




## ORIGINAL RESEARCH

# White matter hyperintensities associate with cognitive slowing in patients with systemic lupus erythematosus and neuropsychiatric symptoms

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## ABSTRACT

**Objective** To compare cognitive function between patients with different phenotypes of neuropsychiatric systemic lupus erythematosus (NPSLE) and assess its association with brain and white matter hyperintensity (WMH) volumes.

**Methods** Patients attending the Leiden University Medical Centre NPSLE clinic between 2007 and 2015 without large brain infarcts were included (n=151; 42±13 years, 91% women). In a multidisciplinary consensus meeting, neuropsychiatric symptoms were attributed to systemic lupus erythematosus (SLE) (NPSLE, inflammatory (n=24) or ischaemic (n=12)) or to minor/non-NPSLE (n=115). Multiple regression analyses were performed to compare cognitive function between NPSLE phenotypes and to assess associations between brain and WMH volumes and cognitive function cross-sectionally.

**Results** Global cognitive function was impaired in 5%, learning and memory (LM) in 46%, executive function and complex attention (EFCA) in 39% and psychomotor speed (PS) in 46% of all patients. Patients with inflammatory NPSLE showed the most cognitive impairment in all domains (p≤0.05).

Higher WMH volume associated with lower PS in the total group (B: -0.14 (95% CI -0.32 to -0.02)); especially in inflammatory NPSLE (B: -0.36 (95% CI -0.60 to -0.12)). In the total group, lower total brain volume and grey matter volume associated with lower cognitive functioning in all domains (all: 0.00/0.01 (0.00;0.01)) and lower white matter volume associated with lower LM, EFCA and PS (all: 0.00/0.01 (0.00;0.01)).

**Conclusion** We demonstrated that an association between brain and WMH volumes and cognitive function is present in patients with SLE, but differs between (NP) SLE phenotypes. WMHs associated with PS especially in inflammatory NPSLE, which suggests a different, potentially more severe underlying pathophysiological mechanism of cognitive impairment in this phenotype.

## INTRODUCTION

Cognitive impairment is reported in up to 95% of patients with systemic lupus erythematosus (SLE).<sup>1</sup> SLE-specific factors (such

## Key messages

### What is already known about this subject?

- Cognitive dysfunction is common in patients with systemic lupus erythematosus (SLE), but the underlying causes remain largely unknown.

### What does this study add?

- Our findings show that changes in brain structures are involved in the pathogenesis of cognitive dysfunction in SLE.
- White matter hyperintensities (WMHs) are common in patients with SLE and are associated with reduced cognitive function, especially reduced psychomotor speed.
- This effect is most pronounced in patients with inflammatory neuropsychiatric SLE.

### How might this impact on clinical practice or future developments?

- Our findings highlight the role of WMHs in cognitive dysfunction in patients with SLE, and call for future studies to examine treatment to prevent (progression of) WMHs.

as certain cytokines and autoantibodies) and factors associated with chronic disease (such as fatigue, mood disorders and medication) may play a role in the occurrence of cognitive impairment. In general, neuropsychiatric symptoms can be caused by SLE itself and require specific treatment (neuropsychiatric systemic lupus erythematosus (NPSLE)) or can be caused by the burden of a chronic illness, by other diagnoses or by minor involvement of SLE requiring solely symptomatic or supportive treatment (minor/non-NPSLE).<sup>2</sup> A recent meta-analysis showed that patients with NPSLE have greater cognitive impairment than patients without NPSLE.<sup>3</sup>

There are different phenotypes of NPSLE, based on the underlying aetiology: inflammatory, ischaemic or a combination thereof.<sup>4</sup> Based on the knowledge about the multitude of causes of neuropsychiatric symptoms in patients with SLE, cognitive impairment might also occur through different pathophysiological mechanisms. The hypothesised underlying aetiology of inflammatory NPSLE is a breach of a neuroimmune interface, such as the blood–brain barrier or the blood–cerebrospinal fluid (CSF) barrier, leading to the influx of inflammatory mediators in the central nervous system.<sup>5</sup> This leads to neuroinflammation, which is associated with cognitive impairment in other autoimmune inflammatory brain diseases, such as multiple sclerosis.<sup>6</sup> In ischaemic NPSLE, brain infarcts are often present, which are associated with cognitive impairment.<sup>7</sup> It is unknown to what extent cognitive impairment is present in patients with ischaemic NPSLE without clear brain infarcts. Microstructural brain changes in patients with SLE have been previously associated with cognitive impairment.<sup>8,9</sup>

