Cognition, apathy, and gait dysfunction in cerebral small vessel disease: A shared neural basis?

Hao Li, Mengfei Cai, Anil Man Tuladhar*

Cerebral small vessel disease (SVD) represents a range of pathological changes in the small blood vessels of the brain. SVD can be detected on MRI, which includes white matter hyperintensities, lacunes, and cerebral microbleeds (Duering et al., 2023). Patients with SVD exhibit significant clinical heterogeneity, often presenting with cognitive impairment, apathy, gait dysfunction, and lacunar stroke (Wardlaw et al., 2019). The chronic and progressive symptoms, such as cognitive and motor complaints, as well as mood disorders, continuously affect SVD patients. This, in turn, often results in a loss of functional independence and a diminished quality of life (Wardlaw et al., 2019). Previous studies have focused on unraveling the underlying mechanisms, the trajectory, and the potential clinical outcomes of these specific symptoms (e.g., cognitive impairment, apathy, and gait dysfunction) in SVD (Wardlaw et al., 2019). However, these studies typically investigated each symptom individually, without integrating these symptoms to provide a comprehensive understanding.

A shared neural basis underlying cognition, apathy, and gait dysfunction in small vessel disease: Recently, we systematically investigated cognitive impairment, apathy, and gait dysfunction using a comprehensive cognitive test battery including processing speed, executive function, and memory, the Apathy Evaluation Scale, and motor tests, including mean time and step numbers in the Timed Up and Go test in 213 participants with sporadic SVD from the Radboud University Nijmegen Diffusion tensor and Magnetic resonance imaging Cohort study (Li et al., 2024). Our study was built on the assumption that cognitive impairment, apathy and gait dysfunctions occur simultaneously and may therefore be interrelated with each other. This assumption has been partly supported by previous findings. For example, a previous study has shown that apathy was associated with cognitive impairment in SVD (Lohner et al., 2017). Additionally, neuropsychological research on sporadic SVD and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, a rare monogenetic form of SVD, demonstrated that dysfunctional effort-based decision-making might be a cognitive basis for apathy (Le Heron et al., 2018). Moreover, gait dysfunction was linked to cognitive impairment in individuals with SVD (Cai et al., 2022), and to apathy in those with subcortical vascular dementia (Moretti et al., 2015). On the basis of these findings, we further related cognition, apathy, and gait dysfunction together by showing close correlations among these measurements for cognition, apathy, and gait in our study sample. Using principal component analysis, an advanced dimension-reduction statistical approach, we identified a common component for these three symptoms, with higher values indicating worse composite performance in cognition, apathy, and gait. This principal component analysis-derived component indicates that cognition, apathy, and gait are not only inter-related statistically, but carry important implications clinically.

Given the observation of a common component underlying cognitive impairment, apathy and gait dysfunction in SVD, we argued that a shared neural basis for these three symptoms may exist. Although the direct evidence is limited, previous studies suggested that grey matter atrophy or white matter microstructural damage within the dopamine reward circuit could be the potential mechanism of apathy in sporadic SVD (Tay et al., 2019), genetic SVD (Le Heron et al., 2018), and cerebral amyloid angiopathy (Chokesuwattanaskul et al., 2023), another type of SVD characterized by the cerebrovascular accumulation of amyloid-β. Additionally, the dopaminergic system in the brain, especially the meso-cortical and meso-limbic pathways, is known to be key structures for cognitive control, mood regulation, and motor function. Therefore, we employed the neuroimaging fiber tracking (i.e., tractography on diffusion-weighted images) and reconstructed white matter tracts within the meso-cortical pathway and meso-limbic pathway. We found that white matter damages, quantified by the diffusion metric (i.e., free water), within the meso-cortical pathway were related to cognitive impairment, apathy, gait dysfunction, as well as to the common principal component in our SVD sample.

These findings have provided preliminary evidence suggesting that cognitive impairment, apathy, and gait dysfunction in SVD are interrelated and exist as a common component, representing a composite performance in these three symptoms. Furthermore, damage to the meso-cortical white matter pathway may serve as the shared neural basis underlying these three clinical features (**Figure 1**).

Clinical relevance of these findings: This study is of clinical relevance. First, given the fact that the three major symptoms are closely related to each other, their composite performances may serve as a more comprehensive and effective outcome measure in related clinical trials. In addition, clinicians should be aware of the increased risk of other symptoms developing when a patient presents with one of these symptoms. Second, the dopamine system function in the brain may serve as a potential therapeutic target for these symptoms in SVD. Dopaminergic medications have been employed clinically to improve cognitive decline and gait disturbances. These medications have also shown potential efficacy against apathy in several clinical trials for Alzheimer's disease and Parkinson's disease, though results have been inconsistent (Cummings et al., 2024). Therefore, our findings, along with previous evidence, provide a basis for further investigation into dopamine-targeted treatments to mitigate cognitive decline, apathy, and gait dysfunction, thereby improving clinical outcomes and quality of life in SVD.

