Topical Review

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# White Matter Microstructural Damage on Diffusion Tensor Imaging in Cerebral Small Vessel Disease

## Clinical Consequences

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Cerebral small vessel disease (SVD) is a major health problem for its contribution to ≈45% of dementias, and about a fifth of all strokes worldwide, representing one of the most important causes of disabilities.[1] The term SVD refers to a group of pathological processes with various etiologies that affect the small arteries, arterioles, venules, and capillaries of the brain. The most common forms are age- and hypertension-related SVD and cerebral amyloid angiopathy (CAA).[2] Vessel wall changes may lead to both ischemic and hemorrhagic consequences: (1) a state of chronic hypoperfusion or vascular dysfunction responsible for incomplete infarction,[3,4] (2) acute focal necrosis (lacunar infarct), or (3) vessel rupture manifesting as hemorrhagic SVD. The clinical consequences of SVD are various and mainly consist of cognitive, mood, and motor dysfunctions leading to functional disability in the late stages of the disease.

Magnetic resonance imaging (MRI) has become crucial in the diagnosis of SVD enabling the evaluation of the disease progression both in the clinical and research settings. However, correlations between clinical features of SVD and conventional MRI measures have been partially discordant. Some authors suggested that the cumulative effect of SVD lesions, rather than the individual lesions themselves determines the clinical impact,[5] whereas others suggested that the presence and severity of alterations nonvisible on conventional MRI might also be an explanation.[6]

In the past decade, diffusion tensor imaging (DTI) has been increasingly used for the evaluation of SVD patients because it is sensitive to tissue damage and can show abnormalities in both areas of white matter hyperintensities (WMH) and in normal appearing WM (NAWM). Despite the high sensitivity in detecting cerebral damage, DTI has a low specificity in detecting the underlying cause. In fact, we can only infer that DTI changes reflect a loss of WM integrity because of damage to structures that restrict molecular movement along the primary axis of the axons, such as axonal cell membranes, myelin sheaths, and neurofilaments. Growing evidences indicate definite structural vascular abnormalities associated with WMH, strengthening the argument that WMH have a vascular pathogenesis.[7] DTI is suited to study cortical disconnection because it provides indices of microstructural integrity within interconnected neural networks. Most DTI studies evaluated WM microstructural damage in aging, Alzheimer disease and mild cognitive impairment patients, but recently, studies in SVD patients have documented a significant association between WM microstructural damage and clinical features, providing new insight in the biological basis of this condition.[8–10]

The aim of this review is to analyze the evidence of the role of WM microstructural damage beyond the standard structural MRI sequences, evaluated with DTI, in the clinical consequences of cerebral SVD. Although some definitions have been proposed,[11] it is explicitly not our intention to clinically define a SVD patient, as SVD is often accompanied by other processes, such as aging and neurodegeneration, leading to a broad spectrum of clinical manifestations. Our review is based on those studies that enrolled patients with a predominant SVD pathology and does not include those that enrolled non-SVD participants (eg, healthy aging, Alzheimer disease, and mild cognitive impairment) even though they evaluated the association between SVD markers and WM microstructural damage.

The first part of this review briefly examines the methodological aspects of DTI, the role of DTI in understanding SVD pathophysiology and the relationship between risk factors and WM microstructural damage. In the second part, we review clinical studies that reported on the association between DTI and different clinical manifestations of SVD, focusing on cognition, mood disorders, and motor dysfunctions. The last part of the review outlines possible future applications of DTI, in

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particular its role as a sensitive marker to evaluate SVD progression in clinical trials.

## Article Search Strategy

Articles were identified through Pubmed searches using these terms: DTI, diffusion, WM microstructural damage, WM integrity, structural network, brain connectivity AND each of the following: SVD, subcortical small vessel, Binswanger, vascular cognitive impairment, CAA, Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL), vascular dementia, motor symptoms, gait, falls, balance, parkinsonism, depression, depressive symptoms, mood, smoking, hypertension, blood pressure, diabetes mellitus, blood glucose, body mass index, hypercholesterolemia, physical activity, leukoaraiosis, and lacunes, from any date to November 15, 2015.

## Methodological Aspects

DTI is a quantitative MR technique that measures the movement of water within the tissue microstructure applying a magnetic diffusion gradient in more directions (at least 6) to acquire a diffusion tensor.[12] From the tensor, 2 commonly derived quantitative measures that provide information about the in vivo WM microstructure are fractional anisotropy (FA) and mean diffusivity (MD). FA is a measure of anisotropic water diffusion, which reflects the degree of directionality of cellular structures within the WM tracts and ranges from 0 (diffusivity equal in all directions) to 1 (entirely unidirectional). MD is the average rate of diffusion in the noncollinear directions and an increasing value represents an increase in water diffusion. A lower FA and corresponding higher MD are generally believed to reflect lower microstructural connectivity. Other tensor indices have been proposed as markers of neuronal damage, such as axial diffusivity and radial diffusivity. Once FA and MD maps are generated, postprocessing procedures start with mainly 3 approaches: region of interest (Figure [A]), tract-based spatial statistics (TBSS; Figure [B]), and voxel-based analysis (Figure [C]). Each of these techniques has pro and cons. Technical aspects related to brain network analysis are briefly described in the figure (Figure [D]).

## DTI and Cerebral SVD

Among DTI studies in patients with sporadic SVD, mainly defined as presence of moderate/severe WMH and lacunar infarcts not related to a monogenic disease, the predominant findings are that FA is decreased and MD is increased both in NAWM and WMH suggesting decline in the composition and integrity of the WM.[13] Similar results have been reported also in CADASIL patients (Table I in the online-only Data Supplement).

A substantial loss of anisotropy in the regions of WMH compared with NAWM has been reported,[14] whereas NAWM showed lower FA values close to WMH compared with more distant areas[15] For this reason, the term WM penumbra has been proposed to describe the area just surrounding the WMH which is still composed of NAWM based on conventional MRI, but with already lower structural integrity as compared with more remote areas of WM.[15]

A positive correlation has been reported between the total WMH load and diffuse WM injury in NAWM, suggesting WM damage to be more widespread rather than region specific. Normal WM, WMH penumbra, and WMH all show a similar decline in WM integrity over time.[15,16] Accordingly, NAWM regions that ultimately converted into WMH had already significant lower FA and higher MD at baseline in both growing WMH (defined as WMH expanding from already present WMH at baseline) and de novo WMH (defined as a new WMH not adhering to an already present WMH at baseline) compared with persistent NAWM.[17] These results highlight that WMH develop gradually, and that WMH are only the tip of the iceberg of WM pathology.

