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Distinct profiles of cognitive impairment associated with different silent cerebrovascular lesions in hypertensive elderly Chinese☆

Manman Zhang[a,b], Bingjiao Xie[b], Junling Gao[c], Henry Ka Fung Mak[d], Alfred Siu Kei Kwong[e], Dicken Chin Ping Chan[e], Raymond Tak Fai Cheung[b,f,*]

[a] Department of Neurology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China
[b] Department of Medicine, The University of Hong Kong, Hong Kong
[c] Centre of Buddhist Studies, The University of Hong Kong, Hong Kong
[d] Department of Diagnostic Radiology, The University of Hong Kong, Hong Kong
[e] Sai Ying Pun Jockey Club General Out-patient Clinic, Hong Kong
[f] Research Centre of Heart, Brain, Hormone & Healthy Aging, The University of Hong Kong, Hong Kong

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ABSTRACT

Background/objectives: Silent cerebrovascular lesions (SCLs) and their underlying pathology are now recognized as important causes of cognitive impairment in the elderly. However, the distinct profile of cognitive deficits associated with each type of SCLs remains unclear.

Methods: Of 497 otherwise healthy hypertensive elderly Chinese, 398 participants (mean age 72.0, ranging from 65 to 99, SD = 5.1) successfully completed a battery of structured neuropsychological tests and a multi-sequence 3 T MRI scanning. SCLs were rated independently. Correlations between each MRI marker and cognitive function were assessed using a series of linear regression models.

Results: Strictly lobar cerebral microbleeds were linked to impaired language function ($B = -0.231, p < 0.05$). Silent lacunes were associated with poor executive function, but the association disappeared after additional adjustment for white matter hyperintensities. White matter hyperintensities (especially periventricular hyperintensities) were associated with poor executive function ($B = -0.126$, $p < 0.05$) and slower information processing speed ($B = -0.149$, $p < 0.05$).

Conclusion: Different SCLs were associated with different patterns of cognitive deficits, indicating that different SCLs may have distinct impacts on cognitive performance.

1. Introduction

Silent cerebrovascular lesions (SCLs) are neuroradiologic findings in patients without overt clinical events. MRI is superior to CT in detection of SCLs. Common SCLs include white matter hyperintensities (WMHs), silent lacunes (SLs) and cerebral microbleeds (CMBs). These markers could indicate an early stage of cerebral small vessel disease which may or may not progress to an advanced stage with symptomatic lacunar stroke plus confluent WMHs. SCLs are common in the general elderly population and were previously regarded as benign pathologies. SCLs have recently been found to be strongly associated with cardiovascular and cerebrovascular diseases [1,2] and have increasingly been recognized as predictors of functional impairment and cognitive decline [3,4]. Impaired executive function (EF) and reduced information processing speed (IPS) are the most frequently reported cognitive deficits in people with cerebral small vessel disease [5,6]. However, the independent spectrum and magnitude of cognitive impairment related to SCLs remain unclear, largely due to inconsistent results from different studies. Participants of previous studies were typically recruited from hospitals. As these participants probably had severe cardiovascular or neurological diseases, the reported associations may be biased [7–9]. Moreover, most of these studies have focused on Caucasian populations. Similar research data from Chinese populations are scarce. Studying a relatively large, pure and representative cohort can provide useful

Abbreviations: CMBs, cerebral microbleeds; DWMHs, deep white matter hyperintensities; EF, executive function; IPS, information processing speed; PVHs, periventricular hyperintensities; SCLs, Silent cerebrovascular lesions; SLs, silent lacunes, WMHs - white matter hyperintensities

☆ The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) for human research. All participants were informed of the scope of the study before signing the consent form.

* Corresponding author at: Department of Medicine, The University of Hong Kong, Hong Kong.
E-mail address: rtcheung@hkucc.hku.hk (R.T.F. Cheung).

