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Superficial white matter microstructure affects processing speed in cerebral small vessel disease

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Abstract

White matter hyperintensities (WMH) are a typical feature of cerebral small vessel disease (CSVD), which contributes to about 50% of dementias worldwide. Microstructural alterations in deep white matter (DWM) have been widely examined in CSVD. However, little is known about abnormalities in superficial white matter (SWM) and their relevance for processing speed, the main cognitive deficit in CSVD. In 141 CSVD patients, processing speed was assessed using Trail Making Test Part A. White matter abnormalities were assessed by WMH burden (volume on T2-FLAIR) and diffusion MRI measures. SWM imaging measures had a large contribution to processing speed, despite a relatively low SWM WMH burden. Across all imaging measures, SWM free water (FW) had the strongest association with processing speed, followed by SWM mean diffusivity (MD). SWM FW was the only marker to significantly increase between two subgroups with the lowest WMH burdens. When comparing two subgroups with the highest WMH burdens, the involvement of WMH in the SWM was accompanied by significant differences in processing speed and white matter microstructure. Mediation analysis revealed that SWM FW fully mediated the association between WMH volume and processing speed, while no mediation effect of MD or DWM FW was observed. Overall, results suggest that the SWM has an important contribution to processing speed, while SWM FW is a sensitive imaging marker associated with cognition in CSVD. This study extends the current understanding of CSVD-related dysfunction and suggests that the SWM, as an understudied region, can be a potential target for monitoring pathophysiological processes.

KEYWORDS

cerebral small vessel disease, diffusion magnetic resonance imaging, extracellular free water, processing speed, superficial white matter, white matter hyperintensities

Shuyue Wang and Fan Zhang contributed equally to the study and are co-first authors of this paper.

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1 | INTRODUCTION

Cerebral small vessel disease (CSVD) is the most important vascular contributor to cognitive decline and the cause of nearly 50% of dementia worldwide (Wardlaw et al., 2019). CSVD-related cognitive impairment is often characterized as deficits in executive function and speed of information processing (Duering et al., 2014; Hamilton, Backhouse, et al., 2021; Hamilton, Cox, et al., 2021). White matter hyperintensities (WMH), the most prevalent feature of CSVD on magnetic resonance imaging (MRI) (Vergoossen et al., 2021), appear as hyperintense patches in the white matter on T2-weighted (T2w) and T2-FLAIR images (Fazekas et al., 1987; Wardlaw et al., 2013). Widespread microstructural changes in the white matter are a key manifestation in CSVD and have been consistently associated with cognitive deficits (Cremers et al., 2016; Hamilton, Backhouse, et al., 2021; Hamilton, Cox, et al., 2021; Vergoossen et al., 2021).

The most commonly used method to study the white matter microstructure is diffusion MRI (dMRI) (Basser et al., 1994), which measures diffusion properties of water molecules in vivo and in a non-invasive way. dMRI studies have found widespread white matter microstructural alterations and significant associations with cognition in CSVD (Table 1). Many studies have focused on conventional diffusion measures, where a decrease in the anisotropy of water diffusion (fractional anisotropy [FA]) and an increase in the extent of water diffusion (mean diffusivity [MD]) are generally considered indicative of damaged white matter microstructure (Baykara et al., 2016; van Norden et al., 2012). Using these conventional diffusion measures, previous studies have suggested that potential pathological processes

TABLE 1 Summary of dMRI studies that explore associations between white matter microstructure and cognitive performance (processing speed or executive function) in cerebral small vessel disease

CSVD dMRI study methodology	
Conventional diffusion measures (e.g., FA, MD)	Baykara et al. (2016), Chen et al. (2019), Du et al. (2021), Huang et al. (2020), Lawrence et al. (2013), Liu et al. (2020), Moonen et al. (2017), Nitkunan et al. (2008), O'Sullivan et al. (2005), O'Sullivan, Markus, et al. (2004), O'Sullivan, Morris, et al. (2004), Quinque et al. (2012), Schmidt et al. (2010), Tozer et al. (2018), Tuladhar (2015), Vergoossen et al. (2021), Wei et al. (2019), and Zeestraten et al. (2017)
Advanced diffusion measures (e.g., FW, NODDI, DKI, IVIM)	Duering et al. (2018), Gesierich et al. (2020), Konieczny et al. (2021), Zhang, Wong, van de Haar, et al. (2017), and our current study
Structural network measures	Boot et al. (2020), Du et al. (2021), Gesierich et al. (2020), Heinen et al. (2018), Lawrence et al. (2014), Liu et al. (2020), Reijmer et al. (2016), Tuladhar et al. (2016, 2017), van Leijsen et al. (2019)
Study findings: White matter regions related to cognitive performance in CSVD	
Global findings	
In the entire white matter or entire white matter skeleton	Baykara et al. (2016), Du et al. (2021), Konieczny et al. (2021), Moonen et al. (2017), Nitkunan et al. (2008), Wei et al. (2019), and Zeestraten et al. (2017)
Localized findings	
Within WMH	O'Sullivan, Markus, et al. (2004), O'Sullivan, Morris, et al. (2004), and Schmidt et al. (2010)
In normal-appearing white matter	Jokinen et al. (2013), Lawrence et al. (2013, 2014), O'Sullivan, Markus, et al. (2004), O'Sullivan, Morris, et al. (2004), Schmidt et al. (2010), Tozer et al. (2018), Tuladhar (2015), and Zhang, Wong, Uiterwijk, et al. (2017)
In particular fiber tracts or deep white matter regions	O'Sullivan et al. (2005), Quinque et al. (2012), Tuladhar (2015), Chen et al. (2019), Huang et al. (2020), Liu et al. (2020), Vergoossen et al. (2021), and our current study
Superficial white matter regions	Our current study
Network findings	
Global network	Du et al. (2021), Gesierich et al. (2020), Heinen et al. (2018), Lawrence et al. (2014), van Leijsen et al. (2019), Tuladhar et al. (2016)
Local (sub)network	Boot et al. (2020), Du et al. (2021), Lawrence et al. (2014), Liu et al. (2020), and Reijmer et al. (2016)
Peripheral white matter connections	van Leijsen et al. (2019)

Note: For each study, the methodology used to evaluate white matter microstructure and the locations of findings are reported.
Abbreviations: CSVD, cerebral small vessel disease; DKI, diffusion kurtosis imaging; FA, fractional anisotropy; FW, free water; IVIM, intravoxel incoherent motion imaging; MD, mean diffusivity; NODDI, neurite orientation dispersion and density imaging; TBSS, tract-based spatial statistics; WMH, white matter hyperintensity.

underlying WMH may be related to demyelination and reduced axonal density (Muñoz Maniega et al., 2017; Wardlaw et al., 2015). Furthermore, studies indicate that an increase of extracellular free-water (FW) (Pasternak et al., 2009), measured using dMRI, may be an early pathological process in CSVD (Duering et al., 2018; Humphreys et al., 2021; Wardlaw et al., 2019) and is a sensitive marker of cognitive performance in aging (Maillard et al., 2019). While associations between white matter microstructure and cognitive performance are found throughout the white matter in CSVD (Table 1), thus far the superficial white matter microstructure has not been specifically investigated.