In a recent study, we demonstrated that patients with inflammatory NPSLE have reduced brain volumes and increased white matter hyperintensity (WMH) volume compared with other NPSLE phenotypes.<sup>10</sup> Whether structural brain changes in patients with different NPSLE phenotypes are associated with cognitive dysfunction remains to be elucidated.

Therefore, in this study we aimed to compare cognitive dysfunction between patients with SLE with different phenotypes of (NP)SLE and cross-sectionally assess its association with brain and WMH volumes in patients without large brain infarcts.

## PATIENTS AND METHODS

The Leiden University Medical Center (LUMC) NPSLE clinic is a tertiary referral centre for patients with a (suspected) diagnosis of SLE and neuropsychiatric symptoms. All patients are evaluated with a standardised evaluation, which includes assessment by a rheumatologist, neurologist, clinical neuropsychologist, psychiatrist, vascular internal medicine expert and advanced nurse practitioner. In addition, extensive laboratory assessment as well as brain MRI assessment is performed in order to exclude other diseases. In a multidisciplinary consensus meeting, the presence of NPSLE is defined based on factors as described by the Systemic Lupus International Collaborating Clinics (SLICC) decision rules and the NPSLE attribution model, among others.<sup>11,12</sup> If NPSLE is present, a phenotype is assigned based on the suspected underlying pathogenetic mechanism: inflammatory, ischaemic or a combination thereof. Clinical, laboratory and radiological features are discussed and taken into account when assigning the underlying phenotype. In case there are signs of inflammation, such as complement consumption and other SLE manifestations, the inflammatory phenotype is assigned. In case of signs of ischemia and/or the presence of the antiphospholipid syndrome

(APS), the ischaemic phenotype is assigned. Subsequent treatment is started according to the suspected underlying pathogenetic mechanism (immunosuppressive or anticoagulant therapy). If the phenotype was not clearly reported, phenotype was retrospectively assigned to patients with the diagnosis of NPSLE based on the initiated treatment. In some cases a relationship with SLE cannot be excluded, but the symptoms are mild and do not require specific immunosuppressive or anticoagulant therapy: these patients are classified as minor/non-NPSLE. An elaborate explanation of the phenotypes has been published previously.<sup>13</sup>

Patients visiting the LUMC NPSLE clinic between September 2007 and April 2015 with the clinical diagnosis of SLE and age  $\geq 18$  years who signed informed consent were included in this study. Patients with an uncertain diagnosis, change of initial diagnosis at follow-up or a combined NPSLE phenotype were excluded. In addition, patients with alternative diagnoses on brain MRI or brain infarcts  $>1.5$  cm were also excluded, as we aimed to study cognitive function in patients without overt brain abnormalities. Twenty patients were excluded because of large brain infarcts ( $>1.5$  cm): nine minor/non-inflammatory NPSLE, six patients with inflammatory NPSLE and five patients with ischaemic NPSLE.

## Patient and public involvement

No patients were involved in this study design.

## Clinical data

Clinical characteristics were obtained during clinical interview and later retrieved from electronic medical files. SLE disease activity was calculated using the SLE Disease Activity Index 2000 (SLEDAI-2K, range 0–105)<sup>14</sup> and SLE damage was calculated using the SLICC/American College of Rheumatology (ACR) Damage Index.<sup>15</sup> The presence of APS was defined according to the revised classification criteria.<sup>16</sup> Education level was categorised as follows: low (0–6 years), middle (6–12 years) or high ( $>12$  years). Hypertension was considered present if this was diagnosed by the vascular internal medicine expert at baseline visit and diabetes was considered present if antidiabetic medication was used at the time of the baseline visit.