DTI tractography can be used to spatially characterize WM diffusion abnormalities along the pathway of a specific tract. Using a reconstructed WM tract containing a lacunar infarct, Reijmer et al[18] showed that WM microstructural damage attenuates with increasing distance from the primary lesion. This finding was replicated also in CAA patients.[19] Duering et al[20] applied serial cortical thickness measurements and tractography in CADASIL patients and showed focal cortical thinning in cortical regions with high probability of connectivity with the incident infarct. This result provided evidence for cortical neurodegeneration after subcortical ischemia as one mechanism for brain atrophy in cerebrovascular disease. The same group has replicated this finding in a non-CADASIL cohort.[21]

Recently, new advances in network analysis have been used to study the whole brain connectivity using graph theory. This can be applied after structural networks have been reconstructed from diffusion tensor tractography (Figure [D]). SVD patients have been reported to have networks less densely connected, and reductions in both global and local efficiency, compared with controls, especially in interhemispheric and prefrontal tracts.[22] A similar approach showed network disturbances, most pronounced in the occipital, parietal, and posterior temporal lobes, in CAA patients.[5]

## Risk Factors for Microstructural Damage Within the WM in SVD

To date, the Radboud University Nijmegen Diffusion Tensor and Magnetic resonance Cohort (RUN DMC) is the only study investigating cross-sectionally the role of vascular risk factors on microstructural changes in SVD (Table II in the online-only Data Supplement).[23,24] Increased blood pressure (average of 3 measurements of systolic and diastolic blood pressures) and hypertension (defined as blood pressure >140/80 mm Hg and use of blood pressure–lowering agents) were associated with loss of WM integrity in both the NAWM and WMH.[23] In particular, hypertension was associated with lower FA in the splenium of the corpus callosum and higher MD in both the anterior body and the splenium of the corpus callosum. These associations disappeared after adjustment for other SVD markers, such as WMH volume, lacunes, and gray matter atrophy, evoking the possible role of mediator of SVD between hypertension and low microstructural integrity.[24]

In one SVD cohort, both history and duration of smoking were associated with a low WM microstructural integrity, and diffusion values were comparable between those who had quit smoking more than 20 years and those who had never smoked.