The superficial white matter (SWM) is the thin layer of WM underneath the cortex. It includes short-range association connections (u-fibers) that connect adjacent gyri, and this region is also traversed by terminations of long-range tracts (Liu et al., 2016). Autopsy and MRI studies have reported that the short association fibers make up 57%–67% of all white matter fibers, and their estimated volume is much larger than the volume of the long-range projections (Liu et al., 2016; Schüz & Braitenberg, 2002; Vergani et al., 2014). The SWM plays an important role in processing speed and other functions such as working memory and visuomotor attention (Nazeri et al., 2013, 2015; Phillips et al., 2018). In recent years, dMRI studies have suggested the importance of the SWM in aging (Cox et al., 2016; Nazeri et al., 2015; Phillips et al., 2013), Alzheimer's disease (Bigham et al., 2020; Contarino et al., 2021; Phillips et al., 2016), and neuropsychiatric disease (D'Albis et al., 2017; d'Albis et al., 2018). In CSVD, dMRI tractography studies of the entire brain as a network have implicated the SWM (Table 1): two studies found reduced SWM connectivity (in short peripheral tracts; Tuladhar et al., 2017; and some superficial white matter u-fibers; Lawrence et al., 2014), while one study found that a decline in peripheral connection strength was associated with cognition (van Leijsen et al., 2019). However, despite the well-known decline in processing speed (Hamilton, Backhouse, et al., 2021; Hamilton, Cox, et al., 2021; Peng, Geriatric Neurology Group, Chinese Society of Geriatrics and Clinical Practice Guideline for Cognitive Impairment of Cerebral Small Vessel Disease Writing Group, 2019; Prins et al., 2005), which is associated with widespread white matter changes in CSVD (Konieczny et al., 2021; Vergoossen et al., 2021), the abnormalities in the SWM are poorly understood.

Therefore, we believe that studying white matter abnormalities in the SWM may shed light on the mechanisms underlying cognitive dysfunction in CSVD. Several lines of evidence suggest that the SWM may be affected. First, the effect of WMH is widespread. A recent review summarizes postmortem histological and MR imaging studies of CSVD, which have reported extensive white matter lesions with SWM involvement (Humphreys et al., 2021). In addition, progression of WMH is known to spread from deeper to more superficial white matter regions during the course of CSVD (Lambert et al., 2016; van Leijsen et al., 2018).

In this study, our primary goal is to employ imaging markers to investigate the impact of the SWM on processing speed, the main cognitive deficit in CSVD (Hamilton, Backhouse, et al., 2021; Hamilton, Cox, et al., 2021; Vergoossen et al., 2021). To this end, we perform several analyses to study the role of white matter microstructure in CSVD and its relationship to cognitive performance. First, we assess the effect of WMH burden on the SWM and DWM microstructure. Second, we assess the contribution of abnormalities in the SWM and the DWM toward processing speed. Third, we assess differences of SWM and DWM microstructure and processing speed between groups with different levels of WMH burden. Fourth, we perform mediation analysis to further determine whether SWM and DWM microstructure could mediate the association between WMH burden and processing speed.

2 | MATERIALS AND METHODS

2.1 | Subjects

This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine. Written informed consent was obtained from each subject.

We recruited patients admitted to the Department of Neurology, the Second Affiliated Hospital, Zhejiang University School of Medicine, who received brain MRI and were diagnosed with CSVD between December 2015 and December 2020. CSVD was defined as the presence of lacunes and/or WMH on MRI according to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) (Wardlaw, Smith, Biessels, et al., 2013). More details about the cohort can be found in previously published studies (Huang, Zhang, Jiaerken, Wang, Hong, et al., 2021; Wang et al., 2020). Visual assessment of WMH presence (Fazekas scores) was performed by two neuroradiologists (R.Z. and H.H.) according to the STRIVE standards (Wardlaw, Smith, Biessels, et al., 2013). Inclusion criteria were as follows: (a) visible WMH on T2-FLAIR; (b) age > 40; (c) normal vision and hearing. Exclusion criteria were as follows: (a) WM lesions of nonvascular origin (immunological-demyelinating, metabolic, toxic, infectious, etc.); (b) severe head motion during MRI scanning; (c) history of stroke, multiple sclerosis, Alzheimer's disease, Parkinson's disease, or head trauma; (d) image quality issues. Starting from a total of 365 subjects who had MRI data, we first excluded 63 subjects with possible other brain disorders under the exclusion criteria. Of the remaining 302, there were 145 subjects with the processing speed assessment. Four subjects were further excluded due to insufficient image quality. Finally, a total of 141 subjects were included in the present study. Demographic information and vascular risk factors, including age, sex, diabetes, hypertension, hyperlipidemia, heart disease, smoking, and drinking histories, are summarized in Table 2.

2.2 | Neuropsychological assessments

Each subject's neuropsychological condition was assessed by the mini-mental state examination (MMSE) and Montreal Cognitive Assessment (MoCA). Processing speed was evaluated with the Trail Making Test Part A (TMT-A) (Bowie & Harvey, 2006). The completion time for TMT-A was evaluated by scoring the time in seconds, and the

TABLE 2 Characteristics of subjects ($N = 141$)

Age, mean (SD)	67.48 (±9.34)
Males	84 (59.57%)
Diabetes	20 (14.18%)
Hypertension	94 (66.67%)
Hyperlipidemia	17 (12.06%)
History of heart disease	12 (8.51%)
History of smoking	37 (26.24%)
History of drinking	28 (19.86%)
Education, mean (SD)	7.86 (±4.42)
MMSE, mean (SD)	26.71 (±3.11)
MoCA, mean (SD)	22.82 (±4.90)
TMT-A completion time, median (IQR)	79.80 (63.07–121.76)
WMH-total volume, mean (SD)	19.16 (16.68)
WMH-SWM volume, mean (SD)	4.26 (5.50)
WMH-DWM volume, mean (SD)	9.65 (8.83)
ICV, median (IQR)	1438.58 (1345.32–1528.37)

Abbreviations: DWM, deep white matter; ICV, intracranial volume (cm^3); IQR, interquartile range; MMSE, Mini-mental State Examination; MoCA, Montreal Cognitive Assessment; SWM, superficial white matter; SD, standard deviation; TMT-A, Trail Making Test Part A (second); WMH-total volume, white matter hyperintensity volume (cm^3).

maximum was limited to 180 s according to the administration procedure and interpretive guideline (Bowie & Harvey, 2006; Thompson et al., 1999). Then, the TMT-A completion time was log-transformed to reduce the skewness (Sudre et al., 2019; Yano et al., 2017).

2.3 | MRI data acquisition and preprocessing

All subjects underwent multimodal MRI on a 3.0 T MR scanner (MR750; GE Healthcare, Milwaukee, USA) equipped with an eight-channel brain phased array coil. The scanned modalities for each subject included T1-weighted imaging (T1w), T2-FLAIR imaging and dMRI. T1-weighted imaging was acquired using spoiled gradient echo sequences with TR/TE = 7.3/3.0 ms, TI = 450 ms, flip angle = 8°, slice thickness = 1 mm, matrix = 250 × 250, field of view (FOV) = 250 mm × 250 mm. The sequence parameters of T2-FLAIR were TR/TE = 8400/152 ms, TI = 2100 ms, flip angle = 90°, slice thickness = 4 mm without slice gap, matrix size = 256 × 256, FOV = 240 mm × 240 mm. dMRI was acquired with a single shot, diffusion-weighted spin echo echo-planar imaging sequence. Thirty non-collinear directions were acquired with a *b*-value of 1000 s/mm^2. Five additional volumes were acquired without diffusion weighting (*b*-value = 0 s/mm^2). Other parameters of dMRI were as follows: TR/TE = 8000/80.8 ms, flip angle = 90°, slice thickness = 2 mm without slice gap, isotropic voxel size = 2 × 2 × 2 mm^3, matrix size = 128 × 128, FOV = 256 mm × 256 mm. All dMRI data were preprocessed using MRtrix3 (http://www.mrtrix.org) (Tournier et al., 2019), including signal denoising, Gibbs ringing removal, eddy-current and head motion correction, and bias field correction.

