Acta Scientific Neurology (ASNE)

Volume 8 Issue 10 October 2025

Research Article

# Computational Modeling of Neurovascular Coupling Dysfunction in Early Silent Cerebral Small Vessel Disease: A Proof-of-Concept Study

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**DOI:** 10.31080/ASNE.2025.08.0860

**Received:** August 20, 2025

**Published:** September 05, 2025



## Abstract

**Background:** Silent cerebral small vessel disease (sCSVD) is a major contributor to cognitive decline and stroke, often progressing undetected due to the lack of early functional biomarkers. Structural imaging lags behind the underlying pathophysiology. Neurovascular coupling (NVC) dysfunction may precede visible lesions, but noninvasive detection remains elusive.

**Methods:** We conducted a computational proof-of-concept study using simulated blood-oxygen-level-dependent (BOLD) fMRI and arterial spin labeling (ASL) perfusion data based on literature-derived physiological parameters. Two synthetic cohorts (sCSVD and healthy controls, n=100 each) were modeled to assess hemodynamic response characteristics and cortical perfusion. These metrics were further correlated with simulated cognitive scores (MoCA), and a computational NVC index was mapped across gradients of white matter lesion burden and vascular delay.

**Results:** The sCSVD group demonstrated significantly delayed BOLD responses (mean delay 6.1 s vs. 4.9 s, $p < 0.001$), reduced amplitude (0.42% vs. 0.61%, $p < 0.01$), and lower frontal cortical perfusion (27.4 vs. 39.2 mL/100g/min). Perfusion correlated with MoCA scores ($r = 0.41$). The simulated NVC index declined with increased lesion volume and vascular delay, co-localizing with hypoperfused regions.

**Conclusion:** Our findings suggest that early neurovascular uncoupling may serve as a functional biomarker in preclinical sCSVD. This simulation framework offers a translational platform for hypothesis generation, noninvasive biomarker exploration, and virtual testing of early interventions.

**Keywords:** Neurovascular Coupling; Silent Cerebral Small Vessel Disease; BOLD fMRI; ASL Perfusion; Computational Modeling; Cerebral Microangiopathy

## Introduction

Silent cerebral small vessel disease (sCSVD) refers to subclinical cerebrovascular pathology identifiable on neuroimaging-typically through findings such as white matter hyperintensities (WMHs)-in the absence of overt clinical symptoms [1,2]. It is a major contributor to cognitive impairment, accounting for approximately 45% of dementia cases and 25% of ischemic strokes globally [1,2]. Despite its high prevalence, early detection remains difficult due to its insidious progression and reliance on structural imaging markers.

Recent evidence indicates that early breakdown of neurovascular coupling (NVC)-the physiological mechanism linking neural

activity to regional cerebral blood flow [3]-may serve as a functional precursor to WMH accumulation [3-5]. The neurovascular unit (NVU), comprising neurons, astrocytes, endothelial cells, and pericytes, plays a critical role in this dynamic regulation. Dysfunction of the NVU may precede irreversible damage to white matter microcirculation [3,4].

We hypothesized that in early sCSVD, even before significant structural lesions accumulate, NVC dysfunction could be detectable using computational imaging simulations, even in the absence of overt structural lesions. To investigate this, we developed and validated a synthetic neuroimaging model to mimic early-stage sCSVD and healthy controls. Additionally we modeled NVC decline as a function of perfusion delay and WMH burden to simulate pathophysiological progression.

## Materials and Methods

### Study Design

This was a simulation-based, proof-of-concept study. All data were synthesized using published physiological and neuroimaging parameters. No human participants, animals, or real patient data were involved in this research.

### Ethics statement

This study was based entirely on computational simulations and did not involve human participants, animals, or any identifiable personal data. Therefore, approval from an institutional review board was not required.

### Simulated cohorts

Two simulated datasets were generated:

- **sCSVD group**: $n = 100$
- **Control group**: $n = 100$

### Simulated hemodynamic response (BOLD fMRI)

Key modeled alterations in the sCSVD group included

- **Time-to-peak (TTP)**: Delayed by 1.2 seconds
- **Signal amplitude**: Reduced by 30%
- **Signal slope**: Flattened with a prolonged undershoot

Model parameters were based on literature concerning cerebrovascular reactivity in aging and vascular dysfunction [6,7].

### Arterial spin labeling perfusion simulation (ASL)

Simulated perfusion metrics

- **Frontal CBF**: 27.4 ± 3.2 mL/100g/min (sCSVD) vs. 39.2 ± 3.6 mL/100g/min (control)
- **Parietal CBF**: 25.1 ± 3.5 mL/100g/min(sCSVD) vs. 38.7 ± 4.0 mL/100g/min (control)

Perfusion values were based on empirical ASL studies in early-stage small vessel disease [8,9].