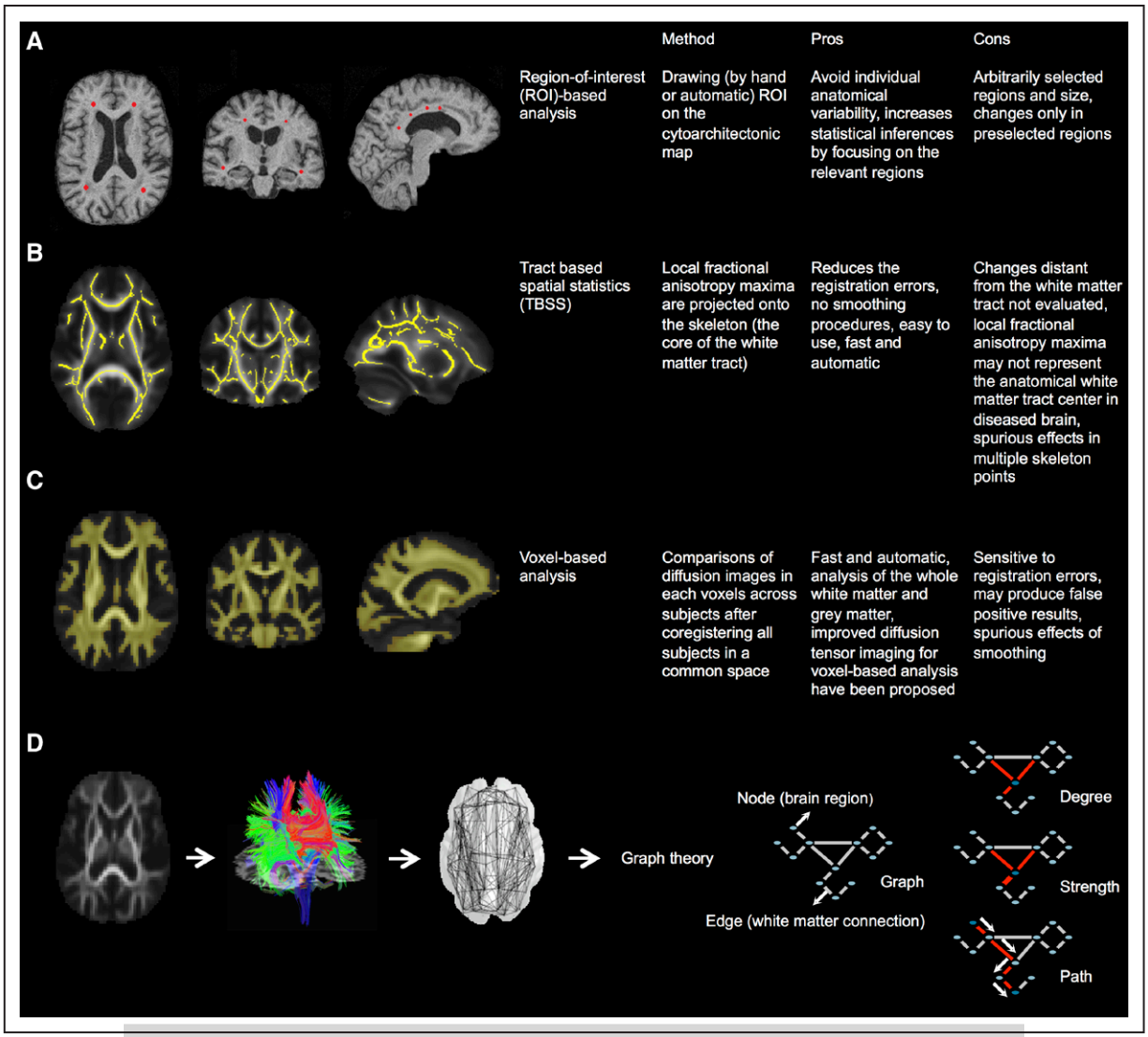


**Figure.** Diffusion tensor imaging (DTI) post processing techniques with pros and cons, construction of structural network based on diffusion tensor tractography and network measures. **A**, Region-of-interest-based analysis, (**B**) tract-based spatial statistics, (**C**) voxel-based analysis. **D**, Construction of structural network based on DTI followed by tractography. Each individual network is represented as a graph, a mathematical model of a network with nodes (brain regions) linked by edges (white matter connections), which can then be explored using graph theory. There is a wide variety of network measures, only some of which are depicted in the figure. Basic network measures, including degree and strength of a node, are depicted in the figure. Degree of a node represents the number of connections linked to a node in a network. Strength of a node is defined as the sum of the weights of all edges connected to a node. Characteristic path length is defined as the shortest path or the minimum number of connections between 2 given nodes. Efficiency is inversely related to path length, which is easier to use in a disconnected graph. ROI indicates region-of-interest; and TBSS, tract-based spatial statistics.

This may suggest a beneficial role of quitting smoking on WM structural integrity.[25]

One cross-sectional study, using TBSS, investigated the relationship between physical activity and WM microstructural integrity showing that poor physical activity was associated with lower microstructural integrity in almost all voxels of the TBSS skeleton.[26]

No study has to date investigated the association between diabetes mellitus and microstructural damage specifically in a SVD population. A recent review, however, reported on 5 cross-sectional studies examining the relation between DTI parameters and diabetes mellitus and all found lower microstructural integrity in patients with type 2 diabetes mellitus compared with controls, adjusted for different confounders.[27]

Taken together, these studies may suggest that vascular risk factors could damage WM integrity in elderly patients with SVD and that their control might be associated with better DTI parameters. This may not apply to normal aging because recently in a population-based cohort cardiovascular risk factors were not associated with longitudinal changes in white matter microstructure.[28]

## Clinical Expressions of SVD and WM Microstructural Damage

### Cognition

SVD patients are prone to develop cognitive impairment and their neuropsychological profile is generally characterized by

a predominant impairment of executive functions, attention, and psychomotor speed. One of the most accepted mechanisms of cognitive impairment in SVD is based on the disconnection theory by which it is hypothesized that impairment in attention, processing speed, and executive function is related to the disruption of fronto-subcortical circuits. Indeed, it has been demonstrated in both sporadic SVD and CADASIL patients that the forceps minor and the thalamic radiation are strategic WM tracts for processing speed.[29,30]

O'Sullivan et al[13] demonstrated that in SVD patients DTI indices, especially in NAWM, correlated more strongly with cognitive function than T2-lesion volume, after controlling for conventional MRI parameters. Similarly, diffusion changes predict faster decline in psychomotor speed, executive functions, and working memory regardless of conventional MRI findings.[31] Other groups have confirmed the strong association between WM microstructural damage and cognitive impairment in sporadic SVD patients, especially in terms of executive functions, attention, and psychomotor speed (Table III in the online-only Data Supplement). In CADASIL patients, executive performances were reported to be correlated with MD in the frontal WM and through the major antero-posterior fasciculus of the cingulum bundle.[32]

A further contribution to the understanding of the relationship between WM microstructural damage and cognition comes from the RUN DMC study in which more than 500 independently living, nondemented patients with cerebral SVD, aged between 50 and 85 years, were enrolled. In this large cohort, the microstructural integrity of both WMH and NAWM was related to global cognitive function, memory, and executive function.[33] Moreover, TBSS postprocessing analyses were performed and corpus callosum especially in the genu and splenium showed the highest significant relation with global cognitive index. Analyses for each cognitive domain showed the strongest relationship between (1) cingulum bundle microstructural integrity and verbal memory performance and (2) frontal WM and psychomotor speed.[8] However, in the same cohort, the main predictors for the development of incident dementia at 5 years were WM and hippocampal volumes,[34] whereas baseline WM integrity was not associated with decline in cognitive performances[35]

In the Vascular Mild Cognitive Impairment Tuscany study, WM microstructural damage was more strongly reflected in Montreal cognitive assessment than mini mental status examination performances,[36] possibly for the presence in Montreal cognitive assessment of items reflecting executive functions and psychomotor speed.

Interesting insights in the development of cognitive impairment related to SVD come from the evaluation of network connectivity. In both SVD and CAA cohorts, the importance of network disruption as a mediating mechanism between SVD MRI burden and cognitive dysfunction, especially in executive functions, has been demonstrated.[5,22,37] Moreover, it has been shown that structural network efficiency is a predictor of conversion to dementia.[38]

### Depressive Symptoms

Previous cross-sectional studies showed a positive association between conventional SVD characteristics and depressive symptoms in older age, both at a cross-sectional level[39] and prospectively[40] DTI studies performed in patients with late life depression consistently showed lower microstructural integrity in the fronto-striatal and limbic networks.[41]

To date, 4 studies investigated the role of the WM microstructure in SVD in relation to depressive symptoms (Table IV in the online-only Data Supplement).[9,42–44] The first study found that microstructural WM damage, measured by median FA, at least partially mediated the association between SVD and depression.[42] The second study, using TBSS, showed that low WM microstructural integrity in the genu and body of the corpus callosum, bilateral inferior fronto-occipital fasciculus, uncinate fasciculus, and corona radiata was associated with depressive symptoms. These associations almost fully disappeared after adjustment for WMH and lacunes, suggesting that the visible SVD drives the association.[9] The third study reported an association between WM microstructural damage and depressive symptoms in mild cognitive impairment patients with SVD independently of disability or cognitive or motor impairment.[43] The last study evaluated the relationship between FA and both apathy and depression, finding that only apathy was related to damage of cortical–subcortical networks.[44]

The majority of these studies suggest that the association between WM microstructural damage and depressive symptoms might be mediated by the underlying SVD and to a lower extent by other factors, such as disability.

