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Small vessel disease burden and functional brain connectivity in mild cognitive impairment

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ABSTRACT

Background: The role of small vessel disease in the development of dementia is not yet completely understood. Functional brain connectivity has been shown to differ between individuals with and without cerebral small vessel disease. However, a comprehensive measure of small vessel disease quantifying the overall damage on the brain is not consistently used and studies using such measure in mild cognitive impairment individuals are missing.

Method: Functional brain connectivity differences were analyzed between mild cognitive impairment individuals with absent or low (n = 34) and high (n = 34) small vessel disease burden using data from the Parelsnoer Institute, a Dutch multicenter study. Small vessel disease was characterized using an ordinal scale considering: lacunes, microbleeds, perivascular spaces in the basal ganglia, and white matter hyperintensities. Resting state functional MRI data using 3 Tesla scanners was analyzed with group-independent component analysis using the CONN toolbox.

Results: Functional connectivity between areas of the cerebellum and between the cerebellum and the thalamus and caudate nucleus was higher in the absent or low small vessel disease group compared to the high small vessel disease group.

Conclusion: These findings might suggest that functional connectivity of mild cognitive impairment individuals with low or absent small vessel disease burden is more intact than in mild cognitive impairment individuals with high small vessel disease. These brain areas are mainly responsible for motor, attentional and executive functions, domains which in previous studies were found to be mostly associated with small vessel disease markers. Our results support findings on the involvement of the cerebellum in cognitive functioning.

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1. Introduction

The term cerebral small vessel disease (SVD) is used to describe a syndrome of clinical, cognitive, neuroimaging, and neuropathological findings, that is found in up to 45 % of dementia cases [1,2]. The neuroimaging lesions characteristic of SVD include small subcortical infarcts, white matter hyperintensities and lacunes of presumed vascular origin, perivascular spaces, cerebral microbleeds, superficial siderosis, and brain atrophy [2]. These lesions are thought to lead to clinical features such as cognitive impairment and abnormal behavior through functional and structural brain network changes and brain atrophy [3].

Brain functional network integrity can be assessed *in-vivo* using resting state functional MRI (rs-fMRI), which measures brain activation during rest by using blood-oxygenated-level-dependent imaging (BOLD). Brain functional connectivity, as derived from rs-fMRI, is a measure of temporal correlation between BOLD signals from different brain areas [4]. Individuals from the Alzheimer's Disease spectrum with cortical infarcts, two or more lacunes, and confluent white matter lesions were shown to have different functional connectivity phenotypes, measured with rs-fMRI, compared to those without lesions [5]. Also, white matter hyperintensities seemed to disrupt the integrity of brain functional networks of healthy individuals and individuals with mild cognitive impairment (MCI) [6]. Evidence of brain functional connectivity changes in the presence of SVD has been recently summarized and highlights disturbed connectivity in the default mode network, frontoparietal control network, and salience network [7].

The presence of SVD has been recognized as a risk factor for dementia and Alzheimer's disease in the general population [8]. Additionally, small vessel neuropathology, namely arteriosclerosis, was associated with higher odds of Alzheimer's disease dementia and worse cognition in a postmortem study [9]. While this relationship is established, the role of SVD in the development of dementia is still not completely understood. Individuals with mild cognitive impairment are a relevant group to further investigate the role of SVD since vascular mechanisms could be in play before and as early as mild cognitive changes begin [10]. As recently reviewed, [7], most studies examining functional connectivity differences in the presence of SVD compare individuals with MCI and SVD to cognitively unimpaired individuals rather than to MCI individuals with different SVD burdens. Additionally, only one or two markers of vascular lesions have been used in these studies to characterize SVD. Previous studies, however, have claimed that considering all SVD markers allows quantifying the overall brain damage resulting from SVD on the brain, so more comprehensively than by using the individual features separately [11,12].

In this study, we hypothesize that the presence of SVD might lead to alterations in neuronal networks in individuals with MCI. We examine brain activity and functional connectivity differences between MCI individuals with absent or low SVD burden and those with high SVD burden. By confirming our hypothesis, deeper insights will be gained into the role of SVD in cognitive impairment and the brain regions affected by SVD at the MCI stage.

2. Materials and methods

Results are reported according to the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) for reporting studies in cerebral SVD [13].

2.1. Sample

Participants were included between November 2009 and May 2016 from the Health-RI Parelsnoer Neurodegenerative Diseases Biobank (PND; https://www.health-ri.nl/initiatives/parelsnoer), a collaboration between eight Dutch University Medical Centers. For the data needed in the current study, only three centers had available information. PND aims to investigate the role of imaging-derived parameters and biomarkers in early neurodegenerative disease diagnosis and disease monitoring. This multi-center cohort study focuses on data obtained from individuals who visited one of the medical centers with memory complaints. Eligible participants completed a clinical evaluation by a neurologist, were administered neuropsychological tests and behavioral questionnaires by trained staff members, and biobank data were acquired (i.e., MRI, blood, DNA, and CSF).

The general inclusion and exclusion criteria of the study are described in detail in the study protocol [14]. In summary, individuals referred to a memory clinic for the assessment of cognitive problems, with a clinical dementia rating scale (CDR) score of 0, 0.5, or 1, and a Mini Mental State Examination score of 20 or higher, were included. Exclusion criteria comprised conditions like Normal Pressure Hydrocephalus; Morbus Huntington; Transient Ischemic Attack or Cerebrovascular Accident within the past two years followed by cognitive decline within three months; a history of schizophrenia; bipolar disorder, or unspecified psychotic symptoms, or prior treatment for these conditions; current major depressive disorder; cognitive issues attributed to alcohol abuse; brain tumor; epilepsy; encephalitis; mental incapacity to make a participation decision; absence of a reliable informant; or the anticipation that a follow-up assessment after one year would not be feasible. Additional inclusion criteria for the current study were: availability of a resting state functional MRI sequence, a T1- or T2-weighted sequence, as well as a T2-weighted fluid-attenuated inversion recovery (FLAIR) turbo/fast spin-echo sequence; a Hachinski ischemic score $\leq$ four; availability of the clinical dementia rating scale score and MCI diagnosis. For the diagnosis of MCI, while in the original protocol the McKhann et al. [15] criteria were used, we updated this classification based on the criteria of Petersen [16] and used the CDR score, considering individuals as having mild cognitive impairment if having a CDR score of 0.5. More information on the neuropsychological, behavioral, CSF, and brain volume data collection is reported in Supplementary Material.

