Stroke

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Dissociable Contributions of Thalamic-Subregions to Cognitive Impairment in Small Vessel Disease

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BACKGROUND: Structural network damage is a potentially important mechanism by which cerebral small vessel disease (SVD) can cause cognitive impairment. As a central hub of the structural network, the role of thalamus in SVD-related cognitive impairments remains unclear. We aimed to determine the associations between the structural alterations of thalamic subregions and cognitive impairments in SVD.

METHODS: In this cross-sectional study, 205 SVD participants without thalamic lacunes from the third follow-up (2020) of the prospective RUN DMC study (Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort), which was initiated in 2006, Nijmegen, were included. Cognitive functions included processing speed, executive function, and memory. Probabilistic tractography was performed from thalamus to 6 cortical regions, followed by connectivity-based thalamic segmentation to assess each thalamic subregion volume and connectivity (measured by mean diffusivity [MD] of the connecting white matter tracts) with the cortex. Least absolute shrinkage and selection operator regression analysis was conducted to identify the volumes or connectivity of the total thalamus and 6 thalamic subregions that have the strongest association with cognitive performance. Linear regression and mediation analyses were performed to test the association of least absolute shrinkage and selection operator-selected thalamic subregion volume or MD with cognitive performance, while adjusting for age and education.

RESULTS: We found that higher MD of the thalamic-motor tract was associated with worse processing speed (β=−0.27; P<0.001), higher MD of the thalamic-frontal tract was associated with worse executive function (β=−0.24; P=0.001), and memory (β=−0.28; P<0.001), respectively. The mediation analysis showed that MD of thalamocortical tracts mediated the association between corresponding thalamic subregion volumes and the cognitive performances in 3 domains.

CONCLUSIONS: Our results suggest that the structural alterations of thalamus are linked to cognitive impairment in SVD, largely depending on the damage pattern of the white matter tracts connecting specific thalamic subregions and cortical regions.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cerebral small vessel disease ■ cognitive impairments ■ cortical regions ■ thalamus ■ white matter

Cerebral small vessel disease (SVD) is the leading vascular cause of cognitive impairment and dementia.[1] Magnetic resonance imaging (MRI) features of SVD include white matter hyperintensities (WMHs), lacunes, and cerebral microbleeds (CMBs).[2] Although these MRI markers are associated with cognitive impairment, studies have shown that their dose-response relation with cognitive impairment is modest.[3] Recent studies highlighted that SVD can be considered a diffuse brain disease causing global brain dysfunction.[4]

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Nonstandard Abbreviations and Acronyms

BPF	brain parenchymal fraction
CMB	cerebral microbleed
IQR	interquartile range
MD	mean diffusivity
SVD	small vessel disease
TMT	Trail Making Test
VIF	variance of inflation factor
WM	white matter
WMH	white matter hyperintensity

Cognitive decline in SVD patients is probably a result of widespread white matter network disruption,[5] especially between the highly connected hubs. In this regard, structural alterations of the thalamus, being one of the central hubs, might be important contributors to cognitive impairment in SVD.

Several studies, especially in multiple sclerosis, have shown that thalamic atrophy and thalamocortical disconnections were associated with impairments in processing speed, executive function and memory.[6–9] In SVD, studies have reported that lacunes in the thalamus and WMH accumulation in the tracts connecting thalamus and prefrontal cortex were associated with lower processing speed and worse executive functions.[10–13] However, studies on the relation between the thalamus structural changes and cognitive impairment in SVD patients without thalamic lacunes are lacking. The thalamus is a complex structure with several subcomponents, each having different functions depending on their connections to specific cortex.[14] Studies considering the different thalamic subregions and specific cognitive domains are crucial to characterize the role of thalamus in SVD.

Therefore, we hypothesized that the volumes and connectivity of each thalamic subregion may display specific associations with different cognitive domains in SVD patients without thalamic lacunes. In addition, considering the white matter damage is the predominant feature of SVD, we further hypothesized that the effect of thalamic atrophy on cognitive performances is mediated by the disrupted thalamic connectivity. To test our hypothesis, we assessed the volume and connectivity of thalamic subregions and their association with each cognitive domain (processing speed, executive function, and memory) in 205 SVD participants without thalamic lacunes.

METHODS

The data of this study are available from the corresponding author, depending on reasonable request from qualified investigators after permission of appropriate regulatory bodies.

Study Population

The study is a part of RUN DMC (Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort). We included participants meeting the following criteria: (1) age between 50 and 85 years, (2) WMHs or lacunes on MRI, (3) cognitive and motor symptoms that could be attributed to SVD. Baseline data were collected in 2006, with 3 follow-up assessments in 2011, 2015, and 2020. At baseline 503 participants were included, however, due to the change of MRI scanners, we only used the data from the third follow-up assessment to perform cross-sectional analyses in the present study. Out of 230 participants in the third follow-up, 25 participants were excluded due to thalamic lacunes (n=21), uncompleted MRI scans (n=2), low-quality of MRI images (n=1), and image processing failure (n=1), resulting in 205 participants included in the present study (Figure S1). The study was approved by the Medical Review Ethics Committee Region Arnhem-Nijmegen, and written informed consent was obtained from all participants. Detailed information of the RUN DMC has been described in previous studies.[15,16]

Neuropsychological Assessment

All participants underwent a detailed cognitive assessment in 3 domains: processing speed, executive function, and memory. Processing speed was assessed using the Trail Making Test-A and Symbol-Digit Modalities Test; executive function was assessed using the Trail Making Test-A, Trail Making Test-B, and Verbal Fluency test; memory was assessed using the forward and backward of Digit Span test, the immediate and delayed recall of the Rey Auditory Verbal Learning Test and the immediate and delayed recall of Rey-Osterrieth Complex Figure Test. The raw test scores were scaled as *Z*-scores. Next, compound scores were computed per cognitive domain (Table S1).

