Decreased Cerebrovascular Reserve is the Initial Cause of White Matter Hyperintensity Related Cognitive Decline

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Research

Keywords: white matter hyperintensity, cerebrovascular reserve, cognitive decline, resting-state functional MRI, pathogenesis

DOI: https://doi.org/10.21203/rs.3.rs-35534/v1

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Abstract

**Background:** Increasing evidences have demonstrated the progressions of white matter hyperintensity (WMH) are associated with cerebrovascular reserve (CVR) and cognitive decline. The present study hypothesized that impaired CVR is associated with WMH progression and may lead to cognitive decline through WMH.

**Methods:** A total of 244 WMH subjects were recruited and were categorized into WMH-I (n=112), WMH-II (n=76) and WMH-III (n=56) groups according to Fazekas rating scale. The individual CVR was measured using blood-oxygenation level-dependent (BOLD) signal fluctuations obtained from resting-state functional MRI (rs-fMRI). We compared maps of the CVR and clinical features among the three groups. Multiple linear regression analysis was performed to investigate the correlations of WMH volume with impaired CVR and cognitive functions indifferent domains controlling for age, sex, years of education, vascular risk factors, numbers of lacunas and cerebral microbleeds in all WMH individuals.

**Results:** Compared with the WMH-I group, both WMH-II and WMH-III groups showed CVR decline in the left frontal and occipital areas. Multiple linear regression analysis showed WMH volume was negatively associated with CVR impairments in left frontal/occipital areas and cognitive functions including global cognitive function (GCF), executive function (EF), information processing speed (IPS), memory and visuospatial processing function (VPF) (all P<0.05). Additionally, mediation analysis revealed CVR impairments in left frontal and occipital areas didn’t directly lead to cognitive decline, but indirectly caused cognitive decline in multiple domains through increasing WMH burdens (all 95% confidence intervals didn’t contain zero).

**Conclusion:** The CVR decline initially resulted in WMH progression, which is responsible for the following development of cognitive decline. This study shed lights on exploring the pathogenesis of WMH progression and underlying mechanisms of WMH-related cognitive decline.

Background

White matter hyperintensity (WMH) presented as the hyperintense of the subcortical white matter on T2-weighted MRI image or fluid-attenuated inversion recovery (FLAIR) sequence is frequently observed in elderly individuals [1]. Epidemiologic studies have revealed that WMH can be observed in 72–96% European individuals over 60 years old [2], and 70% Chinese individuals over 50 years old [3]. Additionally, with each additional year of age, the morbidities of periventricular white matter hyperintensity and deep white matter hyperintensity increase by 0.2% and 0.4% respectively [4]. According to Fazekas rating scale, WMH can be classified into four grades (Grade 0, no WMH; Grade 1, focal or punctate lesions; Grade 2, beginning confluent lesions; Grade 3, confluent lesions), among which the WMH of Grade 2–3 can lead to disconnection syndromes [5].

A great number of studies have reported that WMH can cause vascular cognitive impairment (CI), especially in domains of executive function, attention, working memory and information processing...
speed. Furthermore, WMH is correlated closely with increased prevalence of stroke, dementia, and death [6, 7]. WMH is known to be highly related to age [8], as well as independently related to risk factors for cardiac and cerebral vascular disease [9, 10]. However, the exact pathogenesis of WMH and the pathologic mechanism of CI caused by WMH remain to be elucidated.

Cerebrovascular reserve (CVR) is also called cerebrovascular reactivity, which is defined as the change of cerebral blood flow induced by a vasoactive stimulus, and has been thought as an indicator of vascular reserve [11] and autoregulatory efficiency [12]. CVR provides important information about vascular health in a range of brain conditions and diseases. Impaired CVR is correlated closely with normal aging [13] and might be a sensitive early predictor of Alzheimer's disease [14]. In addition, it is reported that impaired CVR is the most reliable neuroimaging predictor of impending cerebrovascular disease [15, 16], and could be a neuroimaging marker guiding the treatment and prevention of stroke and cerebral small vessel disease (CSVD) [17, 18]. Furthermore, increasing evidences have demonstrated that CVR function is associated with subtle perfusion and microstructure changes in normal-appearing white matter (NAWM) [19], and has been involved in the pathophysiology disruption of the brain network connectome in individuals with WMH [20]. All these studies suggest that CVR might be an initial factor leading to WMH and cognitive decline. However, there are few studies exploring the development pattern of CVR reduction from normal individuals to WMH, which leads to cognitive decline and the exact relationship among CVR, WMH and cognitive performance remains unclear.