Fig. 1 summarizes the participants' selection process in detail. The local eight Dutch Medical Ethics Committees approved the Parelsnoer study, and the current study protocol was approved in April 2018 by the Parelsnoer Institute review board. The study was performed abiding by the Declaration of Helsinki, patient anonymity was ensured, and all patients provided written informed consent.

2.2. Imaging

2.2.1. Functional MRI acquisition

MR image acquisition was performed with 3.0 Tesla scanners (i.e., Siemens MAGNETOM Trio 3T, A Tim System; General Electric Signa HDxt 3.0T MR system; Philips Achieva 3.0T X-Series MRI system). The same head coils were used throughout the study at each site for each individual scanner [14]. High-resolution volumetric T1-weighted imaging was acquired using a 3D ultra-fast gradient echo sequence (i.e., MP-RAGE for Siemens systems, FSPGR for GE systems, and T1-TFE for Philips systems), with whole-brain coverage and $1 \times 1 \times 1$ mm voxel resolution, slab thickness 180 mm, and 180 partitions. A T2-weighted FLAIR was acquired using a 2D turbo/fast spin-echo sequence. The rs-fMRI images were acquired using a single shot T2*-weighted EPI sequence. The scan time for rs-fMRI was 7–10 min and participants kept their eyes open and fixated on a point displayed on a screen for the entire scanning period. Further details on the protocol of the sequences used can be found in Table 1.

MRI data were acquired in three centers: 34 participants from Maastricht University Medical Center (site number 208), 15 from Radboud Medical Center (site number 608), and 19 from VUmc Amsterdam (site number 808). In the low or absent SVD group, 11 participants came from site 208, 9 from site 608, and 14 from site 808. In the high SVD group, 23 subjects came from site 208, 6 from site 608, and 5 from site 808. From its start, the consortium aimed at using harmonized protocols for the data from different sites to be analyzed together. This has been

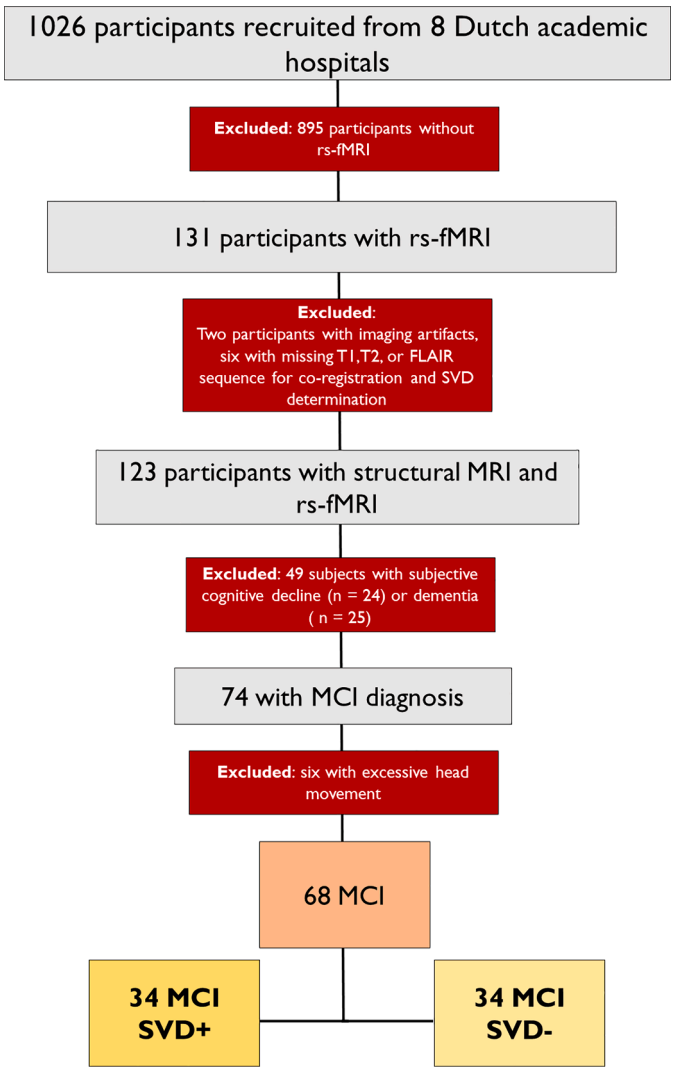

Fig. 1. Participants selection flow diagram. (A) Flow diagram displaying the selection process of individuals with mild cognitive impairment (MCI) with high small vessel disease (SVD+) and absent or low small vessel disease burden (SVD-).

additionally checked during a denoising step (through carpet plots, motion control) where we found that no differences were shown among the three sites. It was therefore possible to use data from all three sites and additionally, scanner ID was used as a covariate in the models.

2.2.2. Resting state functional MRI image pre-processing, processing, and analyses

The rs-fMRI image pre-processing was performed using the SPM 12 software package (Wellcome Trust Centre for Neuroimaging, University College London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm/software) implemented in MatLab 2018b [17]. All preprocessing steps were performed using the CONN toolbox (RRID: SCR_009550, release 21a, McGovern Institute for Brain Research, Massachusetts Institute of Technology, http://www.nitrc.org/projects/conn) following the default preprocessing pipeline for volume-based analyses [18]. The preprocessing steps consisted of (1) realignment and unwarping, (2) slice-timing correction, (3) structural segmentation and normalization, (4) functional normalization, (5) outlier identification and denoising, and (6) functional smoothing. This rs-fMRI pre-processing pipeline has been previously described by our group [19]. Quality assessment was performed as part of the denoising step using the automated quality assessment graphs provided by CONN and verified visually through carpet plots.

Table 1
MRI protocol.