MRI Acquisition

Participants were scanned on a 3T MRI scanner (MAGNETOM Prisma, Siemens) with a 32-channel head coil, including the following sequences: 3D T1-weighted Magnetization Prepared 2 Rapid Acquisition Gradient Echoes, multi-shell diffusion weighted imaging, 3D fluid-attenuated inversion recovery images, susceptibility-weighted images. Details were provided in the Supplemental Material and previous study.[17]

MRI Markers for SVD

MRI markers of SVD (WMH, lacunes, CMBs) and brain atrophy were assessed according to the Standards for Reporting Vascular changes on neuroimaging.[2] WMH was segmented using a previously validated convolutional network algorithm.[16] WMH volumes were calculate and normalized for the intracranial volume. A visual rating of WMH was performed according to the modified Fazekas scale (mild: 0–1 score, moderate: 2 score, severe: 3 score).[16,18] Gray matter, white matter (WM), and cerebrospinal fluid volumes were calculated based on T1-weighted images. Due to the similar intensities between WMH and gray matter, WMH mask was employed to correct the gray matter/WM segmentation. The total brain volume was calculated as the sum of gray matter and WM volumes. Brain parenchymal fraction (BPF) was determined as the ratio of total brain volume and intracranial volume and employed to

assess brain atrophy. Last, a simple total SVD score consisting of WMH, lacunes, and CMBs was generated to assess the total SVD burden.[19] Since our cohort lacked information regarding perivascular spaces and the perivascular space counts showed no association with cognitive impairment in previous study,[20] we did not include the perivascular spaces in the simple SVD score. In this simple SVD score without perivascular spaces, one point was respectively assigned for WMH Fazekas score ≥2, lacunes number ≥3, the presence of CMBs.[19]

Segmentation of Thalamus and Cortical Regions

The thalamus was segmented using Freesurfer 7.2.0.[21] The thalamus segmentation was manually corrected. The total thalamic volume was calculated. The 6 cortical regions connected to the thalamus were derived based on the Harvard-Oxford cortical atlas and included: frontal cortex, motor cortex, temporal cortex, sensory cortex, posterior parietal cortex, and occipital cortex (Table S2). Afterward, the thalamus and 6 cortical regions in the native T1-space were registered to diffusion space through the linear and nonlinear transforms using FMRIB Software Library (v6.0.1; Figure 1). All segmented and transformed images were visually inspected. Details in the Supplemental Material.

Diffusion MRI Processing

Diffusion MRI data were preprocessed for denoising, removal of Gibbs artifacts, correction of head motion, eddy currents-induced distortion, susceptibility-induced distortion, and intensity bias.[22–26] Next, multifiber directions within each voxel were estimated using the ball-and-two-sticks model. Fractional anisotropy and mean diffusivity (MD) images for each participant were obtained from the processed images (only b=0 and b=1000 s/mm^2).

Probabilistic Tractography and Connectivity-Based Thalamic Segmentation

Probabilistic tractography were performed from thalamus to 6 cortical regions, respectively. The resulting connectivity maps were normalized by dividing the total streamlines number and then thresholded at 0.01 to generate tract masks.[27] The mean MD values of each tract mask were calculated to measure the white matter integrity of the tract as a proxy of thalamocortical structural connectivity of each thalamic subregion. The 6 tracts were also combined to form a total thalamocortical tract mask and applied to extract mean MD values as the total thalamocortical structural connectivity. The MD index was preferentially selected over the fractional anisotropy index because MD is less affected by the crossing fibers and has showed stronger association with cognitive impairments in SVD.[3,28] The total thalamus was segmented into 6 subregions based on the thalamic-cortical connectivity pattern.[14] The resulting segmentations were thresholded at 50 samples (5000 samples were initiated per seed voxel) and used to calculate each thalamic subregion volume (Figure 1). Details in the Supplemental Material.

Statistical Analysis

Continuous variables were described by mean (SD) or median (interquartile ranges [IQRs]), according to their distribution. When non-normally distributed data were used as response variables, we used the "bestnormalized" package in R to perform the normalizing transformations. The volumes of total thalamus and thalamic subregions were normalized by dividing intracranial volume.

To assess the effects of total SVD burden and each SVD marker on the total thalamic volume and thalamocortical connectivity, we divided all participants into 2 groups according to the total SVD score (splitting at score 1), normalized WMH volumes (splitting at the median volume), lacunes (splitting by the presence), CMBs (splitting by the presence), and BPF (splitting at the median value), respectively. Two-sample *t*-tests were used to examine the group differences of normalized total thalamic volume and thalamocortical MD. Next, using the Kendall rank correlation, we assessed the intercorrelation among normalized total thalamic volumes, thalamocortical MD and each SVD MRI marker and BPF across the total sample.