## Neuropsychological assessment

All patients underwent extensive standardised neuropsychological assessment, adapted from the neuropsychological test battery as suggested by the 1999 ACR NPSLE nomenclature and case definition system.<sup>17</sup> For this study, four cognitive domains were assessed using the following test components:

1. Global cognitive function: Minimal Mental State Exam (MMSE),<sup>18</sup> total score (range: 0–30);
2. Learning and memory: Wechsler Memory Scale,<sup>19</sup> total score (range: 0–94);
3. Executive function and complex attention: Stroop Color and Word Test (STROOP)<sup>20</sup> card 3 (time), trail making test part B<sup>21</sup> (time);

4. Psychomotor speed: STROOP card 1+2 (time),<sup>20</sup> trail making test part A<sup>21</sup> (time).

Cognitive impairment was defined as a global cognitive function score  $\leq 25/30$ . For the other cognitive domains, impairment was defined as an average of the tests within that domain of  $\geq 1$  SD lower than the Dutch general population (T-score  $\leq 40$ ).<sup>22</sup>

### MRI protocol

All patients underwent a brain MRI (body transmit radiofrequency coil and an 8-Channel receive head coil array) on a Philips Achieva 3T MRI scanner (Philips Healthcare, Best, the Netherlands). All participants were scanned with a standardised scanning protocol, that included a 3-D T1-weighted scan (voxel size =  $1.17 \times 1.17 \times 1.2$  mm<sup>3</sup>; repetition time (TR)/ echo time (TE) = 9.8/4.6 ms) and a 2-D or 3-D fluid-attenuated inversion recovery (FLAIR) scan. A total of 109 participants were scanned with a 2-D-multislice FLAIR scan (voxel size =  $1.0 \times 1.0 \times 3.6$  mm<sup>3</sup>; TR/TE/ inversion time (TI) = 10 000/120/2800 ms) and 54 participants were scanned with a 3-D FLAIR scan (voxel size =  $1.10 \times 1.11 \times 0.56$  mm<sup>3</sup>; TR/TE/TI = 4800/576/1650 ms) (for more details see<sup>10</sup>). The change in the FLAIR scan occurred in February 2013.

### Image processing

Firstly, 2-D and 3-D FLAIR scans were registered to the 3-D T1-weighted scans by using the Linear Image Registration Tool from the FMRIB Software Library V.5.0, which required upsampling for the 2-D FLAIR scans.<sup>23</sup> Secondly, WMH segmentations were performed to generate WMH probability maps on the registered FLAIR scans by using the lesion prediction algorithm, a toolbox of the Lesion Segmentation Toolbox V.2.0.15 (LST) for the statistical parametric mapping software (SPM12) (Wellcome Institute of Neurology, University College London, UK). A threshold of 0.2 was applied to the WMH probability maps to generate WMH masks. This threshold was chosen after testing different thresholds between 0.1 and 0.5 on a random selection of patients where a threshold of 0.2 resulted in the best visual performance of WMH segmentation accuracy. Additionally, these masks were filled on the 3-D T1-weighted scans with the LST. Lastly, the resulting lesion-filled 3-D T1-weighted scans were used to segment and calculate the grey matter, white matter and cerebral-spinal fluid volumes using the CAT12 toolbox from the SPM12.<sup>23</sup> WMH volume was determined using LST. Intracranial volume was determined as the sum of grey matter, white matter and cerebral-spinal fluid volumes. Total brain volume was calculated as the sum of grey matter and white matter volumes.

All MRI images as well as all the segmentations (grey matter, white matter, cerebral-spinal fluid and WMH maps) were visually inspected for segmentation errors and artefacts by a trained researcher (FI) and a neuroradiologist experienced in brain segmentation (JdB), both blinded to the clinical data.