Sagittal 3D T1-weighted gradient-echo sequence (6–9 min).
Correction for non-linear gradients (if applicable) TE and TR according to local settings- giving good grey matter – white matter contrast Slab thickness 180 mm, 180 partitions, 1.0 mm effective slice thickness In-plane resolution 1.0 mm
2D T2-weighted turbo/fast spin-echo sequence (3–5 min)
TR 2,000 - 4,000 ms, TE 80–120 ms Slice thickness 3 mm, no gap Number of slices 48 In-plane resolution 0.5 –1.0 mm
2D T2-weighted FLAIR turbo/fast spin-echo sequence (3–5 min)
TR 8,000 – 12,000 ms, TE 100–150 ms, TI 2,200 – 2,800 ms Slice thickness 3 mm, no gap Number of slices 48 In-plane resolution 0.5 – 1.0 mm
2D Resting state functional-MRI (optional) (7–10 min)
3.0 Tesla scanner: TR 1,800–2,200 ms, TE 30–40 ms, Flip Angle 80 ° Slice thickness 2.0 – 2.5 mm, gap 10 % Number of slices 38–54 In-plane resolution 2.0 – 2.3 mm Number of volumes 200 (excluding run-in scans)

All scans have full brain coverage except resting state functional-MRI that had coverage of at least 105 mm. All scans were in the transverse orientation except the 3D T1w gradient echo sequence, which was in the sagittal orientation.

Following preprocessing, rs-fMRI data were processed using the CONN toolbox. Firstly, a group-independent component analysis (ICA) was used to determine functional connectivity networks in a data-driven manner. Calhoun et al., [20] have described how ICA can be used to identify independent spatiotemporal sources organizing brain regions with similar time course of activity into spatially independent patterns of BOLD signal represented as independent components. Thus, ICA maps represent different networks with a measure of within-network connectivity at each voxel, per CONN toolbox definition of fastICA methods. Twenty independent components were chosen *a priori* and later adjusted setting the threshold at $Z = 3.3$ according to the Dice similarity coefficients (Supplementary Fig. 3) to find a one-to-one correspondence between independent components and the resting-state brain networks as described by Yeo et al., [21]. For the group-ICA, groups were compared using two sample *t*-tests on mean regional activation maps; the statistical significance was set at $p < 0.05$ false discovery rate (FDR) corrected for voxel-level and cluster size. The localization and size of the activation clusters, FDR corrected p-value, and overall effect sizes will be reported in the results.

Secondly, to assess between-group connectivity differences, a region of interest to region of interest (ROI-to-ROI) functional connectivity analysis was run. The ROI-to-ROI analysis (referred to in the manuscript as seeds-to-targets) was performed using the regions of the brain that displayed differences in the group-ICA analysis (seeds). The selected seeds were the 17 cerebellar and two thalamus and caudate nucleus Oxford-Harvard atlas-defined regions. The targets of interest were the default mode network (i.e., four subregions: right and left lateral parietal, posterior cingulate cortex, medial prefrontal cortex), the sensorimotor network (i.e., three subregions: superior, right, and left lateral motor cortex), the visual network (i.e., four subregions: medial, occipital, right and left lateral visual cortex), the salience network (i.e., seven subregions: anterior cingulate cortex, bilateral insular cortex, bilateral rostral prefrontal cortex, and bilateral supramarginal gyrus) the dorsal attention network (i.e., four subregions: bilateral frontal eye fields and bilateral intraparietal sulcus), the frontoparietal network (i.e., four subregions: bilateral lateral-prefrontal cortex and bilateral posterior

parietal cortex), the language network (i.e., four subregions: bilateral inferior frontal gyrus and bilateral posterior superior temporal gyrus), and the cerebellar network (i.e., two subregions: anterior and posterior cerebellum). Functional connectivity was assessed with a weighted generalized linear model using a bivariate correlation for each seed and target region. We corrected for sex, age, educational level, CSF t-tau, CSF p-tau, and CSF amyloid levels by including subject-level regressors in the design matrix (i.e., one-way ANCOVA covariate control analysis in CONN); results remained the same when correcting only for sex and age. Cluster inferences were determined using a threshold-free cluster enhancement (TFCE) method, which is a non-parametric statistical technique used to correct for Type I error inflation from multiple comparisons [22]. Connection thresholds were considered significant at *p-FDR* corrected < 0.05. For a more detailed (pre-) processing protocol we refer the reader to the Supplementary Material section. In summary, we first detected brain regions that differed between groups in a data-driven manner. After that, we used these regions as seeds. The rationale for that was that, as reported in the CONN manual ([23]; page 93), to reduce the false positive rate, it is advised to focus on connections sharing similar results.

A brain tissue and white matter hyperintensity segmentation method developed by Quantib B.V., based on de Boer et al., [24], is applied to the T1-weighted and fluid attenuation inversion recovery (FLAIR) scans to obtain total grey and white matter volume, white matter hyperintensity volume, and intracranial volume (ICV).

2.2.3. Small vessel disease burden score

The SVD burden was calculated using a previously described scoring system [25]. The SVD burden score ranged from 0 to 4 on an ordinal scale where one point was given for each of the following: (1) the presence of one or more lacunes in any location; (2) the presence of one or more microbleeds in any location; (3) moderate/severe presence of perivascular spaces in the basal ganglia (score 2–4), and; (4) Fazekas score 3 in periventricular white matter and/or Fazekas score 2-3 in deep white matter. Two independent neuroradiologists assessed the T2-weighted and T2-weighted FLAIR sequences to identify these features. The inter-rater reliability ratio was 0.92; when two scores differed, a third neuroradiologist was consulted to reach a consensus. For this study, after the SVD burden score was calculated for each participant, two groups were identified: (1) absent or low SVD burden group (i.e., SVD burden score 0 and 1); and (2) high SVD burden group (i.e., SVD burden score 2–4). Dichotomization was necessary to maintain power and have sufficient individuals in each SVD group.

The SVD burden score was previously found to be related to behavioral and psychological symptoms in MCI and mild dementia patients [26], to worse cognitive functioning in cognitively unimpaired individuals [27], and to gait disturbance in community-dwelling elderly individuals [28]. Additionally, individuals with higher SVD burden were found to have faster decline in cognitive functioning, grey matter density and white matter integrity [29].