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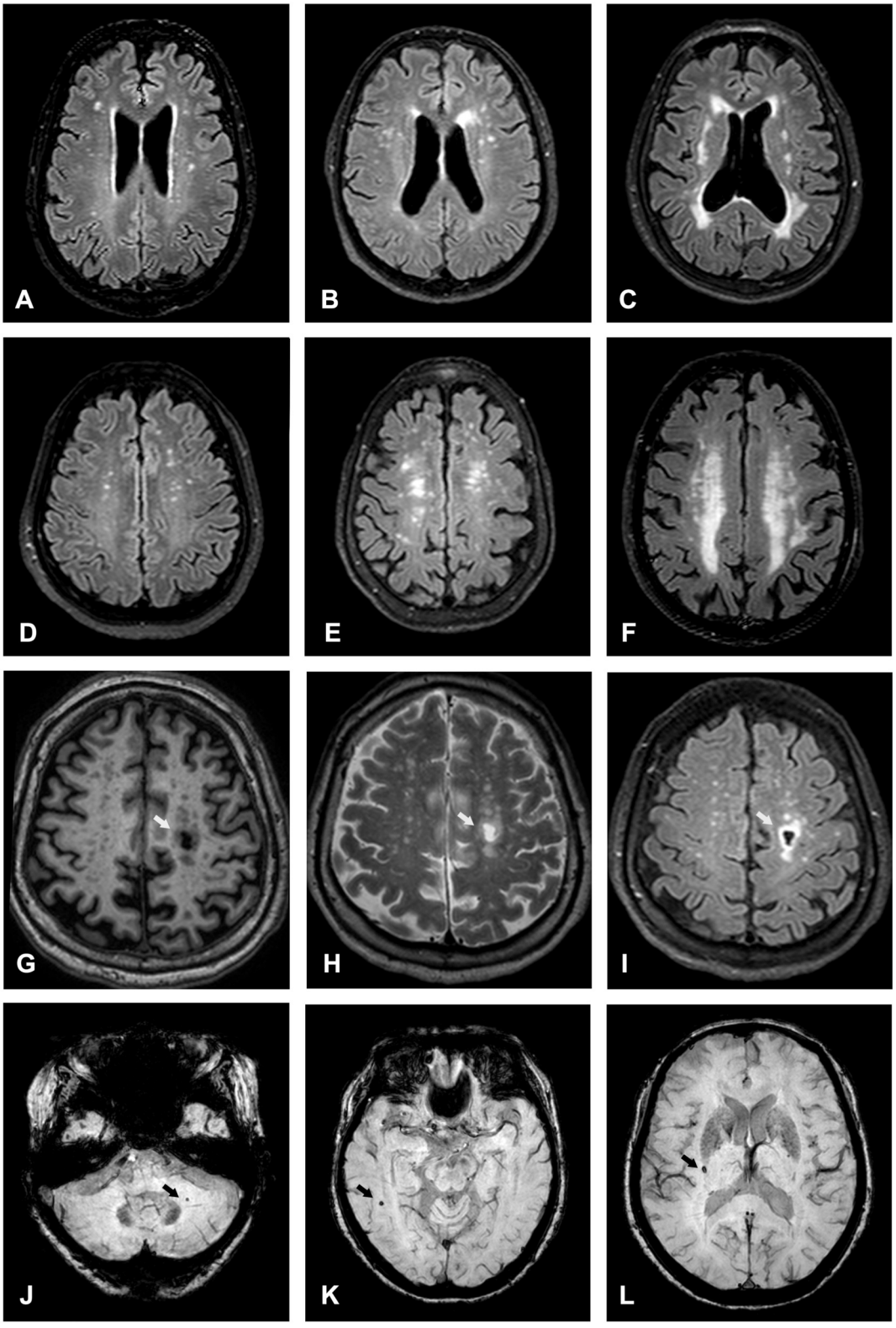

Fig. 1. These FLAIR images show increasing degrees of periventricular hyperintensities (A, B and C) and deep white matter hyperintensities (D, E and F) as rated on the Fazekas scale. The T1-weighted (G), T2-weighted (H) and FLAIR (I) images show the same silent lacune. Three microbleeds of different locations (J, cerebellum; K, temporal lobe and L, basal ganglia) are shown on susceptibility-weighted imaging.

epidemiological data to guide clinicians and neuropsychologists in subsequent intervention and rehabilitation.

