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Blood pressure in old age : exploring the relation with the structure, function and hemodynamics of the brain

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Chapter 6

Influence of small vessel disease and microstructural integrity on neurocognitive functioning in older persons: the DANTE Study Leiden

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Submitted

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Abstract

Background

Small vessel disease (SVD) is a major cause of neurocognitive dysfunction at old age. SVD may manifest as white matter hyperintensities (WMH), lacunar infarcts, cerebral microbleeds and atrophy, which features are visible on conventional MRI, or as microstructural changes, determined by diffusion tensor imaging (DTI). The aim of this study was to investigate whether microstructural integrity is associated with neurocognitive dysfunction in older persons regardless of conventional features of SVD.

Methods

This study included 195 participants who were ≥ 75 years old and underwent conventional 3-Tesla MRI with DTI to assess fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AxD) and radial diffusivity (RD). Cognitive tests were administered to assess cognitive domains, and the Geriatric Depression Scale-15 (GDS-15) and Apathy Scale to assess symptoms of depression and apathy, respectively. The association between DTI measures and neurocognitive function was analysed using linear regression models.

Results

A lower FA and higher MD, AxD and RD in grey matter were associated with worse executive function, psychomotor speed, and overall cognition, and in white matter additionally with memory. Findings were independent of WMH, lacunar infarcts and cerebral microbleeds, but after additional adjustment for normalized brain volume, only lower FA in white and grey matter and higher grey matter RD remained associated with executive functioning. DTI measures were not associated with GDS-15 or Apathy Scale scores.

Conclusion

Microstructural integrity was associated with cognitive, but not psychological dysfunction. Associations were independent of conventional features of SVD, but attenuated after adjusting for brain volume.

Introduction

The occurrence of small vessel disease (SVD), seen on conventional MRI as white matter hyperintensities (WMH), lacunar infarcts, cerebral microbleeds, and brain atrophy,¹ increases with advancing age.² SVD is a major cause of cognitive³ and possibly of psychological dysfunction.⁴ Nevertheless, the relationship between these overt signs SVD and cognitive and psychological dysfunction is modest and inter-individual variability is high. It has been suggested that these visible lesions only represent the tip of an iceberg, when in fact SVD may also cause more subtle diffuse microstructural changes in the brain. Microstructural integrity can be determined with diffusion tensor imaging (DTI), which measures diffusion of cerebral water molecules. Diffusion changes have been observed not only in lesions visible on standard MRI but also in the surrounding normal –appearing brain tissue.⁵⁻⁷ The pathological processes underlying changes in DTI measures include axonal degeneration and ischemic demyelination,^{7,8} which may lead to disruption of white matter tracts that connects brain regions involved in cognitive functions.

Previous studies have demonstrated that DTI measures of WM microstructural integrity may add additional value in explaining variance in cognitive function beyond conventional MRI features of SVD.⁹ Other studies demonstrated that microstructural integrity is an independent predictor of cognitive function beyond other features of SVD. Cross-sectional studies in older persons (mean age: 60-70 years) found that diffusion signal abnormality in WMH and particularly in normal appearing white matter was associated with cognitive dysfunction, regardless of WMHs, lacunar infarcts or brain volume.¹⁰⁻¹² A longitudinal study in older persons (mean age: 74 years) demonstrated that diffusion signal abnormalities in normal appearing grey or white brain tissue, rather than microstructural damage in WMH, predicted faster cognitive decline 3 years later, regardless of conventional SVD features.¹³ Furthermore, a cross-sectional study (mean age: 69 years) found that, compared to controls, older persons with psychological dysfunction had diffusion signal abnormalities, also after the exclusion of WMH from the DTI measurements.¹⁴

As yet there are no data available determining the role of microstructural integrity as independent predictor in the oldest old, in whom overt features of SVD and

in particular atrophy are more prevalent. The aim of this cross-sectional study is to investigate whether microstructural integrity is independently associated with cognitive and psychological dysfunction in an older study population (mean age 81 years) beyond other features of SVD.

