RESEARCH PAPER

Mapping the contribution and strategic distribution patterns of neuroimaging features of small vessel disease in poststroke cognitive impairment

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ABSTRACT

Objectives Individual neuroimaging features of small vessel disease (SVD) have been reported to influence poststroke cognition. This study aimed to investigate the joint contribution and strategic distribution patterns of multiple types of SVD imaging features in poststroke cognitive impairment.

Methods We studied 145 first-ever ischaemic stroke patients with MRI and Montreal Cognitive Assessment (MoCA) examined at baseline. The local burdens of acute ischaemic lesion (AIL), white matter hyperintensity, lacune, enlarged perivascular space and cross-sectional atrophy were quantified and entered into support vector regression (SVR) models to associate with the global and domain scores of MoCA. The SVR models were optimised with feature selection through 10-fold cross-validations. The contribution of SVD features to MoCA scores was measured by the prediction accuracy in the corresponding SVR model after optimisation.

Results The combination of the neuroimaging features of SVD contributed much more to the MoCA deficits on top of AILs compared with individual SVD features, and the cognitive impact of different individual SVD features was generally similar. As identified by the optimal SVR models, the important SVD-affected regions were mainly located in the basal ganglia and white matter around it, although the specific regions varied for MoCA and its domains.

Conclusions Multiple types of SVD neuroimaging features jointly had a significant impact on global and domain cognitive functionings after stroke, and the joint contribution and strategic distribution patterns of different SVD features in poststroke cognitive impairment are still unknown.

A recent study combined the neuroimaging features of SVD (in terms of ‘total SVD burden’) and tested for associations with cognitive performance in community-dwelling older adults. In fact, this total SVD score could only describe the overall severity of different SVD features as it was based on the global rating scales of each feature. The location of the SVD neuroimaging features, which is also a key determinant of cognitive impairment, cannot be captured in such a composite SVD score.

In this case, we proposed a study that quantified the local burden of typical neuroimaging features of SVD (regional lesion volumes for WMH, lacune and EPVS, and volume ratio for cross-sectional atrophy) and applied support vector regression (SVR) to associate these individual SVD features and their combinations with cognitive impairment after stroke. SVR is a widely used machine learning tool for regression problems and predictions of real values, and featured with good generalisation ability to unseen data. We measured the contribution of the SVD features to poststroke cognitive impairment by the prediction accuracy (Pearson correlation between the predicted and real cognitive scores) of the SVR model that included the corresponding SVD features as predictors. Furthermore, we visualised the important SVD-affected regions for global cognition and each cognitive domain in a similar manner with lesion–symptom mapping.

METHODS

Subjects

Participants were patients of the ongoing Chinese University—Stroke Registry Investigating Cognitive Decline (CU-STRIDE) study, which recruited 1013 consecutive acute stroke/TIA patients that were admitted to the Prince of Wales Hospital in Hong Kong between 2009 and 2010. Written informed consent from all participants was obtained. Among the 510 patients who were examined by MRI, we only included the patients with acute ischaemic lesions (AILs). In addition, we further excluded the patients without fluid-attenuated inversion recovery (FLAIR), T2-weighted or T1-weighted images...
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Figure 1  Flow chart of patient inclusion. TIA, transient ischaemic attack; ASU, acute stroke unit; FLAIR, fluid-attenuated inversion recovery; MoCA, Montreal Cognitive Assessment; STRIDE, Stroke Registry Investigating Cognitive Decline.

Neuropsychological assessment

The cognitive functions were assessed using the Hong Kong version of Montreal Cognitive Assessment (MoCA).14 Items of Hong Kong-MoCA were identical to the standard version with the exception of several cultural and linguistic modifications.14 We subdivided MoCA into five cognitive domain scores including memory (delayed recall, orientation, digit span forward), language (animal picture naming, sentence repetition), attention (serial 7s, digit vigilance), executive function (digit span backward, trail-making test, word similarities, category fluency) and visuospatial function (cube draw, clock draw), using a method published previously.15

