintain adequate performance, and BOLD response may decrease. This phenomenon has also been observed in other diseases such as dysthymic disorder[32] and schizophrenia[33]. In addition, the interpretation of the results may be relatively limited because of the small sample and we will expand the sample size to conduct in-depth research and analysis.

Our study showed that the bilateral hippocampal/parahippocampal gyrus were abnormally activated. Earlier investigations have revealed evidence of hippocampal atrophy in patients with SLE[34]. The hippocampus is mainly involved in consolidation of explicit or declarative but not implicit or nondeclarative memory[35]. It means the hippocampus does not encode, store, or retrieve memory independently without the help of other brain regions, such as the PFC. Therefore, it follows that this research has shown an attenuated activation of the hippocampus consistent with PFC BOLD changes.

Notably, another finding was the abnormalities of the activation pattern negatively related to disease duration in non-NPSLE patients. Similarly, Mackay, *et al*[36] showed that non-NPSLE patients with shorter disease duration had increased responses in the DLPFC and SMA cortex, which may be attributed to the protective nature of the blood-brain barrier (BBB). The BBB is likely to be different from other organ systems that are more vulnerable to circulating cytokines, autoantibodies, and activated lymphocytes. These results provide direct evidence that significant injury to brain functioning is already present in non-NPSLE patients, highlighting the necessity of early intervention and maintenance of patients at the early stages of SLE. In addition, our findings indicated the BOLD response in the ROI is not significantly influenced by SLEDAI, SLICC/DI, or glucocorticosteroid (GC) dosage. The absence of associations found between DI and BOLD activation intensity suggests that the DI is not a useful indicator of brain dysfunction and that susceptibility of the brain to damage is different from other organs. However, it is worth noting that SLEDAI was previously found to correlate with functional connectivity in the frontoparietal cortex during the resting state[8], while GC dosage was reported to correlate with brain structural changes[37]. Conversely, 1 study found no significant correlations between GC dosage and abnormalities in brain volume in SLE[38]. Further investigations are warranted to explore the potential influence of SLEDAI and GC on cerebral function of non-NPSLE patients.

This pilot study has some limitations. The study population was relatively small; therefore, the explanation of the results was limited. As our study goes on, more patients will take part and the results will be more sufficient statistically to validate our hypothesis. In addition, more neuropsychological tests should be taken to evaluate the real cognitive function of participants.

To our best knowledge, this is the first study using MOCA-CR, the n-back task, and BOLD-fMRI technology to investigate the spatial WM function and the brain activity network of non-NPSLE patients. The findings showed that spatial WM was processed by a network of frontoparietal lobe and subcortical structures. Moreover, non-NPSLE patients already have WM hypofunction, and the miopragia of the DLPFC/PA/PreMA network might be one of the neural mechanisms responsible for this spatial WM impairment. Additionally, the inverse correlation between disease duration and activation intensity of brain areas supports the proposal that patients with longer disease duration would be expected to show increased brain damage, and early intervention

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and maintenance are of great importance to even those non-NPSLE patients.

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