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# Hippocampal and Amygdala Size in Patients with Ischemic Stroke: Does Small Vessel Disease Play a Role?

**Yang-Kun Chen[1,2,3], Vincent Mok[2], Defeng Wang[4], Lin Shi[4], Winnie CW Chu[4], Ka Sing Wong[2], GS Ungvari[5], Xiangxin Liu[1], Wai Kwong Tang[1,*]**

[1]Department of Psychiatry, the Chinese University of Hong Kong, Hong Kong SAR, China
[2]Department of Medicine and Therapeutics, the Chinese University of Hong Kong, Hong Kong SAR, China
[3]Department of Neurology, Dongguan People`s Hospital, Guangdong Province, China
[4]Department of Diagnostic Radiology and Organ Imaging, the Chinese University of Hong Kong, Hong Kong SAR, China
[5]Graylands Hospital/School of Psychiatry & Clinical Neurosciences, University of Western Australia, Perth, Australia

***Corresponding author:** Wai Kwong Tang, Department of Psychiatry, Shatin Hospital, Shatin, N.T., Hong Kong, China; Tel: +852-2636-7760, Fax: +852-2648-3394; E-mail: tangwk@cuhk.edu.hk

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## Abstract

**Objective:** The effect of Small Vessel Disease (SVD) on the size of the hippocampus and amygdala remains uncertain. We carried out an MRI volumetry study to investigate the association between the volume of White Matter Lesions (WMLs) and the size of the hippocampus and amygdala.

**Methods:** One hundred patients with ischemic stroke were recruited in this study, with their MRIs analyzed using automatic volumetry. The volumes of the hippocampus, amygdala, Cortical Gray Matter (CGM), and WMLs were measured and standardized with intracranial volume. The subjects were divided into two groups stratified by smaller and larger hippocampus, amygdala, and CGM volumes (with the median as the cut-off), respectively. The demographic, clinical, and imaging variables of the two groups were compared in term of smaller and larger volumes in these three regions.

**Results:** Multivariate logistic regression showed that WML volume (odds ratio [OR] = 1.869, p=0.004) and sex (male, OR=5.714, p=0.004) were significant predictors of a smaller hippocampus. Age (OR=1.062, p=0.033) was the only significant predictor of a smaller amygdala. Age and sex were predictive of a smaller CGM volume.

**Conclusions:** The hippocampus may be vulnerable to SVD in patients with ischemic stroke, suggesting that hippocampal atrophy may result from a mixture of ischemic and degenerative pathologies. Whether SVD plays a role in atrophy of the amygdala remains uncertain.

**Keywords:** Hippocampus; Stroke; White Matter Hyperintensities; MRI

## Introduction

Brain atrophy is common in patients with ischemic stroke, and may arise from both aging and ischemic lesions. Cortical Gray Matter (CGM) atrophy has been linked to age, hypertension, and white matter lesions (WMLs)[1]. WMLs are generally considered to be features of Small Vessel Disease (SVD), although in a previous study we found vulnerability to SVD to differ in the frontal, parietal, and temporal lobes[2]. In subjects with SVD, the common presence of memory impairment (although less prominent than executive dysfunction) and behavioral symptoms suggests that the structures involved in the limbic system may be affected by SVD.

The hippocampus is a limbic system structure that is essential for learning and declarative memory. Hippocampal atrophy is generally considered to be an early feature of Alzheimer's Disease (AD)[3], and hippocampal size has been shown to be a predictor of dementia in individuals with mild cognitive impairment[4]. Hippocampal atrophy has also been

documented in other forms of dementia, including Vascular Dementia (VaD)[5], and is predictive of dementia in patients with Subcortical Ischemic Vascular Disease (SIVD)[6] and poststroke cognitive decline[7,8]. Pathological studies have suggested that the hippocampal atrophy seen in VaD is related to ischemic pathology rather than AD pathology[9,10]. However, a study comparing the hippocampal volume of a group of stroke or Transient Ischemic Attack (TIA) subjects with or without dementia and that of a group of healthy controls found no significant difference between them[11].