Resting-state functional MRI (rs-fMRI) is a non-invasive imaging technique used to explore the aberrant intrinsic functional architecture of the brain and have been increasingly utilized to investigate functional alterations related to the onset of CI in WMH[21, 22]. It can offer a unique window to obtain quantitative mapping of CVR information based on intrinsic fluctuations in the blood-oxygenation level-dependent (BOLD) signal [23, 24]. Meanwhile, it does not require hypercapnia related tasks including carbon dioxide inhalation, breath-holding and cued deep breathing which is necessary for traditional technology [25, 26]. It can therefore be used to assess vascular reactivity in a wide range of clinical and research conditions. Recently, rs-fMRI has been applied to explore CVR in cerebral large vessel diseases including carotid artery stenosis carotid or occlusion, Moyamoya disease [24, 27–29]. Furthermore, emerging studies used BOLD signal technology to evaluate CVR in WMH individuals and found that impaired CVR was associated with WMH [20, 30, 31]. However, all these studies didn't further explore whether impaired CVR can leads to cognitive decline through WMH.

Therefore, in the present study, we applied rs-fMRI to evaluate CVR function in WMH-I, WMH-II and WMH-III populations. We investigated the relationships among WMH burden, impaired CVR and cognitive decline. We hypothesized that CVR decline caused WMH progression and might lead to cognitive decline through WMH.

**Methods**

**Participants**
This present research was a part of the Study on Register and the Diagnosis, Therapy and Prognosis of Cerebral Small Vessel Disease, an ongoing longitudinal study of CSVD (Registration number: ChiCTR-OOC-17,010,562), which was carried out in accordance with the latest version of the Declaration of Helsinki and approved by the Nanjing Drum Tower Hospital. Overall, from January 2017 to April 2019 in inpatients and outpatients of neurological department, Nanjing Drum Tower Hospital, a total of 244 WMH subjects were recruited and were divided into WMH I (n = 112), WMH II (n = 76), and WMH III (n = 56) according to Fazekas rating scale (Fig. 1). WMH was categorized independently and unanimously by two radiologists, who visually evaluated MRI without knowledge of the participants’ clinical profiles. All participants were provided written informed consents and underwent multimodal MRI scans and standardized diagnostic evaluations, including demographic data, vascular risk factors and an examination of neuropsychological status.

The inclusion criteria for WMH subjects were as follows: 1) age between 47 and 81 years; 2) presence of mild to severe WMH on FLAIR; 3) without MRI contraindications; 4) no recent small subcortical infarction. Exclusion criteria were as follows: 1) a history of ischemic stroke with infarct size more than 1.5 cm in diameter or cardiogenic cerebral embolism; 2) cerebral hemorrhage; 3) internal carotid artery or vertebral artery stenosis (> 75%) or coronary atherosclerosis heart disease; 4) WMH due to immune-mediated demyelinating disease (multiple sclerosis, neuromyelitis optical, acute disseminated encephalomyelitis), metabolic leukodystrophy and genetic leukoencephalopathy; 5) other neurological disorders, such as AD, Parkinson, epilepsy; 6) systemic disease, such as cancer, shock, anemia and systemic lupus erythematosus; 7) prominent impairments of audition or vision.

Neuropsychological examination

Each subject underwent a standardized neuropsychological test protocol, including the mental status, global cognitive function, and multiple cognitive domain examinations. Hamilton depression rating scale (HAMD) and Hamilton anxiety rating Scale (HAMA) were used to test the mental status of all subjects. Global cognitive function (GCF) was evaluated by Mini Mental State Examination (MMSE) and Beijing version of the Montreal cognitive assessment (MoCA-BJ). The raw rest scores were converted to Z-scores which calculate the compound cognitive index. Executive function (EF) is a compound score of the average Z-scores of Trail Making Test-B (TMT-B) and Stroop Color and Word Tests-C (SCWT-C), Information processing speed (IPS) was calculated as the average Z-scores of TMT-A, SCWT-A and B. Memory was calculated as the mean of the Z-scores of Wechsler Memory Scale-Visual Reproduction-delayed recall (VR-DR) and Auditory Verbal Learning Test-long delayed recall (AVLT-DDR) representing visual memory and verbal memory respectively. Visuospatial processing function (VPF) was a compound score that included the mean of the Z-scores of Clock Drawing Test (CDT) and Visual Reproduction-copy (VRC).

MRI scanning

Each participant was examined on a Philips 3.0-T scanner (Philips Medical Systems, Netherlands). The examination protocol included the high-resolution
T1-weighted turbo gradient echo sequence \([\text{repetition time (TR)} = 9.8 \text{ ms}, \text{flip angle (FA)} = 8^\circ, \text{echo time (TE)} = 4.6 \text{ ms}, \text{FOV} = 250 \times 250 \text{ mm}^2, \text{number of slices} = 192, \text{acquisition matrix} = 256 \times 256, \text{thickness} = 1.0 \text{ mm}],\) the FLAIR sequence \([\text{TR} = 4500 \text{ ms}, \text{TE} = 333 \text{ ms}, \text{time interval (TI)} = 1600 \text{ ms}, \text{number of slices} = 200, \text{voxel size} = 0.95 \times 0.95 \times 0.95 \text{ mm}^3, \text{acquisition matrix} = 270 \times 260]\) and the gradient-recalled echo planar imaging sequence \([\text{TR} = 2000 \text{ ms}, \text{FA} = 90^\circ, \text{TE} = 30 \text{ ms}, \text{number of slices} = 35, \text{acquisition matrix} = 64 \times 64, \text{FOV} = 240 \times 240 \text{ mm}^2, \text{thickness} = 4.0 \text{ mm}].\)