Image acquisition

Brain MRI was performed within 1 week of hospital admission on the patients. All MRI examinations were performed on a 1.5T scanner (Sonata; Siemens Medical, Erlangen, Germany) or a 3.0T scanner (Achieva 3.0T TX Series; Philips Medical System, Best, the Netherlands) using standard protocols. The applied MRI sequences in the proposed study included diffusion-weighted imaging (DWI), axial spin echo T1-weighted fast field echo, T2-weighted and axial fluid-attenuated inversion recovery (FLAIR). Their imaging parameters were previously described.16

MRI analysis

An AIL was defined by the presence of a hyperintense DWI lesion with corresponding hypointensity in the apparent diffusion coefficient map. The neuroimaging features of SVD, including WMH, lacune, EPVS and atrophy (cross-sectional) were defined according to the Standards for Reporting Vascular Changes on Neuroimaging for reporting studies in SVD1 (see online supplementary method for more details).

The AILs and lacunes were manually delineated on DWI and FLAIR scans, respectively. The WMHs were automatically segmented on FLAIR scans17 with manual correction when necessary. Regarding EPVS, we first manually segmented them roughly in a region of interest on T2-weighted image, and then refined them by an intensity-based thresholding to eliminate the false positives with isointensity surrounding individual EPVS.18

Cross-sectional atrophy was measured by the ratio of regional brain volumes to the intracranial volume of each patient, which were quantified by FreeSurfer imaging analysis suite (http://surfer.nmr.mgh.harvard.edu/) through volumetric segmentation of the T1-weighted images in individual space.20

Statistical analysis

To model the multivariate relationship of SVD imaging features and poststroke cognition, we applied SVR, which is a machine learning tool with a good generalisation ability for predictions of real values. The independent variables (predictors) of SVR were the global and regional volumes of the AIL, WMH, lacune, FLAIR, fluid-attenuated inversion recovery on 20 April 2018 by guest. Protected by copyright.
EPVS and the local atrophy measures (in volume ratios), as well as age, gender and education year (the number of year of education). Here, we projected the normalised lesion masks of AILs, WMHs, lacunes and EPVS to two widely used brain atlases with predefined regions of interest (ROIs) that covered the whole brain (AAL atlas and ICBM-DTI-81 white matter tract atlas), and quantified their regional volumes in these ROIs (WMHs were only quantified in the white matter regions as defined by ICBM-DTI-81 atlas). The dependent variable (outcome) was the MoCA score to be predicted, which was linearly transformed to a deficit score. Specifically, if we define $y$ as the deficits of MoCA scores, then $y = 1 - (Z - \min(Z))/(\max(Z) - \min(Z))$, where $Z$ are the MoCA scores (total score and domain scores). This linear transformation helps to get positive predictive weights for the ROI-based lesion features that contribute to MoCA deficits, which is easier for interpretation of the strategic lesion distribution map. Here, we used linear kernel rather than non-linear kernel for SVR to retain the ability to plot predictive weights back to brain anatomy. The contributions of different SVD features and their combinations to poststroke cognitive impairment were measured as the prediction accuracy of MoCA deficit scores from an SVR model that included these SVD imaging features as predictors. The prediction accuracy was calculated as the Pearson correlation coefficient between the predicted score and the real score. To compare the cognitive impact of different SVD imaging features, we designed several SVR models with corresponding SVD imaging features measured in the predefined ROIs: (1) model 1 with only demographic characteristics (age, gender and education year); (2) model 2 with demographic characteristics and regional AIL volumes; (3) model 3 with predictors of model 2 and regional WMH volumes; (4) model 4 with predictors of model 2 and regional lacune volumes; (5) model 5 with predictors of model 2 and regional EPVS volumes; (6) model 6 with predictors of model 2 and regional atrophy measures; (7) model 7 with predictors of model 2 and the combination of ROI-based SVD lesion measures (including WMH, lacune and EPVS); and (8) model 8 with predictors of model 7 and regional atrophy measures (the complete combination of different SVD imaging features).