The amygdala, also part of the limbic system, is a central structure in the control of emotion and affective behavior. It also plays a role in learning and memory through the influence of emotional valence on memory[12]. Neuroimaging studies have confirmed the amygdala's role in anxiety disorders, particularly posttraumatic stress disorder and social anxiety disorder[13], and in major depressive disorders[14]. In addition, significant amygdala atrophy has been detected on the MRIs of patients with early AD[15,16]. However, the amygdala has rarely been studied in stroke subjects, although Sachdev[17] found it to be smaller in stroke or TIA patients, particularly those with cognitive impairment. Both hypertension and atrial fibrillation were found to be significant predictors of amygdala volume[17].

The effect of SVD on the hippocampus and amygdala remains uncertain. As SVD is prevalent in stroke patients and the community-dwelling elderly[18], examination of its role in these two critical structures is of considerable importance. The aim of the MRI volumetric study reported herein was to compare the effect of SVD on hippocampus and amygdala volumes, with CGM as a reference. We hypothesized that the three structures would exhibit different degrees of vulnerability to SVD.

## Methods

Three hundred and thirty-seven patients with acute ischemic stroke were admitted to the Acute Stroke Unit (ASU) of the Prince of Wales Hospital in Hong Kong and underwent MRI examination between June 2006 and June 2007. Among them, 147 patients were recruited for a poststroke psychiatric interview three months after the index stroke. Patients attended the post stroke psychiatric interview if they were: (1) 18 years or older, (2) had an acute first or recurrent ischemic stroke, (3) scored 15 or higher on the Cantonese version of the Mini-Mental State Examination (MMSE) on admission, and (4) were of Chinese descent and fluent in the Cantonese dialect. Patients were excluded if they (1) had a central nervous system disease other than stroke, or (2) significant aphasia or dysarthria. Of the 147 subjects who attended interviews, we excluded 34 with large vessel infarctions and 10 with cardioembolic infarctions, and three additional subjects were excluded because their MRI quality was too poor for volumetry. The MRIs of 100 patients were thus analyzed using volumetry. Their recruitment was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong, and all participants signed a consent form.

Basic socio-demographic and clinical data, including age, sex, education (years), hypertension, diabetes mellitus, previous stroke, ischemic heart disease, and smoking history, and National Institutes of Health Stroke Scale (NIHSS) score at admission, were retrieved from the Stroke Registry at the ASU. Hypertension was defined as repeated blood pressure measures of ≥140/90mm Hg or the need for chronic antihypertensive medication; diabetes mellitus was defined as fasting blood glucose ≥7.0mmol/l, postprandial blood glucose ≥11.1mmol/l, or current treatment for the disease. The Cantonese version of the MMSE[19] and Geriatric Depression Scale (GDS) [20] were administered by a research assistant at three months post stroke.

### MRI measurements

MRI assessment was performed on each subject in a 1.5T MR scanner (Sonata, Siemens Medical, Erlangen, Germany) within seven days of the index stroke. DWI spin echo EPI (TR/TE/excitation=180/122/4, matrix=128×128, FOV=230 mm, slice thickness/gap=5 mm/1 mm, EPI factor=90, acquisition time=55 s) with three orthogonally applied gradients were used with b values of 1000 and 500. Axial gradient echo images were acquired as the second sequence with imaging parameters of TR/TE/excitation=350/30/2, flip angle=30 u, slice thickness/gap=5 mm/0.5 mm, FOV=230 mm, matrix 256×256 and acquisition time=5 min 4 s. Axial SE T1 (TR/TE/excitation=425/14/2, FOV=230 mm, slice thickness/gap=5 mm/0.5mm, matrix=256×256, acquisition time=4 min 28 s) and TSE T2 (TR/TE/excitation=2500/120/1, turbo factor =15, FOV=230mm, slice thickness/gap=5mm/0.5mm, matrix =256×256, acquisition time=1 min 39 s) images were also acquired. Finally, whole-brain volume was also measured using a T1-weighted FLASH sequence.

### Brain infarcts and cerebral microbleeds

The measurement of brain infarcts and cerebral microbleeds (CMBs) was conducted by a neurologist (YKC) experienced in neuroimaging. Old infarctions of the brain were identified on the T1-weighted images and confirmed on the corresponding T2-weighted images, with the volumetric measurements carried out on the former. The area of old infarcts in each visible slice was measured with manual outlines, and the total volume was calculated by multiplying the total area by the sum of the slice thickness and gap. The number of old infarcts was also recorded. New infarctions were not assessed, as they did not affect the correlation between SVD and brain atrophy, abnormalities that existed before the index stroke. Inter- and intra-rater agreement was good in the infarct measurement (volume of infarcts: inter-rater intra-class correlation coefficient [ICC] =0.86; intra-rater ICC=0.95; number of infarcts: inter-rater ICC=0.93; intra-rater ICC= 0.96).