Critical interpretation of these findings: We acknowledge several limitations of our study before drawing definitive conclusions. Due to the limited sample size (n = 213) and the lack of specific criteria used to identify patients with cognitive impairment, we were unable to accurately estimate the prevalence of each clinical symptom individually or the prevalence of overlapping symptoms (i.e., the co-occurrence of two or three symptoms among cognitive impairment, apathy, and gait dysfunction) in SVD. A validation study with a larger sample size or a meta-analysis would be beneficial in providing a more accurate estimate of the co-occurrence of these three symptoms in the SVD population. In addition, previous studies have shown that apathy in SVD could predict all-cause dementia in this population (Tay et al., 2020), and that there was a faster progression of gait dysfunction

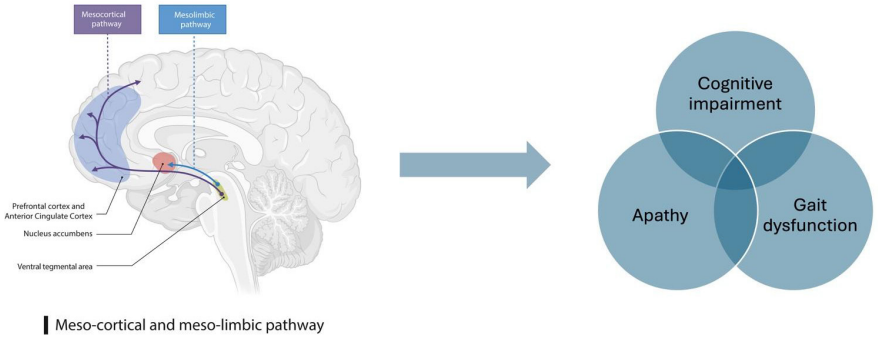

Figure 1 | **Relation between meso-cortical and meso-limbic pathway damage and cognitive impairment, apathy and gait dysfuction in cerebral small vessel disease.**
Meso-cortical pathway (purple solid line): white matter tracts projecting from the ventral tegmental area to the prefrontal cortex and anterior cingulate cortex; meso-limbic pathway (blue solid line): white matter tracts projecting from the ventral tegmental area to the nucleus accumbens. Created with BioRender.com.

among SVD patients who eventually developed dementia (Bergkamp et al., 2024). Therefore, it is crucial to assess whether the onset of apathy or gait dysfunction accelerates cognitive decline and the development of dementia, as well as to determine the effect size of this acceleration. Such investigations may help identify patients at high risk of dementia and optimize early-stage management strategies for these patients. When investigating the neural underpinnings of cognitive impairment, apathy, and gait dysfunction in SVD, we focused on the white matter tracts within the mesocortical and mesolimbic pathways. Our analyses established a potential link between the mesocortical pathway damage and these symptoms, suggesting such damage may serve as a common neural basis for these manifestations in SVD. However, interpreting mesocortical white matter pathway damage as indicative of dopamine dysfunction should be made with caution. The identification of these tracts within the meso-cortical and meso-limbic pathways was achieved solely using the tractography on diffusion imaging, incorporating constraints from several anatomical regions within the dopamine circuit. Although these tracts are primarily innervated by dopaminergic neurons, some spatial overlaps with fibers innervated by other neurotransmitters may exist, such as glutamatergic thalamic projections. Future studies employing dopamine-specific PET imaging are crucial to assist in identifying dopaminergic fibers within the mesocortical and mesolimbic systems, thereby further validating our findings.

Other potential structural underpinnings and future directions: In addition to the damage to white matter tracts within the mesocortical and mesolimbic pathways, our previous study suggested an association between striatal atrophy and both apathy and cognitive impairment in another independent sporadic SVD cohort (Li et al., 2023). Consequently, it can be hypothesized that volume loss, microstructural abnormalities, and other pathological changes in the gray matter nuclei of the dopamine circuit may serve as additional neural mechanisms underlying these symptoms (i.e., cognitive impairment, apathy, and gait dysfunction) in SVD. Moreover, a previous study has suggested that damage to the cholinergic system was associated with these symptoms in Parkinson's disease (Bohnen and Albin, 2011). It would be interesting to reconstruct the cholinergic white matter pathway similar to those used in our study and assess whether cholinergic deficits could also lead to impaired performance in SVD. Nevertheless, additional studies are required to elucidate the impact of neurotransmitter functions, particularly those of the dopaminergic and the cholinergic systems, on these clinical manifestations in SVD. This might help to identify new treatment targets and lead to the development of novel therapeutic approaches for SVD.

In addition to these hypothesis-driven analyses, data-driven whole-brain analyses may facilitate an exploration of the neural basis of these three symptoms in SVD. For example, lesion-symptom mapping, combined with the recent developed neuroimaging approach of lesion-network mapping, which analyzes the locations of brain lesions and determine how these lesions disrupt connectivity within the brain's functional or structural networks (Joutsa et al., 2022), could be instrumental in identifying strategic lesions and lesion-related networks that significantly contribute to the three symptoms and their common components in SVD. Furthermore, the use of Voxel-Based Morphometry or Tract-Based Spatial Statistics can identify these regions in brain that significantly associated with each symptom of cognitive impairment, apathy, and gait dysfunction in SVD. The identification of these regions could further delineate the overlapping areas associated with both these symptoms in SVD, thereby offering a deeper and more comprehensive understanding of the shared neural basis of these conditions.