## Statistical analyses

### Cognitive function

Z-scores were used to compare cognitive function across different NPSLE phenotypes and to assess the association between cognitive function and brain volumes. The Z-score for each cognitive domain was derived by calculating the mean of the Z-scores for tests comprising that domain. If individual test scores were missing, the domain Z-score was based only on the available tests. Three tests were not normally distributed and were transformed using squaring (MMSE) or natural log transformation (trail making test part B and STROOP card 3). The summary Z-scores of the four different cognitive domains were compared between different NPSLE phenotypes using multiple regression analyses, corrected for age, sex and education. Results are presented as B (95% CI). This B represents how much the (transformed) Z-score of the cognitive domain changes in the presence of a specific NPSLE phenotype.

### Brain volumes, WMH and cognitive function

Multiple regression analyses were used to assess the association between brain volumes (white matter, grey matter and total brain volume) and WMH volume with the cognitive domains, corrected for age, sex and intracranial volume. In secondary analyses these regressions were additionally corrected for diabetes and hypertension. For these analyses, the WMH was multiplied by 1 000 000 and natural log transformed, because of non-normal distribution. Results are presented as B (95% CI). This B represents how much the (transformed) Z-score of a cognitive domain changes when the brain volume changes one unit. The analyses were performed for the total group and for the (NP)SLE phenotypes separately.

### Sensitivity analyses

Multiple sensitivity analyses were performed, in which comparisons of cognitive function across different NPSLE phenotypes were repeated using an alternative calculation for the cognitive domains executive function and complex attention, psychomotor speed and learning and memory (see online supplemental files).

All analyses were performed using STATA V.16. College Station, Texas, USA: StataCorp LLC.

## RESULTS

### Study population

A total of 196 consecutive patients with the clinical diagnosis of SLE were eligible for inclusion in this study. Forty-five patients were excluded, because of uncertainty of NPSLE diagnosis (n=8), combined NPSLE phenotype (n=8), change of diagnosis at follow-up (n=20), motion artefacts on MRI (n=3), presence of other brain diseases (n=2: a brain tumour and a large arachnoid cyst) and lack of neuropsychological assessment (n=4).

Of the 151 SLE included patients without large brain infarcts (91% female), 115 had minor/non-NPSLE (76%;  $42 \pm 13$  years), 24 had inflammatory NPSLE (16%;  $40 \pm 16$

**Table 1** Baseline characteristics of patients visiting the neuropsychiatric systemic lupus erythematosus (NPSLE) clinic between 2007 and 2015

	All patients (n=151)	Minor/non-NPSLE (n=115)	Inflammatory NPSLE (n=24)	Ischaemic NPSLE (n=12)
Female	138 (92)	106 (92)	22 (92)	10 (83)
Age	41.9±13.3	42.3±13.0	39.5±15.5	42.2±11.5
Duration of SLE, years	5 (0–30)	7 (0–30)	1 (0–21)	7 (1–29)
SLEDAI-2K	4 (0–34)	4 (0–18)	8 (0–34)	4.5 (0–8)
SDI	1 (0–5)	0 (0–5]	1 (0–4)	1 (0–4)
BMI	24.6±4.5	24.6±4.4	24.1±5.2	25.9±4.7
Current smoking	49 (32)	39 (34)	6 (25)	4 (33)
<b>Education</b>				
Low	7 (5)	4 (4)	1 (4)	2 (17)
Middle	90 (60)	70 (61)	12 (50)	8 (67)
High	54 (36)	41 (36)	11 (46)	2 (17)
<b>Comorbidities</b>				
Hypertension	53 (35)	38 (33)	10 (42)	5 (42)
Diabetes	4 (3)	4 (4)	0 (0)	0 (0)
Antiphospholipid syndrome	19 (13)	13 (11)	3 (13)	3 (25)
<b>Brain volumes (in mL)</b>				
White matter volume	481±56	485±51	473±53	483±57
Grey matter volume	561±60	564±44	562±63	561±61
Total brain volume	1045±108	1046±111	1028±94	1050±107
WMH volume	0.7 (0–48)	0.6 (0–48)	1.1 (0–30]	1.1 (0–10)

Data represent n (%), mean±SD or median (range).