In the present study, we recruited a cohort of otherwise healthy hypertensive elderly Chinese subjects from a primary care service. We first studied the profiles of cognitive decline according to each type of SCLs concerning their presence, load and location, if applicable. Next, the independent impact of each type of SCLs was analyzed after adjustment for other SCLs and vascular risk factors.

2. Materials and methods

2.1. Study population

Data from 398 participants of the **S**ilent cerebrovascular lesions in healthy **H**ypertensive **E**lderly **C**hinese **P**roject (SHECP) were analyzed in this cross-sectional study. The SHECP project is a prospective cohort study investigating the risk factors, incidence and consequences of SCLs among otherwise healthy elderly (over 65 years old) Chinese residents who have attended the general out-patient clinic in western district of Hong Kong Island for hypertension of five years or more. This clinic provides cardiovascular risk assessment for patients with essential hypertension on an annual basis.

The exclusion criteria included a history of dementia, stroke (ischemic stroke, subarachnoid hemorrhage and primary hemorrhagic stroke), transient ischemic attack, encephalitis, brain tumor, other neurological diseases, schizophrenia, depression, and other psychiatric diseases. Patients with atrial fibrillation, coronary heart disease, diabetes mellitus and other severe medical illnesses, individuals with contraindications for MRI scan and those unable to complete the cognitive assessments were also excluded.

2.2. Procedures

All participants underwent a face-to-face interview and a multi-sequence 3 T MRI scanning at baseline. The time interval between the interview and MRI scanning was within one month. Demographic and clinical data were collected during the interview, and additional information was extracted from the medical records. The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster for human research. All participants were informed of the scope of the study before signing the consent form.

2.3. MRI acquisition

All participants of SHECP underwent baseline MRI scanning using a 3.0 Tesla field strength machine (Philips Medical Systems, Best, The Netherlands). The MRI protocol included an axial three dimensional T1-weighted magnetization prepared rapid gradient echo (TR = 7000 ms; TE = 3.2 ms, 155 contiguous 1-mm-thick axial slices, acquisition matrix size = 240 × 240), an axial proton density/T2 turbo spin echo run twice (PD/T2; TR = 5000 ms; TE = 16/80 ms, 50 contiguous 2.5-mm-thick axial slices, acquisition matrix size = 480 × 480), and an fluid attenuated inversion recovery sequence (TR = 11,000 ms; TE = 120 ms, inversion time = 2800 ms, 50 1-mm-thick axial slices, acquisition matrix size = 768 × 768), susceptibility weighted imaging (TR = 27.9 ms; TE = 23 ms, 135 2-mm-thick axial slices, acquisition matrix size = 704 × 704), and other sequences (diffusion tensor imaging, 3D time-of-flight cerebral angiography, carotid T1-weighted black-blood fat-suppression imaging, and 3D TOF carotid angiography).

2.4. Independent rating of SCLs

Two neurologists (B. XIE and M. ZHANG) under the supervision of an experienced neuroradiologist (H.K.F. MAK) carried out the visual rating of lacunes, CMBs and WMHs on the anonymous MRI images independently and separately (Fig. 1). Both raters reassessed the same MRI images independently three months later. The inter- and intra-rater reliability were good, as reflected by Cohen κ values between 0.60 and 0.86. Any disagreement between the two raters would be adjudicated by the neuroradiologist.

A lacune was defined as a 3 to 15 mm diameter hypointense focus on both the T1-weighted and FLAIR sequences with high signal intensity on the corresponding T2-weighted images. Both the presence and the location (deep or lobar) of the lacune were recorded. A CMB was defined as a 2–10 mm diameter round or oval punctuate hypointense focus on the susceptibility-weighted imaging. The Brain Observer MicroBleed Scale (BOMBS) was used to visually score the load and the location of CMBs [10]. When lacunes and CMBs were only seen in the lobar white matter, they were referred to as strictly lobar lacunes and CMBs, respectively; deep lacunes and CMBs were used, respectively, when both lobar and deep lacunes and CMBs were present [11,12]. WMHs were defined as bilateral symmetrical hyperintense foci on FLAIR and T2-weighted sequences with an isointense or hypointense signal on the corresponding T1-weighted images. The severity of WMHs was visually rated on the FLAIR images according to the Fazekas white matter scale, generating separate WMH scores for periventricular hyperintensities (PVHs) and deep white matter hyperintensities (DWMHs) [13].