2.3. Statistical analyses

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) Version 28 [30]. Sample characteristics (age, education, sex, ethnicity, marital status, and APOE genotype) were analyzed using independent *t*-tests for continuous normally distributed variables (means and standard deviations displayed), Mann-Whitney U test for continuous non-normally distributed variables (median and interquartile range displayed), chi-square tests for categorical variables (percentages displayed).

2.4. Data availability

The data that support the findings of this study have been obtained from the Parlesnoer consortium (BBMRI-NL Catalogue). Upon request and evaluation from the consortium's board, this data can be made available.

3. Results

A total of 68 MCI individuals fulfilled the inclusion criteria, the selection process can be seen in detail in Fig. 1. Of these, 34 participants were classified as having an absent or low SVD burden (i.e., SVD burden score 0 and 1) and 34 participants were classified as having a high SVD burden (i.e., SVD burden score 2–4; details on each participant's score composition are provided in Supplementary Table 1). Sample characteristics are displayed in Table 2. Groups did not differ in age, education, sex, ethnicity, marital status, or APOE genotype ($p > 0.05$). Total grey matter, white matter, CSF, and ICV volume did not differ between SVD burden groups ($p > 0.05$), but white matter hyperintensity volume did ($p < 0.001$), with the high SVD burden group having significantly higher white matter hyperintensity volume compared to the absent or low SVD

Table 2
Sample characteristics.

		Absent or low SVD burden ($n = 34$) Mean ± SD	High SVD burden ($n = 34$) Mean ± SD	Total ($N = 68$) Mean ± SD	*p*-value *p*
Age		66.5 ± 8.9	70.3 ± 9.1	68.4 ± 9.1	0.09
		Median (IQR)	**Median (IQR)**		***p***
Education		12 (5)	12 (7)		0.90
		%	**%**	**%**	***p***
Sex	**Female**	32.4 %	23.5 %	27.9 %	0.42
Genotype APOEε	**ε2 ε 3**	3 %	0 %	1.5 %	0.37
	ε2 ε4	6.1 %	11.8 %	9 %	
	ε3 ε3	27.3 %	44.1 %	35.8 %	
	ε3 ε4	45.5 %	29.4 %	37.3 %	
	ε4 ε4	18.2 %	14.7 %	16.4 %	
Ethnicity	**Caucasian**	100 %	100 %	100 %	
Marital Status	**Unmarried**	2.9 %	5.9 %	4.4 %	0.64
	Married or partnership	79.4 %	85.3 %	82.4 %	
	Widowed	11.8 %	8.8 %	10.3 %	
	Divorced	2.9 %	0 %	1.5 %	
	Other	2.9 %	0 %	1.5 %	
SVD markers	**One or more lacunes in any location**				
	Yes	2.9 %	64.7 %		
	No	97.1 %	35.3 %		
	One or more microbleeds in any location				
	Yes	5.9 %	47.1 %		
	No	94.1 %	52.9 %		
	Moderate/severe perivascular spaces in basal ganglia				
	Yes	52.9 %	94.1 %		
	No	47.1 %	5.9 %		
	Fazekas 3 in periventricular white matter and/or Fazekas 2–3 in deep white matter				
	Yes	2.9 %	73.5 %		
	No	97.1 %	26.5 %		

APOE, Apolipoprotein E Gene; ε, Allele; IQR, Interquartile Range; SD, Standard Deviation; SVD, Small Vessel Disease.

group ($p < 0.001$), as displayed in Supplementary Table 2. Within the absent or low SVD group, 15 individuals had a score of 0 and 19 had a score of 1; within the high SVD group, 21 had a score of 2, 9 individuals had a score of 3, and 4 had a score of 4. Additional information on the sample's neuropsychological, behavioral, CSF, and brain volume data is displayed in Table 3.

3.1. Independent component analysis

Twenty independent components were identified using the default voxel-to-voxel one-sample *t*-tests ICA spatial overlap map with a 3.3 Z-score threshold. The cerebellar network was identified in components 1 and 9; the visual network in components 2, 5, 11, 13, and 15; the default mode network in components 3 and 7; the dorsal attention network in components 4 and 18; the frontoparietal network in components 6, and 8; the language network in components 10 and 14; the salience network in components 12 and 17; the sensorimotor in components in components 16 and 19; and lastly, the CSF in component 20 (Supplementary Fig. 1 and 2). After a Dice similarity coefficient for the spatial correlation maps was set at $Z = 3.3$, suprathreshold areas of components 6, 9, 11, 12, and 14 were no longer observable in the spatial maps; however, after visual inspection of the independent components after adjusting the suprathreshold, only component 9 was no longer observable. The spatial correlation overlap map of independent components to the template is displayed in Supplementary Fig. 3. Activity differences between MCI individuals with absent or low SVD burden and MCI with high SVD burden were seen in three regions of the cerebellum, the thalamus and the caudate nucleus. The cerebellar region comprised a cluster of 4541 voxels (+20 -74 -38) consisting of the left cerebellum crus II, right cerebellum crus II, and left cerebellum lobule VIII. MCI patients with absent or low SVD burden had increased activity in the cerebellum compared to MCI patients with high SVD burden ($p\text{-}FDR < 0.001$, F (1,49)). The region of the right thalamus and right caudate nucleus had an activation cluster of 218 voxels (+22 -28 +20); again, MCI patients with absent or low SVD burden had increased activity of this region compared to MCI patients with high SVD burden ($p\text{-}FDR < 0.001$, F (2,79)). Visual representations of the group-ICA results are depicted in Fig. 2.

3.2. Functional connectivity differences

Functional connectivity between-group differences were observed between MCI individuals with absent or low SVD burden and MCI individuals with high SVD burden. Overall, 1830 connections were analyzed among 61 ROIs (seeds and targets). Patients with absent or low SVD burden generally had greater connectivity than those with a higher disease burden. These differences were specifically observed in the connection between two brain seeds and targets. The first seed is the vermis subdivision VIII, while the second seed comprises the vermis subdivision IX and bilateral cerebellum subdivision IX. MCI individuals with absent or low SVD burden had higher functional connectivity than MCI individuals with high SVD burden between (1) the vermis VIII and the right cerebellum subdivisions VII and VIII ($TFCE = 48.05$, $p\text{-}FDR = 0.044$) and (2) the vermis IX and the bilateral cerebellum X and brain stem ($TFCE = 45.36$, $p\text{-}FDR = 0.044$), and between bilateral cerebellum subdivision IX and the bilateral cerebellum X and brain stem ($TFCE = 45.36$, $p\text{-}FDR = 0.044$). Detailed information on the effect sizes for each connection is described in Table 4 and the connectome ring functional connectivity and glass display representation are displayed in Figs. 3 and 4, respectively.