Considering that entering large number of ROIs-based features would inevitably induce many irrelevant features or noises, we also performed feature selection for the SVR models to improve the model performance. In detail, we attempted two feature selection schemes: one that only captures the task-oriented (TO) information (only screens the predictors that each have independent contributions to the outcome), and the other captures both the TO and self-representation (TS) information (screens the predictors that jointly have contribution to the outcome). Model training was subsequently implemented for the SVR models preprocessed with different feature selection schemes. Within the data of the 145 patients with stroke, we performed 20 times 10-fold cross-validations (each of the 10-folds was once used for testing and the remaining 9-folds used for training) for each of these models, which aimed to optimise their mean prediction accuracy of a specific MoCA deficit score. Paired t-test was performed to compare the prediction accuracies (generated during cross-validations) of these optimised SVR models with different SVD features and feature selection schemes.

In addition to comparing the cognitive impact of different SVD imaging features, the applied SVR also facilitated to display the strategic distribution patterns of SVD features in a similar manner with multivariate lesion–symptom mapping (to measure the spatial relationship between the presence of a lesion on a voxel or in an ROI and the outcome). Here, the SVR model with the best prediction accuracy was used to visualise the ROI-based SVD features that survived feature selection, where the predictive weights of these ROI-based features were encoded in colours. Statistical inference was further performed through permutation test to measure the significance level of these ROI-based features. In details, we shuffled the observations of MoCA deficit scores to create pseudo weight coefficients for each ROI-based SVD feature, and the significance level was calculated by counting the number of pseudo weights smaller or larger than the real weight in 1000 permutations.

Further details about the statistical analysis are provided in online supplementary method.

### RESULTS

Clinical characteristics of the patients in this study are provided in table 1. The lesion volumes of AIL, WMH, lacune and EPVS were measured in the standard space (MN152). The median AIL volume was 2.57 mL, indicating that most patients had relatively small acute infarcts rather than large infarcts. The ROI-based distribution of AIL and SVD imaging features in the study cohort is illustrated by the lesion prevalence maps in figure 2. The distribution of AILs covered most parts of the cerebral in ROI-based scale and the most affected regions were mainly near basal ganglia. WMHs of the patients covered most regions in white matter, and lacunes were mainly located in the basal ganglia and the white matter near it. EPVS covered most part of the brain (including all the typical regions, namely basal ganglia, centrum semiovale and mid-brain) and were most frequent in basal ganglia. The voxel-wise lesion distribution of

<table>
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<tr>
<th>Table 1 Patient characteristics</th>
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<tr>
<td><strong>Characteristics</strong></td>
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<tr>
<td>Demographic characteristics</td>
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<tr>
<td>Age, mean ± SD (years)</td>
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<tr>
<td>Education, mean ± SD (years)</td>
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<tr>
<td>Female, n (%)</td>
</tr>
<tr>
<td>Stroke subtype</td>
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<tr>
<td>Large artery atherosclerosis, n (%)</td>
</tr>
<tr>
<td>Small artery occlusion, n (%)</td>
</tr>
<tr>
<td>Cardioembolism, n (%)</td>
</tr>
<tr>
<td>Others, n (%)</td>
</tr>
<tr>
<td>Vascular risk factors</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
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<tr>
<td>Hypertension, n (%)</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
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<tr>
<td>Lesion measures</td>
</tr>
<tr>
<td>Median acute infarct volume, mL (range)</td>
</tr>
<tr>
<td>Median white matter hyperintensity volume, mL (range)</td>
</tr>
<tr>
<td>Median lacune volume, mL (range)</td>
</tr>
<tr>
<td>Median enlarged perivascular space volume, mL (range)</td>
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<tr>
<td>Cognitive measures (max): MoCA score</td>
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<tr>
<td>Global (30), median (Q1–Q3)</td>
</tr>
<tr>
<td>Memory (12), median (Q1–Q3)</td>
</tr>
<tr>
<td>Language (5), median (Q1–Q3)</td>
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<tr>
<td>Attention (4), median (Q1–Q3)</td>
</tr>
<tr>
<td>Executive (5), median (Q1–Q3)</td>
</tr>
<tr>
<td>Visuospatial (4), median (Q1–Q3)</td>
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</table>

Q1 and Q3 indicate the first and third quartiles, respectively (in ascending order).

MoCA, Montreal Cognitive Assessment.

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the relevant imaging features (as in figure 2) is also displayed in online supplementary figure S1.