Methods

Participants

Participants for this cross-sectional study were included from the MRI sub-study of the Discontinuation of Antihypertensive Treatment in Elderly people (DANTE) Study Leiden.¹⁵ Between June 2011 and August 2013 community-dwelling persons were included when they were aged ≥ 75 years, had a Mini Mental State Examination (MMSE) score between 21 and 27, were on antihypertensive medication, and had a current systolic blood pressure ≤ 160 mmHg. Participants with a clinical diagnosis of dementia, or serious current angina pectoris, cardiac arrhythmia, heart failure, myocardial infarction or a coronary reperfusion procedure less than 3 years ago, a history of stroke or transient ischemic attack were excluded. A more detailed description of procedures used has been published previously.¹⁵

The Medical Ethical Committee of the Leiden University Medical Center approved the study and written informed consent was obtained from all participants. A total of 236 participants underwent a MRI scan of the brain, of whom 16 were excluded due to incidental MRI findings (cortical infarcts $n=8$, aneurysms $n=2$, normal pressure hydrocephalus $n=2$, meningioma $n=1$, cavernoma $n=2$, internal carotid artery occlusion $n=1$). In addition 25 were excluded due to having DTI images of insufficient quality, leaving 195 participants for analysis.

Demographic and clinical characteristics

Demographic characteristics were assessed at baseline using standardized interviews and blood pressure was measured.¹⁵ General practitioners used structured questionnaires to obtain medical history and medication use.

MRI Acquisition and processing

All MRI scans were acquired on a whole-body magnetic resonance system operating at a field strength of 3-Tesla (Philips Medical Systems, Best, The

Netherlands), equipped with a 32-channel head coil. DTI images were acquired with repetition time/echo time=9592/56 ms, flip angle=90°, Field Of View = 220'220'128 mm, matrix size 112'110, voxel dimensions = 2 mm (isotropic), 64 slices, 32 measurement directions and b-value=1000. MRI scans were analysed with FMRIB Software Version 5.0.1. Library. Using the FDT (FMRIB's Diffusion Toolbox) individual fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AxD) and radial diffusivity (RD) images were created.¹⁶ Using FLIRT to a non-diffusion-weighted reference volume, original images were corrected for effects of head movement and eddy currents in the gradient coils. A diffusion tensor model was fitted to the corrected images to create individual FA, MD, AxD and RD images. For global quantification of brain tissue FA, MD, AxD, and RD in white or grey brain tissue (that included WMH and other features of SVD) 3DTI images were skull-stripped,¹⁷ segmented,¹⁸ and aligned into MNI152 using FLIRT. Lower FA and higher MD, AxD and RD indicate poorer microstructural integrity.

Microbleeds were assessed using T2*-weighted MRI (TR/TE=45/31 ms, FA=13°, FOV=250'175'112 mm, voxels dimension 0.8 mm (isotropic) and were defined as focal areas of signal void (on T2-MRI), which increased in size on T2*-weighted images (blooming effect) compared with corresponding T2-weighted images (TR/TE=4200/80 ms, FA=90°, FOV=224'180'144 mm, matrix size 448'320, 40 slices, 3.6 mm thick). Symmetric hypointensities in the basal ganglia, likely to represent non-haemorrhagic iron deposits were disregarded. MRI acquisition, image processing and analysis of WMH volume, brain volume and lacunar infarcts has been described previously.^{19;20}

Cognitive and psychological function

Global cognitive function was assessed with the MMSE, ranging from 0-30 points with higher scores indicating better performance.²¹ Furthermore, a battery of cognitive tests was administered from which cognitive domain compound scores were calculated.¹⁵ Executive function was assessed with the interference score of the abbreviated Stroop Colour Word Test,²² and the difference between the time to complete the Trail Making Test part A and B (TMT delta).²³ The immediate (3 trials) and delayed recall (1 trial) on the 15-Word Verbal Learning Test (15-WVLT), and the visual Association Test (VAT)²⁴ were used to measure memory. Psychomotor speed was evaluated with the Letter-Digit Substitution

Test (LDST).²⁵ All of the six aforementioned tests were combined in the overall cognition compound score. The Geriatric Depression Scale (GDS)-15²⁶ was used to measure symptoms of depression (range 0-15 points, with higher scores indicating more symptoms) and the Apathy Scale²⁷ to measure symptoms of apathy (range 0-42 points, with higher scores indicating more symptoms).