4. Discussion

In this study, differences in brain functional activity and connectivity were analyzed between MCI individuals with absent or low SVD burden and MCI individuals with high SVD burden. SVD burden was determined using a comprehensive score [25]. Using a data-driven approach, we observed higher activity in the cerebellum, the thalamus, and the caudate nucleus in the absent or low SVD burden group compared to the high SVD burden group. Additionally, the absent or low SVD group showed higher functional connectivity with regions of the cerebellum, the thalamus and the caudate nucleus compared to the high SVD burden group. Our findings might suggest that in MCI individuals with absent or low SVD burden, functional connectivity is more intact than when SVD burden is high.

Activity differed between the two groups in a large cluster in the cerebellum; its involvement in cognitive decline has been previously documented [31], and this is thought to exhibit as deficits in the

Table 3
Additional sample information.

		Absent or low SVD burden ($n = 34$)		High SVD burden ($n = 34$)		Total	*p*-value
ANCOVA	***n***	**Mean ± SD**	***n***	**Mean ± SD**	***n***	**Mean ± SD**	***p***
WLT (immediate)	34	30.2 ± 11.9	34	32.8 ± 11.4	68	31. ± 11.6	0.37
Digit span (backward + forward)	34	13.2 ± 3.2	34	13.2 ± 3.3	68	13.2 ± 3.2	0.91
GDS	34	2.7 ± 1.8	34	3.50 ± 2.85	68	3.09 ± 2.41	0.16
P-tau	22	64.1 ± 27.4	19	39.31 ± 22.99	41	52.56 ± 28.10	**0.00*****
T-tau	22	540.3 ± 251.4	19	350.3 ± 241.5	41	452.3 ± 262.0	**0.02***
CSF volume (ml)	33	279.3 ± 46.6	34	297.3 ± 60.6	66	288.3 ± 54.4	0.68
Grey matter volume (ml)	33	638.3 ± 62.9	33	644.3 ± 62.9	66	641.3 ± 62.5	0.92
White matter volume (ml)	33	475.5 ± 64.9	33	478.5 ± 52.5	66	477.0 ± 58.6	0.32
Intracranial volume (ml)[+]	33	1396.8 ± 131.2	33	1436.0 ± 109.1	66	1416.4 ± 121.3	0.19
Mann-Whitney	***n***	**Median (IQR)**	***n***	**Median (IQR)**	***n***		***p***
MMSE	34	26(6)	34	28(2)	68		0.13
VAT (short version)	34	11(6)	34	12(0)	68		0.56
DAD total (ratio)	34	.87(0.17)	34	.90(0.15)	68		0.43
NPI (total)	31	14(15)	31	16(17)	62		0.68
Amyloid beta-42	22	542(281)	19	690.5(328)	41		0.30
WMH volume (ml)	33	1.8(3.3)	33	15.9(14.6)	66		**0.00*****

ANOVA, Analysis of Variance; CSF, Cerebral Spinal Fluid; DAD, Disability Assessment of Dementia; IQR, Interquartile Range;GDS, Geriatric Depression Scale; MCI, Mild Cognitive Impairment; MMSE, Mini Mental State Examination; NPI, Neuropsychiatric Inventory; SD, Standard Deviation; SVD, Small Vessel Disease; VAT, Visual Association Test; WLT, World Learning Test; WMH, White Matter Hyperintensities.
***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.
[+] Intracranial volume is calculated as the sum of CSF, grey and white matter, and WMH volume.