Then, we examined the associations between the total thalamic volume and thalamocortical connectivity, and cognitive function. Linear regression analyses were performed between each cognitive domain (ie, processing speed, executive function, and memory) and normalized total thalamic volumes and thalamocortical MD. Different adjustments were included in the models: model 1: age and education; model 2: model 1 plus SVD MRI markers (ie, normalized WMH volumes, the presence of lacunes, the presence of CMBs), and BPF; model 3: model 2 plus vascular risk factors (ie, hypertension, diabetes, hypercholesterolemia, and smoking). These regression models were checked for multicollinearity using the variance of inflation factors (VIFs).

In addition, to test if the relation between thalamic volume and each cognitive domain was mediated by the disrupted thalamic connectivity, we performed mediation analyses while controlling for age and education. We also tested an alternative mediation model in which thalamic volume mediated the relationship between thalamic connectivity and cognition.

To identify the volumes or connectivity of total thalamus and 6 thalamic subregions that have the strongest association with each cognitive domain, we employed the least absolute shrinkage and selection operator regression analysis while adjusting for age and education. Next, the association of least absolute shrinkage and selection operator-selected volumes/connectivity of the thalamic subregion with each cognitive domain were tested in 3 linear regression models (model 1, model 2, and model 3). This was then followed by mediation analyses as described above to assess the relation between volume and connectivity of each thalamic subregion, and each cognitive domain.

All statistical analyses were completed using R software (version 4.1.0). The significant level was set at a 2-tailed *P* value <0.05. Details in the Supplemental Material.

There were no missing data for outcome variables in this study, except for 1% to 6% (Table S3) of participants, who were missing one or more cognitive tests. The missing data were imputed by the mean of the available participants to fully utilize available information.

RESULTS

A total of 205 SVD participants without thalamic lacunes were included in this study. The median age was 73.0 (IQRs, 69.0–79.0) years and 89 (43.4%) were women. The raw and normalized volume of WMH were 3.8 (IQRs,

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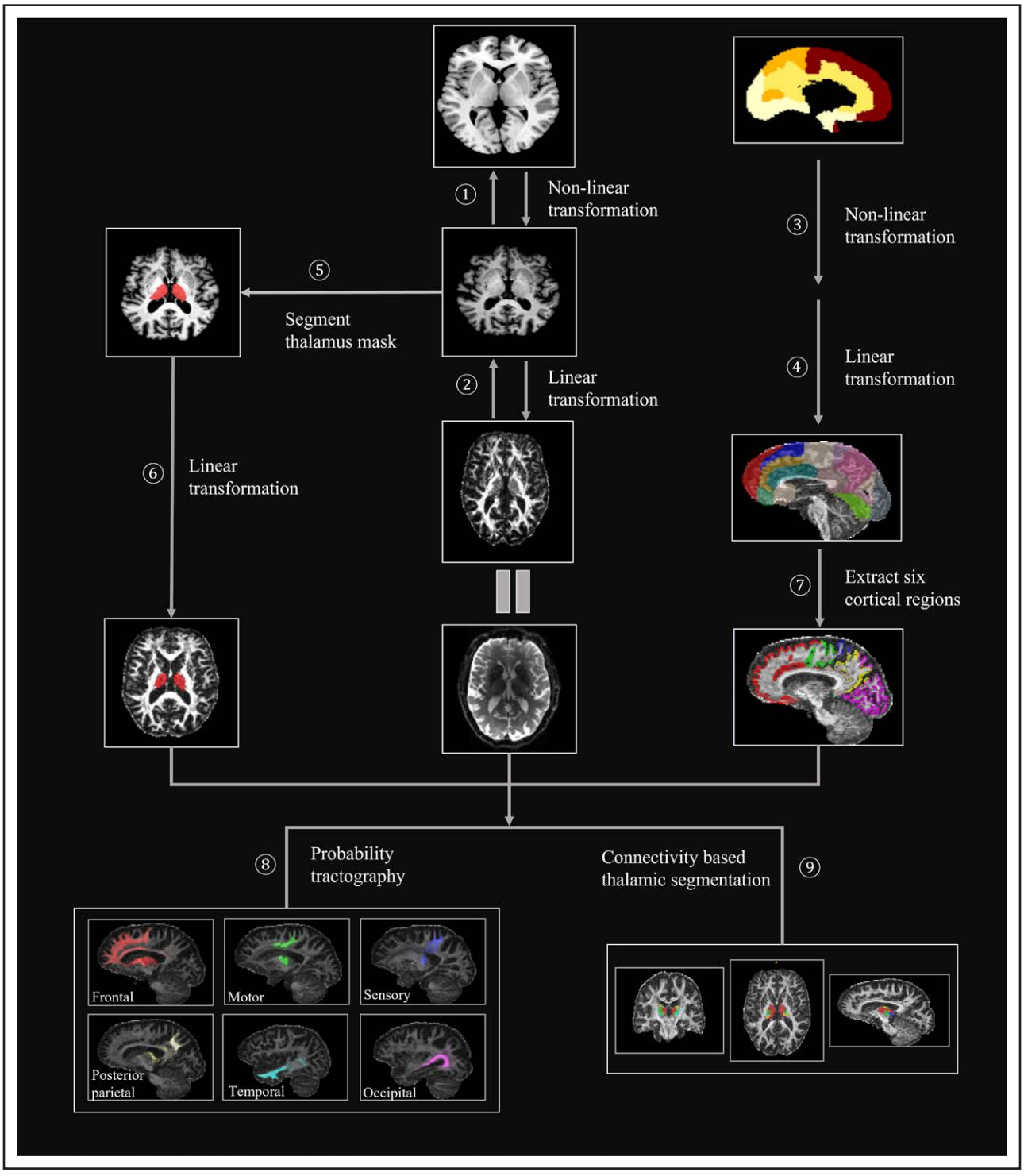