Rs-fMRI was acquired by a gradient-echo-planar imaging (GRE-EPI) sequence: \([\text{repetition time} = 2000 \text{ ms}, \text{echo time} = 30 \text{ ms}, \text{flip angle} = 90^\circ, \text{matrix} = 64 \times 64, \text{voxel size} = 3 \times 3 \times 3 \text{ mm}, \text{field of view} = 192 \times 192 \text{ mm}, \text{thickness} = 4.0 \text{ mm}, \text{gap} = 0 \text{ mm}, \text{and number of slices} = 35.\) The total scan duration was 8 min and 7 s and participants were instructed to keep their eyes closed and stay as still as possible, not to fall asleep or think of anything in particular. Additionally, axial T2-weighted, diffusion weighted imaging (DWI) sequence and susceptibility weighted imaging were collected to detect acute or subacute infarctions, cerebral microbleeds.

**Brain, WMH and hippocampus volumetry**

Briefly, the volumes of total brain, gray matter and white matter were calculated using a VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm8) based on 3D-T1 images. The WMH volumes were semi-automatically quantified by the Wisconsin White Matter Hyperintensity Segmentation Toolbox (https://sourceforge.net/projects/w2mhs) based on 3D-T1 and 3D-FLAIR images. The hippocampus (left and right) was isolated using automated anatomical labeling implemented through the rs-fMRI Data Analysis Toolkit 1.7 software (http://restfmri.net/forum/index.php). Then, the hippocampal regions were interpolated to the same sizes, dimension and origins with T1 images. And a mean volume index of all voxels within the hippocampal region (left and right) was extracted for each subject. Finally, the hippocampal volume was obtained by multiplying the mean volume index by the size of each voxel \((1.5 \times 1.5 \times 1.5 \text{ mm})\) and the number of voxels within the hippocampal region.

**Cerebrovascular reserve assessment**

Rs-fMRI data were preprocessed and analyzed using Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm/) and in-house MATLAB (MathWorks, Natick, MA) scripts. The preprocessing procedures included: 1) head motion correction; 2) spatial smoothing by means of convolution \(9\) with an isotropic Gaussian kernel of \(8 \text{ mm}\); 3) linear detrending. Given that the global BOLD fluctuations in the frequency range of \(0.02–0.04 \text{ Hz}\) mostly contributed to natural variation in end-tidal \((\text{Et})\) CO2 levels \([32]\), the rs-fMRI data was temporally filtered with a band-pass filter of \(0.02\) to \(0.04 \text{ Hz}\). The average whole-brain rs-BOLD signal was calculated as reference time course. A general linear model was
employed on a voxel-wise way with the reference time course as the independent variable and each voxel's time course as the dependent variable, yielding a CVR index map, then the CVR index map was furtherly normalized to the reference time course, yielding a relative CVR map. The relative CVR maps were then spatially normalized to the standard Montreal Neurologic Institute (MNI) template, with a resampled voxel size of $3 \times 3 \times 3$ mm$^3$, so that a global voxel-wise between-subject comparison was able to be conducted.

**Statistical analysis**

Normality of continuous variables was checked by the Kolmogorov–Smirnov test and WMH volumes were log-transformed to normalize the distribution. Differences in demographic, clinical, volume data and neuropsychological data across the three groups were analysed using one-way analysis of variance, Chi-squared ($\chi^2$) test or Kruskal-Wallis test in the case of non-normality which all were conducted using SPSS 22.0 software (IBM Corp., Armonk, NY). $P < 0.05$ was considered statistically significant.

The group differences of CVR among the three groups were analyzed by using a voxel-wise one-way analysis of covariance (using DPABI v2.3, the voxel Z threshold $< 0.001$), controlling for age, gender and years of education with Gaussian Random Field (GRF) correction (voxel p threshold for the minimum cluster size $< 0.001$ and cluster p threshold $< 0.01$) for multiple comparison correction. Subsequently, for the GRF corrected statistically significant brain regions, a post-hoc analysis was performed to investigate group differences between any two groups, additionally correcting for multiple comparisons with Bonferroni correction which is standard in SPSS 22.0 when covariates are entered into the model. Then, multiple linear regression analysis was performed to investigate the correlations of log-transformed WMH volume with impaired CVR and cognitive functions in multiple cognitive domains controlling for age, sex, years of education, vascular risk factors, numbers of lacunas and cerebral microbleeds in all WMH individuals.