BMI, body mass index; SDI, SLICC/ACR Damage Index; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; WMH, white matter hyperintensity.

years) and 12 had ischaemic NPSLE (8%; 42±12 years), as shown in [table 1](#). A difference in SLE duration was present between inflammatory NPSLE (median: 1 year) and the other phenotypes (median: 7 years). In addition, patients with inflammatory NPSLE showed more disease activity (median SLEDAI-2K: 8) compared with ischaemic and minor/non-NPSLE (median SLEDAI-2K: 4.5 and 4, respectively). Details on the NPSLE syndromes are provided in online supplemental table 1.

### Cognitive function

Impairment was infrequent in the domain global cognitive function, but common in all other cognitive domains, as shown in [table 2](#). In patients with inflammatory NPSLE, the cognitive domain learning and memory was impaired in 58% of the patients, whereas executive function and complex attention and psychomotor speed were impaired in 50% of patients. In patients with minor/non-NPSLE cognitive impairment was respectively present in 44%, 38% and 49% of patients in these domains and in patients with ischaemic NPSLE (without large brain infarcts) this was 50%, 17% and 17%, respectively. Raw scores and Z-scores of the cognitive domains are provided in online supplemental table 2.

Patients with inflammatory NPSLE had lower cognitive scores than patients with minor/non-NPSLE in all domains (no statistical significance; see [table 3](#)). In addition, patients with inflammatory NPSLE also performed worse than patients with ischaemic NPSLE without large brain infarcts: B: −0.80 (−1.44 to −0.17) for global cognitive function (indicating a 0.8 lower transformed Z-score on this cognitive domain in the presence of an inflammatory phenotype), B: −0.74 (−1.37 to −0.12) for learning and memory, B: −0.98 (−1.56 to −0.41) for executive function and complex attention and B: −0.79 (−1.41 to −0.16) for psychomotor speed. No differences in cognitive function were found between patients with ischaemic NPSLE without large brain infarcts and patients with minor/non-NPSLE.

### Association between brain and WMH volumes and cognitive function

In the total population, lower brain volumes associated with lower cognitive function in different cognitive domains: lower total brain volume and grey matter volume associated with lower cognitive function in all domains (all B's: 0.00/0.01 (95% CI 0.00 to 0.01)); lower white matter volume associated with lower cognitive



**Table 2** Cognitive impairment in patients with systemic lupus erythematosus and neuropsychiatric symptoms of different origins

	Global cognitive function	Learning and memory	Executive function and complex attention	Psychomotor speed
All patients (n=151)*	8 (5)	70 (46)	57 (39)	69 (46)
Minor/non-NPSLE (n=115)	5 (4)	50 (44)	43 (38)	55 (49)
Inflammatory NPSLE (n=24)	3 (13)	14 (58)	12 (50)	12 (50)
Ischaemic NPSLE (n=12)	0 (0)	6 (50)	2 (17)	2 (17)

Data represent n (%) of patients with cognitive impairment (defined as a T-score ≤40).

\*The percentages were calculated from total number of patients with available scores. Minor/non-neuropsychiatric systemic lupus erythematosus (NPSLE): 113/115 for global cognitive function, psychomotor speed and executive function and complex attention; Inflammatory NPSLE: 23/24 for global cognitive function; Ischaemic NPSLE: all tests available.

function in all domains (all B's: 0.00/0.01 (95% CI 0.00 to 0.01)), with the exception of global cognitive function (table 4). In addition, an inverse association was found between higher WMH volume and lower psychomotor speed (B: -0.14 (95% CI -0.32 to -0.02)).

In patients with minor/non-NPSLE, there was an association between brain volumes and cognitive function similar to the analyses of the total cohort (all B's: 0.00/0.01 (95% CI 0.00 to 0.01)). However, no association between WMH volume and any of the cognitive domains was found in patients with minor/non-NPSLE. In patients with inflammatory NPSLE, higher WMH volume (B: -0.36 (95% CI -0.60 to -0.12)) and lower white matter volume (B: 0.02 (95% CI 0.00 to 0.03)) were associated with lower psychomotor speed. In patients with ischaemic NPSLE (without large brain infarcts), no associations were found between brain volumes or WMH volume and cognitive function.