### Motor Problems

Only a small number of studies have investigated the relation between WM integrity and motor impairment (gait, parkinsonism, falls, and balance) in SVD using DTI (Table V in the online-only Data Supplement).[5,10,45–51] Loss of WM integrity, most pronounced in the corpus callosum, especially the genu,[46,47] was associated with lower gait velocity at a cross-sectional level.[5,45–47] This association with gait was seen for both NAWM and WMH. Network efficiency was also related to gait velocity in CAA patients, suggesting a role of network disruption in this relation.[5] Other studies investigated the cross-sectional associations between microstructural integrity and a clinical scale measuring extrapyramidal motor deficits,[48] extrapyramidal movement disorders, such as freezing of gait,[49] and mild Parkinsonian signs.[10] Three studies found an association between extrapyramidal motor symptoms and low microstructural integrity in both supratentorial (frontal lobes)[10,50,51] and infratentorial (pedunculopontine nucleus) regions. A prospective study showed a low baseline microstructural integrity of several bifrontal WM tracts involved in movement control in participants with incident vascular parkinsonism in comparison to those without[51] also after adjustment for SVD characteristics.

These studies uniformly support the notion that, in SVD, disturbances of frontal WM microstructure, especially the genu of the corpus callosum, are associated with motor deficits, and related to incident vascular parkinsonism.

## Future Directions and Conclusions

The evaluation of WM microstructural damage has gained attention during the past 15 years in the study of SVD because

it provides in vivo an understanding of the pathogenesis of important clinical and neuroimaging consequences of SVD. The majority of the studies that have used DTI demonstrated a good correlation between WM microstructural damage and several clinical measures linked to SVD such as cognition, mood disorders and motor performances. In the studies where a multimodal approach was used, DTI indices were generally strongly associated with clinical outcome measures also after correction for multiple conventional neuroimaging markers of SVD. Furthermore, longitudinal studies showed that changes in DTI parameters could be detected during a period of 1 or 2 years.[52,53] In CADASIL patients, for example, Molko et al[54] found important changes in DTI parameters during a period of 20 months, whereas no changes were detected in the control group. These findings suggest that DTI might be considered a sensitive biomarker to monitor the progression of WM damage in patients with SVD. This may be particularly relevant because DTI indices were shown to be predictors of clinical progression in both sporadic SVD and CADASIL.[52–55] Therefore, the measurement of diffusion will possibly become one important surrogate marker in future preventive trials in SVD.

There are at least 3 possible ways in which DTI can be of aid in a better understanding of the pathogenesis and clinical consequences of SVD: (1) It may provide new insights in the understanding of the mechanisms of the main clinical consequences of SVD, particularly by evaluating the structural integrity of the cerebral WM architecture; (2) it may furnish a reliable surrogate marker, especially in clinical trials, of SVD progression over time to appreciate the effects of beneficial therapeutic interventions; (3) it may help to better appreciate the real SVD burden and its progression.

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## Disclosures

None.

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# White Matter Microstructural Damage on Diffusion Tensor Imaging in Cerebral Small Vessel Disease: Clinical Consequences

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# Supplemental Material

## White matter microstructural damage on diffusion tensor imaging in cerebral small vessel disease: clinical consequences

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**Supplemental Table I.** White matter microstructural damage in CADASIL.

| Study | Sample size and age (years±SD) | DTI Method | Adjustments | Significant associations with cognition | Other results |
|---|---|---|---|---|---|
| O'Sullivan, 2005[1] | CADASIL pts: 18<br>46.3±11.3 | Voxel based analyses, WM MD and FA | None | - MD, FA in the left cingulum bundle and left precuneus: Trail making Test B and Symbol digit | |
| Chabriat, 1999[2] | CADASIL pts: 16<br>59.3±7.6<br>Controls pts: 10<br>54.6±7.2 | ROI, NAWM and WMH, MD | Age | - WMH MD: MMSE | - NAWM MD and FA in SVD differ significantly from controls<br>- WMH MD differed between patients mild vs severe impairment |
| Holtmannspotter, 2005[3] | **Longitudinal study:**<br>CADASIL pts: 62<br>44±9 | Whole brain WM MD (average value, peak height and location) | Age, sex, systolic blood pressure, homocysteine level, T2-lesion volume | - Whole brain WM MD: SIDAM scale | - MD at baseline significant predictor for changes of the Rankin score, of the SIDAM score and newly occurring strokes<br>- 1 year follow up: average values and peak locations of MD significantly increased |
| Viswanathan, 2010[4] | CADASIL pts: 147<br>51.8±11.2 | Whole brain DWI ADC histogram | Age, sex, education level, WMH, brain volume, normalized lacunes volume, microbleeds | - Whole brain mean ADC histogram: Mattis Dementia Rating scale (also MMSE, results not shown) | - Brain atrophy plays the most important role in disability and cognitive impairment |
| Jouvent, 2007[5] | CADASIL pts: 42<br>69.1±7.8 | Whole brain DWI ADC histogram | Age, hypercholesterolemia, sex, WMH, lacunes, microbleeds | - Not evaluated | - Brain volume was significantly associated with whole brain mean ADC |
| Molko, 2002[6] | **Longitudinal study**<br>CADASIL pts: 22<br>54±11<br>Controls pts: 12<br>51±11<br>14 CADASIL pts and 5 controls repeated MRI at 21±6 months (average time)<br>7 CADASIL underwent a third MRI | Whole brain DTI, trace of the diffusion tensor [Trace (D)]. | None | - Diffusion parameters: baseline MMSE<br>- In the subgroup of 14 patients, these correlations remained significant at both the 1st and 2st scan times. | - Whole brain mean value of Trace (D) was higher in patients than in controls.<br>- An increase in the mean Trace (D) value and a decrease in the peak height of Trace (D) histograms were observed overtime in patients, while no change was found in the control group |

DTI: diffusion tensor imaging, Pts: patients, WMH: white matter hyperintensities, NAWM: normal appearing white matter, WM: white matter, SIDAM : structured Interview for the diagnosis of Dementia of the Alzheimer Type, multi-infarct dementia and other type of dementia. MMSE: mini-mental state examination test, DWI: diffusion weighted imaging, MD: mean diffusivity, FA: Fractional Anisotropy, ROI: Region of Interest