2.4 | Image processing and estimation of imaging markers

Figure 1 gives an overview of the image processing steps for the computation of imaging markers of interest. We computed two types of imaging markers in the SWM, including (1) WMH volume to assess the burden of WMH and (2) diffusion measures to assess microstructural abnormalities. For comparison, we also computed the imaging markers in the DWM. The major image processing steps included (a) regional white matter segmentation, (b) WMH segmentation, and (c) diffusion measure computation, as described below in detail.

2.4.1 | White matter segmentation

The entire white matter was segmented into deep white matter (DWM) and superficial white matter (SWM). This was done by registering DWM and SWM atlases defined in the standard MNI space to each subject's diffusion MRI space. Specifically, DWM was defined as the white matter region comprising the JHU-ICBM-DTI-81 white matter atlas (Mori et al., 2005). SWM was defined according to the atlas created in the study by Nazeri et al. (2015), which was shown to be successful in defining the SWM across the adult lifespan (18–86 years of age). This SWM atlas was created to be used together with the JHU DWM atlas, thus it excludes the DWM regions. It has been successfully applied to study the relationship between diffusion measures in SWM and cognitive performance in aging (Nazeri et al., 2015). The standard-space DWM and SWM masks were aligned to each subject's diffusion space via a nonlinear registration between the standard-space T1w template and the subject's b0 image using the Normalization toolbox in Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm). All registered masks were visually inspected in each subject.

We also further segmented the SWM according to the brain lobes to investigate lobar SWM abnormalities. Brain lobes were defined using a standard atlas (Mayo Clinic Adult Lifespan Template, MCALT, www.nitrc.org/projects/mcalt) (Schwarz et al., 2018). A total of eight lobar regions were studied, including the bilateral frontal, occipital, temporal, and parietal lobes. The standard-space lobar masks were aligned to each subject's diffusion space via a registration between the standard-space T1w template and the subject's b0 image. Image registration was conducted using SPM. After visual inspection for registered lobar masks, lobar SWM regions were defined according to the subject's lobar masks and the SWM mask.

2.4.2 | WMH segmentation and WMH volume computation

White matter hyper-intense (WMH) regions were segmented using the T2-FLAIR images. The lesion prediction algorithm (LPA) of the Lesion Segmentation Toolbox (http://www.applied-statistics.de/lst.html) in SPM was used to automatically segment WMH lesions in the T2-FLAIR image of each subject under study. Previous studies (Cedres et al., 2020; Vanderbecq et al., 2020; Wang et al., 2020; Zhang

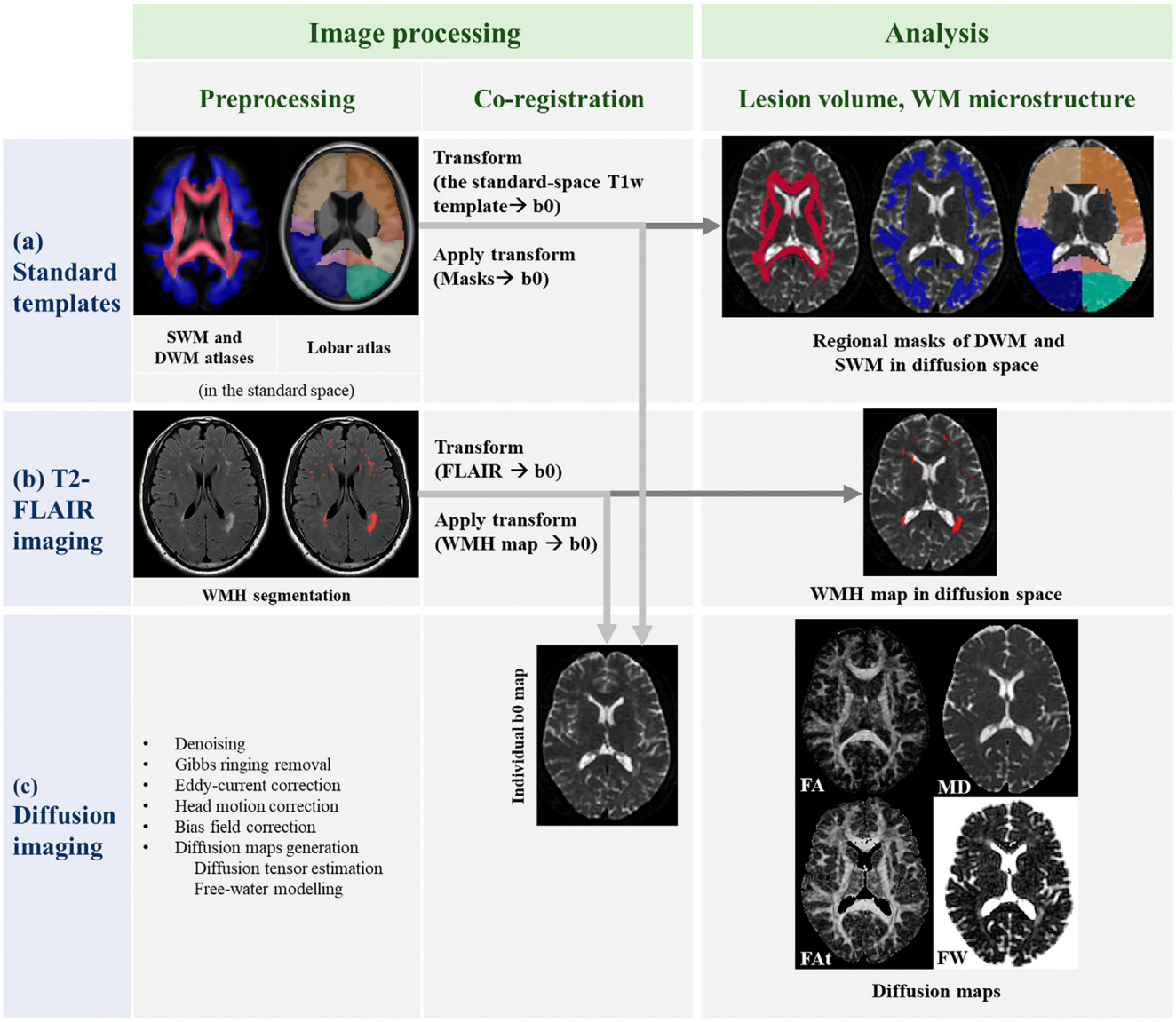

FIGURE 1 Schematic illustration of the multimodal image processing and analysis pipeline. CSF, cerebrospinal fluid; DWM, deep white matter; SWM, superficial white matter; WMH, white matter hyperintensity

et al., 2021) have shown successful applications of the LPA algorithm in WMH segmentation using T2-FLAIR. Each segmented result was visually inspected and manually corrected by expert readers (S.W. and H.H.) in ITK-SNAP (http://www.itksnap.org) according to the STRIVE (Wardlaw, Smith, Biessels, et al., 2013). One neuroradiologist (R.Z.) reviewed all the corrected lesion maps. Then, the segmented WMH lesion map was registered to the individual diffusion space by performing a registration between the T2-FLAIR image and the first b0 diffusion image using SPM.