Additionally, mediation analysis was performed to explore whether WMH volume involved in the relationship between decreased CVR and cognitive function controlling for age, sex, years of education, vascular risk factors, numbers of lacunas and cerebral microbleeds. The primary estimates of interest were the degree of the changes in the direct path between decreased CVR and cognitive performance, labelled $c$ in the bi-variate models and $c'$ in the full mediating models, and the indirect path from decreased CVR to cognitive performance through WMH volume: the product of path $a$ and $b$. We computed the bias-corrected 95% confidence intervals for the size of the mediating effects with bootstrapping ($k = 5000$ samples). The mediating effect is said to be present if the 95% confidence intervals does not contain zero. All the mediation analyses were conducted in PROCESS for the SPSS 22.0 framework.

**Results**
Demographic, clinical, and cognitive data among the three groups

Demographic, vascular risk factors, the volume data, and mental data across the three groups were showed in Table 1. There were no significant differences in gender, years of education, vascular risk factors, the number of lacunars and cerebral microbleeds, HAMD and HAMA scores, TIV, gray and white matter volume, left and right hypothalamus volume among the three groups (all $P > 0.05$) except for ages and WMH volume ($P < 0.05$). We hereby removed age effect in all the following analyses. With the Fazekas score increased, the volume of WMH increased simultaneously ($P < 0.05$). As showed in Table 2, when compared with WMH-I subjects, WMH-III and WMH-II subjects exhibited poorer GCF, EF and IPS, memory (all $P < 0.05$). In contrast with WMH-II, WMH-III subjects showed worse EF ($P < 0.05$). WMH-III subjects showed worse VPF than WMH-I subjects ($P < 0.05$).

CVR differences among the three groups

Atlas maps of CVR based on BOLD signal for each group were showed in Fig. 2. As shown in Table 3 and Fig. 3, the three groups displayed significant different CVR in left frontal and occipital areas (including gray matter and white matter areas) controlling for age, sex, years of education with GRF correction (voxel $p$ threshold for the minimum cluster size $< 0.001$ and cluster $p$ threshold $< 0.01$) for multiple comparisons correction. Post hoc analysis showed there was a decreasing trend of CVR in left frontal and occipital areas among the three groups. WMH-II and WMH-III groups displayed lower CVR in left frontal area than WMH-I group, ($P = 0.003$ in WMH-II group, $P < 0.001$ in WMH-III group vs. WMH-I group, Bonferroni-corrected, Fig. 4A), as well as left occipital area ($P = 0.002$ in WMH-II group, $P < 0.001$ in WMH-III group vs. WMH-I group, Bonferroni-corrected, Fig. 4B). Relative to WMH-II group, WMH-III group showed lower CVR in the left frontal and occipital areas. However, it did not achieve statistical significance.

Correlations of WMH volume with left Occipital/Frontal CVR and cognitive performance

We conducted multiple linear regression analysis to explore the correlations of log-transformed WMH volume with impaired CVR and cognitive functions controlling for age, sex, years of education, vascular risk factors, numbers of lacunars and cerebral microbleeds. As shown in Table 4, we found WMH volume was negatively associated with CVR in the occipital area ($\beta=-0.212, P < 0.001$) and frontal area ($\beta=-0.215, P < 0.001$), as well as cognitive functions including GCF ($\beta=-0.283, P < 0.001$), EF ($\beta=-0.364, P < 0.001$), IPS ($\beta=-0.326, P < 0.001$), VPF ($\beta=-0.184, P < 0.0014$), and memory ($\beta=-0.170, P < 0.024$).

Decreased CVR in left Occipital/Frontal regions caused cognitive decline through increasing WMH volume

To further explore whether decreased CVR lead to cognitive decline through WMH burdens, we performed mediation models among decreased CVR value, log-transformed WMH volume and cognitive performance controlling for age, sex, years of education, vascular risk factors, numbers of lacunars and...
cerebral microbleeds. Firstly, we found the relationship between left occipital CVR and cognitive performance was significantly mediated by WMH volume. Briefly, the indirect effect from decreased CVR in left occipital area to cognitive functions through WMH volume was 0.1354 in GCF (95% confidence interval: 0.0523, 0.2509, Fig. 5A), 0.1389 in EF (95% confidence interval: 0.0600, 0.2580, Fig. 5B), 0.1377 in IPS (95% confidence interval: 0.0542, 0.2803, Fig. 5C), 0.0919 in VPF (95% confidence interval: 0.0256, 0.2015, Fig. 5D), and 0.0691 in memory (95% confidence interval: 0.0018, 0.1681, Fig. 5E). Secondly, we found the associations between left frontal CVR and cognitive performance was significantly mediated by WMH volume. The detailed mediation paths were as follows: (1) indirect effect from decreased CVR in left frontal area to GCF through WMH volume was 0.1535 (95% confidence interval: 0.0591, 0.2979, Fig. 6A); (2) indirect effect from decreased CVR in frontal area to EF through WMH volume was 0.1607 (95% confidence interval: 0.0755, 0.2907, Fig. 6B); (3) indirect effect from decreased CVR in frontal area to IPS through WMH volume was 0.1596 (95% confidence interval: 0.0672, 0.3253, Fig. 6C); (4) indirect effect from decreased CVR in frontal area to VPF through WMH volume was 0.0948 (95% confidence interval: 0.0196, 0.2077, Fig. 6D); (5) indirect effect from decreased CVR in frontal area to general memory through WMH volume was 0.1607 (95% confidence interval: 0.0755, 0.2907, Fig. 6E).