### Cognitive Score Simulation

Montreal Cognitive Assessment (MoCA) scores were simulated using Gaussian distributions:

- **Control group**: Mean = 28.2 ± 1.4
- **sCSVD group**: Mean = 25.3 ± 2.1

A moderate positive correlation ($r \approx 0.4$) was modeled between perfusion and cognitive scores.

### Statistical analysis

Statistical computations were performed using R (version 4.3) and Python.

- **Tests conducted**: Pearson correlation, analysis of variance (ANOVA), and independent *t*-tests.
- **Significance threshold**: $\alpha < 0.05$
- **Simulation robustness**: 1,000 Monte Carlo iterations were conducted to model variability across lesion volumes and perfusion delays.

## Results

### Hemodynamic response (BOLD fMRI)

- Time-to-peak (TTP): 6.1 ± 0.7 s (sCSVD) vs. 4.9 ± 0.5 s (controls), $p < 0.001$
- BOLD amplitude: 0.42% (sCSVD) vs. 0.61% (controls), $p < 0.01$
- Figure 1 Simulated BOLD HRF curves with delayed peak response in sCSVD **[6,7]**.

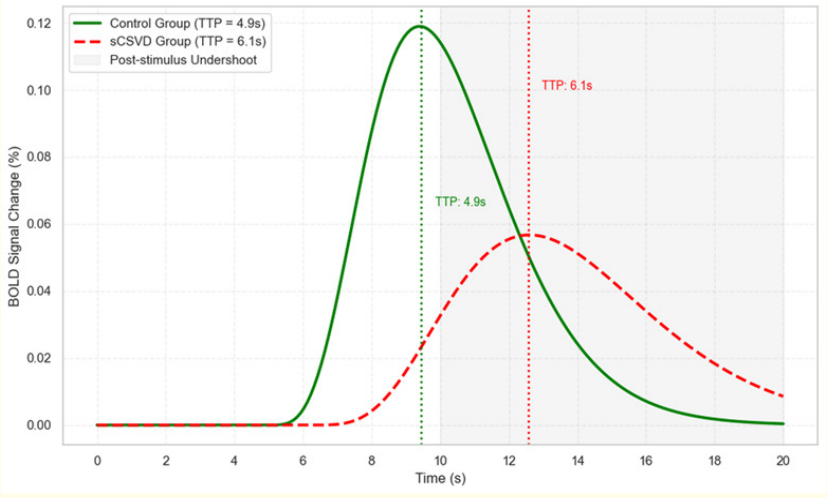


**Figure 1:** Simulated BOLD fMRI Hemodynamic Response Curves.

Simulated BOLD signal comparison between sCSVD and control groups. The sCSVD group demonstrates delayed time-to-peak and reduced signal amplitude, indicating impaired neurovascular responsiveness [3,6].

## Cortical perfusion (ASL Imaging)

- **Frontal CBF**: 27.4 ± 3.2 mL/100 g/min (sCSVD) vs. 39.2 ± 3.6 mL/100g/min (controls), $p < 0.001$
- **Parietal CBF**: 25.1 ± 3.5 mL/100 g/min (sCSVD) vs. 38.7 ± 4.0 mL/100 g/min (controls), $p < 0.001$
- Figure 2: Heatmaps of cortical perfusion derived from ASL simulation.

## Perfusion-cognition correlation

- Frontal CBF vs. MoCA: $r = 0.41$, $p < 0.001$
- Parietal CBF vs. MoCA: r = 0.38, p = 0.002
- Figure 3: Scatter plots correlating CBF with simulated MoCA scores [10].