**Supplemental Table II.** White matter microstructural damage in cerebral small vessel disease and vascular risk factors**.**

| Study | Sample size and age (years±SD) | SVD definition | Risk factors | DTI method | Adjustments | Significant association with vascular risk factor | Other |
|---|---|---|---|---|---|---|---|
| Gons, 2010[7] | SVD pts: 499<br>65.6±8.8 | Presence of WMH and/or lacunes | Blood pressure (>140/90 and/or use of anti-hypertensive medication) | ROI:<br>Mean FA and mean MD in NAWM and WMH, and lobar ROI's | Age, sex, DM hypercholesterol-aemia, smoking and BMI | - Mean FA and MD in the WMH: both systolic and diastolic blood pressure<br>- Mean FA in the NAWM: both systolic and diastolic blood pressure<br>- Mean MD in the NAWM: systolic blood pressure<br>- Hypertensive subjects had lower mean FA and higher mean MD in WMH and NAWM than normotensives | - Treated uncontrolled had lower mean FA and higher mean MD values than the treated controlled subjects |
| Gons, 2012[8] | SVD pts: 499<br>65.6±8.8 | Presence of WMH and/or lacunes | Blood pressure (>140/90 and/or use of anti-hypertensive medication) | ROI<br>mean FA and mean MD in the genu, anterior body, posterior body and splenium of the CC | Age, sex and cardiovascular risk factors<br>Additionally GM volume, number of lacunes and WMH | - Low FA in the splenium and high MD in the anterior body and splenium of the CC and presence of hypertension<br>- Treated uncontrolled subjects had both lower FA and higher MD in both the anterior body and splenium | - FA and MD in the genu, anterior body and splenium were associated with global cognitive and executive functions |
| Gons, 2011[9] | SVD pts: 499<br>65.6±8.8 | Presence of WMH and/or lacunes | Cigarette smoking (pack-years, and status never/ former/current) | ROI<br>Mean FA and mean MD in NAWM and WMH | Age, sex, alcohol intake, education and cardiovascular risk factors, including DM hypercholesterol-emia, HT and BMI | - MD in WMH and NAWM and smoking status Lower MD and higher FA in the NAWM and years of smoking cessation<br>- Smoking cessation >20 years had identical MD and FA values compared with never smokers | - MD and FA in the NAWM and global cognition (by cognitive index) |
| Gons, 2013[10] | SVD pts: 440<br>Age range 50-85 | Presence of WMH and/or lacunes | Physical activity, MET | TBSS<br>MD, AD, RD and FA<br>And ROI: mean FA and MD in the NAWM and WMH | Age, sex, education, normalized TBV, and cardiovascular risk factors. | - MD in the WMH and NAWM and physical activity<br>- In almost all voxels of the skeleton MD, AD and RD related to physical activity, whereas no association with FA | - Association remained present after adjustment for confounders |

SVD: small vessel disease, HT: hypertension, HC: healthy controls; WMH: white matter hyper intensities, MRI: Magnetic Resonance Imaging, DTI:Diffusion Tensor Imaging, MRS: Magnetic Resonance Spectroscopy, NAA: N-acetylaspartate, tCho: total cholines, tCr: total creatines, mI: myo-inositol, MD: mean diffusivity, FA: Fractional Anisotropy, ROI: Region of Interest, DM: diatbetes mellitus, BMI: Body Mass Index, CC: corpus callosum, MET: metabolic equivalent, TBV: total brain volume

**Supplemental Table III.** White matter microstructural damage and cognition in cerebral small vessel disease.

| Study | Sample size and age (years±SD) | SVD definition | Cognitive Tests | DTI Method | Adjustments | Significant associations with cognition | Other results |
|---|---|---|---|---|---|---|---|
| Lawrence, 2013[11] | SVD pts: 121<br>70.0±9.7<br>Controls: 57<br>70.4±9.2 | Clinical lacunar stroke + lacunar infarct on MRI and WMH (Fazekas ≥ 2) | Verbal fluency, modified Wisconsin card sort test, Grooved Pegboard Task, digit symbol substitution, BMIPB Speed of Information Processing | Whole brain NAWM: FA, MD, AD, RD (mean, median, interquartile range, SD, skew, kurtosis, peak height and location) | Age, sex , premorbid IQ, WMH, lacunes, brain volume | - Peak height MD: psycomotor speed<br>- Peak height RD: executive functions | - Mean FA < in SVD than controls<br>- Mean MD > in SVD than controls<br>- RD more altered than AD in SVD |
| O'Sullivan, 2004[12] | SVD pts: 36<br>69.5±8.8<br>Controls: 24<br>71.6±7.5 | Diffuse/confluent WMH + clinical lacunar stroke | MMSE, WAIS-R digit span, digit symbol, full scale IQ, WCST, Reitan trail making, verbal fluency, WAIS-R digit symbol and digit span backwards, logical memory, paired associate learning subtests, Benton facial recognition | ROIs in WMH and NAWM: FA, MD | Age, sex, WMH volume, parenchymal volume | - NAWM MD: IQ and WCST | - NAWM MD and FA in SVD differ significantly from controls |
| List, 2003[13] | SVD pts: 20<br>72.3±4.3<br>Controls: 20<br>70.6 ±3.6 | WMH (Fazekas ≥ 2) | TMT A+B, verbal and semantic fluency, AVLT, ROCF, digit span and block tapping, working memory performance | Whole brain WM, ROIs: mean FA | Age | - Mean whole brain WM FA: executive functions, working and verbal memory | - In SVD, FA of all brain areas, except cerebellum < than controls |
| Nitkunan, 2008[14] | **Longitudinal study:**<br>Baseline:<br>SVD pts: 35<br>68.8±9.3<br>1 year Follow-up<br>SVD pts: 27 | Lacunar stroke (at least 3 months before the enrollment)+ Fazekas≥ 2 | National adult reading test, WAIS: vocabulary and matrix reasoning subtests, MMSE, Wechsler Memory scale III (verbal memory, digit span), verbal fluency, TMT B, Trails Motor Speed subtest from the Delis-Kaplan Executive Function System | Whole brain WM: FA and MD (peak height, median, mode) | WMH volume, brain volume, lacunar infarcts age, sex, and premorbid IQ | - Peak height FA: executive functions (composite score). | - 1-year follow-up: increase in median MD, MD at peak height, and reduction in peak height FA |
| Xu, 2010[15] | SVD pts: 42<br>Age: 69.1±7.8 | Moderate and severe WMH + lacunar infarct | MMSE, TMT, Stroop color word test, category verbal fluency test, RAVL test, ROCF, Boston naming test | Whole brain WMH or NAWM: FA, MD | Age, sex, education | - Whole brain WMH and NAWM DTI indices: attention, executive and memory functions | - Cognitive impairment pts had > MD and <FA in both WMH and NAWM than pts without cognitive impairment |
| Zhou, 2011[16] | SVD pts:<br>- 18 with cognitive impairment no dementia<br>-18 no cognitive impairment | WMH + ≥ 1 lacunar infarct | TMT A, B, Stroop color word test, category verbal fluency test, AVLT, ROCF, Boston naming test (30 words) | VBA: MD and FA average value, histogram peak height and location | None | - FA peak location, average MD, and mean MD peak location of WM: general intellect (composite z-scores) | - SVD pts with cognitive impairment had < FA in bilateral frontal lobes, occipital lobes, temporal lobes, and insula than no cognitive impairment SVD pts |