Statistical analyses

Characteristics of participants are presented as mean (standard deviation [SD]), median (interquartile [IQR] range), or as number (percentage), where appropriate. Education was dichotomized at primary education (6 years of schooling). The distribution of WMH volume was skewed, which required transformation by natural log. Linear models were used wherein DTI measures in white and grey matter (standardized FA, MD, AxD and RD) were entered as independent variables, and standardized cognitive domain scores, or GDS-15 and Apathy Scale scores as dependent variables. These analyses were adjusted for age, gender and education in model 1, additionally for number of lacunar infarcts and microbleeds and WMH volume in model 2, and furthermore for normalized brain volume in model 3. The F-test was used to compare the fit (the R-squared; explained variance) of the different models. Voxel-wise statistical analysis of the FA, MD, RD and AxD data was carried out using Tract-Based Spatial Statistics (TBSS)²⁸ part of FSL. TBSS projects all subjects' FA data onto a mean FA tract skeleton, before applying voxelwise cross-subject statistics. Exploratory local DTI analyses were performed in the hippocampus^{29;30}, thalamus³¹, putamen^{20;32;33} and pre- and postcentral gyrus^{31;33}, as previous research associated these areas with cognitive dysfunction. To explore the associations between DTI measures in white and grey matter and features of SVD linear or logistic regression models were used adjusted for gender and age. The SPSS software for Windows (version 20.0.0.1; SPSS, Chicago, IL, USA) was used for statistical analyses. A p-value of < 0.05 was considered statistically significant.

Results

Table 1 presents the characteristics of the study population; mean age was 80.7 (SD 4.1) years and 41.5% was male.

The FA, MD, AxD and RD in white matter were all related to WMH, lacunar infarcts, cerebral microbleeds, and normalized brain volume (all $p < 0.01$) (Supplementary table 1). Furthermore, in grey matter, higher FA was associated with lower volume of WMH and less lacunar infarcts. A higher MD, AxD and RD in grey matter were associated with the presence of lacunar infarcts and microbleeds and, most strongly, with a lower normalized brain volume.

Table 2 present the associations between DTI measures in white matter with cognitive and psychological function. In model 1, MD, AxD and RD in white matter were associated with worse executive function, memory, psychomotor speed, and overall cognition (all $p < 0.05$). FA was associated with executive function and overall cognition. To assess the impact of diabetes mellitus and hypertension to our findings, we separately added the covariates to model 1, which did not change the results (data not shown). Additional adjustment for conventional features of SVD in model 2 yielded similar effect estimates. After further adjustment for brain volume in model 3, all these associations strongly attenuated, with only the association between FA in white matter and executive functioning remaining. Results for DTI measures in grey matter (see supplementary table 2) followed a similar pattern as for white matter, with the exception of the lack of any association with memory. After adjustment for normalized brain volume, only FA and RD in grey matter remained associated with executive functioning.

To assess the individual contribution of each covariate to overall cognitive functioning, the standardized beta coefficients for each variable in the fully adjusted model for one DTI measure (FA in white matter) are presented in supplementary table 3. The largest effect estimates were found for education and normalized brain volume. Model 3 fitted significantly better (F-test < 0.05) than model 2 for executive function, psychomotor speed and overall cognition as indicated by * in table 2 and supplementary table 2.

Table 1. Characteristics of participants (n=195)