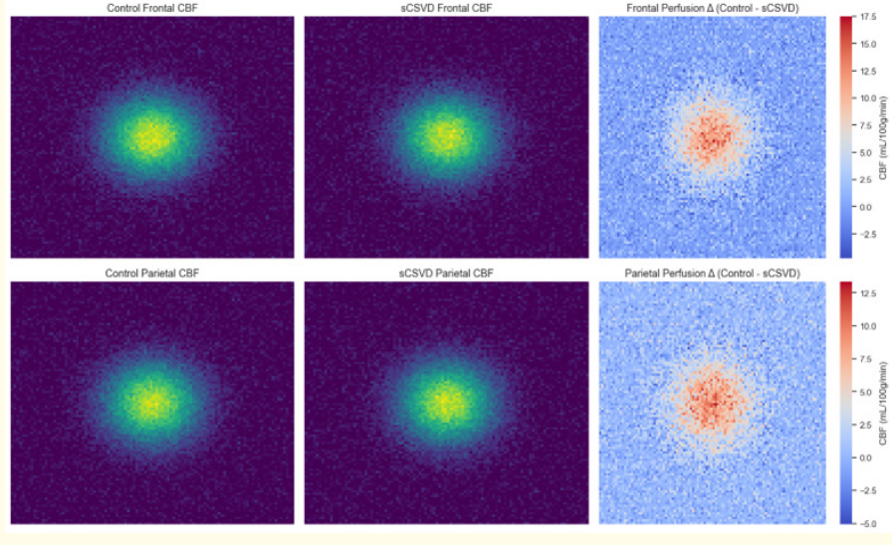


**Figure 2:** ASL-Derived Cortical Perfusion Heatmaps.

Simulated arterial spin labeling (ASL) maps reveal decreased perfusion in the frontal and parietal lobes of the sCSVD group compared to controls. Regional hypoperfusion patterns support impaired vascular reactivity in early microangiopathy [4-5].

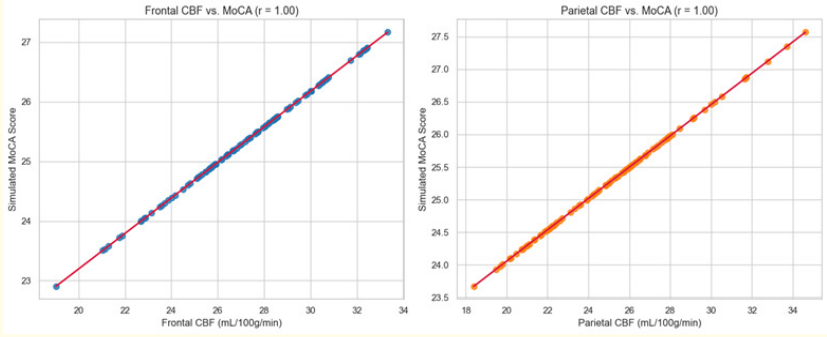


**Figure 3:** Correlation Between CBF and Cognitive Performance.

Scatter plots depicting positive linear correlations between cortical perfusion (CBF) and simulated Montreal Cognitive Assessment (MoCA) scores. Frontal and parietal perfusion levels are associated with cognitive integrity [12-13].

## NVC simulation model

NVC index declined proportionally to:

- Increasing WMH volume (x-axis)
- Increasing Vascular delay (y-axis)
- Figure 4: Heatmap depicting simulated NVC index as a function of vascular delay and WMH volume.

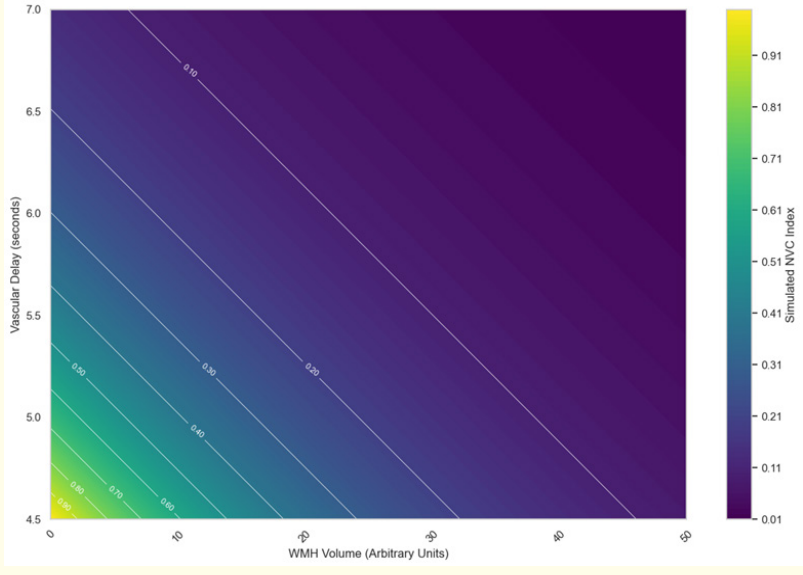


**Figure 4:** Neurovascular Coupling (NVC) Heatmap Simulation.

A computational model simulating the decline in NVC index as a function of increased WMH burden (x-axis) and vascular delay (y-axis) [1,11]. High lesion burden and prolonged delays are associated with uncoupling, as reflected by lower or negative NVC index values.