Post hoc mediation model from WMH to cognitive performance through deceased CVR

In consideration of a potential factor associated with both WMH and CVR value in lead to a spurious mediation effect. We also performed post hoc mediation modal which hypothesis hypothesize CVR value results from WMH lesion, which leads to cognitive performance. We didn’t find any mediation effect in this pathway (all 95% confidence interval contains zero, Supplementary Table 1), suggesting that the mediation effect is specific to the hypothesized sequential order.

Discussion

In the present study, we used BOLD signal based on rs-fMRI to calculate the CVR in different grades of WMH subjects. We firstly found that with the degree of WMH aggravated, the CVR of left frontal and occipital areas decreased, and the cognitive tests score decreased. In all WMH subjects, mediation analysis revealed that impaired CVR in left frontal and occipital areas led to cognitive decline in different domains through WMH, suggesting that impaired CVR may be the initial cause of WMH, and then leading to WMH-related cognitive decline. Our results suggested that the CVR based on BOLD data could be used to monitor impaired brain regions in the potential risk of WMH and WMH-related cognitive decline. Additionally, this study provided a comprehensive understanding of the pathophysiology mechanisms regarding WMH progression and WMH-related cognitive decline.

Consistent with previous cross-sectional studies [33, 34], our study revealed that the brain CVR decreased in moderate or severe WMH individuals including gray matter and white matter areas. It remains unknown whether WMH causes reduced CVR due to decreased metabolic demand or whether reductions in CVR lead to the development of WMH. Animal models demonstrated cerebrovascular dysfunction appeared months ahead of the first histological evidence of white matter injury, including oligodendrocyte loss and
glial activation [35, 36]. Previous clinical studies followed up moderate-severe WMH patients for one year and found in comparison with contralateral normal appearing white matter (NA WM) that did not progress, NAWM that progressed to WMH had significantly decreased CVR value [30, 31]. This result suggested that impaired dynamic cerebrovascular response to hypercapnia precedes the occurrence of WMH and may result in the development of WMH. It is interesting to note that in our study, decreased CVR wasn’t directly related to cognitive decline, but caused cognitive decline through WMH, which indirectly indicating that the decrease of CVR may precede the occurrence of WMH. In terms of etiology, we can conclude that hemodynamic disorder represented by CVR may be an etiological factor of WMH, as well as WMH related cognitive decline.

Sequential evidences indicated that endothelial dysfunction may result in increased blood-brain barrier permeability with leakage of blood constituents into the vessel wall and white matter, and lead to increased arterial stiffness and persistent vasodilation/reconstruction that impairs vasoreactivity [37], which was crucial driver of CSVD [38–40]. The decrease of CVR represents low perfusion of brain tissue which may be a manifestation of endothelial dysfunction and impaired blood-brain barrier [41]. Therefore, assessment of CVR can provide early warning of the occurrence and development of WMH and WMH-related cognitive decline. Assessment of CVR by breath-holding index of middle cerebral arteries via transcranial doppler ultrasound has found global CVR decreased as the severity of WMH increased and associated with cognitive performance [34]. Findings from BOLD-based CVR studies remain controversial [16]. Some studies reported whole brain CVR was not related to WMH [42, 43], but others showed decreased CVR at baseline can predict the process of WMH lesions [18, 44, 45]. Based on previous studies, the current study confirmed that WMH was associated with decreased CVR again. What’s more, we further explore the relationships among decreased CVR, WMH and cognitive performance in different cognitive domains and found decreased CVR in left frontal and occipital areas was the initial cause of WMH related cognitive decline, suggesting that hemodynamic impairment may contribute to the pathogenesis and progression of WMH related cognitive decline.