CMBs were defined as small (2-10 mm) hypointense lesions on the T2-weighted gradient echo sequence, with symmetric basal ganglia calcification and flow void artifacts of the pial blood vessels excluded[21]. The presence and number of CMBs were recorded. Inter- and intra-rater agreement was good (presence of CMBs: inter-rater kappa=0.78; intra-rater kappa=0.85; number of CMBs: inter-rater ICC =0.91; intra-rater ICC=0.95).

## Volumetry of brain regions and WMLs

Volumetry analysis of subjects' brain regions was performed by two radiological engineers (DW and LSH) using an automatic image analysis program, the Insight Segmentation and Registration Toolkit (http://www.itk.org). Tissue classification was performed using the supervised k-nearest neighbors' classifier to classify the entire 3-D image. The initial classification was defined by a set of samples generated from prior tissue probability maps in the standard brain space. After sufficient quality control, the volumes of white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) were calculated as the number of voxels multiplied by the size of each voxel. WMLs were defined as high intensities observed on the T2-weighted MRI images and FLAIR images within the cerebral WM (including the periventricular and subcortical regions). A fully automated clustering-based quantitative WML detection technique was adopted to analyze the FLAIR intensities on the WM mask, which was generated from the segmentation result of T1 images co-aligned with FLAIR data [22]. The regional brain volume was evaluated specifically for the hippocampus and amygdala, and the Talairach atlas was constructed by manually delineating the deep brain structures and intracranial region of a single subject. These brain structure labels were then transformed into input data non-rigidly (using demon registration)[23]. This technique allowed the hippocampus and amygdala to be segmented, and their volumes quantified. The intracranial volume (ICV) was also calculated using this approach. Finally, the volumes of all three brain regions, GM, and WMLs were standardized by ICV (=1000×raw volume/ICV).

## Statistical analysis

The subjects were divided into two groups stratified by a smaller and larger hippocampus volume, defined as a volume at or below the median and above the median, respectively. The proportional differences between the two groups were analyzed with the $\chi 2$ test. Continuous data were compared with t-tests (normally distributed) or Mann-Whitney U tests (distorted), as appropriate. Variables with a p value <0.1 were then entered into a multivariate logistic regression to identify the significant correlates of smaller hippocampal volume. The same analysis was performed for amygdala and CGM. The level of significance in the logistic regressions was set at $p<0.05$ (two-tailed). Finally, the Pearson's correlations between WML volume (log-transformed) and hippocampus, amygdala, and CGM volume were calculated. All statistical analyses were performed using SPSS Version 16.0 (SPSS, Chicago, USA).

# Results

One hundred patients with ischemic stroke were evaluated in this study. The patients excluded from the study (237 cases) were older (73.9(12.1) vs. 69.0(8.7) years, $p<0.001$), more likely to be female (52.4% vs. 38.0%; $p=0.016$), and had a higher NIHSS score (10.2(9.5) vs. 4.5(3.1), $p < 0.001$). Eleven (11.0%) of the 100 patients included in the study had a history of prior stroke, and none had an infarct larger than 15 mm in diameter. The mean (s.d.) ICV and CGM volume were 1446.82 (173.62) and 574.12 (75.31)cm3, respectively, with a CGM/ICV ratio of 0.397. The mean (s.d.) volumes (sum of the left and right sides) of the hippocampus and amygdala were 7.36 (0.91) and 2.81 (0.42)cm3, respectively, and the mean (s.d.) WML volume was 5.44 (4.22)cm3. The patients' characteristics are presented in Table 1.

| Variables | Mean (s.d.)/n(%) |
|---|---|
| Age | 69.0±8.7 |
| Sex(male) | 62(62.0%) |
| Education years | 5.1±3.6 |
| Hypertension | 71(71.0%) |
| Diabetes | 32(32.0%) |
| Smoking history | 51(51.0%) |
| Prior stroke | 11(11.0%) |
| NIHSS on admission | 4.5±3.1 |
| MMSE | 25.8 (3.2) |
| GDS | 4.5 (3.9) |
| Intracranial volume ($cm^3$) | 1446.82 (173.62) |
| Grey matter volume ($cm^3$) | 574.12 (75.31) |
| Grey matter / intracranial volume | 0.397 |
| Hippocampal volume ($cm^3$)* | 7.36 (0.91) |
| Amygdala volume ($cm^3$)* | 2.81 (0.42) |
| White matter lesions volume ($cm^3$) | 5.44 (4.22) |