**Supplemental Table III. (Continued)**

| Study | Sample size and age (years±SD) | SVD definition | Cognitive Tests | DTI Method | Adjustments | Significant association with cognition | Other results |
|---|---|---|---|---|---|---|---|
| Tuladhar, 2015[17] | SVD pts: 444<br>65.3±8.9 | Presence of WMH and/or lacunes | MMSE, 1-letter subtask of the paper–pencil memory scanning task, Stroop test, symbol–digit, RAVL, ROCF, verbal fluency, verbal series attention test | TBSS, ROIs (corpus callosum): FA, MD | Age, sex, education, depressive symptoms, normalized TBV, WMH and number of lacunes | - WM MD, FA: psychomotor speed, concept shifting.<br>- WM FA: cognitive index, verbal memory<br>- cingulum bundle and corpus callosum FA: verbal memory<br>- integrity of genu and splenium of the corpus callosum: cognitive index, executive domains, psychomotor speed and concept shifting<br>- integrity of body of corpus callosum: memory | - Association of MD and cognition in corpus callosum resulted driven by changes in RD, and not AD |
| Van Norden, 2012[18] | SVD pts: 499<br>65.6±8.8 | Presence of WMH and/or lacunes | Same as reference [17] | WMH and NAWM FA, MD | Age, sex, education, depressive symptoms, TBV, lacunes and WMH | - WMH MD, FA: attention, concept shifting<br>- WMH MD: global function, psychomotor speed.<br>-NAWM MD, FA: concept shifting, psychomotor speed, attention, verbal memory<br>- NAWM MD: visuospatial memory, fluency | - Pts with severe WMH had MD and FA changes more related to worst performances in many cognitive domains than those with mild or moderate WMH |
| Van der Holst, 2013[19] | SVD pts: 440<br>65.2± 8.9 | Presence of WMH and/or lacunes | Same as reference [17] | TBSS, ROIs (cingulum): FA MD | Age, sex, educational level, depressive symptoms TBV, hippocampal volume, WMH, lacunes | - FA and MD in the cingulum, corpus callosum: immediate memory, delayed recall, delayed recognition and overall verbal memory performance<br>- mid/posterior (ROI approach): cingulum FA and memory | - MD, FA of all ROIs differed significantly between pts with good and poor hippocampal integrity |
| Pasi, 2015[20] | SVD pts: 76<br>75.8±6.8 | WMH (Fazekas ≥ 2) and MCI | MoCA test, MMSE | Whole brain WM: median FA, MD | Age, education level, sex, lacunar infarcts, WMH, global cortical atrophy, medial temporal lobe atrophy | FA, MD: MoCA test | - No correlation was found between MD, FA and MMSE |

**Supplemental Table III. (Continued)**

| Study | Sample size and age (years±SD) | SVD definition | Cognitive Tests | DTI Method | Adjustments | Significant association with cognition | Other results |
|---|---|---|---|---|---|---|---|
| O'Sullivan, 2001[21] | SVD pts: 30<br>69.7±8.9<br>Controls: 17<br>71.8±7.9 | WMH + history of a clinical lacunar event | MMSE, Wisconsin Card Sorting test | ROI: NAWM MD, FA (anterior and posterior PV, centrum semiovale) | None | - Anterior PV FA and MMSE<br>- Centrum semiovale: executive functions (Wisconsin card sorting test) | - FA in PV NAWM < in SVD |
| Kim SH, 2011[22] | SVD pts: 61<br>73.3±6.9<br>- MCI: 27<br>- Demented: 34 | WMH: PV cap or band ≥ 10 mm + deep lesion ≥ 25 mm and MCI or dementia | ROCF, Seoul verbal learning test, Boston naming Test, digit span test, word fluency tests, and Stroop color reading test | VBM: FA, MD | Age, education | - MD values in temporal area: delayed recall<br>- FA in the splenium of the corpus callosum and FA and MD in posterior PV areas: praxia<br>- FA in the left medial temporal area: language<br>- FA, MD in PVWM and deep WM: digit span<br>- FA and MD in the left PVWM: phonemic fluency<br>- FA in the posterior PVWM and MD in right medial temporal, corpus callosum, anterior cingulate gyrus and lingual gyrus: attention | - Disruption of the posterior WM integrity is related to poor performance on cognitive tests in the task for frontal functioning. |
| Li, 2012[23] | SVD pts: 20<br>65.1±7.0<br>Controls: 20<br>65.8±8.0 | WMH + history of a clinical lacunar event | MMSE, TMT B, verbal fluency (phonemic and meaning), digit span backwards, digit symbol | ROI: mean MD, FA (anterior, posterior horn) | None | - Anterior PV WM FA: executive functions<br>- Anterior PV WM MD: executive functions, fluency, memory, MMSE<br>- Posterior PV WM: MD and executive functions | - MD > and FA < in PV WM in SVD |
| Lin, 2015[24] | SVD pts: 50<br>VCIND pts: 22<br>72±6.8<br>NC pts: 28<br>70.9±8.2 | Moderate WMH + lacunar infarcts | MoCA test | ROI: FA, MD | None | - FA and MD values of all projections, commissural and associational fibers: MoCA score | - MD > VMCI than NC<br>- FA < VMCI than NC |
| Jokinen, 2013[25] | SVD pts: 340<br>73.9±5.1 | Mild to severe WMH | MMSE, VADAS, Stroop test and TMT A and B-A | DWI: WMH mean ADC | Age, sex, education, WMH, lacunes, global brain atrophy | - WMH mean ADC: TMT A | - WMH mean ADC related to a faster rate of decline in the TMT A scores |
| Della Nave, 2007[26] | SVD pts: 36<br>77±4.5 | Mild to severe WMH | MMSE, Stroop test, Symbol digit, Maze Task and Verbal Fluency Test | VBM FA histograms and whole brain MD | None | - Whole brain MD:Stroop test, Maze task, digit and verbal fluency | |