Frontal and occipital areas are the main watershed regions bordered by the distal territories of the anterior, middle, and posterior cerebral arteries. In an event of hemodynamic compromise, peripheral circulation and small blood vessels in watershed areas are most susceptible to hypoperfusion, resulting in cerebral ischemia and hypoxia and thus more likely to develop ischemic lesion. A previous study revealed that the magnitude of the CVR decreased significantly with age in frontal white matter regions comprising the ACA-MCA watershed area[46]. Another study found hypertension with diabetes patients had decreased CVR in bilateral occipitoparietal areas [47]. In the present study, we found the CVR decline in left frontal and occipital areas may precede the occurrence of WMH. Therefore, combined with previous research findings and hemodynamic theory, we can conclude that CVR in frontal and occipital areas is more vulnerable to CVR damage and leading to WMH.

The current study is innovative and receivable for some of reasons. Firstly, we used BOLD signal based on rs-fMRI that does not require any specialized cooperation, resulting in higher patient compliance and research accuracy. Secondly, we enrolled patients with relatively homogeneous WMH subjects restricted
to CSVD populations. In order to rule out the effects of severe cerebral microbleeds, lacunar and other vascular risk factors, brain/hippocampus volume on cognitive function and cerebral perfusions in comparisons among groups, we used semiquantitative classification to group WMH patients in attempting to match the confounding factors of each group, so that these factors did not influence the conclusion. Additionally, in the regression analysis and mediation analysis, we controlled for all possible potential confounders including age, gender, education, numbers of cerebral microbleeds and lacunars, and other vascular risk factors.

This is an initial cross-sectional study investigating the effects of decreased CVR on WMH progress and WMH-related cognitive decline using BOLD signal based on re-fMRI. Several limitations should be addressed. Firstly, BOLD signal based on re-fMRI was just validated in large artery disease, Moyamoya disease and healthy individuals, which was not validated by clinically established prospective CO$_2$ targeting CVR method. So that, further studies with CO$_2$ validation should be recommended. Secondly, because our study population came from outpatients and inpatients in department of neurology, no healthy controls were included. A previous study via transcranial doppler ultrasound indicated that no significant difference in CVR between WMH-0 and WMH-I groups [34]. Whatever, future works should recruit healthy controls to verify whether CVR declines have existed in WMH-I subjects compared to healthy controls. Finally, the nature of this study is cross-sectional. No causal inferences, or directionality can be made. We are continuing to follow-up them to validate our findings.

**Conclusion**

The decreased CVR in left frontal and occipital areas derived from BOLD signal based on rs-fMRI is associated with WMH progress and is the initial cause of cognitive decline related to WMH, which suggesting that impaired CVR may contribute to the pathogenesis and progression of WMH and WMH related cognitive decline. Taking CVR analysis approach into consideration may be beneficial for early warning and diagnosis of WMH and WMH related cognitive decline, as well as providing a new insight into the pathophysiology of WMH.

**Abbreviations**

AVLT-DDR, auditory verbal learning test-long delayed recall; CDT, clock drawing test; CI cognitive impairment; CSVD, cerebral small vessel diseases; DTI, diffusion tensor imaging; EF, executive function; FLAIR, fluid-attenuated inversion recovery; GCF, global cognitive function; HAMA, Hamilton anxiety rating scale; HAMD, Hamilton depression rating scale; IPS, information processing speed; MMSE, mini mental state examination; MoCA-BJ, Beijing version of the Montreal cognitive assessment; SCWT, Stroop Color and Word Tests; TBV, total brain volume; TMT, trail making test; VPF, visuospatial processing function; VR-C, visual reproduction-copy; VR-DR, visual reproduction-delay recall; WMH, white matter hyperintensity.

**Declarations**
Ethics approval and consent to participate

This research was approved by the ethics committee of the Affiliated Drum Tower Hospital of Nanjing University and conducted in accordance with the principles of the Declaration of Helsinki. All subjects gave their informed consent prior to their inclusion in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have declared that no competing interest exists.

Founding

This research was supported by the National Key Research and Development Program of China (2016YFC1300504), the National Natural Science Foundation of China (81630028), the Key Research and Development Program of Jiangsu Province of China, Jiangsu Province Key Medical Discipline (ZDXKA2016020).

Authors’ contributions

YX designed this study. DY and LC wrote the manuscript. DY statistically analysed the data. HHX, LN helped analyse MRI data. RMQ, JYM, PFS, LLH, CML, MCL, ZLY, XNS, B helped collect data. YX and MJZ revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