In a secondary analysis, additional correction for the presence of diabetes and hypertension yielded identical results (see online supplemental table 3).

### Sensitivity analyses

Multiple sensitivity analyses were performed, as described in online supplemental tables 4 and 5. Alternative approaches for calculating the Z-scores of the cognitive domains yielded similar results to the main analyses.

### DISCUSSION

We demonstrate that cognitive impairment is common in patients with (NP)SLE without large brain infarcts and that patients with inflammatory NPSLE have reduced cognitive function compared with patients with ischaemic and minor/non-NPSLE. WMHs are associated with reduced psychomotor speed, especially in patients with inflammatory NPSLE. Furthermore, reduced brain

**Table 3** Comparison of cognitive function between patients with minor/non-neuropsychiatric systemic lupus erythematosus (NPSLE), inflammatory NPSLE and ischaemic NPSLE

	Global cognitive function	Learning and memory	Executive function and complex attention	Psychomotor speed
	B (95% CI)	B (95% CI)	B (95% CI)	B (95% CI)
Inflammatory versus minor/non-NPSLE (R)	-0.43 (-0.87 to 0.01)	-0.34 (-0.71 to 0.03)	-0.35 (-0.74 to 0.05)	-0.24 (-0.62 to 0.15)
Ischaemic versus minor/non-NPSLE (R)	0.01 (-0.57 to 0.59)	0.15 (-0.34 to 0.64)	0.42 (-0.10 to 0.94)	0.48 (-0.04 to 0.99)
Inflammatory versus ischaemic NPSLE (R)	-0.80* (-1.44 to -0.17)	-0.74* (-1.37 to -0.12)	-0.98* (-1.56 to -0.41)	-0.79* (-1.41 to -0.16)

Data represent B's and 95% CI's resulting from multiple regression analyses corrected for age, sex and education. These values represent how much the (transformed) Z-score of the cognitive domain differs in the presence of a specific NPSLE phenotype. \*P<0.05. R, reference value.

**Table 4** Association between cognitive function and brain volumes including white matter hyperintensity (WMH) volume in patients with systemic lupus erythematosus and neuropsychiatric symptoms of different origins

	Global cognitive function		Learning and memory		Executive function and complex attention		Psychomotor speed	
	B	(95% CI)	B	(95% CI)	B	(95% CI)	B	(95% CI)
<b>All patients (n=151)</b>								
Total brain volume	0.00*	0.00 to 0.01	0.00*	0.00 to 0.01	0.00*	0.00 to 0.01	0.01*	0.00 to 0.01
Grey matter volume	0.01*	0.00 to 0.01	0.01*	0.00 to 0.01	0.01*	0.00 to 0.01	0.01*	0.00 to 0.01
White matter volume	0.00	-0.00 to 0.01	0.00*	0.00 to 0.01	0.01*	0.00 to 0.01	0.01*	0.00 to 0.01
WMH volume*	-0.05	-0.18 to 0.09	-0.07	-0.18 to 0.05	-0.11	-0.24 to 0.01	-0.14*	-0.32 to -0.02
<b>Minor/non-NPSLE (n=115)</b>								
Total brain volume	0.00	-0.00 to 0.01	0.00*	0.00 to 0.01	0.00*	0.00 to 0.01	0.00*	0.00 to 0.01
Grey matter volume	0.01*	0.00 to 0.01	0.01*	0.00 to 0.01	0.01*	0.00 to 0.01	0.01*	0.00 to 0.01
White matter volume	0.00	-0.00 to 0.01	0.00	-0.00 to 0.01	0.01*	0.00 to 0.01	0.01*	0.00 to 0.01
WMH volume*	0.02	-0.14 to 0.17	-0.03	-0.17 to 0.10	-0.07	-0.22 to 0.07	-0.07	-0.22 to 0.07
<b>Inflammatory NPSLE (n=24)</b>								
Total brain volume	0.00	-0.01 to 0.02	0.01	-0.00 to 0.02	0.01	-0.01 to 0.01	0.01	-0.00 to 0.02
Grey matter volume	0.00	-0.01 to 0.02	0.00	-0.01 to 0.02	0.00	-0.01 to 0.02	0.01	-0.01 to 0.02
White matter volume	-0.01	-0.02 to 0.03	0.01	-0.00 to 0.03	0.02	-0.00 to 0.04	0.02*	0.00 to 0.03
WMH volume*	-0.14	-0.49 to 0.21	-0.11	-0.43 to 0.20	-0.22	-0.52 to 0.08	-0.36*	-0.60 to 0.12
<b>Ischaemic NPSLE (n=12)</b>								
Total brain volume	0.00	-0.02 to 0.01	0.00	-0.02 to 0.01	0.00	-0.01 to 0.01	0.00	-0.01 to 0.01
Grey matter volume	0.00	-0.03 to 0.02	0.00	-0.03 to 0.03	-0.00	-0.02 to 0.02	0.00	-0.01 to 0.02
White matter volume	0.00	-0.01 to 0.02	0.00	-0.04 to 0.03	0.00	-0.02 to 0.03	0.00	-0.01 to 0.03
WMH volume*	-0.02	-1.00 to 0.96	-0.12	-1.14 to 0.89	-0.28	-1.08 to 0.52	-0.21	-0.86 to 0.44