2.5. Neuropsychological tests

The interview also included a battery of neuropsychological tests (as detailed in the supplemental materials). For more meaningful comparison, related items of different tests were grouped into six cognitive domains: attention, language-related function, memory, visuospatial function, IPS and EF (Table 1). All these neuropsychological tests were administered by the same researcher (M. ZHANG).

2.6. Statistical analysis

First, the raw score from each test item was *Z*-transformed (i.e. first subtract the mean from the raw score and then divide the difference by the standard deviation). The reversed Z scores were used in the Stroop tests (i.e., –Z) so that higher values indicate better performance. Next, the mean Z score of all test items was generated for each cognitive domain as a compound score.

The association between cognitive function and each type of SCL (SLs, CMBs, PVHs and DWMHs) was assessed separately using linear regression models. The numbers of CMBs were highly skewed, thus we performed additional analysis after categorizing the numbers of microbleeds into groups as described in previous articles [11]. All the analyses were adjusted for age, sex, and educational level. Additional adjustments were made for vascular risk factors (i.e., body mass index, hyperlipidemia, impaired glucose tolerance, smoking, drinking, systolic

Table 1
Neuropsychological tests of different cognitive domains.

Domains	Tests
Attention	Forward digit span, backward digit span
Language-related function	Verbal fluency, MoCA naming, MoCA repetition
Memory	MoCA verbal learning test
Visuospatial function	MoCA drawing a cube, MoCA drawing a clock
Information processing speed	Stroop color naming subtask, Stroop neutral color subtask, symbol digit modalities written test, symbol digit modalities oral test
Executive function	Backward digit span, verbal fluency, Stroop interference subtask

MoCA, Montreal cognitive assessment.

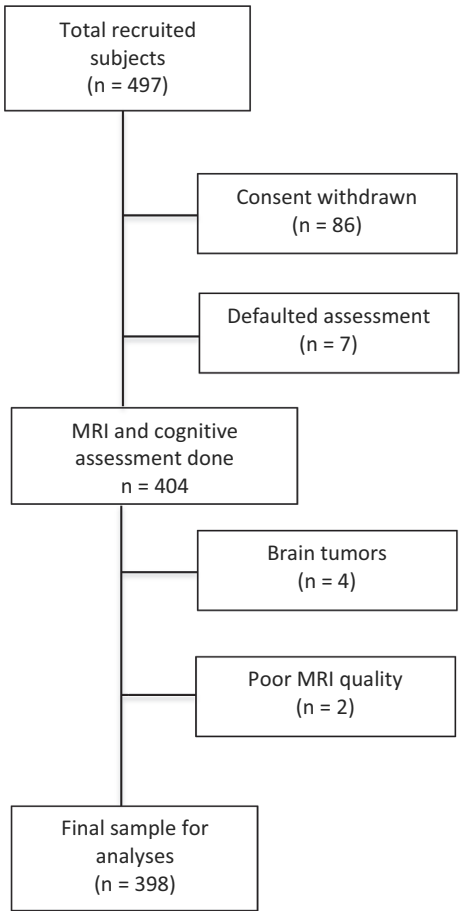

Fig. 2. Flow chart of subject recruitment.

blood pressure and diastolic blood pressure).

In order to elucidate whether the correlation between each type of SCL and cognitive performance is independent of the other types of SCLs, analyses were repeated after adjusting for the other types of SCLs. For each type of SCLs, only the parameters with a significant correlation in the single variable models were entered in the multiple variables models to control for multicollinearity.

All analyses were performed using the statistical package SPSS 22.0. A p value < 0.05 was taken to infer statistical significance.