Figure 1. Flowchart of the performed neuroimaginsg analysis; ①, nonlinear transformation between individual's T1-weighted image and MNI152 standard space; ②, linear transformation between individual's T1-weighted image and individual's diffusion tensor imaging space; ③ and ④, the transformation matrix from step ① and ② were used to transform Harvard-Oxford cortical atlas from standard MNI space to individual's diffusion tensor imaging space; ⑤, extract thalamic mask in individual's T1-weighted images; ⑥, the transformation matrix from step ② were used to transform thalamic mask from individual's T1 space to individual's diffusion-weighted imaging space; ⑦, 6 cortical regions were extracted in Harvard-Oxford cortical atlas in individual's diffusion-weighted imaging space: frontal cortex (red), motor cortex (green), sensory cortex (blue), posterior parietal cortex (yellow), temporal cortex (light blue), and occipital cortex (pink); ⑧, probability tractography from thalamus to 6 cortical regions; ⑨, thalamic segmentation based on the thalamic-cortex connectivity pattern.

1.8–8.7) mL and 0.3 (IQRs, 0.1%–0.6%), respectively. Forty-four (21.5%) participants had lacunes, 70 (34.1%) participants had CMBs, and the median simple SVD score was 1.0 (IQRs, 0.0–1.0) (Table 1; Table S3). The raw and normalized mean volume of total thalamus was 11.1 (SD, 1.1) mL and 0.8 (SD, 0.1)%, respectively. The mean MD value of the thalamocortical tract was 7.9 (SD, 0.7)×10^{-4} mm^2/s. The mean volumes of the 6 thalamic-subregions and mean MD values of the 6 tracts connecting thalamic-subregions and cortical regions were shown in Table S4.

Thalamic Volume, Thalamocortical MD, and SVD Burden

The group with high SVD burden, which assessed by the presence of lacunes or lower BPF showed smaller normalized thalamic volume than the group with low SVD burden. The group with high SVD burden assessed by the simple SVD score ≥1, higher normalized WMH volumes, the presence of lacune, the presence of CMBs or lower BPF showed higher thalamocortical MD than the group with lower SVD burden (*P*-uncorrected <0.05; Figure 2A; Figure S2). Higher normalized thalamic volume was significantly correlated with higher BPF (*r*=0.42), lower thalamocortical MD (*r*=–0.18), and the presence of lacunes (*r*=–0.12). Higher thalamocortical MD was significantly associated with lower BPF (*r*=–0.36), higher normalized WMH volumes (*r*=0.52), the presence of lacunes (*r*=0.32), and the presence of CMBs (*r*=0.18; Figure 2B).

Table 1. Demographic, Clinical, and Imaging Characteristics of the Study Cohort

	N=205
Demographic	
Age, y, median (IQR)	73.0 (69.0 to 79.0)
Female, n (%)	89 (43.4%)
Education, y, median (IQR)	10.0 (10.0 to 15.0)
Vascular risk factors	
Hypertension, n (%)	133 (64.9%)
Diabetes, n (%)	28 (13.7%)
Hypercholesterolemia, n (%)	108 (52.7%)
Smoking history, n (%)	130 (63.4%)
Cognition function	
MMSE score, median (IQRs)	29.0 (27.0 to 30.0)
Processing speed, *Z* score, median (IQRs)	0.3 (–0.8 to 1.2)
Executive function, *Z* score, median (IQRs)	0.1 (–0.3 to 0.4)
Memory, *Z* score, mean (SD)	0.0 (1.9)
SVD markers	
Raw WMH volumes, mL; median (IQRs)	3.8 (1.8 to 8.7)
Normalized WMH volumes, %, median (IQRs)	0.3 (0.1 to 0.6)
WMH Fazekas score ≥2, n (%)	89 (43.4%)
Lacunes, n (%)	44 (21.5%)
CMBs, n (%)	70 (34.1%)
Simple SVD score, median (IQRs)	1.0 (0.0 to 1.0)
Brain volume, mL; mean (SD)	1085.5 (115.8)

CMB indicates cerebral microbleed; IQR, interquartile range; SVD, small vessel disease; and WMH, white matter hyperintensity.

Thalamic Volume, Thalamocortical MD, and Cognitive Function

Normalized thalamic volume was not related to processing speed, executive function, and memory (Table 2). Higher thalamocortical MD was related to worse cognitive functions while adjusting for age and education (model 1): processing speed (β=–0.248; *P*<0.001), executive function (β=–0.235; *P*=0.001), and memory (β=–0.301; *P*<0.001). The relation between thalamocortical MD and memory remained significant after additionally adjusted SVD MRI markers, BPF and vascular risk factors (model 2: β=–0.332; *P*=0.003; model 3: β=–0.346; *P*=0.002) but not for processing speed and executive function (Table 2).

The mediation *P* showed that thalamocortical MD mediated the relations between normalized thalamic volume and 3 cognitive domains (Figure 3), while normalized thalamic volume showed no mediating effects in the relations between the thalamocortical MD and each cognitive domain (Figure S3).