Performance of SVR models with different SVD features and feature selection schemes

The model performance (prediction accuracy) with different feature selection schemes is shown in figure 3 for the SVR models with typical neuroimaging features of SVD and their combinations. The number of ROI-based features included in these models is provided in supplementary table S1. The results of comparison in feature selection schemes are shown in supplementary table S2, where the prediction accuracies (generated in the 20 times 10-fold cross-validations) of the SVR models with different feature selection schemes were compared with paired t-tests. In general, TS feature selection outperformed the other feature selection schemes to improve the model performance (in terms of prediction accuracy of MoCA deficit scores, with P<0.001 in general), especially in the model with the complete combination of SVD features. Furthermore, TS feature selection helped to distinguish the contributions of individual SVD features and their combinations to MoCA deficits on top of AILs, where other feature selection schemes failed (figure 3).

Regarding the comparison of the cognitive impact of typical types of SVD features, the paired t-test results are provided in supplementary table S3. The model with the complete combination of SVD features generally outperformed the other models that only considered atrophy measures or lesion features of SVD (P<0.001 in general), especially in the model with the complete combination of SVD features. Furthermore, TS feature selection helped to distinguish the contributions of individual SVD features and their combinations to MoCA deficits on top of AILs, where other feature selection schemes failed (figure 3).

Important SVD-affected regions for cognitive impairment after stroke

As the SVR models that combined all the SVD features achieved the best prediction accuracy of MoCA deficits, we further visualised the involved ROI-based SVR features (predictors in the models) that contributed to the impairment in global cognition and each cognitive domain. The ROI-based features of AIL, WMH, lacune, EPVS and atrophy for global cognitive impairment (that survived TS feature selection) are shown in figure 4 (with their weighting coefficients labelled in colour). The feature ROIs for impairment in cognitive domains (memory, language, attention, executive and visuospatial function) are shown in online supplementary figures S3–S7, respectively.

Regarding the global cognitive functioning, the important regions affected by AILs that survived TS feature selection were mainly in the frontal and parietal cortex, basal ganglia and the white matter near basal ganglia. The important regions of WMH,
lacune, EPVS and atrophy that were associated with global cognitive impairment were generally different, but they consistently involved basal ganglia structures and the white matter around them (figure 4 and online supplementary table S6). With statistical inference, only AILs in the left tapetum, right fornix, right retrolenticular part of internal capsule and right superior corona radiata were significantly associated with global cognitive impairment after stroke (P<0.05 in the 1000 permutations). In addition, there were still several SVD-affected regions that were significantly associated with global cognitive impairment, such as EPVS in the right inferior fronto-occipital fasciculus and left posterior thalamic radiation, and local atrophy in the left putamen (figure 4).

Regarding the impairment in cognitive domains after stroke, the important regions of AIL and SVD features screened by TS feature selection were generally located in the basal ganglia and white matter around it, although the detailed strategic regions varied (online supplementary figures S3–S7 and supplementary tables S7–S11). In addition, at least one type of SVD imaging feature was significant in the statistical inference regarding the associations between their regional measures with cognitive domains: memory (WMH, lacunes, EPVS, atrophy), language (lacune, EPVS), attention (lacune, EPVS, atrophy), executive function (WMH, EPVS) and visuospatial function (atrophy).

For a specific MoCA deficit, many important ROI-based features of different SVD imaging features (that survived feature selection) overlapped with the same regions, and some had positive contribution to the deficit score while the others had...
Table 2: Prediction accuracy of Montreal Cognitive Assessment scores with different combinations of regions of interest-based features

<table>
<thead>
<tr>
<th>Model</th>
<th>Features in the model</th>
<th>Prediction accuracy (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Global</td>
</tr>
<tr>
<td>1</td>
<td>Age, gender, education year</td>
<td>0.5241</td>
</tr>
<tr>
<td>2</td>
<td>Model 1 + AIL</td>
<td>0.6170</td>
</tr>
<tr>
<td>3</td>
<td>Model 2 + WMH</td>
<td>0.6362</td>
</tr>
<tr>
<td>4</td>
<td>Model 2 + lacune</td>
<td>0.5909</td>
</tr>
<tr>
<td>5</td>
<td>Model 2 + EPVS</td>
<td>0.5696</td>
</tr>
<tr>
<td>6</td>
<td>Model 2 + atrophy</td>
<td>0.4763</td>
</tr>
<tr>
<td>7</td>
<td>Model 2 + SVDL</td>
<td>0.7102</td>
</tr>
<tr>
<td>8</td>
<td>Model 2 + SVDL + atrophy</td>
<td>0.8882*</td>
</tr>
</tbody>
</table>