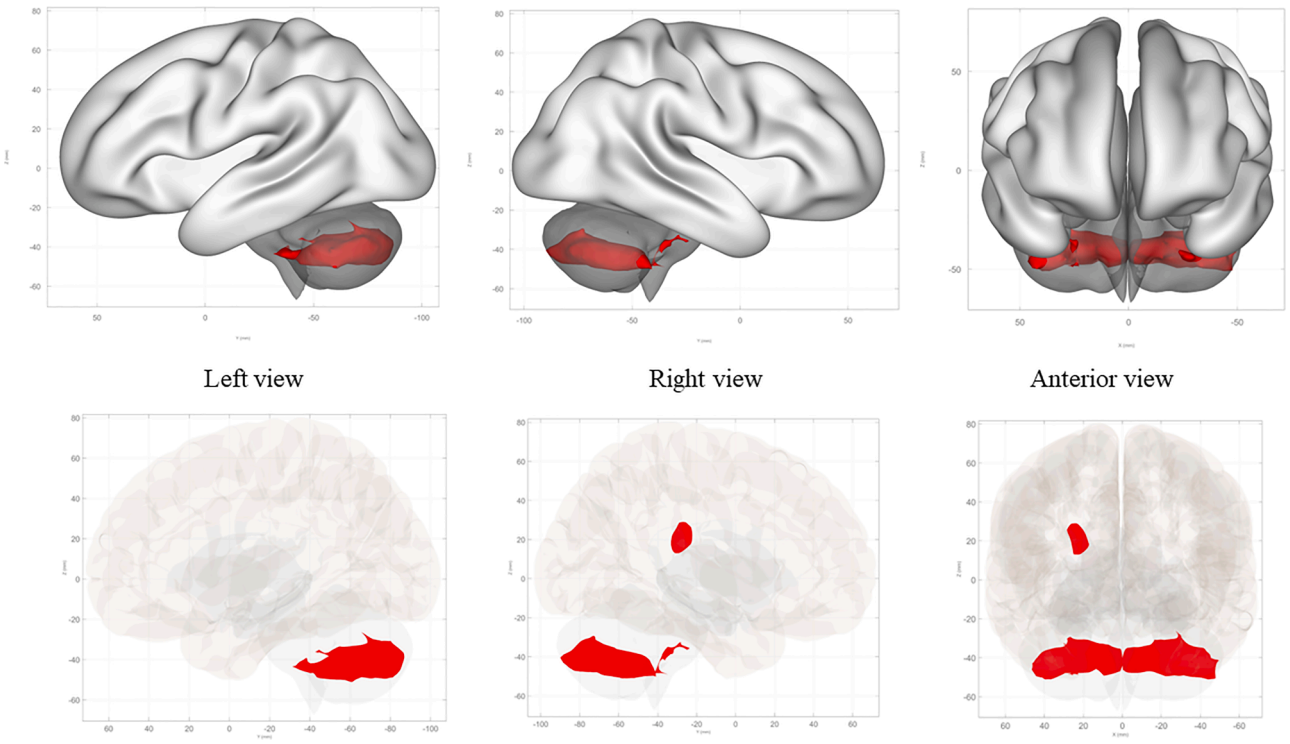

Fig. 2. Group independent component analysis: differences between MCI with low or absent SVD burden and MCI with high SVD burden.

Table 4
Functional brain connectivity cluster-based inferences.

ROI-to-ROI connection	Statistic	*p*-uncorrected	*p-FDR*	*p-FWE*
Vermis -Right Cerebellum	*TFCE* = 48.05	0.000348***	0.044137*	0.044000*
Vermis VIII - Right Cerebellum VII	*T*(66) = 3.80	0.000321***		
Vermis VIII - Right Cerebellum VIII	*T*(66) = 3.27	0.001722**		
Vermis-Bilateral Cerebellum-Brain stem	*TFCE* = 45.36	0.000444***	0.044137*	0.048000*
Vermis IX – Right Cerebellum X	*T*(66) = 4.12	0.000108***		
Vermis IX – Left Cerebellum X	*T*(66) = 3.14	0.002514**		
Right Cerebellum IX – Right Cerebellum X	*T*(66) = 2.84	0.005972**		
Left Cerebellum IX – Brain stem	*T*(66) = 2.66	0.009681**		
Right Cerebellum IX – Left Cerebellum X	*T*(66) = 2.61	0.011136*		
Left Cerebellum IX - Left Cerebellum X	*T*(66) = 2.61	0.011177*		
Right Cerebellum IX – Brain stem	*T*(66) = 2.58	0.012076*		
Left Cerebellum IX - Right Cerebellum X	*T*(66) = 2.43	0.017853*		
Vermis IX – Brain stem	*T*(66) = 2.37	0.020620*		

***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.
FDR: False Discovery Rate; *FWE*: Family-Wise.

modulation of cognitive and behavioral functions [32]. The cerebellum is involved in the control and coordination of movements [33–35], as well as in cognitive functions, leading to deficits in language, spatial processing, and working memory when lesioned [36]. A recent study found impairments in frontal executive functioning, verbal fluency, and processing speed in cerebellar stroke patients, leading the authors to support the Cerebellar Cognitive and Affective Syndrome hypothesis proposed by Schmahmann [37,38]. In a previous study, comparing cognitively unimpaired individuals with and without SVD, using a rs-fMRI data-driven whole-brain analysis, the same cerebellar hubs as in our study, crus II and lobule VIII, were identified as different, namely with increased connectivity in the patient group [39]. The crus II was previously found to be activated during language, executive functioning, and working memory tasks [40] as well as during emotion processing tasks [41]. Lobule VIII has been described to be active in motor tasks [41], specifically finger tapping [34]. Although, Schaefer et al., [39] findings are in the opposite direction compared to ours, since increased eigenvector centrality was found in the group with SVD compared to the one without, as well as decreased connectivity in frontal areas. The authors argue that cerebellar increased connectivity in the presence of SVD would compensate for frontoparietal decreased connectivity. Since in our study we include individuals with MCI, this might suggest that in the presence of a high SVD burden when cognitive impairment also arises, no decreased frontoparietal connectivity is seen, but decreased cerebellar connectivity. In our study, we also found that increased connectivity was present between several cerebellar subdivisions in the absent or low SVD group compared to the high SVD. This might indicate that functional connectivity within the cerebellum is more intact in the group with absent or low SVD burden. Several previous studies have found anatomical connections between the cerebellum and brain regions supporting higher functions, namely prefrontal, and parietal association cortices [36]. Our findings did not show any functional connectivity differences between the two groups between the cerebellum and other canonical networks; suggesting that at the MCI stage, these connections are not affected. Our results also hint that in the study of cognitive decline, where overall cerebellum volume is often used as