Characteristic	n=195
Demographic and clinical	
Age (years)	80.7 (4.1)
Male	81 (41.5%)
Education >6 years	137 (70.3%)
Current smoking	13 (6.7%)
Diabetes mellitus	39 (20.0%)
Cardiovascular disease ^a	17 (8.7%)
Systolic blood pressure (mmHg)	147.5 (20.5)
Diastolic blood pressure (mmHg)	81.2 (10.5)
Cerebrovascular pathology and brain volumes	
WMH volume, cc	22.5 (8.1-56.3)
Lacunar infarcts present ^b	52 (26.7%)
Cerebral microbleeds present	50 (26.2%)
Brain volume total, cc	1000.0 (92.7)
Grey matter volume, cc	497.2 (48.1)
White matter volume, cc	502.8 (52.5)
Microstructural integrity in white and grey matter	
Fractional anisotropy	
White	0.24 (0.02)
Grey	0.17 (0.01)
Mean diffusivity, $\times 10^{-3}$ mm ² /s	
White	1.01 (0.06)
Grey matter	1.15 (0.07)
Axial diffusivity, $\times 10^{-3}$ mm ² /s	
White	1.24 (0.05)
Grey	1.34 (0.07)
Radial diffusivity, $\times 10^{-3}$ mm ² /s	
White	0.89 (0.06)
Grey	1.05 (0.07)
Cognitive and psychological measures	
Mini mental state examination	26.0 (25.0-27.0)
Executive ^c	
Delta Trial Making Test (seconds)	130.8 (66.6)
Stroop interference score (seconds)	39.28 (32.7)
Memory	
15-Word Verbal Learning Test (words remembered)	
Immediate recall score	16.7 (5.6)
Delayed recall score	4.8 (2.8)
Visual Association Test (pictures remembered)	12 (10-12)
Psychomotor speed	
Letter-Digit Substitution Test (digits coded)	31.0 (9.4)
Geriatric Depression Scale ^c	1.0 (0-3.0)
Apathy Scale ^c	10.7 (4.4)

The data are presented as mean $\pm$ standard deviation, median (interquartile range) or as number (percentage) where appropriate. Abbreviations: cc, cubic centilitres, WMH, white matter hyperintensities Delta Trial Making Test (TMT) denotes difference between TMT-B and TMT-A.

^a comprises myocardial infarction or coronary intervention procedure ≥ 3 years ago, or peripheral arterial disease.

^b missing for n=4 participants.

^c Higher scores indicate worse functioning.

TBSS demonstrated no associations for microstructural integrity and cognitive and psychological functioning. Supplementary table 4 shows several associations of DTI measures in local brain regions with various cognitive domains. Global or local DTI measures in both white and grey matter were not associated with GDS-15 or Apathy Scale scores.

Discussion

This study reveals that in older persons with mild cognitive deficits, DTI abnormalities in grey matter were associated with worse executive function, psychomotor speed and overall cognition, whereas DTI abnormalities in white matter were additionally associated with memory. These relationships were independent of WMH, lacunar infarcts or cerebral microbleeds, but strongly attenuated after adjusting for brain volume.

In contrast to other studies,^{34,35} we found no global or local associations between microstructural integrity and symptoms of depression or apathy. Also contradictory to our findings, a 3-year follow-up study in persons (mean age: 74 years) has demonstrated that DTI abnormalities in normal-appearing brain tissue predicted worse executive function, memory, and psychomotor speed, independently of WMH, lacunar infarcts and total brain volume.¹³ Furthermore, a large cross-sectional study in older persons (mean age: 67 years) showed that diffusion signal abnormalities were associated with several cognitive domains regardless of brain volume and other conventional features of SVD.¹² Differences in study findings may be explained by that we used different cognitive tests to assess cognitive function and included older participants who were all using antihypertensive treatment. Finally, it is likely that adjustment for brain volume in

Table 2. Associations for DTI measures in white and grey matter and features of SVD (n=195)