3. Results

3.1. Study participants

From February 2012 to February 2015, a total of 497 otherwise healthy hypertensive elderly Chinese subjects were recruited into SHECP, and data for analysis were available from 398 subjects (Fig. 2). Table 2 summarizes the participants' demographic characteristics and vascular risk factors. Their mean age was 72.0 (ranged from 65 to 99, SD = 5.1) years old, and 53.5% of them were male. Their mean cognitive performance and the prevalence and distribution of different types of SCL were included in the supplemental materials (Supplemental Tables 1 and 2).

3.2. CMBs and cognition

A larger number of CMBs was significantly associated with worse performance in the tests on language-related function (Table 3). More specifically, this association was attributable to the failure in neuropsychological tests of verbal fluency and repetition rather than naming (Supplemental Table 2). Further analysis according to different groupings of loads of CMBs supported a dose-dependent effect. Furthermore, we found a stronger association between worse performance on language-related function and the presence of strictly lobar CMBs but not deep CMBs (Table 3).

Additional adjustment for vascular risk factors did not alter the association between the presence of strictly lobar CMBs and worse performance on language-related function. This association also persisted after correcting for the presence of deep SLs and the severity of PVHs (Table 5).

Table 2
Clinical characteristics of study participants (n = 398).

Characteristics	
Mean age (SD) in years	72.0 (5.1)
Male (%)	213 (53.5)
Median educational level (IQR) in years	8 (6)
BMI distribution (%)	
< 25	228 (57.3)
25–29.9	146 (36.7)
≥30	24 (6.0)
Mean blood pressure on drugs (%) in mmHg	
SBP level	
< 120	21 (5.3)
120–139	302 (75.8)
≥140	75 (18.9)
DBP level	
< 80	265 (66.6)
80–89	114 (28.7)
≥90	19 (4.7)
Smoking status (%)	
Never	314 (79.0)
Past	62 (15.4)
Current	22 (5.6)
Alcohol consuming	
Never or occasional	331 (83.2)
Mild to moderate	53 (13.3)
Heavy	14 (3.5)
Impaired glucose tolerance (%)	70 (17.6)
Hyperlipidemia (%)	165 (41.5)
Median GDS (IQR)	1 (2)

BMI, body mass index; DBP, diastolic blood pressure; GDS, Geriatric Depression Scale; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation.

3.3. SLs and cognition

The presence of SLs was significantly associated with worse performance on EF (Table 4). Excluding participants with strictly lobar SLs did not affect the association (Table 4). This association persisted after additional adjustment for vascular risk factors but disappeared after correcting for the presence of strictly lobar CMBs and the severity of PVHs (Table 5).

3.4. WMHs and cognition

The Fazekas scores of PVHs and DWMHs were separately evaluated for their associations with cognitive performance using linear regression models (Table 4). The severity of PVHs was associated with language-related function, IPS and EF. In contrast, the severity of DWMHs was not associated with any compound score of the six cognitive domains.

Additional adjustment for vascular risk factors did not alter the associations. The associations with IPS and EF but not language-related function persisted after correcting for the presence of strictly lobar CMBs and the presence of deep SLs (Table 5).

Table 3
Association between the number or location of CMBs and the Z score of the cognitive domains using single variable linear regression models controlled for age, gender and educational levels.