To assess the burden of disease, we measured the volume of WMH (the larger the volume, the heavier the burden of disease). The volume of the segmented WMH region (referred to as the WMH-total volume), as well as the volume of WMH in the SWM and DWM regions (referred to as the WMH-SWM and WMH-DWM volumes, respectively), were calculated for each subject using the *fslstats* tool in the FMRIB Software Library (FSL, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki).

2.4.3 | Diffusion measure computation

Four diffusion measures of interest were computed from the DWI data, including: conventional fractional anisotropy (FA) and mean diffusivity (MD) (Pierpaoli & Basser, 1996), and extracellular free-water (FW) and FW-corrected intracellular tissue FA (FAt) (Pasternak et al., 2009). FA and MD were computed using the conventional diffusion tensor model (Pierpaoli & Basser, 1996). This was done by fitting the preprocessed DWI data to a diffusion tensor image using a linear regression in the FSL *dtifit* tool. FA and MD images were then computed from the estimated diffusion tensor in

each voxel using the FSL *fslmaths* tool. FW and FAt were computed using free-water (FW) imaging (Pasternak et al., 2009). FW imaging is a model-based approach that applies a regularization framework to fit a two-compartment model to diffusion-weighted images. The two compartments estimated in the FW model are (1) an isotropic FW compartment, which quantifies the contribution of extracellular FW to the signal, and (2) a tissue compartment, modeled using a single diffusion tensor, which is corrected for FW. FW provides a putative index of unrestricted extracellular water content. FAt is calculated from the FW-corrected intracellular tissue compartment and more closely reflects changes in myelination and axonal membrane health than the conventional DTI metric FA (Pasternak et al., 2009, 2018). FW modeling was performed using a nonlinear regularized minimization process implemented in MATLAB as previously described (Di Biase et al., 2020; Pasternak et al., 2009). The fractional volume of the FW compartment was estimated to produce a FW map. Then FAt map was calculated from the FW-corrected tensor using FSL.

For each subject, the mean diffusion measures (FA, MD, FW, and FAt) were calculated by averaging their values across all voxels within the identified DWM and SWM regions using the FSL *fslstats* tool. In the same way, the mean of each diffusion measure was calculated for each lobar SWM region.

2.4.4 | Estimation of intracranial volume

T1-weighted images were processed using the default "Recon-all" pipeline in the FreeSurfer software (version 6.0, http://surfer.nmr.mgh.harvard.edu/fswiki). The intracranial volume (ICV) of each subject was calculated and extracted as a covariate.

2.5 | Statistical analyses

We performed four analyses to investigate abnormalities in SWM and their effects on processing speed in the CSVD patients under study. We also performed the corresponding analyses in the DWM for comparison. All statistical analyses were performed in SPSS (version 23.0), R (version 4.0.5), and MATLAB (version R2019b). Covariates included age, sex, and ICV, with the addition of years of education for analyses involving processing speed. These covariates are frequently employed in studies of CSVD due to their relevance to cognitive impairment (Hamilton, Backhouse, et al., 2021; Hamilton, Cox, et al., 2021). The statistical significance level was set at $\alpha < .05$, with correction for multiple comparisons using the false discovery rate (FDR) method (the Benjamini and Hochberg procedure) (Benjamini & Hochberg, 1995).

2.5.1 | Effect of WMH burden on white matter microstructure

First, we investigated the microstructure of the SWM (and DWM) under increasing WMH burden. WMH-total volume was set as the independent variable, and we investigated its associations with the four diffusion measures in the SWM and DWM using simple linear regression analyses. There were eight comparisons in this experiment, and results were corrected for multiple comparisons using FDR. The standardized β coefficient of each variable was reported for each regression model.

2.5.2 | Association of each imaging marker with processing speed

Second, we investigated whether imaging markers in the SWM (and DWM) were associated with processing speed in CSVD. Imaging markers included WMH-total, WMH-SWM, and WMH-DWM volumes, as well as the four diffusion measures in the SWM and DWM. To do so, we first assessed the association between each imaging marker and processing speed using linear regression analyses. In each regression model, the imaging marker was set as the independent variable, and the TMT-A completion time was set as the dependent variable. All results were corrected for the number of comparisons (three comparisons for the WMH volume analyses and eight comparisons for the diffusion measure analyses) using the FDR method.

In addition to the association analysis for each image marker independently, we also performed a multivariable regression analysis to assess the explanatory power of all imaging markers together. Considering the presence of potential collinearity among these imaging markers (see Figure S1 for intercorrelations between all variables using Pearson correlation analysis), we performed random forest regression with conditional inference trees (Strobl et al., 2007), an advanced machine learning based technique to estimate importance of each variable while accounting for all other variables. Compared to the commonly used multiple linear regression, conditional forest regression offers increased robustness against multicollinearity (Hothorn et al., 2006) and is unbiased when subsampling, avoiding potentially biased estimates in the presence of high interactions among different types of predictions (such as categorical and continuous variables) (Strobl et al., 2007). Conditional forest regression has been successfully applied in dMRI studies to assess the contributions of multiple imaging markers (Finsterwalder et al., 2020; Konieczny et al., 2021; Nemy et al., 2020; Pechtel et al., 2014), including dealing with cognition in association with multiple microstructural measures (Konieczny et al., 2021) and diffusion measures of different tracts (Nemy et al., 2020), as well as associations among multiple imaging markers (Finsterwalder et al., 2020). The R package "party" (version 1.3–7) was applied (Strobl et al., 2007). We calculated 1501 conditional inference trees with unbiased variable selection (unbiased resampling scheme) (Hothorn et al., 2006) using standard parameters (five randomly preselected variables for each split). From these trees, we next calculated a conditional permutation importance from 400 repetitions (Duering et al., 2018). The resulting importance of each variable was calculated as the increase in the mean squared error (MSE) of the predicted response variable (i.e., TMT-A completion time in our study), where an important variable would produce a large increase in MSE (Strobl et al., 2007). To further investigate the

robustness of the results from the conditional forest regression, we also performed a standard random forest regression that did not include conditional inference trees. Results are reported in Supplementary Methods S1, where we showed that the overall importance ranking of variables corresponded across both analyses (Figure S3 in Supplementary and Figure 2 in Section 3).

To assess the effect of lobar SWM microstructure on processing speed, we examined associations between processing speed and the four diffusion measures in each of eight lobar SWM regions using simple linear regression analyses. The standardized β coefficient of each variable was estimated for each regression model. Results were corrected for 32 (4*8) comparisons using the FDR method.

2.5.3 | Abnormalities of SWM and DWM in different levels of disease

Third, we assessed microstructures in the SWM (and DWM) and cognitive performance in different levels of disease. The subject sample was split into four subgroups with different levels of WMH burden, according to the quartiles of WMH-total volume (the first quartile and the fourth quartile of patients had the lowest and the highest WMH burden, respectively). We compared demographic and clinical characteristics among the four subgroups using the chi-square test, one-way analysis of variance (ANOVA) or Kruskal–Wallis test, depending on the type and distribution of dependent variables. Imaging markers in the SWM and the DWM were calculated in each subgroup. The processing speed measures and diffusion measures were compared among the four subgroups using ANOVA and Tukey's post hoc tests. We identified the disease levels in which processing speed and imaging markers had significant between-group differences.