These data represent B's and 95% CI's corrected for age, sex and intracranial volume. \* $p \leq 0.05$ . The B's shown represent how much the (transformed) Z-score of a cognitive domain changes when the brain volume changes one unit.

\*WMH volume: expected negative association with cognitive function, whereas all other domains are expected to have a positive association.

NPSLE, neuropsychiatric systemic lupus erythematosus.;

volumes are associated with reduced function across different cognitive domains in patients with SLE and neuropsychiatric symptoms.

Previous studies have demonstrated that patients with SLE have impaired cognitive function in multiple cognitive domains, including visual attention, cognitive fluency, immediate visual memory and visual reasoning.<sup>24</sup> Patients with NPSLE showed more cognitive impairment than general patients with SLE and also showed impairment in other domains, such as attention, visuomotor coordination and executive function.<sup>3 25</sup> Cognitive function in different phenotypes of NPSLE has not been previously studied. In our study, we confirmed a high level of impairment in executive function (present in about half of the patients), but impairment differed across NPSLE phenotypes. Studying patients without large brain infarcts, we showed that cognitive impairment was most common in patients with inflammatory NPSLE. Nearly half of the

patients with inflammatory NPSLE showed impairment in the domains learning and memory, executive function and complex attention and psychomotor speed. These domains were also strongly affected in minor/non-NPSLE, but not in patients with ischaemic NPSLE. This is most likely explained by the selection of ischaemic patients with NPSLE in our cohort, as patients with large brain infarcts (>1.5 cm) were excluded in order to focus on patients without overt brain abnormalities. Small infarcts and other brain abnormalities in patients with ischaemic NPSLE in our cohort therefore appear to have a limited effect on cognitive function. Overall, we demonstrate that cognitive impairment is frequent, but differs across NPSLE phenotypes in patients with relatively normal conventional brain MRI. This might be explained by differences in brain abnormalities due to possible other underlying pathophysiological processes across phenotypes.

An association between brain volume and cognitive function has been demonstrated in both normal ageing and disease.<sup>26</sup> Decrease in brain volume is generally thought to be associated with a decline in cognitive function through neuronal death or atrophy and loss of neuronal connections, which might be caused by immune-mediated inflammation in patients with SLE.<sup>27</sup> Only a limited number of studies have previously focused on the association between cognitive function and brain volumes on MRI in patients with SLE without major nervous system involvement ('non-NPSLE').<sup>28–37</sup> Several studies found an association between global cognitive impairment and reduced grey matter<sup>36</sup> or white matter volume<sup>28 30 36</sup> and in one study this association was not found.<sup>31</sup> In our study, we demonstrated that brain volumes were indeed associated with cognitive function (all domains) in patients with SLE, but differences were present between NPSLE phenotypes.