Thalamic Subregions and Cognitive Domain

Least absolute shrinkage and selection operator regression analyses showed that MD of the thalamic-motor tract was associated with processing speed, and MD of the thalamic-frontal tract with executive function and memory (Table S5). Linear regression models confirmed the results showing that higher MD of the thalamic-motor tract was associated with lower processing speed (model 1: β=–0.27; *P*<0.001), higher MD of the thalamic-frontal tract was associated with worse executive function (model 1: β=–0.24; *P*=0.001) and memory (model 1: β=–0.28; *P*<0.001), respectively (Figure 4). Further adjustments for SVD MRI markers, BPF (model 2), and vascular risk factors (model 3) had little effects on these relations (Tables S6 and S7).

Mediation analyses showed that MD of the thalamic-motor tract mediated the relation between the normalized volume of thalamic-motor subregion and processing speed; MD of the thalamic-frontal tract mediated the relations between the normalized volume of thalamic-frontal subregion and executive function and memory, respectively; while the normalized volume of these thalamic subregions showed no mediating effect in the relations between MD of the thalamic-cortex tracts and each cognitive domain (Figure 4).

DISCUSSION

In the present study, we found that (1) thalamic volume and thalamocortical MD (as a proxy for thalamocortical connectivity) were correlated with SVD burden; (2)

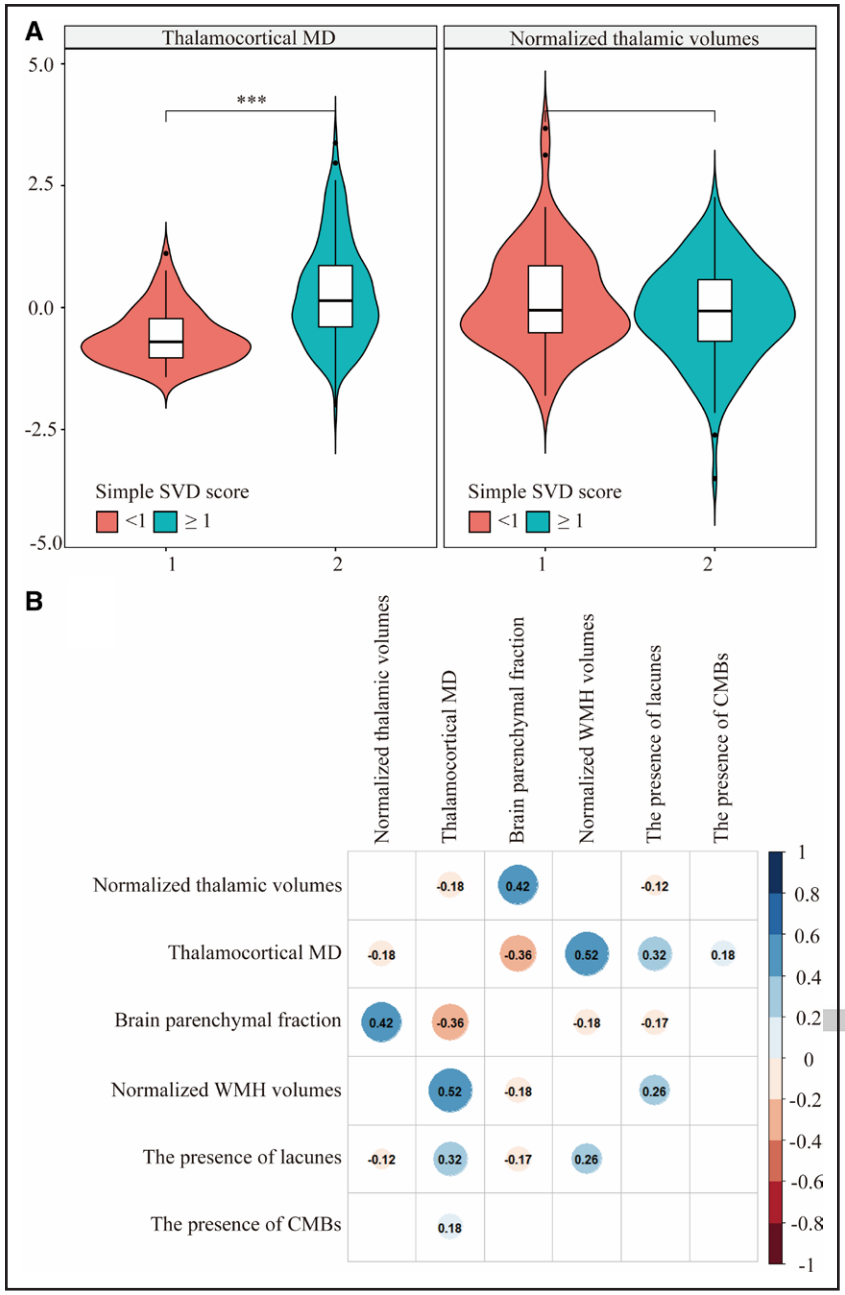

Figure 2. Group differences based on the simple small vessel disease (SVD) score and intercorrelation among total thalamic volume, thalamocortical mean diffusivity (MD), magnetic resonance imaging markers of SVD, and brain atrophy. **A**, Intergroup differences of total thalamic volume, thalamocortical MD based on the simple SVD score; (**B**) intercorrelation among total thalamic volume, thalamocortical MD, magnetic resonance imaging markers of SVD, and brain atrophy. **P*-uncorrected <0.05; ***P*-uncorrected <0.01, ****P*-uncorrected <0.001. All numbers in **B** represent correlation coefficients (*P*-uncorrected <0.05), blank means no statistically significant results (*P*-uncorrected >0.05). CMB indicates cerebral microbleed; and WMH, white matter hyperintensity.