	Attention	Language	Memory	Visuospatial	IPS	Executive
Number of CMBs	0.000 (−0.039, 0.038)	−0.063# (−0.109, −0.017)	0.004 (−0.032, 0.040)	0.027 (−0.004, 0.059)	0.009 (−0.049, 0.031)	−0.013 (−0.045, 0.019)
1 CMB versus none	−0.189 (−0.411, 0.033)	−0.112 (−0.284, 0.020)	0.025 (−0.191, 0.242)	−0.020 (−0.270, 0.170)	0.040 (−0.145, 0.224)	−0.300 (−0.852, 0.251)
≥1 CMBs versus none	−0.026 (−0.600, 0.547)	−0.190# (−0.114, −0.267)	−0.035 (−0.221, 0.152)	0.066 (−0.095, 0.227)	−0.233 (−0.852, 0.386)	−0.162 (−0.718, 0.395)
≥3 CMBs versus none	−0.063 (−0.495, 0.369)	−0.378* (−0.715, −0.040)	−0.022 (−0.402, 0.358)	0.387* (0.056, 0.719)	−0.030 (−0.431, 0.360)	−0.095 (−0.470, 0.280)
≥5 CMBs versus none	−0.183 (−0.344, 0.038)	−0.187* (−0.352, −0.022)	0.043 (−0.433, 0.519)	0.510* (0.091, 0.929)	0.028 (−0.138, 0.197)	−0.106 (−0.266, 0.055)
Presence of strictly lobar CMBs versus none	−0.190 (−0.423, 0.043)	−0.231* (−0.429, −0.032)	−0.072 (−0.298, 0.154)	−0.038 (−0.234, 0.158)	−0.057 (−0.258, 0.144)	−0.166 (−0.360, 0.028)
Presence of deep CMBs versus none	−0.078 (−0.381, 0.226)	−0.104 (−0.354, 0.146)	−0.130 (−0.534, 0.273)	0.295 (−0.057, 0.646)	0.178 (−0.077, 0.432)	0.012 (−0.240, 0.264)

CMBs, cerebral microbleeds; IPS, information processing speed.
Values are expressed as the unstandardized beta coefficient with 95% confidence interval in brackets.
* $p < 0.05$.
# $p < 0.01$.

Table 4
Association between presence of SLs or severity of WMHs and the Z score of cognitive domains using single variable linear regression models controlled for age, gender and educational levels.

	Attention	Language	Memory	Visuospatial	IPS	Executive
SLs	−0.092 (−0.311, 0.127)	−0.155 (−0.409, 0.100)	−0.027 (−0.238, 0.185)	0.042 (−0.142, 0.225)	−0.117 (−0.305, 0.072)	−0.217* (−0.397, −0.032)
Deep SLs	−0.061 (−0.288, 0.166)	−0.168 (−0.363, 0.028)	−0.024 (−0.242, 0.194)	0.036 (−0.154, 0.225)	−0.096 (−0.290, 0.098)	−0.206* (−0.397, −0.018)
PVHs	−0.035 (−0.165, 0.096)	−0.138* (−0.250, −0.027)	−0.004 (−0.131, 0.123)	−0.002 (−0.112, 0.108)	−0.156* (−0.267, −0.046)	−0.132* (−0.241, −0.023)
DWMHs	−0.056 (−0.221, 0.109)	−0.082 (−0.221, 0.057)	0.072 (−0.083, 0.228)	0.064 (−0.071, 0.200)	−0.129 (−0.276, 0.018)	−0.128 (−0.270, 0.014)

DWMHs, deep white matter hyperintensities; IPS, information processing speed; PVHs, periventricular hyperintensities; SLs, silent lacunes; WMHs, white matter hyperintensities.
Values are expressed as the unstandardized beta coefficient with 95% confidence interval in brackets.
* $p < 0.05$.

4. Discussion/conclusion

Evidence for the impact of SCLs on cognition has accumulating swiftly in recent decades. However, many issues remain controversial, as some studies have yielded inconsistent results. One reason for the mixed results regarding the association between SCLs and cognition may have originated from the heterogeneity of the samples assessed in different studies. Some previous studies recruited participants with more complicated conditions like dementia, stroke and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [14–17], and this may influence the association between SCLs and cognition. Other researchers targeted at more advanced conditions such as symptomatic lacunes and confluent white matter leukoaraiosis [18,19]. The problem with focusing on moderate-to-severe cases is that different types of SCLs may evolve into common late-stage pathologies, including axonal injury, demyelination and

Table 5
Association between severity of PVHs, presence of deep SLs or strictly lobar CMBs and the Z score of selected cognitive domains, using single variable linear regression models[1] controlled for age, gender, educational levels and vascular risk factors or multiple variables linear regression models[2] controlled for age, gender, educational levels and the other two types of SCLs.