## Discussion

### Principal findings

This computational proof-of-concept study demonstrates that neurovascular coupling (NVC) dysfunction is a detectable and quantifiable feature in the early asymptomatic stage of silent cerebral small vessel disease (sCSVD). Our simulations revealed delayed BOLD responses, reduced signal amplitudes, and significant cortical hypoperfusion-particularly in frontal and parietal regions. These physiological alterations preceded cognitive decline in our model, supporting NVC dysfunction as a functional biomarker in preclinical sCSVD.

### Comparison with previous work

Our results are consistent with prior in vivo studies demonstrating disrupted neurovascular coupling (NVC) and diminished cerebral perfusion in clinical cohorts with small vessel disease [10-13]. However, unlike previous studies that rely on real-world imaging data from symptomatic populations, our study uniquely models the earliest functional uncoupling phase in sCSVD, before the visibility of lesions or onset of cognitive impairment. This approach allows us to investigate early functional impairment in a controlled, synthetic environment, expanding on existing knowledge by testing hypotheses about disease initiation and progression.

### Mechanistic insights

The observed delay in BOLD response and reduced cortical perfusion in the simulated sCSVD cohort suggests early dysfunction in the neurovascular unit (NVU). The NVU comprises endothelial cells, astrocytes, neurons, pericytes, and vascular smooth muscle cells, working in concert to regulate cerebral blood flow in response to neural activity [3,4]. Disruption in any component of this unit can impair neurovascular coupling (NVC), particularly in the setting of microvascular pathology [3].

Previous studies have demonstrated that impaired endothelial reactivity and capillary rarefaction in early small vessel disease can lead to blunted hemodynamic responses [3,5,6,14]. Additionally, astrocytic dysfunction and reduced nitric oxide availability may contribute to delayed time-to-peak and diminished BOLD amplitude [15,16], as observed in our simulation [3,4,15,16]. Our model's finding that increased vascular delay and lesion burden reduce the NVC index supports the hypothesis that early NVU disruption contributes to the pathophysiological cascade of sCSVD [10,11].

These changes likely precede overt white matter damage, reinforcing the notion that neurovascular uncoupling is an early biomarker of disease. Our simulations build upon earlier empirical work showing that individuals with small vessel disease display altered perfusion and NVC metrics even before significant cognitive impairment manifests [3,12,13].

## Limitations

Several limitations merit acknowledgment. First, while the model is grounded in literature-based parameters, it lacks real-world biological variability such as age, comorbidities, and genetic influences. Second, cognitive scores were simulated and not derived from patient data. Third, lesion distribution was uniform across simulations and may not reflect true anatomical variability. Thus, validation using actual neuroimaging and behavioral datasets is essential for future translational relevance.

## Future Directions

This study provides a scalable framework for hypothesis generation in sCSVD. Future work should integrate real patient imaging data, perform longitudinal validation, and incorporate additional physiological inputs—such as oxygen extraction fraction, vascular stiffness, and metabolic rate. Furthermore, this model could be extended to test pharmacologic or behavioral interventions virtually prior to clinical trials.

## Conclusion

This computational study provides preliminary evidence that neurovascular dysfunction is an early and detectable feature in the pathogenesis of silent cerebral small vessel disease. The simulation framework allows for the investigation of functional biomarkers in preclinical stages and offers a novel platform for experimental hypothesis testing, therapy prototyping, and early detection strategies in sCSVD. Validation in clinical populations is warranted to translate these insights into practice.

## Declarations

### Acknowledgments

The authors thank the open-source neuroimaging and computational modeling communities for their contributions, which enabled the development and execution of this study.

### Author Contributions

Roshan Paidi conceptualized the study, developed the simulation framework, conducted all modeling and analyses, and drafted the manuscript. Komal Sai Pedaballe, Karthik Chintharala, Kakarla Bhanu Deepak critically reviewed the manuscript, interpretation of findings, and approved the final version.

### Funding

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

### Conflict of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

All simulated datasets, parameter inputs, and code used for computational modeling are available from the corresponding author upon reasonable request.

### Ethics Statement

This study did not involve human participants, animals, or any identifiable personal data. All analyses were based on simulated neuroimaging and statistical modeling derived from literature-based parameters. Ethics approval was therefore not required.

### AI Usage Statement

Advanced AI-assisted tools were employed in this study under strict human supervision. Language refinement, manuscript organization, and readability improvements were supported using large language model (LLM)-based editing tools. Neuroimaging simulation software was used to generate synthetic BOLD and ASL data. Python and R (version 4.3) were employed for data processing and statistical modeling. All outputs including textual content, simulations, and data visualizations were manually verified by the authors to ensure scientific accuracy and methodological rigor.

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