thalamocortical connectivity was associated with processing speed, executive function, and memory, while the total thalamic volume was not; and (3) damage to specific white matter tracts projecting from the thalamus to the cortex was related to specific cognitive deficit. Executive function and memory were related to thalamic-frontal connections and processing speed to thalamic-motor connections. Our results suggest that the thalamic volume and the thalamocortical connections are affected in SVD patients without thalamic lacunes and that these thalamic alterations are linked to the cognitive impairment, largely depending on the damage patterns of the white matter tracts connecting thalamic subregions and cortical regions.

The number of studies on the role of thalamus in SVD is limited.[2] Here, we found that the participants with high SVD burden showed lower thalamic volume and thalamocortical connections compared to those with low SVD burden. This is consistent with previous findings showing that SVD patients with more severe WMH have smaller thalamic volumes.[29] This association could be explained by the shrinkage of thalamic dendrites and cell bodies due to the loss of synaptic input,[30] and the accumulation of microvascular damage in the thalamus.[31]

We found that total thalamocortical connectivity was associated with the 3 cognitive domains (ie, processing speed, executive function, and memory). This finding is in line with previous studies showing the associations

Table 2. Association Between Cognitive Function, Total Thalamic Volume, and Thalamocortical MD

	Processing speed		Executive function		Memory	
	β	*P* value	β	*P* value	β	*P* value
Normalized thalamic volume						
Model 1	−0.049	0.446	0.062	0.350	0.121	0.067
Model 2	−0.064	0.383	−0.024	0.760	0.114	0.114
Model 3	−0.039	0.605	−0.018	0.817	0.129	0.099
Thalamocortical MD						
Model 1	−0.248	<0.001*	−0.235	0.001*	−0.301	<0.001*
Model 2	−0.156	0.145	−0.170	0.129	−0.332	0.003*
Model 3	−0.159	0.142	−0.216	0.054	−0.346	0.002*

Adjustments in model 1: age and education; in model 2: model 1 plus MRI markers of SVD (ie, normalized WMH volumes, the presence of lacunes, the presence of CMBs) and BPF; in model 3: model 2 plus vascular risk factors (ie, hypertension, diabetes, hypercholesterolemia, and smoking). BPF indicates brain parenchymal fraction; CMB, cerebral microbleed; MD, mean diffusivity; SVD, small vessel disease; and WMH, white matter hyperintensity.

between WMH accumulation in the thalamic-cortical tract and processing speed.[12,13] However, in our study, the total thalamic volume showed no association with cognition. In the mediation analyses, thalamocortical connectivity mediated the relations between thalamic volumes and the performances in 3 cognitive domains, while thalamic volume showed no mediating effects in the relations between thalamocortical connectivity and cognition. These findings suggest that the effects of thalamic structural abnormalities on cognitive impairments in SVD are mainly linked to the damage of the cortical-subcortical pathways, which may disrupt the complex network underpinning cognitive functions.[32]