Task-oriented and self-representation feature selection was applied for models 2–8 for consistency of comparison. Mean prediction accuracy was provided for each model. The prediction accuracies of different models were compared with paired t-tests (detailed statistics provided in supplementary tables S3, S4 and S5 and boxplots shown in online supplementary figure S2).

Model 8 achieved significantly higher prediction accuracy than the other models (P<0.001 compared with models 2–7 for global, memory, executive and visuospatial function; P<0.001 compared with models 2–6 and P=0.003 compared with model 7 for attention function).

Model 8 achieved significantly higher prediction accuracy than models 2–6 (P<0.001) and presented similar prediction accuracy with model 7 (P=0.986) for language function.

Age, acute ischaemic lesion; EPVS, enlarged perivascular space; SVDL, lesion features of small vessel disease (WMH, lacune and EPVS); WMH, white matter hyperintensity.

AIC, acute ischaemic lesion; EPVS, enlarged perivascular space; SVDL, lesion features of small vessel disease (WMH, lacune and EPVS); WMH, white matter hyperintensity.

P<0.001 compared with models 2–6 and P=0.003 compared with model 7 for attention function.

P<0.001 compared with models 2–7 for global, memory, executive and visuospatial function; P<0.001 compared with models 2–6 and P=0.986 for language function.

We also showed that WMH, lacune, EPVS and atrophy were all involved in the impairment of global cognition and all the cognitive domains (figure 4 and online supplementary figures S3–S7). These findings generally collaborated with previous studies that reported the cognitive impact of individual SVD features in patients with stroke, including WMH,2 3 EPVS6 and atrophy.7

Regarding the lacunes (silent infarcts in our first-ever stroke cohort), researchers have found their strong association with dementia and cognitive decline in patients without stroke,23 24 and it is not surprising that lacunes have additional contribution to cognitive impairment after stroke, as the combination of a clinical stroke (AILs) with subclinical strokes (lacunes as silent infarcts) further increases risk of cognitive deficits.25

Feature selection played an important role to screen cognitive-relevant features for the SVR models and to improve the model performance.13 26 Without appropriate feature selection, we would be overwhelmed by the noises (ROI-based features that are cognitive-irrelevant) and not be able to distinguish the cognitive impact of individual SVD features and their combinations. Of the two feature selection schemes we used, TS feature selection achieved much better improvement of the model performance, and it succeeded to distinguish the cognitive impact of individual SVD features and their combinations while TO feature selection failed. In fact, their different performance resulted from the mechanisms of these two schemes. While TO feature selection discarded the features that were not highly correlated with a given behavioural score, it could potentially discard the features that might be predictive when used in combination with other features at the same time.12 In contrast, TS feature selection additionally considered the intercorrelations among the features and their multivariate relationship with the behaviour score. In this regard, TS outperformed TO feature selection in the methodology paper22 in predicting Alzheimer’s disease using brain regional volumes, which were generally correlated with each other if they presented volume loss. In our study, the situation was similar because the local burdens of different types of SVD features were generally correlated as they represented different aspects of vascular deficits, and that they generally would not present direct high correlation with MoCA scores in an acute stroke cohort.

For the first time, we visualised the important cognitive-relevant regions affected by SVD features on top of strategic AIL locations in an acute stroke cohort, in a similar manner with the