NIHSS=the National Institutes of Health Stroke Scale; BI=Barthle index; MMSE=Mini-Mental State Examination; GDS= Geriatric Depression Scale.
* The sum of left and right

**Table 1:** Demographic and clinical characteristics of the subjects (n=100).

Univariate comparisons between the smaller and larger volume groups in terms of the hippocampus, amygdala, and CGM are presented in Table 2. The subjects with smaller hippocampus, amygdala, and CGM volumes were all significantly older and had a larger WML volume ($p < 0.01$) compared with those with larger such volumes. Subjects with smaller hippocampus and CGM volumes were more likely to be male ($p < 0.05$). Those with a smaller CGM volume ($p=0.035$) also exhibited a larger old infarct volume.

In the multivariate logistic regression of smaller hippocampal volume, sex (male, odds ratio [OR] = 5.714, 95% confidence interval [C.I.]=1.754-18.519; $p=0.04$) and WML volume (OR= 1.896, 95% C.I.= 1.226-2.849, $p=0.004$) were significant predictors, whereas age was the only significant correlate of a smaller amygdala volume (OR=1.062, 95% CI=1.005-1.123; $p=0.033$) (Table 3). WML volume displayed only a predictive trend ($p=0.070$) toward a smaller amygdala, and age and sex (male) were significant predictors of a smaller CGM volume. Scatter plots of the correlations between WML volume and hippocampus, amygdala, and CGM volumes are presented in Figure 1.

# Discussion

Using MRI volumetry, we found WML volume to be a significant predictor of hippocampal size in non-demented stroke patients, independent of age, sex, smoking history, and old

| | Hippocampus | | Amygdala | | Cortical grey matter | |
|---|---|---|---|---|---|---|
| | smaller n=50 | larger n=50 | smaller n=50 | larger n=50 | smaller n=50 | larger n=50 |
| Clinical variables | | | | | | |
| age | 71.9±9.3‡ | 66.1±7.4 | 71.9±8.6‡ | 66.1±8.2 | 71.5±7.9‡ | 66.4±9.1 |
| sex(male) | 38(76.0%)‡ | 24(48.0%) | 34(68.0%) | 28(56.0%) | 37(74.0%)† | 25(50.0%) |
| education years | 5.1±3.5 | 5.2±3.6 | 5.1±3.6 | 5.1±3.5 | 5.2±3.2 | 5.0±3.9 |
| hypertension | 34(68.0%) | 37(74.0%) | 33(66.0%) | 38(76.0%) | 35(70.0%) | 36(72.0%) |
| diabetes mellitus | 17(34.0%) | 15(30.0%) | 14(28.0%) | 18(36.0%) | 17(34.0%) | 15(30.0%) |
| hyperlipidemia | 28(56.0%) | 27(54.0%) | 25(50.0%) | 30(60.0%) | 24(48.0%) | 31(62.0%) |
| ischemic heart disease | 2(4.0%) | 4(8.0%) | 2(4.0%) | 4(8.0%) | 4(8.0%) | 2(4.0%) |
| previous stroke | 7(14.0%) | 4(8.0%) | 7(14.0%) | 4(8.0%) | 6(12.0%) | 5(10.0%) |
| smoking history | 30(60.0%)* | 21(42.0%) | 28(56.0%) | 23(46.0%) | 30(60.0%)* | 21(42.0%) |
| MMSE | 25.6±3.5 | 26.0±3.1 | 25.7±3.2 | 25.9±3.3 | 25.9±3.3 | 25.7±3.2 |
| GDS | 4.2±3.9 | 4.8±3.8 | 4.3±4.1 | 4.7±3.6 | 4.3±3.9 | 4.6±3.8 |
| Imaging variables | | | | | | |
| no of old lacunes | 0.9±1.6 | 0.6±1.0 | 0.8±1.6 | 0.6±1.0 | 0.8±1.4 | 0.6±1.3 |
| no of old infarcts | 1.0±1.6 | 0.7±1.1 | 1.0±1.6 | 0.8±1.1 | 1.0±1.4 | 0.8±1.3 |
| Std. volume of old infarcts | 1.2±3.2* | 0.1±0.1 | 1.0±2.2 | 0.5±2.4 | 1.0±3.0† | 0.3±1.2 |
| Std. WMLs volume | 5.1±3.5‡ | 2.4±1.7 | 4.9±3.6‡ | 2.6±1.8 | 4.0±2.1‡ | 3.5±3.8 |
| presence of CMBs | 14(28.0%) | 12(24.0%) | 12(24.0%) | 14(28.0%) | 16(32.0%) | 10(20.0%) |
| no of CMBs | 1.3±2.9 | 0.9±3.2 | 1.2±2.9 | 0.9±3.1 | 1.3±2.8 | 0.9±3.2 |