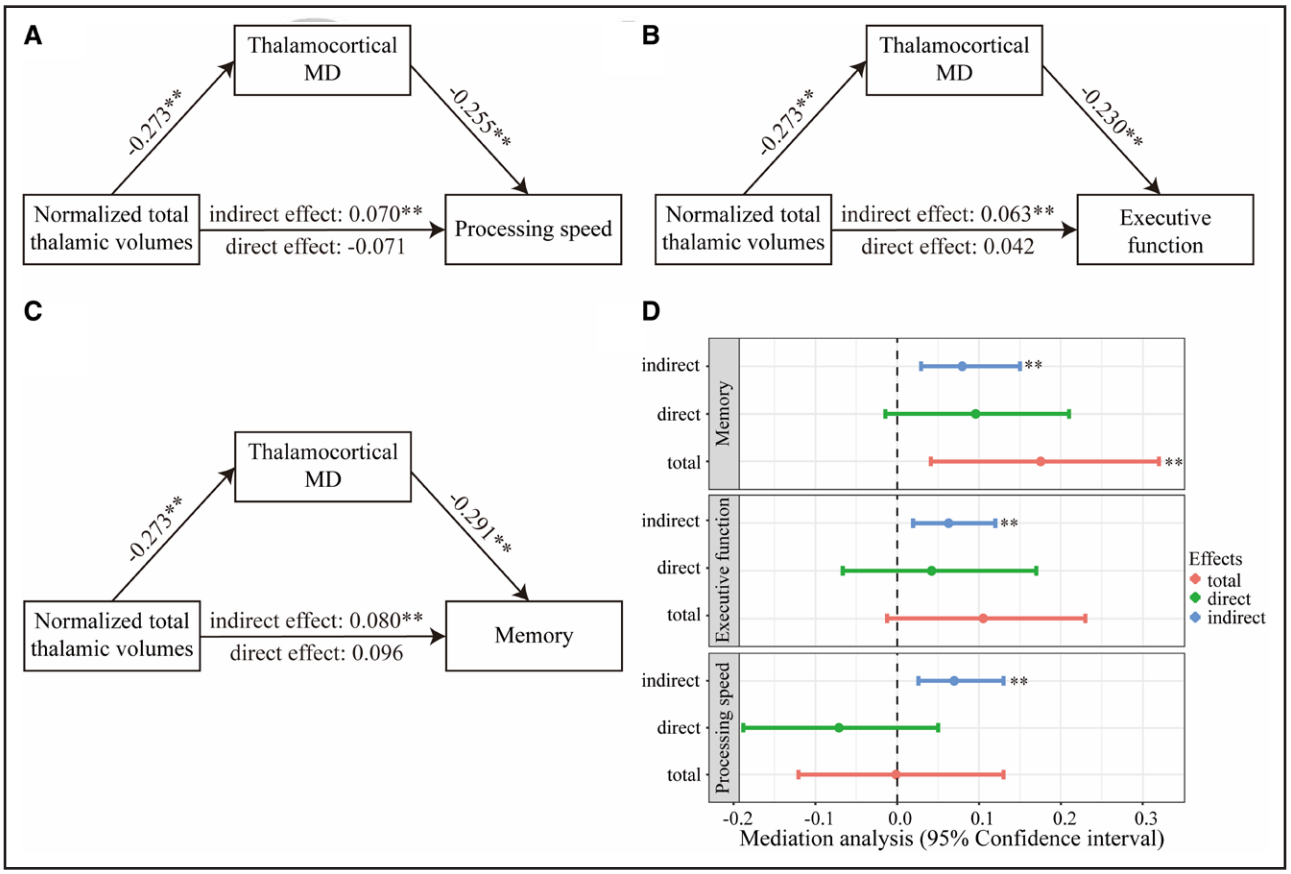

Figure 3. Mediation analysis of thalamocortical connectivity in the relation between thalamic volume and cognitive function. *P<0.05; **P<0.01. **A**–**C**, The path diagrams of 3 mediation models; (**D**) the 95% CIs for indirect effects, direct effects, and total effects using bootstrapping (n=1000 samples).

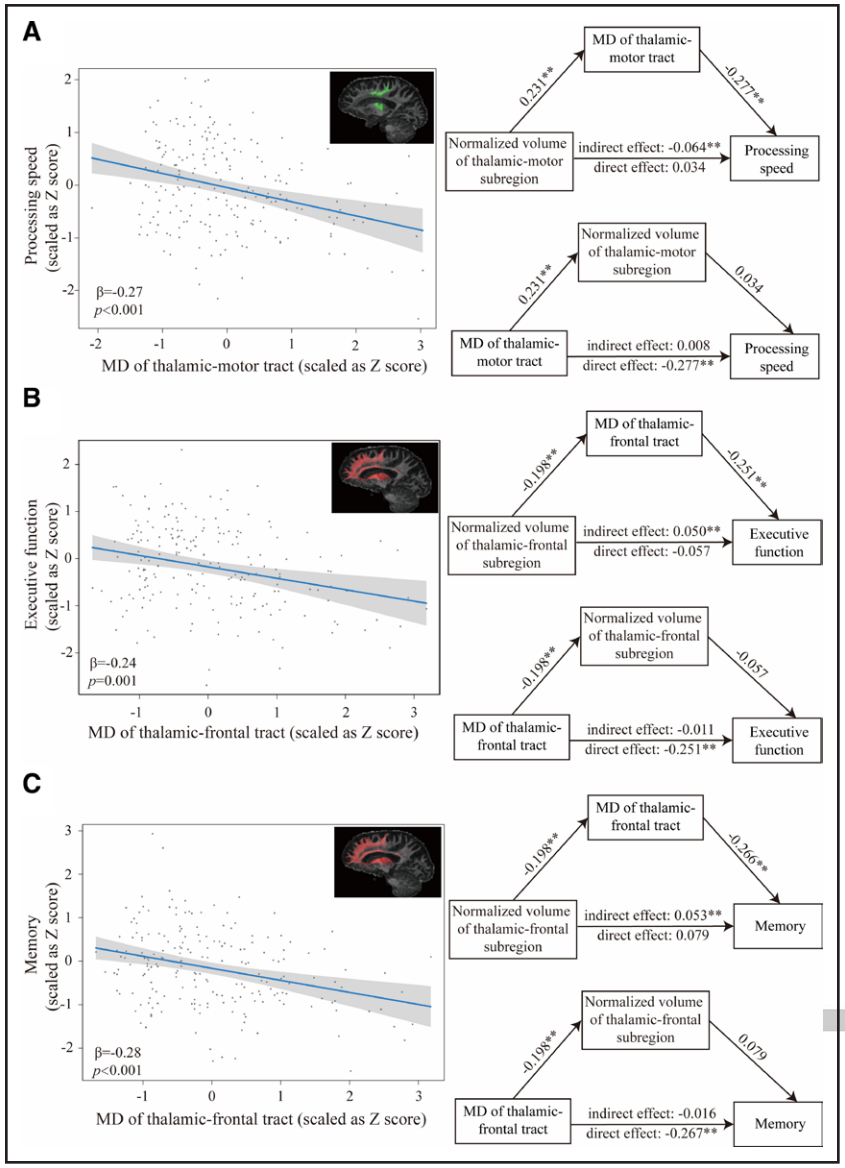

Figure 4. The relation between least absolute shrinkage and selection operator (LASSO) selected thalamic subregion and 3 cognitive domains. **A**, **Left**, linear regression between mean diffusivity (MD) of thalamic-motor tract and processing speed while adjusting for age and education and the visualization of thalamic-motor tract (green); right, the mediation analysis of corresponding thalamic-subregion volumes, connectivity, and processing speed. **B**, **Left**, linear regression between MD of thalamic-frontal tract and executive function while adjusting for age and education and the visualization of thalamic- frontal tract (red); **Right**, the mediation analysis of corresponding thalamic-subregion volumes, connectivity, and executive function; **C**, **Left**, linear regression between MD of thalamic-frontal tract and memory while adjusting for age and education and the visualization of thalamic-frontal tract (red); **Right**, the mediation analysis of corresponding thalamic-subregion volumes, connectivity, and memory. **P*<0.05; ***P*<0.01.