| Supplemental Table III. (Continued) | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Study** | **Sample size and age (years±SD)** | **SVD definition** | **Cognitive Tests** | **DTI Method** | **Adjustments** | **Significant association with cognition** | **Other results** |
| Van Uden, 2015[27] | **Longitudinal study**<br>SVD pts:500<br>65.6±8.8 | Presence of WMH and/or lacunes | Same as reference 17 | NAWM, WMH FA,MD | Age, gender, education, MMSE, WMH, lacunes, MB, GM volumes, hippocampal volumes | - DTI parameters did not predict dementia (42 pts after 5 years) | - WM and hippocampal volume predicted the risk of dementia at 5 years |
| Van Uden 2015[28] | **Longitudinal study**<br>SVD pts: 398 | Presence of WMH and/or lacunes | Same as reference 17 | NAWM, WMH FA,MD | Age, gender, education, depressive symptoms, WMH, lacunes, TBV | - NAWM MD with decline in cognitive index<br>- no significant association after Bonferroni correction | |
| Tuladhar, 2015[29,30] | SVD pts:436<br>65.2±8.8 | Presence of WMH and/or lacunes | Same as reference 17 | Weighted structural connectivity network from DTI | Age, gender, education, depressive symptoms, WMH, lacunes, MB, total brain volume, MD | -Higher global efficiency with higher scores on cognitive index and psychomotor speed<br>- Lower global network efficiency with increased risk of incident all-causes dementia | - WMH, MB, TBV, MD, indirectly related to cognitive index and psychomotor speed via global efficiency<br>- Nodes with the strongest associations with cognitive index and psychomotor speed were in frontal, parietal, occipital lobes |

DTI: diffusion tensor imaging, Pts: patients, MD: mean diffusivity, FA: fractional anisotropy, RD: radial diffusivity, AD: axial diffusivity, TBSS: Tract-based spatial statistics, VBM: Voxel based morphometry, VBA: Voxel based analysis, WMH: white matter hyperintensities, NAWM: normal appearing white matter, ARWMG: age-related with matter changes, SVD: small vessel disease, MCI: mild cognitive impairment, PV: periventricular, VCIND: vascular cognitive impairment, NC: normal cognition, MoCA: Montreal Cognitive Assessment, MMSE Mini-Mental State Examination, IQ: Intelligence quotient, VADAS: Vascular Dementia Assessment Scale–Cognitive Subscale, NABT: Normal appearing brain tissue, BMIPB: Birt Memory & Information Processing Battery, WAISR: Wechsler adult intelligence scale–revised, WCST: Wisconsin card sorting test, TMT: Trail making test, AVLT: Auditory Verbal Learning Test, ROCF: Rey-Osterrieth complex figure test, RAVL: Rey auditory verbal learning test, TBV: Total Brain volume, GM: Gray matter, MB: microbleeds, DWI: diffusion weighted imaging, ROI: region of interest

**Supplemental Table IV.** Microstructural damage in cerebral small vessel disease and depressive symptoms

| Author | Sample size and age (years±SD) | SVD definition | Depression -scale | DTI method | Adjustments | Significant association with depressive symptoms | Other |
|---|---|---|---|---|---|---|---|
| Brookes, 2014[31] | SVD pts: 101<br>71±9.5<br>Controls: 203<br>67.1±9.4 | Clinical lacunar stroke syndrome with radiologic (MRI) confirmation | GDS | TBSS<br>median FA | Global cognitive deficit, functional disability | - Median FA and depression: lower white matter integrity associated with depressive symptoms | - Association between median FA and disability and with global cognition<br>- No association between median FA and quality of life |
| Van Uden, 2014[32] | SVD pts: 438<br>65.1±8.8 | Presence of WMH and/or lacunes | CES-D | TBSS<br>FA, MD, RD, AD | Age, sex, education and TBV<br>Additionally: WMH and lacunes, cognition, anti-depressant use | - Low mean FA, high MD and RD in pts with depressive symptoms compared to those without<br>In pts. with depressive symptoms compared to those without:<br>- FA, AD and RD: genu and body of the CC, bilateral IFOF, UF and corona radiata<br>- For AD and RD(additionally): CB, internal and external capsule, ILF and parietal lobe<br>- For MD: genu and body of the CC, CB, corona radiata | - The associations with FA, AD and RD disappeared after adjustment for WMH and lacunes<br>- Adjustment for use of anti-depressive medication or cognition did not alter the results |
| Pasi, 2015[33] | SVD pts: 76<br>75± 6.8 | Evidence on MRI of moderate to severe degrees of WMH according to the modified version of the Fazekas scale | GDS | Whole brain<br>Mean FA and mean MD | Age, WMH, global cognitive, functional and motor performance, anti-depressant use | - Median FA and MD and depressive symptoms | - This association was not mediated by disability, cognitive, and motor impairment |
| Hollocks, 2015[34] | SVD pts: 118<br>69.9±9.8<br>Controls: 398<br>61.9±13.5 | Clinical lacunar stroke syndrome<br>with radiologic (MRI) confirmation | GDS | VBA<br>FA MD | Age, IQ, global cognitive function and apathy | - Median FA with apathy but not depression | - Association between median FA and quality of life<br>- Association between Median FA and MD and global cognitive function |

Pts: patients, SD: standard deviation, DTI: diffusion tensor imaging,SVD: small vessel disease,GDS: geriatric depression scale, TBSS: tract-based spatial statistics, FA: fractional anisotropy, CES-D: centre for epidemiologic studies depression Scale, WMH: white matter hyperintensities, MD: mean diffusivity, RD: radial diffusivity, AD: axial diffusivity, WM: white matter, CC: corpus callosum, IFOF: inferiorfronto-occipital fasciculus, UF: uncinate fasciculus, ILF: inferior longitudinal fasciculus, CB: cingulum bundle; VBM: voxel based morphometry, VBA: voxel based analysis, IQ: intelligence quotient.