*P<0.1; †P<0.05; ‡P<0.01. MMSE= Mini-mental Status Examination; GDS= Geriatric Depression Scale; Std. WMLs volume = Standardized white matter lesions volume; CMBs= cerebral microbleeds.

**Table 2:** Clinical and imaging characteristics between smaller and larger volume groups in term of hippocampus, amygadala and cortical grey matter.

| Variables | Smaller hippocampal | | Smaller Amygdala | | Smaller CGM volume | |
|---|---|---|---|---|---|---|
| | p | OR (95%C.I.) | p | OR (95%C.I.) | p | OR (95%C.I.) |
| Age | 0.098 | 1.06 (0.989-1.135) | 0.033 | 1.062 (1.005-1.123) | <0.001 | 1.123 (1.055-1.195) |
| Sex(male) | 0.004 | 5.714 (1.754-18.519) | -- | -- | 0.001 | 6.173 (2.105-18.182) |
| Std. WMLs volume | 0.004 | 1.869 (1.226-2.849) | 0.07 | 1.042 (0.997-1.090) | 0.317 | 0.903 (0.740-1.103) |
| Old infarcts volume | 0.139 | 2.919 (0.706-12.074) | -- | -- | 0.204 | 1.151 (0.926-1.431) |
| Smoking history | 0.574 | 0.701 (0.220-2.230) | -- | -- | 0.661 | 0.795 (0.285-2.217) |

CGM= Cortical grey matter; Std. WMLs volume = Standardized white matter lesions volume; OR=odds ratio.

**Table 3:** Logistic regression analysis of smaller volumes of the hippocampus, amygdale and cortical grey matter

infarct volume, although it did not predict CGM volume or amygdala size. This finding suggests that the hippocampus is vulnerable not only to whole brain ischemia, but also to SVD. WMLs have been shown to correlate with hippocampal atrophy in AD patients [24] and the non-demented elderly [25,26], suggesting that indicators of SVD in the brain may be associated with the atrophy of structures affected by AD pathology. In the current study, WMLs predicted a smaller hippocampal size in patients with ischemic stroke. Although this finding has not previously been reported, it is supported by a study showing patients with SIVD to have a smaller hippocampal volume [6], which suggests that hippocampal atrophy may result from a mixture of ischemic and degenerative pathologies. The hippocampus depends largely on input from the cortical association areas by means of projections running through the WM. Interruptions in these connections owing to ischemic WMLs may lead to atrophy of the hippocampus through Wallerian degeneration[27]. Thus, a mixture of AD and VaD pathologies may account for a significant proportion of the dementia seen in stroke patients.

We also assessed the relationship between amygdala size and WML volume, and found age to be the only predictor of the