2.5.4 | Mediation effect of SWM between WMH burden and processing speed

Fourth, we tested whether the relationship between WMH volume and processing speed was mediated by FW, that is, the diffusion measure with the highest association with WMH volume (according to the analysis in Section 2.5.1) and the highest association with processing speed (according to the analysis in Section 2.5.2). To do so, we performed mediation analysis (Avram et al., 2019; Brown et al., 2019; Liu et al., 2016) using PROCESS version 4.0 (https://processmacro.org/index.html) in SPSS (Hayes, 2017). FW of SWM and DWM were introduced as two mediators between total WMH volume and processing speed. We examined whether the total effect (c) of WMH volume on processing speed is due to a significant direct effect (c') or instead is explained by indirect effects (ab) through mediator variables. Effect sizes were calculated as standardized regression coefficients (Brown et al., 2019; Hayes, 2017; Su et al., 2018). A bootstrapping approach with 5000 iterations was used to estimate confidence intervals (CI) (Brown et al., 2019; Gazes et al., 2016). Effects with bootstrapped

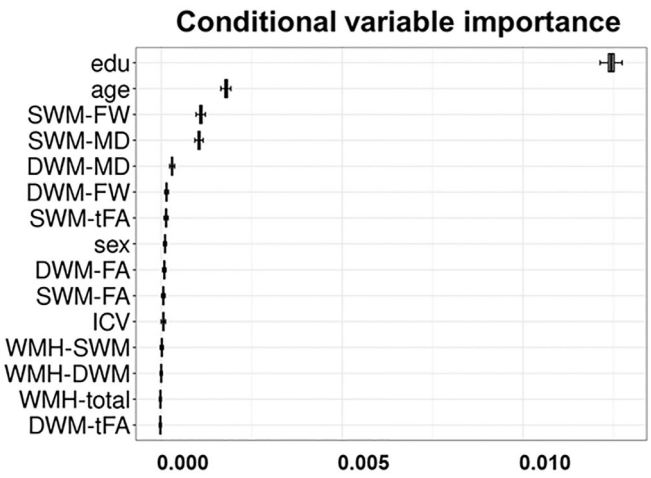

FIGURE 2 Conditional importance of each variable with regard to processing speed (dependent variable) computed using the conditional random forest regression. The plot shows the conditional variable importance with mean values and 95% confidence intervals calculated from 400 repetitions. Variable importance is calculated as the increase in the MSE of the predicted response variable, whereas a larger value indicates a higher variable importance. DWM, deep white matter; FA, fractional anisotropy; FAt, FW-corrected FA; FW, free-water; MD, mean diffusivity; MSE, mean squared error; SWM, superficial white matter; WMH, white matter hyperintensity

95% CI not including zero were considered significant (Avram et al., 2019; Brown et al., 2019; Gazes et al., 2016).

3 | RESULTS

A total of 141 subjects with CSVD were included in the final analysis. Demographic, clinical, and MRI characteristics of subjects are provided in Table 2.

3.1 | FW has the strongest association with WMH burden

To characterize the microstructure in the SWM (and in the DWM) under increasing WM burden, associations of WMH volume with diffusion measures in the SWM and the DWM were analyzed. FA, MD, and FW in SWM and DWM were significantly associated with WMH-total volume (all $p_{FDR} < .001$; Table 3). As the overall disease burden increased (as measured by the WMH-total volume), FA decreased, while MD and FW increased. The FW measure had the strongest association with WMH-total volume in both SWM and DWM. The disease burden (as measured by WMH-total volume) had the largest effect on diffusion measures in the DWM (where a larger lesion volume was observed; see WMH-DWM in Table 1). This effect is indicated by the larger magnitude of the standardized β coefficients of the diffusion measures in the DWM, in comparison to those of the SWM. The free-water-corrected diffusion measure FAt showed no significant association with the WMH-total volume.

3.2 | Association of each imaging marker with processing speed

Next, we investigated if imaging markers in the SWM (and DWM) were associated with processing speed in CSVD.

3.2.1 | Imaging markers in SWM and DWM are associated with processing speed

As shown in Table 4, the WMH burden measures were all significantly associated with processing speed, with similar standardized β coefficients for all regressions.

Furthermore, SWM and DWM diffusion measures (FA, MD, and FW) were significantly associated with processing speed (Table 5). As expected, the poorer the cognitive performance, the lower the FA and the higher the MD and FW. SWM FW was most strongly associated with processing speed, with the largest magnitude standardized β coefficient ($\beta_S = .289$), followed by SWM MD ($\beta_S = .246$). No significant association was found between free-water-corrected diffusion measure FAt and processing speed in SWM or DWM.

3.2.2 | FW in the SWM contributes most to processing speed in multivariable analysis

To assess the contribution of each imaging marker to processing speed while accounting for multicollinearity (see Figure S1 for a matrix of correlations between all variables), we applied conditional random forest regression and calculated the conditional variable importance. Across all imaging markers, significant variables included FW and MD in the SWM, showing high contributions to processing speed (Figure 2). Specifically, the FW in the SWM had the highest variable importance.

3.2.3 | Diffusion measures of SWM in different brain lobes are widely associated with processing speed

To investigate the effects of lobar SWM microstructure on processing speed, we examined associations between processing speed and lobar SWM microstructure. In all lobar SWM regions, FW and MD were strongly associated ($p < .001$) with processing speed (Table S2). In contrast, associations between lobar SWM FA and processing speed were found only in the left frontal and right parietal SWM. No significant association was found for FAt.

3.3 | Comparison of imaging markers of SWM and DWM between different levels of disease

The study sample was split into quartiles according to the total WMH volume, producing four subgroups with different levels of WMH burden. There was no significant difference in age, sex, ICV or education between subgroups (See Table S1 for this information for each group).

TABLE 3 Associations of WMH-total volume with diffusion measures in the SWM and the DWM

	SWM		DWM	
Diffusion measures	β_S	p	β_S	p
FW	.518	**<.001**	.838	**<.001**
MD	.459	**<.001**	.752	**<.001**
FAt	.020	.791	−.083	.368
FA	−.362	**<.001**	−.664	**<.001**

Note: Adjusted for age, sex and ICV. Significant FDR-corrected results are in BOLD.
Abbreviations: β_S, standardized β coefficient; DWM, deep white matter; FA, fractional anisotropy; FAt, FW-corrected FA; FW, free-water; ICV, intracranial volume; MD, mean diffusivity; WMH, white matter hyperintensity; SWM, superficial white matter.

Figure 3a shows the TMT-A completion time and WMH volumes in the SWM and the DWM for subgroups of different WMH burden levels. The WMH-DWM burden significantly increased at all levels of disease burden (i.e., between all compared groups: Groups 1 and 2, Groups 2 and 3, and Groups 3 and 4). However, a significant increase in WMH-SWM was found only between higher levels of disease burden (between Groups 3 and 4). This was accompanied by a significant increase in TMT-A completion time (a decrease in processing speed) at higher levels of disease burden (between Groups 3 and 4).

Figure 3b shows all diffusion measures in the SWM and DWM in the subgroups of different WMH burden levels. DWM-FW and DWM-MD significantly increased at all levels of disease burden (i.e., between all compared groups: Groups 1 and 2, Groups 2 and 3, and Groups 3 and 4). The overall trend of DWM-FA was downward, though not all decreases between groups were significant. In contrast, the between-group differences in diffusion measures in the SWM were less pronounced than those in the DWM. Specifically, only SWM-FW significantly differed in subjects with relatively lower WMH burdens (between Groups 1 and 2), suggesting that the SWM-FW measure is more sensitive than SWM-MD or SWM-FA. Significant increases in SWM-FW and SWM-MD could be observed at higher levels of disease burden (between Groups 3 and 4). Between-group differences in FAt were relatively slight at all levels of disease burden and not significant in the SWM or the DWM.