	Executive function			Memory			Psychomotor speed			Overall cognition			GDS			Apathy Scale		
	B (95% CI)	P		B (95% CI)	P		B (95% CI)	P		B (95% CI)	P		B (95% CI)	P		B (95% CI)	P	
FA																		
Model 1	0.28 (0.13 to 0.42)	<.001		0.12 (-0.03 to 0.26)	.12		0.14 (-0.003 to 0.28)	.06		0.22 (0.08 to 0.36)	.003		0.15 (-0.16 to 0.46)	.34		0.32 (-0.33 to 0.97)	.33	
Model 2	0.28 (0.11 to 0.44)	.002		0.13 (-0.04 to 0.30)	.14		0.16 (-0.01 to 0.32)	.06		0.23 (0.06 to 0.39)	.007		0.15 (-0.22 to 0.52)	.43		0.48 (-0.27 to 1.22)	.21*	
Model 3	0.22 (0.05 to 0.39)	.01*		0.09 (-0.09 to 0.26)	.34		0.08 (-0.08 to 0.25)	.33*		0.16 (-0.01 to 0.32)	.06*		0.18 (-0.21 to 0.56)	.36		0.55 (-0.23 to 1.32)	.17	
MD																		
Model 1	-0.28 (-0.43 to -0.12)	.001		-0.19 (-0.35 to -0.03)	.02		-0.23 (-0.38 to -0.08)	.003		-0.29 (-0.45 to -0.14)	<.001		-0.08 (-0.42 to 0.27)	.66		-0.08 (-0.80 to 0.63)	.82	
Model 2	-0.27 (-0.44 to -0.10)	.002		-0.19 (-0.37 to -0.02)	.03		-0.26 (-0.43 to -0.09)	.002		-0.30 (-0.46 to -0.13)	.001		-0.07 (-0.45 to 0.32)	.74		-0.29 (-1.08 to 0.49)	.47	
Model 3	-0.16 (-0.36 to 0.04)	.12		-0.12 (-0.34 to 0.09)	.26		-0.13 (-0.33 to 0.07)	.19*		-0.18 (-0.38 to 0.02)	.08*		-0.15 (-0.61 to 0.32)	.54		-0.52 (-1.46 to 0.42)	.27	
AxD																		
Model 1	-0.24 (-0.39 to -0.08)	.004		-0.18 (-0.34 to -0.02)	.03		-0.23 (-0.38 to -0.07)	.004		-0.28 (-0.43 to -0.12)	.001		-0.03 (-0.38 to 0.32)	.87		0.04 (-0.69 to 0.76)	.92	
Model 2	-0.22 (-0.39 to -0.05)	.01		-0.18 (-0.36 to -0.01)	.04		-0.24 (-0.40 to -0.08)	.004		-0.26 (-0.43 to -0.10)	.002		-0.02 (-0.40 to 0.37)	.94		-0.18 (-0.95 to 0.60)	.66	
Model 3	-0.09 (-0.29 to 0.11)	.37*		-0.10 (-0.31 to 0.11)	.34		-0.11 (-0.30 to 0.09)	.28*		-0.13 (-0.33 to 0.06)	.18*		-0.07 (-0.53 to 0.38)	.76		-0.36 (-1.29 to 0.57)	.45	
RD																		
Model 1	-0.29 (-0.44 to -0.13)	<.001		-0.18 (-0.34 to -0.03)	.02		-0.23 (-0.38 to -0.08)	.003		-0.30 (-0.45 to -0.14)	<.001		-0.09 (-0.43 to 0.25)	.59		-0.12 (-0.83 to 0.59)	.73	
Model 2	-0.28 (-0.45 to -0.11)	.001		-0.20 (-0.38 to -0.02)	.03		-0.26 (-0.43 to -0.10)	.002		-0.30 (-0.47 to -0.14)	<.001		-0.09 (-0.47 to 0.30)	.66		-0.33 (-1.12 to 0.45)	.41	
Model 3	-0.18 (-0.38 to -0.02)	.07		-0.13 (-0.34 to 0.09)	.24		-0.14 (-0.33 to 0.06)	.17*		-0.19 (-0.39 to 0.01)	.06*		-0.17 (-0.63 to 0.29)	.47		-0.57 (-1.50 to 0.36)	.23	

Beta's represent mean change in cognitive domain z-scores, GDS or Apathy Scale scores per standard deviation increase in DTI measures. Abbreviations: DTI, Diffusion Tensor Imaging; FA, Fractional Anisotropy; MD, Mean Diffusivity; AxD, Axial Diffusivity; RD, Radial Diffusivity; GDS, Geriatric Depression Scale; WMH, white matter hyperintensities. Model 1 = adjusted for gender, age and education.

Model 2 = model 1 + number of lacunar infarcts, number of microbleeds and log WMH volume.

Model 3 = model 2 + normalized brain volume

* F-test <.05; indicating significant improved fit of the model compared to the previous model.

populations with different ages (and different prevalence of brain atrophy) yields different results.