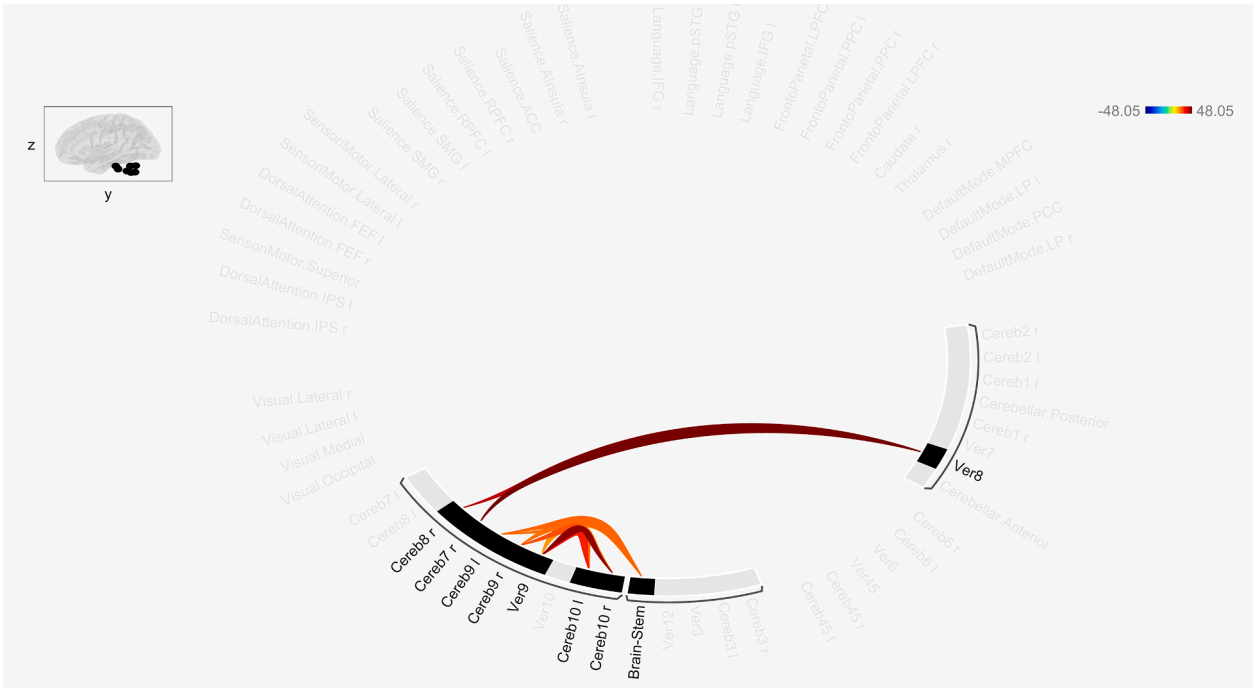

Fig. 3. Connectome ring representation of ROI-to-ROI connectivity. (A) Cereb8 r: Right Cerebellum VIII. Cereb7r: Right Cerebellum VII. Cereb9 l: Left Cerebellum IX. Cereb9 r: Right Cerebellum IX. Ver9: Vermis IX. Cereb10 l: Left Cerebellum X. Cereb10 r: Right Cerebellum X. Ver8: Vermis VIII.

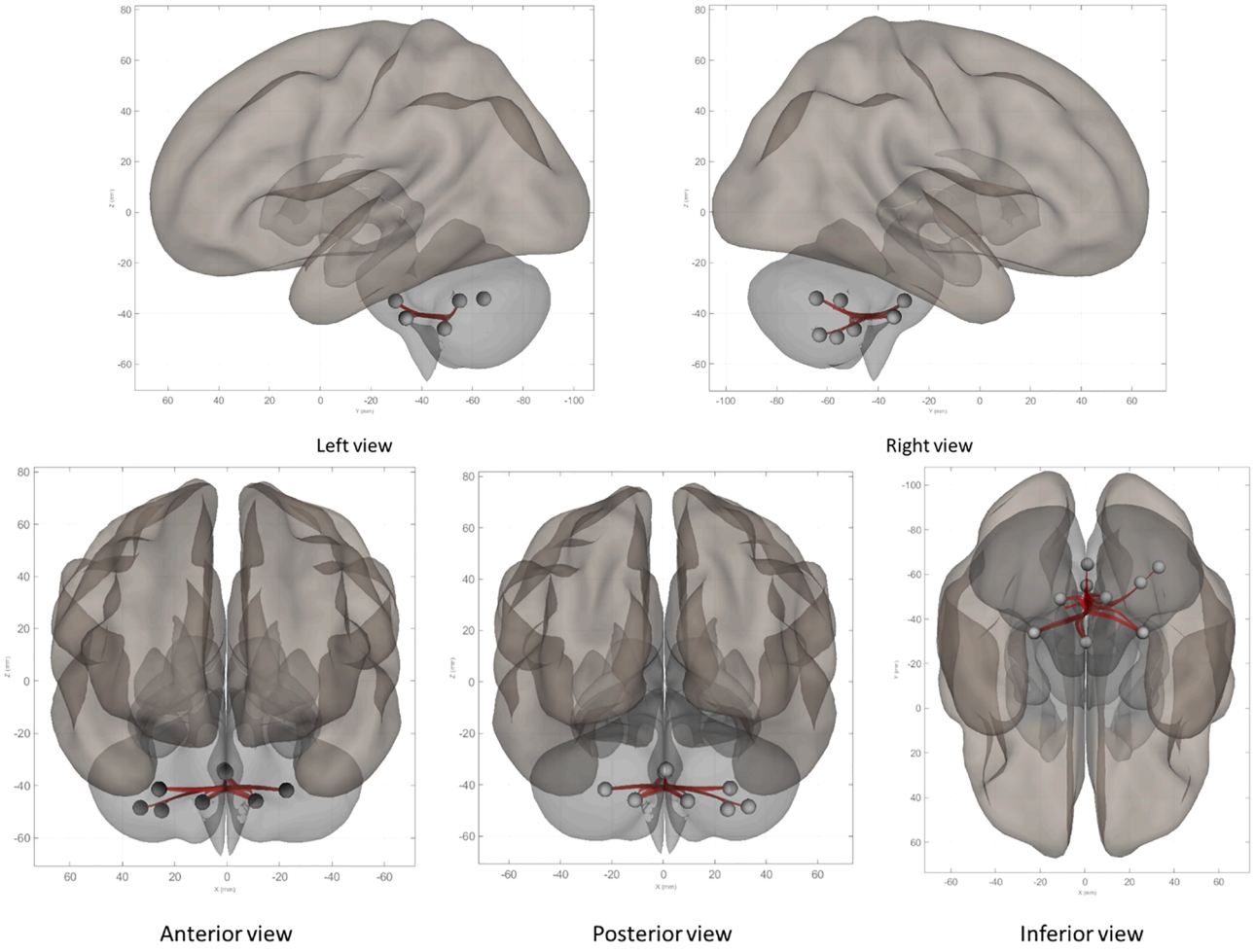

Fig. 4. Glass display representation of ROI-to-ROI connectivity.

reference region, the cerebellum might affect dynamic networks and should be accounted for rather than normed for. Its role in aging and Alzheimer's disease has also been recently reviewed [42]. Furthermore, findings relating it to cognitive functions such as visuospatial, attention, execution, working memory, and language have been recently summarized [43]. Additionally, a recent study has also shown how transcranial magnetic stimulation of Crus II increased cognitive functioning in patients with Alzheimer's Disease [44].