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Tables
### Table 1: Demographic and clinical data among the three groups

| Items                        | WMH-I  | WMH-II | WMH-III | F/x² | P-value |
|------------------------------|--------|--------|---------|------|---------|
| **Demographics**             |        |        |         |      |         |
| Age (years)                  | 64.60±6.89 | 66.75±8.05 | 68.11±6.41<sup>a</sup> | 4.96 | 0.008   |
| Gender, male (% male)        | 59(52.67) | 39(51.32) | 24(42.86) | 1.52 | 0.468   |
| Education (years)            | 9(12,15) | 9(9,12) | 9(9,12) | 4.09 | 0.129   |
| **Vascular risk factors**    |        |        |         |      |         |
| Hypertension, n (%)          | 69(61.61) | 56(73.68) | 38(67.86) | 3.01 | 0.222   |
| Diabetes, n (%)              | 28(25.00) | 18(24.00) | 13(23.21) | 0.069 | 0.966   |
| Smoking, n (%)               | 19(17.75) | 16(23.53) | 12(23.53) | 1.14 | 0.566   |
| hyperlipemia, n (%)          | 20(18.87) | 19(26.76) | 10(19.23) | 1.763 | 0.414   |
| Lacunars, n (%)              | 28(25.00) | 12(15.78) | 19(33.93) | 5.86 | 0.053   |
| microbleeds, n (%)           | 27(24.11) | 29(38.16) | 21(37.50) | 5.33 | 0.07    |
| NO. Lacunars                 | 0(0,5) | 0(0,8) | 0(0,9) | 3.3 | 0.192   |
| NO. microbleeds              | 0(0,8) | 0(0,9) | 0(0,10) | 1.84 | 0.396   |
| **MRI data**                 |        |        |         |      |         |
| TBV (ml)                     | 1405.83±116.18 | 1410.40±133.41 | 1409.35±135.44 | 0.03 | 0.974   |
| WMH volume (ml)              | 2.00±1.42 | 5.38±1.84<sup>a</sup> | 17.59±10.79<sup>ab</sup> | 93.88 | <0.001  |
| Gray matter volume (ml)      | 572.42±47.36 | 567.08±50.51 | 551.45±55.91 | 2.84 | 0.061   |
| White matter volume (ml)     | 473.28±46.79 | 477.23±59.97 | 477.07±58.24 | 0.13 | 0.88    |
| Left hypothalamus volume (ml)| 0.31±0.33 | 0.31±0.32 | 0.31±0.28 | 1.07 | 0.345   |
| Right hypothalamus volume (ml)| 0.34±0.35 | 0.33±0.37 | 0.34±0.38 | 0.99 | 0.375   |
| **Mental status**            |        |        |         |      |         |
| HAMD                         | 5.58±4.60 | 6.18±5.23 | 6.35±4.93 | 0.56 | 0.57    |
| HAMA                         | 7.68±6.47 | 9.53±7.67 | 9.04±7.50 | 1.65 | 0.194   |

Values are presented as means ± standard deviation (SD), median with minimum and maximum.
or absolute numbers with percentages. P < 0.05 appears in bold. a P < 0.05, Statistically different from WMH I. b P < 0.05, Statistically different from WMH-II. HAMA, Hamilton anxiety rating Scale; HAMD, Hamilton depression rating scale; TBV, total brain volume; WMH, white matter hyperintensity.

Table 2 Cognitive evaluations among the three groups

| Cognitive evaluations | WMH-I       | WMH-II      | WMH-III     | F/x²  | P-value |
|-----------------------|-------------|-------------|-------------|-------|---------|
|                       | n=112       | n=76        | n=56        |       |         |
| GCF                   | 0.332±0.531 | -0.166±0.931a | -0.440±1.261a | 16.582 | <0.001  |
| MMSE                  | 0.221±0.532 | -0.091±1.091a | -0.318±1.417a | 6.140  | 0.003   |
| MoCA-BJ               | 0.444±0.652 | -0.243±0.955a | -0.561±1.231ab | 26.685 | <0.001  |
| EF                    | 0.235±0.569 | -0.089±0.777a | -0.350±0.859ab | 13.511 | <0.001  |
| TMT-B (minus value)   | 0.239±0.533 | -0.102±0.932a | -0.340±1.016a | 7.163  | 0.001   |
| SCWT-C (minus value)  | 0.232±0.683 | -0.076±1.100a | -0.361±1.257a | 7.211  | 0.001   |
| IPS                   | 0.276±0.413 | -0.129±0.960a | -0.377±1.960a | 13.851 | <0.001  |
| TMT-A (minus value)   | -0.230±0.533 | -0.072±1.154a | -0.363±1.333a | 7.201  | 0.001   |
| SCWT-A (minus value)  | 0.348±0.473 | -0.148±1.095a | -0.494±1.343ab | 16.250 | 0.001   |
| SCWT-B (minus value)  | 0.250±0.564 | -0.167±1.357a | -0.273±1.011a | 6.967  | 0.001   |
| Memory                | 0.233±0.719 | -0.155±0.799a | -0.254±0.855a | 9.546  | <0.001  |
| AVLT-DDR              | 0.257±0.888 | -0.187±1.078a | -0.261±0.995a | 7.303  | 0.001   |
| VR-DR                 | 0.208±0.974 | -0.124±0.956a | -0.248±1.042a | 4.880  | 0.008   |
| VPF                   | 0.149±0.650 | -0.015±0.758  | -0.278±1.003a | 5.670  | 0.004   |
| VR-C                  | 0.191±0.748 | -0.084±1.030  | 0.267±1.298a  | 4.430  | 0.013   |
| CDT                   | 0.107±0.963 | 0.055±0.869   | -0.289±1.185ab | 3.149  | 0.045   |