WMHs are regularly seen in patients with SLE and appear to be even more frequent in patients with NPSLE.<sup>10 38 39</sup> A recent study demonstrated that patients with SLE with new neuropsychiatric events showed changes on MRI, including an increase of WMHs.<sup>40</sup> Other studies have shown that, in at least a subset of patients, these WMHs are reversible.<sup>41 42</sup> Little is known regarding the exact pathophysiological substrate of WMHs in patients with SLE. The few imaging/histopathological studies performed show that WMHs are usually small resolved or acute infarcts, focal areas of reduced neuronal density, acute microhemorrhages and less frequently focal inflammatory oedema.<sup>43</sup> WMHs have also been associated with the presence of the APS, a common secondary manifestation of SLE.<sup>44</sup> In general, WMHs in patients with SLE are therefore considered a marker of inflammatory and immunologically mediated small vessel disease.<sup>45</sup> Several studies have looked into the association between WMHs and cognitive function in patients with SLE,<sup>8 28 33 46–48</sup> but not in NPSLE. One study showed that composite and verbal memory inversely correlated with WMH number and volume<sup>33</sup> and two studies showed that patients with cognitive dysfunction showed more WMHs.<sup>47 48</sup> Not all studies have confirmed this association between WMHs and cognitive function.<sup>8 46</sup> We demonstrated that WMH volume specifically associates with psychomotor speed, a relationship which is most pronounced in patients with inflammatory NPSLE. This association is in line with studies on damage of the white matter in other diseases, in which an association with psychomotor speed has also been found.<sup>49</sup> The stronger association seen in patients with inflammatory NPSLE might be the result of a different type of WMH in this population. These WMHs may represent both reversible brain abnormalities and irreversible brain damage, that cause a cumulative or increasing damage effect. As WMHs are commonly reported in SLE, appear to influence cognitive function and could be partially reversible,<sup>41 42</sup> WMHs might serve as a biomarker in clinical studies aimed at preventing morbidity due to cognitive impairment.

The strengths of our study include our very well-defined cohort of patients with SLE and neuropsychiatric symptoms: all patients underwent standardised assessment including neuropsychological assessment and a brain MRI. Furthermore, attributing neuropsychiatric symptoms to SLE can be difficult and therefore, the multidisciplinary approach used in our centre is invaluable when studying different NPSLE phenotypes.

One of the limitations of our study is the use of both 2-D and 3-D FLAIR MRI scans, which may have introduced a small measurement bias between patients. To limit the extent of this potential bias, we have used an image processing pipeline that is robust for differences in MRI scans.<sup>50</sup> Another limitation could be circular reasoning in attributing NPSLE phenotype to patients with SLE that present with cognitive complaints. Because of the multidisciplinary assessment (in which information regarding the cognitive status of patients is known), circular reasoning might have led to a higher prevalence of cognitive dysfunction in patients with inflammatory NPSLE. However, neither the separation in cognitive domains or the definition of cognitive impairment based on  $\geq 1$  SD lower than the general population (T-score  $\leq 40$ ) is applied in the multidisciplinary assessment. In addition, as exact brain volumes are unknown during the multidisciplinary meeting, there is no bias due to circular reasoning in the associations between brain volumes and cognitive function and the phenotype. As we only studied patients without large infarcts, it is good to keep in mind that our results are not generalizable to all patients presenting with SLE and neuropsychiatric symptoms. Lastly, as there was a limited sample of patients for some subgroups, future research is necessary to confirm our findings.

In conclusion, we demonstrated that an association between brain and WMH volumes and cognitive function is present in patients with SLE, but differs between (NP) SLE phenotypes. WMHs associated with psychomotor speed, especially in inflammatory NPSLE, which suggests a different, potentially more severe underlying pathophysiological mechanism of cognitive impairment in this phenotype.

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