Next, we used least absolute shrinkage and selection operator and linear regression analyses to identify the volumes and connectivity of thalamic subregions that have the strongest association with each cognitive domain. The connectivity of thalamic-motor tract was related to processing speed in our study, which has been reported in multiple sclerosis.[33] This could be explained by the effects of motor impairment on the processing speed task. However, the lack of association between the connectivity of thalamic-frontal tract and processing speed is inconsistent with previous studies.[12,34] This inconsistency may originate from the differences in the approach used to assess processing speed. Most previous studies employed Trail Making Test-B, instead of Symbol-Digit Modalities Test, to assess processing speed, which may account for the different results. In addition, we found that the thalamic-frontal tract was related to executive function. This is in line with a study showing that WMH located in the anterior thalamic radiations played a strategic role in executive dysfunction in sporadic SVD.[35] Also, we found that the connectivity of thalamic-frontal tract was related to memory. Few studies have examined the role of thalamus in SVD-related memory impairment. The memory impairment following thalamic infarcts has been reported in several cases.[36,37] Studies in Alzheimer disease and multiple sclerosis also proved a role of the thalamus in memory decline.[9,38] The prefrontal cortex and its connections with the mediodorsal thalamus are thought to be crucial for working memory,[39] which is the major impaired part in SVD-related memory damage.[40]

Besides, we found that higher volume of the thalamic-motor subregion was associated with higher MD of the thalamic-motor tract, which was not expected. This finding should be treated with some caution, as we would expect to see facilitation of water diffusion (eg, higher MD) in case of neurodegeneration. Several possible explanations may account for this. First, compensatory enlargement of gray matter in thalamic-motor subregion

may occur in case of disrupted thalamic-motor connections. Second, there may be small registration errors in the image transformations, which will be more obvious in the small-size segmentation (ie, thalamic-motor subregion). Considering this possibility, we combined the subregions connected to the frontal and motor cortex to calculate the volume and then tested the association between volume and connectivity in thalamic-frontal/motor subregion. This result, however, showed that the volume of thalamic-frontal/motor subregion was not associated with the MD of thalamic-frontal/motor tracts (Figure S4).

The main strengths of this study are the quantitative measurement of thalamic volume, thalamocortical connectivity and the connectivity-based thalamic segmentations. Considering the higher rate of crossing fibers within one voxel in subcortical regions, we used the probabilistic tractography, which can better resolve this problem. In addition, using Magnetization Prepared 2 Rapid Acquisition Gradient Echoes sequence and manually adjusting the thalamic mask provided the accuracy of thalamic segmentation. The comprehensive cognitive data in this cohort provided us to better understand the role of thalamus in SVD-related cognitive impairment.

Several limitations should be acknowledged. First, we only used the data of third follow-up of RUN DMC study. RUN DMC study is a long-term longitudinal study. However, due to the change of MRI scanners, we could not use previous MRI data for longitudinal analysis. We were therefore only able to conduct cross-sectional analyses, which limited us to make causal inferences. Future longitudinal studies are needed to test the direction of the observed associations. Second, our cohort does not include the age-matched healthy controls. This limitation makes it difficult to distinguish the observed effects from those of normal aging. To minimize this confounding effect, we adjusted for age and education in the regression models, and we performed group-analyses based on the severity of SVD burden. Third, we have missing data (1%–6%) in some cognitive tests for which we have performed imputation. Also, about a half of the original RUN DMC participants did not participate in the third follow-up due to various reasons, who have more severe SVD burden and are more cognitively impaired. These missing data may cause bias, however, if any, this may lead to an underestimation of the effects of the thalamic volume and connectivity measures. Fourth, we excluded patients with thalamic lacunes. This enabled us to discard the influence of thalamic lacunes and therefore provide solid proof that the thalamic structural alterations, independent of the thalamic lacunes, are related to cognitive impairment, but may also lead to an underestimation of the findings.

In conclusion, our study showed that thalamic volume and thalamocortical connections are lower in participants with high SVD burden compared with participants with low SVD burden and, more importantly, we demonstrated that damage to specific white matter tracts projecting from the thalamus to the cortex are linked to specific cognitive deficit. Our study highlights the importance of studying specific white matter tracts originating from the thalamus in relation to cognitive function and provides additional evidence of the role of the damage of the cortical-subcortical pathways in processing speed, executive function, and memory deficits in SVD patients independent of thalamic lacunes. Further studies preferably with multiple timepoints are necessary to further elucidate the pathophysiology of thalamus alterations and their exact role of cognitive impairments in SVD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Supplemental Methods
Tables S3–S7
Figures S2–S4

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