Additionally, a region involving the right thalamus and right caudate showed more activity in the low or absent SVD group. The thalamus and the caudate are responsible for attentional control and various higher order neurological functions [45]. Notably, attention and executive functions domains are also the most assessed domains in cerebral SVD literature [46] and were found to be the main neuropsychological feature in SVD profiles [47,48]. A previous meta-analysis including individuals with MCI found increased functional connectivity in the thalamus and the caudate compared to healthy controls and suggested that this could be seen as a compensatory mechanism within the salience network in MCI [49]. When focusing on individuals with cognitive impairment and lacunar infarcts, small white matter hyperintensities, and slight atrophy, lower connectivity in the right caudate was also found [50]. While both higher [51] and lower [52] connectivity in the thalamus was found in rs-fMRI studies comparing individuals with SVD, defined based on lacunes and white matter hyperintensities, and healthy controls. In our study, increased connectivity between the thalamus and caudate nucleus and part of the cerebellum was found in the absent or low SVD group compared to the high SVD group.

Blood to the cerebellum, the thalamus, and caudate nucleus is supplied by the posterior circulation. The anterior and posterior circulation have been shown to differ, for instance regarding white matter hyperintensities showing weaker associations with mean blood pressure in the posterior compared to the anterior circulation, leading to different hemodynamic mechanisms [53]. Due to less branching and less dampening pressure, regions supplied by the posterior circulation are more prone to lesions. A previous study has found that posterior brain hypoperfusion during acute increase in arterial pressure is associated with the presence of SVD [54]. Also, in longitudinal studies on small vessel disease, cerebral blood flow decrease was observed more in posterior regions [55].

Although the biomarker data for our sample were not complete, we observed higher phosphorylated and total tau burden in the group with low or absent SVD. We might speculate that a different disease process, more Alzheimer's pathology-like, characterizes the low or absent SVD group and that the reduced functional connectivity in the high SVD group is driven more by SVD than by Alzheimer's pathology. Previous research has shown that SVD is related to pathological changes in the aging brain [56], therefore it remains important to investigate how these interacting phenomena affect functional connectivity at the early stages of disease. Anyhow, in our analyses, we corrected for phosphorylated and total tau, and results remained unchanged, suggesting a main impact of SVD on cerebellar and caudate nucleus and thalamus brain network integrity.

Overall, our findings could indicate that the presence of SVD might affect cortical-subcortical pathways, whose network integrity is needed for cognitive processes [57]. This is especially true for connectivity pathways within the cerebellum and to the thalamus and caudate nucleus, suggesting that these brain regions should be a target in future studies on SVD in cognitively impaired individuals. SVD is thought to originate from a disease impacting the perforating cerebral venules, capillaries, and arterioles leading to brain damage in the white and grey matter [2]. SVD also affects the neurovascular coupling, namely the alterations in local perfusion in response to changes in neuronal activity which are fundamental to supplying energy to brain cells [4]. If the neurovascular coupling is affected, this can influence the BOLD signal, even if neuronal activity is normal, as recently shown in a study on cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), where the BOLD % signal change, specifically the hemodynamic response function, was lower in the CADASIL group compared to controls [58]. Additionally, in early stages of dementia, microvascular heterogeneity at the capillary level could contribute to the observed findings and affect flow patterns and related tissue oxygen delivery, as previously suggested [59,60]. While the simultaneous occurrence of many markers is apparent (as shown in Supplementary Table 1), it would have been valuable to explore whether specific markers exerted a more pronounced influence on the observed connectivity differences. However, given our sample size, we lacked the power to detect connectivity differences creating groups based on the single markers. The same applies if we wanted to stratify our analysis by SVD score (i.e., SVD = 0–4).

Whether individuals with SVD defined using the Klarenbeek et al., [25] scoring system have a higher risk of progression to dementia should be further studied particularly considering cerebellar, thalamic, and caudate connectivity. This should be done using direct measurement of regional perfusion and perfusion heterogeneity with techniques such as dynamic susceptibility contrast MRI, to image additional parameters at the microvascular level [59]. The measurement of local and regional direct microvascular perfusion would help to better understand causality and increase confidence in the connectivity observation.

Previously, the presence of white matter hyperintensities has been linked to a moderate decrease in cognitive functioning in MCI patients and a mild decrease in AD patients; thus, highlighting the role of co-occurring vascular brain injury in MCI and AD [61]. White matter hyperintensities have been associated with a risk of progression from cognitively unimpaired to MCI (i.e., 35 % increased risk), from cognitively unimpaired to AD (i.e., 25–49 % increased risk), and from cognitively unimpaired to vascular dementia (i.e., 73 % increased risk) [62,63]. Also, cerebral microbleeds predict an increased risk of stroke, dementia, and death [64]. Generally, vascular pathologies commonly coexist with AD in the elderly and increase the risk and severity of cognitive impairment [65]. Additionally, mixed pathologies (i.e., most commonly AD and infarctions) have been identified in community-dwelling individuals and multiple neuropathological substrates are associated with three-fold odds increases of dementia [66]. Gait disturbances have been previously related to SVD cross-sectionally and longitudinally [67–70], and to subcortical vascular dementia [71]. While motor function was not assessed in our study, our findings found differences in brain regions responsible for motor functions, making associations between motor functions and SVD in mild cognitive impairment interesting for future investigation. The same applies to cognitive functioning which has not been objective of this study. Whether MCI individuals with SVD also show more impairments in cognitive abilities, such as executive functioning as suggested in individuals with SVD and early cognitive impairment [47], should be further investigated. The current study did not account for the spatial distribution of SVD markers; however, this aspect merits exploration in subsequent research efforts. Future studies incorporating markers' location analyses could offer valuable insights into the impact of SVD markers on functional connectivity. Considering that our sample included only Caucasian individuals, future studies should replicate the findings in other samples. Additionally, previous studies have shown sex differences in cerebral SVD [72]. In our study females were underrepresented and although analyses were corrected for sex, further subgroup analyses were not possible due to a small sample size. Lastly, future studies could further explore the mechanisms of how SVD influences dementia using techniques such as diffusion-weighted imaging to provide further insight into subcortical structural brain connectivity alterations secondary to small vessel vascular injury.

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Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2023.100192.

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