Conclusions: Overall, the current body of evidence suggests the interconnected nature and the existence of common component of cognitive impairment, apathy and gait dysfunction in SVD. Our study found that damage to meso-cortical white matter pathway has the potential to serve as the shared neural basis underlying these specific symptoms in SVD. This finding not only enhances our understanding of the complex mechanisms behind these clinical features, but also opens new avenues for targeted interventions in SVD. Future studies employing neurotransmitter-specific imaging techniques and other advancing methods such as lesion-network mapping, are expected to further clarify the complex interrelations among these symptoms and their neural underpinnings. Ultimately, these insights are poised to drive the development of novel management and therapeutic strategies, aimed at mitigating the profound impact of SVD pathology on patients' cognitive, mood, and motor functions, and overall quality of life.

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Hao Li, Mengfei Cai, Anil Man Tuladhar*
Radboud University Medical Center, Department of Neurology; Radboud Institute for Medical Research and Innovation and Donders Institute for Brain, Cognition and Behavior, Nijmegen, The Netherlands (Li H, Cai M, Tuladhar AM)
Department of Neurology, Guangdong Neuroscience Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou, Guangdong Province, China (Cai M)
***Correspondence to:** Anil Man Tuladhar, MD, PhD, Anil.Tuladhar@Radboudumc.nl.
https://orcid.org/0000-0002-4815-2834 (Anil Man Tuladhar)
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References

Bergkamp MI, Jacob MA, Cai M, Claassen JA, Kessels RPC, Esselink R, Tuladhar AM, De Leeuw FE (2024) Long-term longitudinal course of cognitive and motor symptoms in patients with cerebral small vessel disease. Neurology 102:e209148.

Bohnen NI, Albin RL (2011) The cholinergic system and Parkinson disease. Behav Brain Res 221:564-573.

Cai M, Jacob MA, Norris DG, de Leeuw FE, Tuladhar AM (2022) Longitudinal relation between structural network efficiency, cognition, and gait in cerebral small vessel disease. J Gerontol A Biol Sci Med Sci 77:554-560.

Chokesuwattanaskul A, Zanon Zotin MC, Schoemaker D, Sveikata L, Gurol ME, Greenberg SM, Viswanathan A (2023) Apathy in patients with cerebral amyloid angiopathy: a multimodal neuroimaging study. Neurology 100:e2007-2016.

Cummings J, Lanctot K, Grossberg G, Ballard C (2024) Progress in pharmacologic management of neuropsychiatric syndromes in neurodegenerative disorders: a review. JAMA Neurol 81:645-653.

Duering M, et al. (2023) Neuroimaging standards for research into small vessel disease-advances since 2013. Lancet Neurol 22:602-618.

Joutsa J, Corp DT, Fox MD (2022) Lesion network mapping for symptom localization: recent developments and future directions. Curr Opin Neurol 35:453-459.

Le Heron C, Manohar S, Plant O, Muhammed K, Griffanti L, Nemeth A, Douaud G, Markus HS, Husain M (2018) Dysfunctional effort-based decision-making underlies apathy in genetic cerebral small vessel disease. Brain 141:3193-3210.

Li H, Cui L, Wang M, Liao M, Li JB, Ouyang F, Mei T, Zen H, Fan Y (2023) Apathy is associated with striatal atrophy and cognitive impairment in cerebral small vessel disease. J Affect Disord 328:39-46.

Li H, Jacob MA, Cai M, Kessels RPC, Norris DG, Duering M, de Leeuw FE, Tuladhar AM (2024) Meso-cortical pathway damage in cognition, apathy and gait in cerebral small vessel disease. Brain doi: 10.1093/brain/awae145.

Lohner V, Brookes RL, Hollocks MJ, Morris RG, Markus HS (2017) Apathy, but not depression, is associated with executive dysfunction in cerebral small vessel disease. PLoS One 12:e0176943.

Moretti R, Cavressi M, Tomietto P (2015) Gait and apathy as relevant symptoms of subcortical vascular dementia. Am J Alzheimers Dis Other Demen 30:390-399.

Tay J, Tuladhar AM, Hollocks MJ, Brookes RL, Tozer DJ, Barrick TR, Husain M, de Leeuw FE, Markus HS (2019) Apathy is associated with large-scale white matter network disruption in small vessel disease. Neurology 92:e1157-1167.

Tay J, Morris RG, Tuladhar AM, Husain M, de Leeuw FE, Markus HS (2020) Apathy, but not depression, predicts all-cause dementia in cerebral small vessel disease. J Neurol Neurosurg Psychiatry 91:953-959.

Wardlaw JM, Smith C, Dichgans M (2019) Small vessel disease: mechanisms and clinical implications. Lancet Neurol 18:684-696.

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