DISCUSSION

In this study, we quantified typical neuroimaging features of SVD (WMH, lacune, EPVS and atrophy) as regional volumetric measures and investigated their contribution to poststroke cognitive impairment on top of AILs, using SVR with robust feature selection method. In the models with only individual neuroimaging features of SVD, different individual SVD features presented similar contributions to impairment in global cognition or cognitive domains, and they rarely had additional cognitive impact on top of AILs (online supplementary figure S2). With partial (lesion features of SVD) or complete combination of the SVD features (lesion features of SVD and atrophy measures) considered in the models, their contribution to poststroke cognitive impairment independent of AILs became significant (table 2 and online supplementary figure S2). It indicated that different SVD features might have complementary impact on cognitive impairment in patients with acute ischaemic stroke, and considering only individual SVD features could not well capture their cognitive impact. Of note, the model with the complete combination of SVD features generally outperformed that with partial combination of SVD features (lesion features of SVD), which revealed the additional cognitive impact of atrophy and further confirmed the complementary effect of different SVD features. In the model with the complete combination of SVD features, we would be overwhelmed by the noises (ROI-based features that are cognitive-irrelevant) and not be able to distinguish the cognitive impact of individual SVD features and their combinations. Of the two feature selection schemes we used, TS feature selection achieved much better improvement of the model performance, and it succeeded to distinguish the cognitive impact of individual SVD features and their combinations while TO feature selection failed. In fact, their different performance resulted from the mechanisms of these two schemes. While TO feature selection discarded the features that were not highly correlated with a given behavioural score, it could potentially discard the features that might be predictive when used in combination with other features at the same time.12 In contrast, TS feature selection additionally considered the intercorrelations among the features and their multivariate relationship with the behaviour score. In this regard, TS outperformed TO feature selection in the methodology paper22 in predicting Alzheimer’s disease using brain regional volumes, which were generally correlated with each other if they presented volume loss. In our study, the situation was similar because the local burdens of different types of SVD features were generally correlated as they represented different aspects of vascular deficits, and that they generally would not present direct high correlation with MoCA scores in an acute stroke cohort.

For the first time, we visualised the important cognitive-relevant regions affected by SVD features on top of strategic AIL locations in an acute stroke cohort, in a similar manner with the
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In the optimised SVR model with the complete combination of WMH, lacune, EPVS and atrophy, we displayed the ROI-based SVD features that survived TS feature selection for global and domain cognitive deficits. Although the detailed locations of the SVD features were different that were involved in the contributions to MoCA deficits, they generally covered basal ganglia and the white matter around it, which have been reported as strategic locations of AIL for poststroke cognitive impairment. The distribution pattern of SVD lesion features that significantly affected global cognitive performance was also confirmed in real cases (figure 5). It should be noted that there were also many ROI-based features that have inverse association with the MoCA deficits, especially for the chronic neuroimaging features of SVD. This partly resulted from the feature selection method (TS) we used, as TS feature selection aims to screen the features that jointly have a positive impact on cognitive impairment rather than screening only the features that each have an independent positive impact on cognitive impairment like TO feature selection. Considering the co-occurrence of multiple types of SVD imaging features in some regions, the inverse association of one type of SVD feature in a specific region may also result from the less severe cognitive impact of this SVD feature than some other SVD features in this region. Based on these important ROI-based features that survived feature selection, we further performed statistical inference to highlight the most significant regional imaging features in the multivariate relationship with MoCA deficits. In this analysis, at least one type of SVD feature remained significant for the global or any of the domain cognitive deficits, independent of the regional volumes of AILs, which further confirmed the significant impact of SVD features in poststroke cognitive impairment.

Of note, the interpretations should be cautious regarding our findings about the important regions of cognitive functionings that are affected by AILs or SVD imaging features. In fact, the brain regions that are crucially involved in cognitive functionings but are
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Figure 5 Illustration of the impact of small vessel disease (SVD) features on poststroke cognition. The left columns are the sample slices of a certain subject in the individual space, and the right columns are the normalised lesion maps projected on the 1 mm MNI-152 template (Z coordinates: 0, 9, 17, 28, 40). Cases 1 and 2 indicated the additional contribution of SVD features (white matter hyperintensity (WMH), lacune and enlarged perivascular space (EPVS)) to Montreal Cognitive Assessment (MoCA) deficit on top of acute ischaemic lesion (AIL) in the left basal ganglia when lesion size and location of AIL were similar. Cases 3 and 4 indicated the additional contribution of SVD features (especially EPVS) to MoCA deficit on top of AIL in the right frontal and parietal white matter when lesion size and location of AIL were different. The norm-corrected MoCA is the MoCA score corrected for age, gender and education year among the patients and normalised to have an SD of 1. The range of the norm-corrected MoCA among the patients is −2.781 to 2.159. The sample images and lesion maps are shown in neurological convention (left side is on the left). DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery.