3.4 | Free water in the SWM fully mediates the WMH volume effect on processing speed

Given significant effects of WMH volume and FW on processing speed, we performed mediation analysis to further determine whether FW in the SWM and the DWM could mediate the association between total WMH volume and processing speed. As shown in Figure 4, mediation analysis revealed a significant indirect effect of WMH volume on processing speed via SWM FW ($a1 \times b1 = 0.109$, the bootstrapped 95% CI = [0.018, 0.212]). As a mediator, SWM FW could account for 74.1% of the total effect (c). For FW in the DWM, the bootstrapped 95% CI included zero ([−0.124, 0.450]), indicating

TABLE 4 Associations between global and regional WMH volumes and processing speed

WMH volume	β_S	*p*
WMH-total	.154	**.020**
WMH-SWM	.153	**.020**
WMH-DWM	.146	**.020**

Note: The association analyses are adjusted for age, sex, ICV and education. Significant FDR-corrected results are in BOLD.
Abbreviations: β_S, standardized β coefficient; DWM, deep white matter; ICV, intracranial volume; SWM, superficial white matter; WMH, white matter hyperintensity.

TABLE 5 Associations between each diffusion measure and processing speed

	SWM		DWM	
Diffusion measures	β_S	*p*	β_S	*p*
FW	.289	**<.001**	.240	**<.001**
MD	.246	**<.001**	.245	**<.001**
FAt	−.003	.962	−.027	.771
FA	−.179	**.006**	−.186	**.004**

Note: Adjusted for age, sex, ICV and education. Significant FDR-corrected results are in BOLD.
Abbreviations: β_S, standardized β coefficient; DWM, deep white matter; FA, fractional anisotropy; FAt, FW-corrected FA; FW, free-water; ICV, intracranial volume; MD, mean diffusivity; SWM, superficial white matter; WMH, white matter hyperintensity.

that the mediated effect was not significant. The direct effect of WMH volume on processing speed was not significant after adjusting for the mediators ($c' = -0.112$, $p > .05$), supporting a full mediation model. These results suggest that SWM FW fully mediates the relationship between the WMH volume and processing speed.

4 | DISCUSSION

This study applies multiple imaging markers to assess white matter abnormalities in the SWM and the DWM and investigates their contributions to processing speed in CSVD. The main findings can be summarized as follows: (i) the contributions to processing speed of the SWM (as reflected in imaging markers) are comparable to those of the DWM, despite the fact that the SWM has a lower WMH burden than the DWM; (ii) SWM FW has the strongest association with processing speed among all imaging markers and, unlike the other diffusion MRI measures, significantly increases in subjects with low WMH burden (possibly representing early stages of disease); (iii) under high burden of disease, the involvement of WMH in the SWM is accompanied by significant differences in processing speed and white matter microstructure; (iv) the effect of WMH volume on processing speed is fully mediated by SWM FW, and no mediation effect of DWM FW is observed. Our findings provide new insights into processing speed in patients with CSVD and suggest the SWM as a potential target for future research.

Our results extend the present literature on white matter abnormalities and their impacts on processing speed in CSVD, providing evidence for the importance of the SWM. A number of CSVD studies have found strong associations of cognitive performance with diffusion MRI measures in the DWM (Chen et al., 2019; Huang et al., 2020; Liu et al., 2020; O'Sullivan et al., 2005; Quinque et al., 2012; Tuladhar, 2015; Vergoossen et al., 2021) and in white matter areas without visible WMH (Jokinen et al., 2013; Lawrence et al., 2013, 2014; O'Sullivan, Markus, et al., 2004; O'Sullivan, Morris, et al., 2004; Schmidt et al., 2010; Tozer et al., 2018; Tuladhar, 2015; Zhang, Wong, Uiterwijk, et al., 2017). Although postmortem histological studies have observed white matter abnormalities in the SWM in CSVD (Humphreys et al., 2021), limited dMRI studies have investigated the role of the SWM in CSVD, showing a reduction in SWM connectivity (Lawrence et al., 2014; Tuladhar et al., 2017; van Leijsen et al., 2019). The present study suggests that processing speed in CSVD is particularly related to microstructural abnormalities in the SWM. The significance of the SWM for cognitive performance, especially in executive function, processing speed and visuomotor-attention, has been reported in aging (Nazeri et al., 2015), Alzheimer's disease (Phillips et al., 2016; Reginold et al., 2016) and psychiatric disorders (D'Albis et al., 2017; Nazeri et al., 2013). In the current study, we mainly focused on the processing speed, which is the primary cognitive dysfunction in CSVD (Konieczny et al., 2021; Peng, Geriatric Neurology Group, Chinese Society of Geriatrics and Clinical Practice Guideline for Cognitive Impairment of Cerebral Small Vessel Disease Writing Group, 2019). We found that processing speed was significantly associated with SWM abnormalities measured by imaging markers, including SWM FA, MD, FW, and WMH-SWM. Interestingly, the contributions of SWM imaging markers to processing speed were higher than those of the DWM in multivariable analyses (Section 3.3), despite the fact that the SWM had a lower WMH burden, and diffusion measures in the SWM were less affected by the total WMH burden (see the magnitude of the standardized β coefficients, Table 2). This finding indicates that despite the limited lesion burden in the SWM, the SWM microstructure plays a significant role in cognition. In our study, the potential importance of SWM in CSVD is further emphasized by the result that SWM FW fully mediates the effect of WMH on processing speed (Figure 4). In related work, mediation analyses have shown that global dMRI measures (including FW measured in the entire white matter skeleton; Maillard et al., 2019) and local network efficiency, a property of the entire white matter connectome (Vergoossen et al., 2021) mediate the relationship between WMH volume and cognitive performance measures in aging. In addition, our results indicate that SWM MD shows many similarities with SWM FW (in terms of its association with WMH burden and its conditional importance with respect to processing speed). Therefore, we further investigated whether SWM or DWM MD mediated the relationship between WMH volume and processing speed (Supplementary Methods S1.3). No mediation effects of SWM or DWM MD were found (Supplementary Results S2.5). Overall, our