	Language-related function				Information processing speed				Executive function			
	B	SE	β	*p*-Value	B	SE	β	*p*-Value	B	SE	β	*p*-Value
PVHs[1]	−0.147	0.059	−0.128	0.014*	−0.159	0.059	−0.131	0.007*	−0.143	0.059	−0.130	0.016*
Deep SLs[1]	/				/				−0.235	0.012	−0.121	0.021*
Lobar CMBs[1]	−0.275	0.108	0.134	0.012*	/				/			
PVHs[2]	−0.107	0.062	−0.090	0.088	−0.149	0.064	−0.116	0.020*	−0.126	0.063	−0.106	0.046*
Deep SLs[2]	/				/				−0.197	0.106	−0.098	0.064
Lobar CMBs[2]	−0.202	0.102	−0.098	0.049*	/				/			

B, unstandardized beta coefficient; β, standardized beta coefficient; CMBs, cerebral microbleeds; PVHs, periventricular hyperintensities; SLs, silent lacunes; SCLs, silent cerebrovascular lesions; SE, standard error.
Vascular risk factors include body mass index, hyperlipidemia, impaired glucose tolerance, smoking, drinking, systolic blood pressure and diastolic blood pressure.
* $p < 0.05$.

neuronal loss, and in turn exert a similar impact on cognition. Thus, their distinctive effects on cognition may be more discernable at an early stage of SCLs. In the present study, our participants were recruited from a general clinic and were otherwise healthy hypertensive Chinese elderly subjects. The hypertensive population was chosen because hypertension is very common among the elderly population and since it is an important risk factor of SCLs [20]. Similar studies on Chinese population is scarce. Moreover, most previous studies have focused on one or two types of SCLs. In the current analysis, we tried to identify the distinct association of each type of SCLs with performance in specific cognitive domains.

The impact of CMBs on cognitive performance is a subject of intense debate. Several studies have found evidence for a role of CMBs in cognitive decline across varying populations [11,14,15,17,21,22], while some studies reported an insignificant effect of CMBs [16,23,24]. The present study has provided neuroimaging data from a large Asian sample to support a role of CMBs in cognitive dysfunction. Although single CMB has been shown to have an impact on cognition [11], we did not find any association between single CMB and worse cognitive performance. As the number of cases with single CMB in the present study was small, we cannot exclude a small effect of single CMB on cognition. Single CMB may be a general marker for vascular pathology which in turn interferes with cognitive processes.

CMB-related cognitive deficits are characterized by prominent impairment in psychomotor speed or EF in patients with stroke/TIA or vascular dementia and in non-demented population or community-dwelling individuals [14,15,21]. Some studies have also reported impairment in memory, visuospatial function and other cognitive domains [17,22]. Seo and colleagues previously reported a marginally significant association between the numbers of CMBs and worse performance on the Boston Naming Test [17]. Our data on language-related function have revealed a robust link between the total load of CMBs and worse performance in verbal fluency and repetition. We also found that strictly lobar CMBs have a much stronger and more stable association with language-related function than deep CMBs. This may support the hypothesis that the location of CMBs reflects different etiologies of cognitive impairments [25]. Deep CMBs are linked to hypertensive arteriolosclerosis, whilst strictly lobar CMBs may be a marker of pathologies associated with cerebral amyloid angiopathies or neuritic β-amyloid plaques [26]. These underlying pathologies can various cognitive domains [27–29]. It is plausible that CMBs in various locations can differentially affect the cognitive performance [14]. An alternative hypothesis relating the location of CMBs to cognition is their strategic location in interfering with the cognitive performance. In other words, strictly lobar CMBs may affect the functions of the surrounding cortex, and deep CMBs may cause disconnections between cortical and subcortical structures [30,31]. We postulate that the frontal and/or temporal CMBs may adversely affect language-related function. Further studies are needed to clarify how the location of CMBs could affect specific cognitive domains.