rarely affected by AILs (or lesion features of SVD) would not be identified as strategic regions for poststroke cognitive impairment. Due to the small sample size and insufficient lesion coverage (especially for AILs) in our study, our findings should only be interpreted as a map of strategic regions in which AILs (or lesion features of SVD) are likely to result in poststroke cognitive impairment, rather than an exhaustive map of anatomical correlates with poststroke cognitive impairment. In addition, the anatomical intercorrelations between the presence of AILs and the presence of different SVD imaging features may further limit the generalisability of our findings when applied to a cohort with a very different lesion distribution. In this regard, we cannot draw very strong conclusions about the exact strategic locations of AILs and different SVD imaging features for poststroke cognitive impairment. However, our results about the strategic AIL locations are consistent with the existing studies. Furthermore, the general strategic distribution patterns of multiple SVD imaging features identified in our study are in line with the studies where only one type of SVD imaging feature was investigated regarding its spatial relationship with poststroke cognitive impairment. Further efforts should aim to include thousands of patients with stroke, as suggested even when AILs are considered alone in a large cohort (with >400 patients), to improve the statistical power and generalisability of our findings.

There are several limitations to this study that should be taken into account. First, the sample size of the study cohort is relatively small, as we applied very strict inclusion criteria to enable volumetric measures of almost all the SVD features at the same time, and to remove potential confounders (e.g., prior stroke) that might mediate the multivariate relationship of SVD imaging features and poststroke cognition. The included patients are therefore relatively young with small strokes and the findings are likely to be of less relevance to the patients with more major stroke. Second, we delineated EPVS on T2-weighted images with a thickness (5.5 mm) that was larger than the diameter of EPVS (<3 mm), which influenced the precision of EPVS quantification. However, regarding the routine of MRI scans for patients with acute stroke, T2-weighted images with higher resolution could rarely be available. In fact, we quantified EPVS as regional volumes instead of numbers (which were more influenced by the large gap between slices), and the identified strategic cognitive-relevant regions of EPVS validated the effectiveness of the EPVS quantification in our study. Third, we did not consider CMBs in the analysis, although their associations with global cognitive dysfunction after stroke (especially in attention domain) have been reported. It is because most of the patients were not available for SWI images, and the lesion prevalence of CMBs was very poor. Even if we performed a subanalysis for the patients with SWI, rarely any regional measures of microbleeds could survive the preprocessing guided by lesion prevalence (the candidate ROI-based SVD lesion features for the SVR models should be damaged in at least five patients) due to the sporadic distribution and the small lesion size of CMBs. Finally, we did not test the prediction effect of poststroke cognition from the important ROI-based SVD features on an external validation set (a new cohort not ever used for model training) due to our small sample size. In this regard, the strategic regions of AIL or SVD identified in our study should also be explained with caution.
as aforementioned, as the results were derived from a certain lesion prevalence pattern of the multiple types of lesions.

In conclusion, this study provides a novel perspective to measure the contribution of individual neuroimaging features of SVD and their combinations (on top of AILs) to poststroke cognitive impairment, using SVR with the state-of-the-art of SVD and their combinations (on top of AILs) to poststroke measure the contribution of individual neuroimaging features as aforementioned, as the results were derived from a certain lesion prevalence pattern of the multiple types of lesions.

Funding contributed to study design.

Provenance and peer review
In the peer review process, the manuscript was critically reviewed by an independent expert in the field, ensuring its quality and relevance.

Contributors LS designed the study and experiments and contributed to the main body of the manuscript. LZ performed literature survey, image registration, statistical analysis and prepared the manuscript. FKY ensured the consistency of lesion delineation. SYW, KRTC, MFT, SCC, YCK and KCL performed lesion delineation and contributed to literature survey. KL provided clinical advice on lesion delineation. JMA, BYKL, TWHL and WCWC contributed to data collection. VCTM and IF contributed to study design. VCTM, AYLL and AW contributed to clinical evaluation.

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