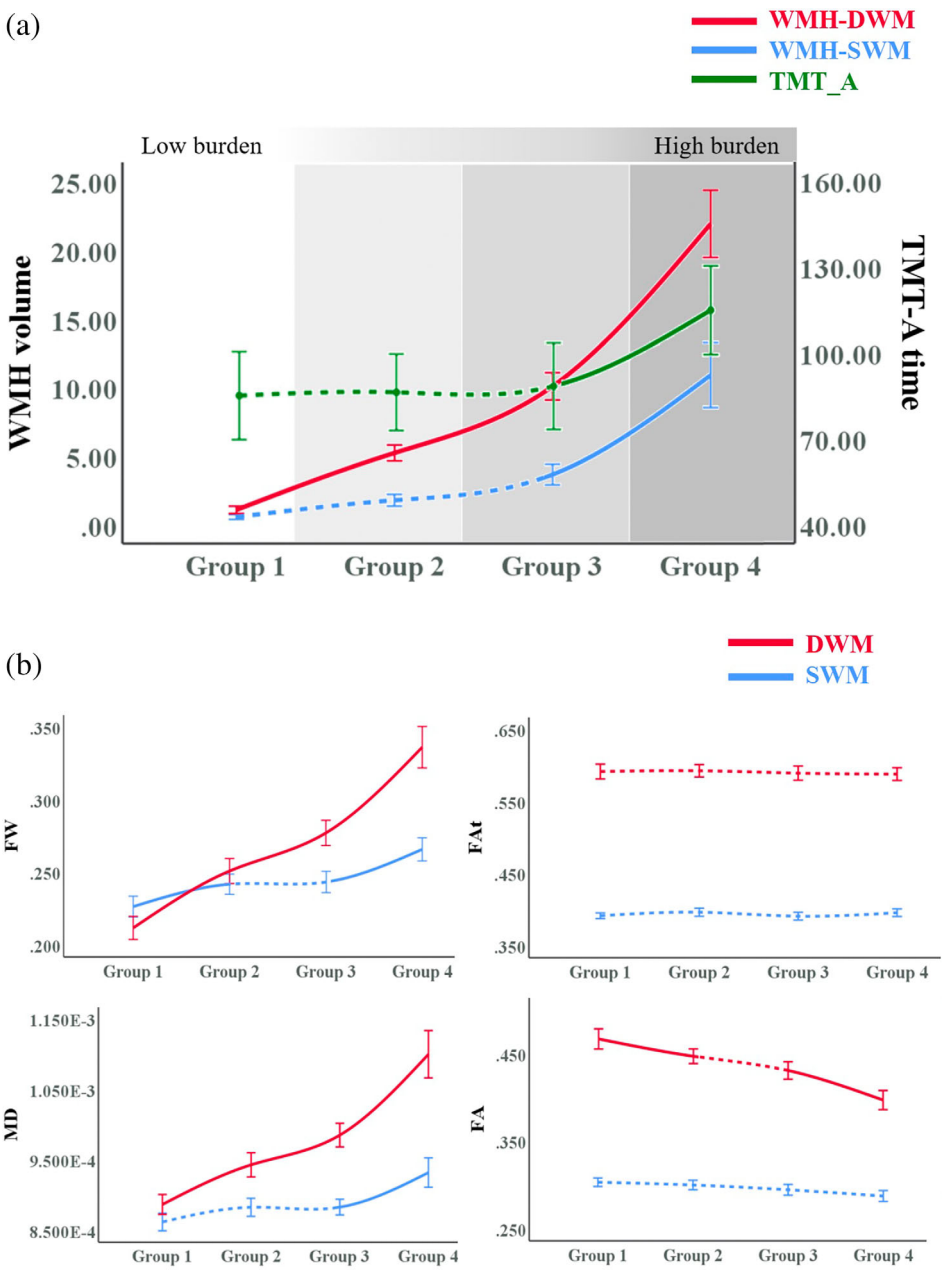

FIGURE 3 The TMT-A completion time and imaging markers in subgroups of different WMH burden levels. (a) the TMT-A completion time and WMH volumes in the SWM and the DWM. The left *y*-axis represents the WMH volume, and the right *y*-axis represents the completion time of TMT-A. (b) Diffusion measures in the SWM and the DWM. Patients in Group 1 and 4 had the lowest and highest level of WMH burden, respectively. Between-group differences were compared. solid line segments indicate that the diffusion measures significantly differed compared to the previous group, while dashed line segments indicate that between-group differences did not reach a statistically significant level. DWM, deep white matter; FA, fractional anisotropy; FAt, FW-corrected FA; FW, free-water; MD, mean diffusivity; SWM, superficial white matter; WMH, white matter hyperintensity

results demonstrate the importance of studying localized dMRI measures in the SWM and suggest that the importance of the SWM may be underestimated in previous studies of CSVD.

SWM imaging markers such as those studied here, in conjunction with previously studied DWM imaging markers, may provide useful information about the disease course in CSVD. Previous CSVD research has linked disease severity to abnormalities in regional white matter (e.g., DWM, normal-appearing white matter and peripheral white matter connections) that were associated with the severity of persisting cognitive impairments (Jokinen et al., 2013; Schmidt et al., 2016; van Leijsen et al., 2017, 2019). In the present study, we identified the WMH burden levels in which processing speed and imaging markers had significant between-group differences. It is worth noting that while the WMH-DWM burden increased from Groups 1 to 4, only between Groups 3 and 4 (with higher WMH burden) did we find significant WMH-SWM and processing speed differences (Figure 3). Our findings suggest that cognitive performance may be related to the involvement of WMH-SWM. This result further shows that the contribution of WMH-SWM to cognitive performance may be a late event. In addition, close associations between microstructural diffusion measures of DWM and SWM (Figure S1) suggest that earlier microstructural abnormalities in the DWM might predict the appearance of later changes in the SWM, which may be an important cumulative factor for a steep difference in processing speed between two groups in the later stages. Considering that the SWM microstructure has a significant effect on cognitive performance, the detection of subtle changes in the SWM is very important. Our results show that SWM microstructural differences can be detected by FW

in the scenario of low WMH burden, which could not be achieved by conventional diffusion measures (Figure 3). Therefore, it is possible that SWM imaging markers may be useful for monitoring the disease course, from early SWM microstructural change (potentially characterized by SWM FW) to late pronounced difference in cognitive performance (potentially characterized by WMH-SWM).

The present study suggests that FW in the SWM may constitute an early marker of white matter microstructural abnormality in CSVD. Although FW was originally estimated to correct for freely diffusing extracellular water (Pasternak et al., 2009), many studies have found that FW is particularly sensitive to disease severity (Duering et al., 2018; Gullett et al., 2020; Huang, Zhang, Jiaerken, Wang, Hong, et al., 2021; Ji et al., 2017; Maillard et al., 2019; Yu et al., 2021). Using FW imaging, increasing evidence suggests a prominent increase in extracellular water in CSVD, with less demyelination and axonal loss than would be suggested by conventional diffusion measures (Duering et al., 2018; Wardlaw et al., 2019). In line with these previous findings, we found that extracellular water in the DWM (DWM-FW) significantly increased in the subgroups with low WMH burden. In addition, our results extended this finding to the SWM, showing that, among all the imaging markers studied, FW was the most sensitive to SWM microstructure. Of note, a significant increase in SWM-FW could be observed in the subgroups with low WMH burden (Groups 1 and 2; Figure 3), while WMH-SWM only slightly increased between these two groups. This finding is consistent with the current view, which suggests that the increased water content in white matter is associated with the early stage of WMH formation (Huang, Zhang, Jiaerken, Wang, Yu, et al., 2021; Muñoz Maniega et al., 2017; Wardlaw et al., 2019). Our results indicate that increased extracellular water, as measured by FW, may be an early sign and main process for SWM microstructural abnormality under low WMH burden.