**Supplemental Table V.** White matter microstructural damage and motor impairment in cerebral small vessel disease

| Author | Sample size and age (years±SD) | SVD definition | Motor score | DTI method | Adjustments | Significant association with motor symptoms | Other |
|---|---|---|---|---|---|---|---|
| Della Nave, 2007[26] | SVD pts: 36<br>77±4.5 | ARWMC changes of any degree | Gait velocity,<br>Single-leg stance test<br>SPPB | VBM<br>FA histograms and whole brain MD | None | - Wide clusters of high MD and smaller clusters of FA in both the corpus callosum and pericallosal WM with 1) gait velocity and 2) SPPB | - No results with single-leg stance test were shown |
| de Laat, 2011[35] | SVD pts: 484<br>65.6±8.9 | Presence of WMH and/or lacunes | Gait velocity,<br>Stride length,<br>Stride width,<br>Tinetti, TUG | ROI based<br>Mean FA and MD in WMH, NAWM | Age, sex, height and TBV additionally: WMH, lacunes | - Higher MD in the WMH: gait speed, cadence, step width, stride width, Tinetti and TUG.<br>Lower FA in the WMH and Tinetti | - Both FA and MD in the NAWM were associated with several gait parameters, of which only the MD in the NAWM remained present after adjustment for WMH |
| de Laat, 2011[36] | SVD pts: 429<br>65.2±8.9 | Presence of WMH and/or lacunes | Gait velocity,<br>Stride length,<br>Stride width,<br>Cadence | TBSS -VBM FA, MD, AD and RD<br>3 ROI's in the CC<br>Mean FA, MD AD and RD | Age, sex and height additionally: WMH, lacunes, TBV | - FA positively associated with gait velocity, stride length and negatively to stride width. MD was negatively associated with the same parameters.<br>- Voxels with the highest relation between FA and MD and gait were located in the total CC, and for MD also in the internal capsule | - After additional adjustment for WMH and lacunes most associations disappeared.<br><br>- DTI parameters in the genu of the CC showed strongest associations with gait |
| Kim, 2011[22] | MCI pts: 27<br>73.6±6.7<br>Dementia pts:34<br>73.0±7.5 | A cap or band ≥10 mm as well as a deep WMH ≥25 mm, as modifed from Fazekas ischemia criteria | Pyramidal and Extra-pyramidal scale for motor deficits | VBM<br>FA and MD | Age | - Low FA with total PEPS score and gait in the brainstem, CC, cerebellum, Corona radiata.<br>- High MD with PEPS in the brainstem, bilateral PVWM and corona radiate.<br>- High MD with extrapyramidal scores in the PVWM and forceps major | - Low FA and high corticospinal score in the internal capsule, corona radiate, CC and posterior PVWM<br>- High MD and corticospinal score in the internal capsule and corona radiate<br>- Corticobulbar symptoms and low diffusion parameters in brainstem |
| Youn, 2012[37] | FOG pts: 14<br>81±5.5<br>Controls: 26<br>79±5.4 | ARWMC 2 or more | Freezing of gait | ROI<br>FA and ADC | FOG and control group did not differ in age, sex, vascular risk factors and ARWMC scale | - Low FA and FOG in the bilateral pedunculopontine nucleus (PPN), superior premotor cortex, right orbitofrontal area and left supplement motor area | - No significant association with ADC values<br>- Compared to controls the FOG group fiber tracking showed lower fiber bundle volume in the PPN ROI |
| Reijmer, 2015[38] | CAA pts: 31<br>68.9±9.9<br>Controls: 29<br>71.3± 7.1 | Probable or definite CAA | Gait velocity (TUG) | DWI; structural brain network by network density, global efficiency | Age, sex, education level, WMH, MB TBV or median FA | - Low global network efficiency was associated with worse gait velocity. This was not independent of median FA | |

| | Supplemental Table V. (Continued) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Author** | **Sample size (n) and age (years±SD)** | **SVD definition** | **Motor score** | **DTI method** | **Adjustments** | **Significant association with motor symptoms** | **Other** |
| De Laat, 2012[39] | SVD pts: 483<br>65.6±8.9 | Presence of WMH and/or lacunes | Mild parkinsonian signs by UPDRS | ROI based<br>Mean FA and MD in WMH, NAWM | Age, sex and TVB WMH and lacunes | - Low FA in the WMH and MPS, independent of WMH volume.<br>- Low FA or high MD in the NAWM increased the presence of MPS 2 fold, which disappeared after adjustment for WMH and lacunes.<br>- Low FA and high MD and MPS in the periventricular ROIs, independent of WMH and lacunes | - In the subcortical ROIs mainly presenting NAWM no association with MPS |
| Van der Holst, 2015[40] | **Longitudinal study**<br>SVD pts: 436<br>65.6±8.8 at baseline | Presence of WMH and/or lacunes | Parkinsonism (clinical diagnosis) | TBSS<br>Mean FA, mean MD | Age, sex, baseline UPDRS score and TBV, WMH, WM, lacunes and MB | - low FA and high MD of bi-frontal WM tracts (CC, CI, SLF, forceps minor, IFOF, cingulum, superior Corona radiata, thalamic radiation) with incident Parkinsonism after 5 years. The association with FA remains present after adjustment for SVD. | - There was no association with high MD and incident parkinsonism after 5 years after adjustment for SVD. |

Pts: patients, SD: standard deviation, DTI: diffusion tensor imaging, SVD: small vessel disease, ARWMC: age-related white matter changes, SPPB: short physical performance battery, VBM: voxel-based morphometry, FA: fractional anisotropy, MD: mean diffusivity, WMH: white matter hyperintensities, NAWM: normal appearing white matter, TUG: timed up and go-test, ROI: region of Interest, TBV: total brain volume, TBSS: tract-based spatial statistics, AD: Axial Diffusivity, RD: Radial Diffusivity, CC: Corpus Callosum, MCI: Mild Cognitive Impairment, PEPS: Pyramidal and Extra-pyramidal scale,MRI: Magnetic Resonance Imaging, PVWM: peri-ventricular white matter, FOG: freezing of gait, ADC: apparent diffusion coefficient, PPN: pedunculopontine nucleus, MPS: mild parkinsonian signs, CAA: cerebral amyloid angiopathy,DWI: diffusion weighted imaging, MB: microbleeds, UPDRS: unified Parkinson's disease rating scale, WM: white matter, CI: internal capsule, SLF: superior longitudinal fasciculus, IFOF: inferior fronto-occipital fasciculus.

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