Values are presented as means ± standard deviation (SD). P < 0.05 appears in bold. a P < 0.05, Statistically different from WMH I group. b P < 0.05, Statistically different from WMH-II group. AVLT-DDR, auditory verbal learning test-long delayed recall; CDT, clock drawing test; EF, executive function; GCF, global cognitive function; IPS, information processing speed; MMSE, mini mental state examination; MoCA-BJ, Beijing version of the Montreal cognitive assessment; SCWT, Stroop Color and Word Tests; TBV, total brain volume; TMT, trail making test; VPF, visuospatial processing function; VR-C, visual reproduction-copy; VR-DR, visual reproduction-delay recall; WMH, white matter hyperintensity.
### Table 3 Brain regions displayed different CVR among the three groups

| Brain areas          | Peak MNI coordinate x, y, z (mm) | Peak F value | Number of cluster voxels |
|----------------------|----------------------------------|--------------|--------------------------|
| Left occipital area  | -30, -60, 21                     | 10.488       | 171                      |
| Left frontal area    | -24, -15, 51                     | 9.701        | 104                      |

The voxel Z threshold <0.001 with Gaussian Random Field (GRF) correction (voxel p threshold for the minimum cluster size < 0.001 and cluster p threshold <0.01) for multiple comparisons. MNI, Montreal Neurological Institute.

### Table 4 Correlations of WMH volume with Occipital/Frontal areas CVR and cognitive performance

| Items            | Standardized Coefficients β | 95% confidence interval       | P-value |
|------------------|-----------------------------|--------------------------------|---------|
| Left occipital area | -0.212                      | -0.368, -0.122                 | <0.001  |
| Left frontal area   | -0.215                      | -0.420, -0.146                 | <0.001  |
| GCF               | -0.283                      | -0.845, -0.319                 | <0.001  |
| EF                | -0.364                      | -0.839, -0.367                 | <0.001  |
| IPS               | -0.326                      | -0.865, -0.326                 | <0.001  |
| memory            | -0.17                       | -0.568, -0.040                 | 0.024   |
| VPF               | -0.184                      | -0.580, -0.066                 | 0.014   |

EF, executive function, GCF, general cognitive function, IPS, information processing speed, VPF, visuospatial processing function.
Figures

Study cohort of CSVD (n=820)

inclusion and exclusion criteria

WMH patients (n=244)

Fazekas rating scale

WMH-I (n=112)  WMH-II (n=76)  WMH-III (n=56)

The baseline data including demographic data, vascular risk factors. Neuropsychological examination and CVR assessment based on rs-fMRI.

Figure 1

Diagrammatic sketch of the screening process. CSVD, cerebral small vessel disease; CVR, Cerebrovascular reactivity; rs-fMRI, resting-statefunctional MRI; WMH, White matter hyperintensity.
Figure 2

Axial atlas images of the CVR magnitude for each WMH cohort. A: WMH-I group, B: WMH-II group, C: WMH-III group.
Figure 3

CVR differences among the three groups. The result was corrected by Gaussian Random Field with setting voxel p threshold for the minimum cluster size < 0.001 and cluster p threshold <0.01.
Figure 4

Post-hoc analyses of CVR differences in left occipital and frontal areas. There was a decreasing trend of CVR in left frontal and occipital areas as the WMH increased. (A) Subjects in the WMH-II and WMH-III group displayed significantly lower CVR in left frontal occipital area than WMH-I group (B) Subjects in the WMH-II and WMH-III group displayed significantly lower CVR in left occipital area than WMH-I group. CVR, cerebrovascular reserve; WMH, white matter hyperintensity.
Figure 5

Path models of decreased CVR in left occipital on cognitive performance through WMH by the mediation analysis. Significant pathways were highlighted in bold characters. For each connection, the standard coefficient (a, b, c, c') and P value were shown. The indirect mediation effect (a×b) and its 95% confidence interval was also showed. EF, executive function; GCF, general cognitive function; IPS, information processing speed; VPF, visuospatial processing function; WMH, white matter hyperintensity.
Figure 6

Path models of decreased CVR in left frontal on cognitive performance through WMH by the mediation analysis. Significant pathways were highlighted in bold characters. For each connection, the standard coefficient ($a$, $b$, $c$, $c'$) and $P$ value were shown. The indirect mediation effect ($a \times b$) and its 95% confidence interval was also showed. EF, executive function, GCF, general cognitive function, IPS, information processing speed, VPF, visuospatial processing function, WMH, white matter hyperintensity.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.xlsx