Our current knowledge about the impact of SLs on cognition is predominantly derived from studies on patients with lacunar stroke. The primary mechanism of the lacune, silent and symptomatic, is assumed to be lipohyalinosis and microatheromatosis of cerebral perforating arteries [32]. Some authors have argued that SLs are similar to lacunar stroke in terms of etiology and pathophysiology and that the non-strategic locations of SLs may explain the absence of lacunar stroke syndromes [33]. Evidence for this notion is scare, and more studies on the cognition of 'asymptomatic' subjects with SLs are needed. Our findings are consistent with previous studies that reported a positive correlation between lacunar stroke and poor executive abilities in elderly populations [18,19,34]. Half of the patients with a first-ever lacunar infarct have been reported to have mild cognitive impairment with subcortical vascular features, and its presence may be a predictor of subcortical vascular dementia in the medium-to-long term [35].

Whereas the association between deep SLs and worse performance on EF was not affected by adjustment for multiple vascular risk factors in the present study, it was attenuated upon correction for WMHs and CMBs. In a previous longitudinal study on patients with deep lacunes and different levels of cognitive deficits, the decline in EF was predicted by the progression in the total volume of lacunar strokes and degree of brain atrophy but not by the load of WMHs on MRI [9]. In contrast, another study reported that the progression of WMHs but not lacunar infarcts was associated with a decline in EF among healthy elderly subjects [36]. Such discrepant findings may be attributable to the differences between the study samples in terms of prevalence and progression of different markers of SCLs as well as in the burden of cognitive impairment.

Associations between the load of WMHs and cognitive decline in the domains of IPS and EF have been reported by other studies [37–39]. These studies also reported less consistent results regarding impairment in global cognition, attention and memory. The present study has also revealed an association between WMHs (mainly PVHs) and language-related function before adjustment for other markers of SCLs. An intriguing finding is that IPS was negatively correlated with the degree of PVHs but not DWMHs. In contrast, several community-based studies have reported that DWMHs were associated with poor performance including EF, IPS and memory tests while PVHs were not related to performance on any of the cognitive functions under investigation [39,40]. PVHs and DWMHs may be different entities with different functional, microstructural and clinical correlates [41]. A closer association between PVHs and cognitive impairment may be partly attributable to the involvement of long association tracts tightly packed in the periventricular region, leading to disconnection among distant and extensive cortices [42–44]. Besides, PVHs affect the corpus callosum, which is the information processing highway for inter-hemispheric communication. Studies using diffusion tensor imaging may provide more evidence by direct identification of white matter tracts traveling through regions with dense WMHs.

The present study has several limitations. Firstly, different neuropsychological assessments have inherent overlap in their tested domains, although our assessment protocols were frequently used for these domains in previous studies [45,46]. More comprehensive and specific tests may be developed and used in future studies to provide data required for reaching specific conclusions. Furthermore, the associations between SCLs and cognition were adjusted for demographic, including educational levels, and vascular characteristics but not for premorbid intelligence. The latter can affect the severity and profile of cognitive impairment. Another potentially relevant silent manifestation of cerebral small vessel diseases is cerebral atrophy, either local or global [47,48]. Future studies can focus on the relationship between SCLs and cerebral atrophy, and analyze the potential impact of cerebral atrophy on the cognition. Finally, the same type of SCLs may exert different impact on cognition because of their strategic locations. Such analyses require better characterization and categorization of the localization of SLs or CMBs.

In conclusion, the impact of SCLs on six cognitive domains was assessed in a cohort of otherwise healthy hypertensive Chinese elderly subjects. CMBs were linked to worse language-related verbal fluency and repetition. The effects were seen in strictly lobar but not deep CMBs. SLs were associated with impaired EF, but the association was not independent of other SCLs. In addition, PVHs but not DWMHs adversely affected EF and IPS. Thus, various SCLs could lead to different profiles of cognitive impairment. These differential effects may reflect differences in etiology, pathology, connectivity and function of the affected neural structures. It should be interesting and valuable to follow up this cohort to assess the progression of SCLs and the evolution of the profiles of cognitive impairment as well as the relationship between different SCLs and specific cognitive impairment.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.06.028.

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