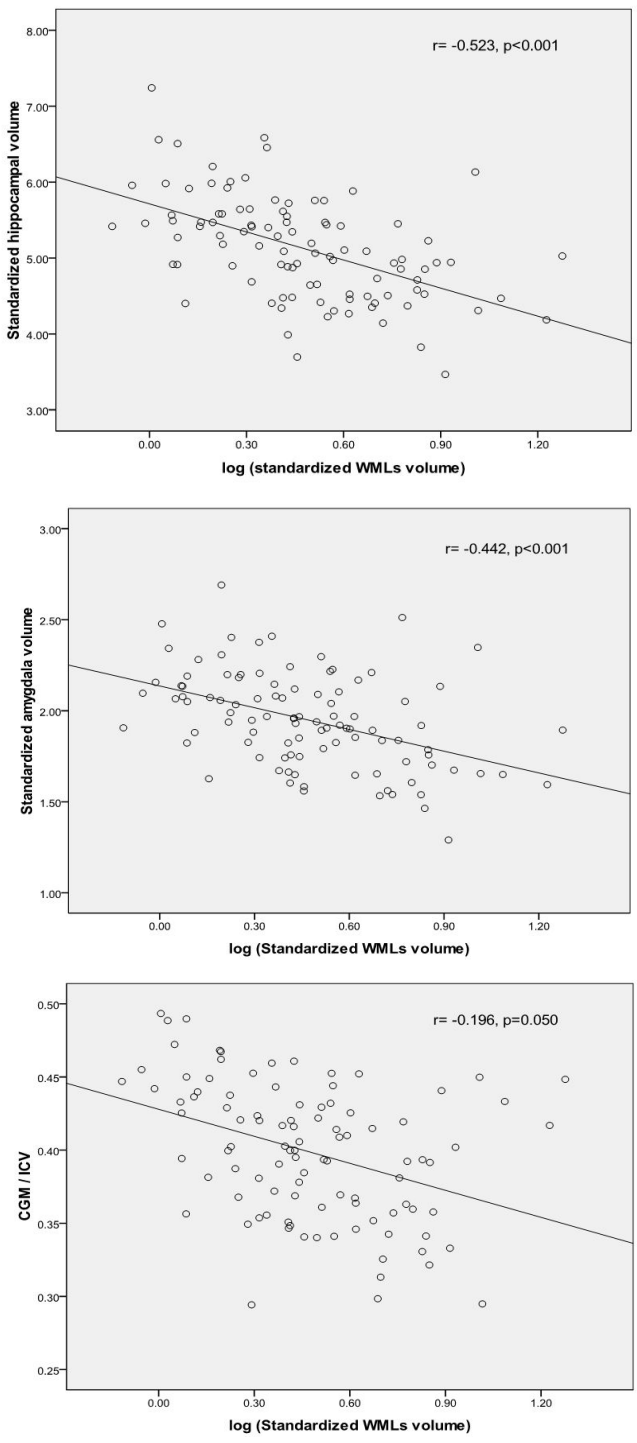


**Figure 1:** Scatter plots of WMLs volume and hippocampus, amygdale and CGM volume

former. Patients with a smaller amygdala had significantly more WMLs. After controlling for age, however, the association was no longer significant (p=0.07). Sachdev[17] reported a similar result, finding WML volume to be significantly associated with amygdala size (r=0.37, p=0.01), but no longer a significant predictor after controlling for age and other confounders in multiple linear regression. However, they did not find amygdala size to be age-dependent, and we were unable to confirm such predictors as hypertension and atrial fibrillation. The discrepancy may result from differences in the clinical characteristics of the study samples. The relationship between WMLs and amygdala size warrants further prospective studies with a larger sample size, as the amygdala is massively connected with other brain regions[28], and these connections may also be affected by WMLs.

Compared with the hippocampus, CGM appears to be primarily dependent on age and sex. WML volume did not contribute to CGM size in this study, which indicates that there may be variations in vulnerability to SVD in different regions of the brain. It can be speculated that SVD has a selective effect on specific cortical regions.

This study suffered a number of limitations. First, its cross-sectional design prevented us from establishing a causal relationship between hippocampal size and WML volume. Second, the subjects may not be representative of a consecutive stroke sample, as they had relatively milder neurologic deficits. Third, we did not divide the WMLs into different regions, and doing so may have provided more interesting information. Finally, we did not take new infarctions into account in volumetry analysis of the three brain regions, i.e., the hippocampus, amygdala, and CGM. However, infarctions involving the hippocampus and amygdala are uncommon, and no subject in our cohort had them in either region. With regard to the CGM measurement, we cannot completely exclude the effects of post-infarction cerebral edema, which led to a slight CGM overestimate. However, as previously noted, we excluded patients with large vessel infarctions and cardioembolic infarctions, which can affect the volumetry of brain regions using automatic image analysis.

In conclusion, the hippocampus may be a structure vulnerable to SVD in patients with ischemic stroke, suggesting that hippocampal atrophy may result from a mixture of ischemic and degenerative pathologies. Whether SVD plays a role in atrophy of the amygdala remains uncertain. Further prospective studies with larger samples are needed to confirm the findings reported herein. In addition, diffusion tensor imaging, which is able to detect the integrity of the WM tract[29], would be a promising technique for investigating the association between these two critical structures and SVD.

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