To our knowledge, FW in the SWM in CSVD was not investigated before, and therefore the factors driving increased SWM FW remain to be determined. Although the exact pathology contributing to the diffusion changes cannot be determined in the current study, there are several potential pathological processes relevant for CSVD that could explain the increased extracellular FW in the SWM. One possible factor is myelin vacuolization, which contributes to white matter rarefaction, and vacuoles in white matter enable interstitial fluid to accumulate (Murray et al., 2012), further increasing the extracellular water. In an animal study of genetic CSVD (Cognat et al., 2014), segmental vacuolization of the white matter was reported as the earliest pathological change. In humans, a postmortem study from Erkinjuntti et al. has found vacuolization in the SWM in nearly half of patients with CSVD-related vascular disorders (Erkinjuntti et al., 1996). This evidence suggests that vacuolization in the SWM may be a pathological process related to small vessel disease. An alternative pathological process that may drive FW is the edema caused by BBB breakdown in WMH, which can increase extracellular water (Di Biase et al., 2021; Duering et al., 2018). It needs to be noted that the aforementioned myelin vacuolization can promote BBB leakage (Cognat et al., 2014). Therefore, the involvement of BBB damage in the SWM may be in the later stages of the disease, which may be a contributor to a steep increase in FW observed in this study (Figure 3, Groups 3 and 4). Another mechanism receiving recent attention is glymphatic dysfunction in CSVD (Benveniste & Nedergaard, 2021). Recent studies found that the impaired drainage of interstitial fluid can increase FW around the perivascular space (Huang, Zhang, Jiaerken, Wang, Yu, et al., 2021; Jiaerken et al., 2021), which is the fluid-filled space surrounding blood vessels (Wardlaw et al., 2020). The increased water content in the dilated perivascular space may be related to WMH formation (Huang, Zhang, Jiaerken, Wang, Yu, et al., 2021; Weller et al., 2015). Although this question did not constitute the objective of our study, it should be noted that the increased water content in the dilated perivascular spaces may partly contribute to the observed increased FW in the SWM. Taken together, our study suggests that SWM FW may be a valuable marker for CSVD.

Our study shifts the focus of CSVD-related white matter abnormalities to the SWM region, and the results highlight the role of the SWM in CSVD-related dysfunction. Some limitations of the study are as follows. First, although the present study provides evidence supporting the role of the SWM in CSVD, the cross-sectional design limits any exploration of longitudinal SWM change and its effects on cognitive decline. Future longitudinal studies of CSVD are needed. Furthermore, the present study lacks healthy controls. Due to the older age of CSVD patients and the involvement of multiple vascular risk factors, studies of CSVD typically have difficulty in identifying matched

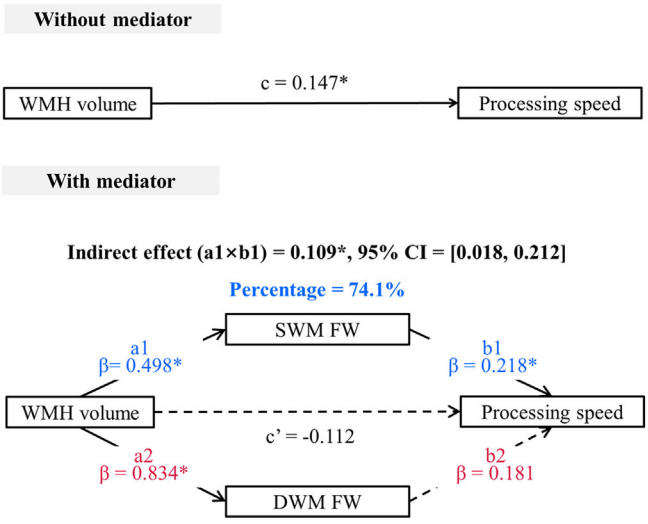

FIGURE 4 Mediation of FW (in the SWM and the DWM) between total WMH volume and processing speed. The effect of WMH volume on processing speed is shown by the direct effect (c) without and the indirect effect (c') with mediators. Standardized β-coefficients of each path (a and b) are shown for two mediators (*p < .05). Significant paths are indicated by solid arrows, and nonsignificant paths are shown by dashed arrows. Indirect effects are statistically significant at the 95% CI when the CI does not include 0. As the direct effect (c') is not significant, SWM FW fully mediates the relationship between WMH volume and processing speed (this analysis controlled for age, sex, ICV, and education.). CI, confidence interval; DWM, deep white matter; FW, free-water; MH, white matter hyperintensity; SWM, superficial white matter

elderly subjects, leading to a lack of healthy controls (De Guio et al., 2020). Second, as hypertension is a key risk factor for CSVD (van Middelaar et al., 2018; Wardlaw, Smith, Biessels, et al., 2013; Wardlaw, Smith, & Dichgans, 2013), associations between SWM microstructure and vascular risk factors merit further study. (We note that we find no significant differences in diffusion measures between subsets of patients with and without hypertension in our current cohort. See Supplementary Methods S1.4 and Supplementary Results S2.6). Third, although processing speed is the primary cognitive function affected in CSVD, other neuropsychological domains, such as memory and depression, need to be investigated in the future. Fourth, our overall motivation for the study was to study the effects of CSVD on the major white matter regions as a whole (deep and superficial); investigation of the localized effects of CSVD on the microstructure within lesions or normal appearing white matter is therefore a promising direction for future work. Fifth, cortical atrophy may contribute to cognitive performance, and its association with abnormalities in the SWM needs to be explored in the future. Sixth, future studies may apply tractography to identify the white matter tracts in the SWM, which may provide a more precise assessment for microstructural changes in the SWM (Guevara et al., 2020; Zhang et al., 2018). Finally, the employed diffusion imaging data uses clinically typical acquisition protocols, with a fairly low resolution (2 mm isotropic). Future studies may employ more advanced or higher resolution imaging protocols to further investigate the role of the SWM in CSVD.

5 | CONCLUSION

In this study, our findings identify SWM abnormalities in CSVD and suggest that the SWM has an important contribution to processing speed. Our results suggest that processing speed decreases in CSVD may be driven by the involvement of WMH lesions in the SWM. Results indicate that SWM FW fully modulates the association between WMH burden and processing speed, while no mediation effect of DWM FW was observed. Overall, FW in the SWM is a sensitive marker of microstructural changes associated with cognition in CSVD. This study extends the current understanding of CSVD-related dysfunction and suggests that the SWM, as an understudied region, can be a potential target for monitoring pathophysiological processes in future research.

AUTHOR CONTRIBUTIONS

Shuyue Wang: Conceptualization, Methodology, Writing – review and editing, Data curation, Data acquisition. **Fan Zhang:** Conceptualization, Methodology, Writing – review and editing, Data curation, Software. **Peiyu Huang**: Conceptualization, Writing – review and editing. **Hui Hong**: Conceptualization, Writing – review and editing, Data acquisition. **Yeerfan Jiaerken**: Conceptualization, Writing – review and editing, Data acquisition. **Xinfeng Yu**: Conceptualization, Writing – review and editing, Data acquisition. **Ruiting Zhang**: Conceptualization, Writing – review and editing, Data acquisition. **Qingze Zeng**: Conceptualization, Writing – review and editing. **Yao Zhang**: Conceptualization, Writing – review and editing, Data acquisition. **Ron Kikinis**: Conceptualization, Writing – review and editing. **Yogesh Rathi**: Conceptualization, Writing – review and editing. **Nikos Makris**: Conceptualization, Writing – review and editing. **Min Lou**: Conceptualization, Writing – review and editing, Data acquisition, Resources. **Ofer Pasternak**: Conceptualization, Methodology, Writing – review and editing, Software. **Minming Zhang**: Conceptualization, Writing – review and editing, Data curation, Resources. **Lauren J. O'Donnell**: Conceptualization, Methodology, Writing – review and editing, Data curation, Software.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

The source of data used in this paper has been described in the Methods section of the paper. The data collected for this study are not publicly available due to ethics and privacy issue. The data is available via a reasonable request with a formal data sharing agreement to the corresponding author. The open-source software tools used in this study are available through their corresponding download sites (please see the Methods section). The code developed in-house will be available upon a reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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