We demonstrated that most associations between DTI measures and cognitive dysfunction attenuated after adjusting for brain volume. It may be that the observed associations were, at least in part, mediated by atrophy. In support of this hypothesis, a longitudinal study showed that midlife white matter diffusion signal abnormalities predicted white matter atrophy.³⁶

However, several DTI measures in global and local brain regions were associated with cognitive functioning regardless of brain volume and overt features of SVD. FA in white and grey matter and grey matter RD remained associated with executive functioning. Furthermore, FA in the putamen as well as MD, AxD and RD in the post-central gyrus remained associated with executive functioning, and MD, AxD, RD in the hippocampus remained associated with memory. These findings may be explained by that microstructural damage to myelin/axons/neurons³⁷ (undetectable by conventional MRI) may lead to disruption of neuronal circuits. These microstructural changes are thought to be secondary to SVD, and are related to vascular risk factors, particularly hypertension.³⁹ Executive function is known to be the cognitive domain most sensitive to subtle diffuse deterioration of microstructural integrity of vascular origin.^{9,39}

To investigate to what extent hypertension contributed to our findings, we added blood pressure as an additional covariate. Adding blood pressure in model I did not affect any of the associations, suggesting that hypertension an unlikely aetiology for DTI abnormalities and cognitive dysfunction in our population. Still, these findings should be interpreted with caution as only participants with a blood pressure ≤ 160 mmHg were included and all participants used antihypertensive treatment, following the strict inclusion criteria from the DANTE Study.

Compared to diffusivity measures, FA had a weaker association with brain volume. The disparity in associations suggests that the DTI measures may reflect different pathophysiology. FA reflects a normalized ratio of diffusion directionality; whereas MD reflects the overall magnitude of water diffusion. Although fundamental research on the underlying pathological substrate is scarce, a lower FA is thought to reflect irreversible structural damage, such as loss of myelin/axons, whereas increased MD may indicate an increase in interstitial or extracellular fluid.⁴⁰

The present results should be interpreted with caution, as we are unable to make any causal inference due to the cross-sectional design. Moreover, due to the strict selection criteria of the DANTE trial, the findings are only generalizable to older persons using antihypertensive treatment, without a history of serious cardiovascular disease or dementia. Finally, we performed multiple testing which can increase the chance of type I errors (wrongfully rejecting the 0-hypothesis). The Bonferroni correction was not applied, as it is considered a too conservative method to use in multiple comparisons with outcomes that are correlated.

The strengths of the study include the extensive assessment of cognitive function and of microstructural integrity using FA, MD, AxD and RD in both white and grey matter. Moreover, in the analyses on the relationship between microstructural integrity and cognitive function, we are the first to adjust for all features of SVD, including the presence of cerebral microbleeds.

In conclusion, DTI measures in white and grey matter were associated with worse functioning on several cognitive domains. Associations were independent of WMH, lacunar infarcts and cerebral microbleeds, but strongly attenuated after adjusting for brain volume. Only white and grey matter fractional anisotropy, and grey matter radial diffusivity were associated with executive functioning, independently of brain volume. Our findings indicate that the relationship between DTI abnormalities and cognitive function is largely explained by brain volume.

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Supplementary material

Supplementary table 1. Associations for DTI measures in white and grey matter and features of SVD (n=195)

	White matter hyper-intensities volume ^a		Presence of lacunar infarcts		Presence of microbleeds		Normalised brain volume	
	B (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	B (95% CI)	P
White matter								
FA	-0.55 (-0.72 to -0.39)	<.001	0.49 (0.34 to 0.72)	<.001	0.59 (0.41 to 0.86)	.006	13.01 (4.95 to 21.07)	.002
MD	0.40 (0.21 to 0.60)	<.001	1.91 (1.29 to 2.83)	.001	2.19 (1.45 to 3.31)	<.001	-33.81 (-41.52 to -26.11)	<.001
AxD	0.33 (0.13 to 0.53)	.001	1.77 (1.20 to 2.61)	.004	2.18 (1.44 to 3.29)	<.001	-35.31 (-42.98 to -27.64)	<.001
RD	0.43 (0.23 to 0.62)	<.001	1.96 (1.33 to 2.90)	.001	2.16 (1.44 to 3.26)	<.001	-32.40 (-40.13 to -24.66)	<.001
Grey matter								
FA	-0.25 (-0.43 to -0.07)	.006	0.55 (0.37 to 0.80)	.002	0.91 (0.64 to 1.29)	.60	5.62 (-2.49 to 13.74)	.17
MD	0.01 (-0.20 to 0.22)	.92	1.61 (1.08 to 2.40)	.02	1.82 (1.20 to 2.74)	.005	-41.95 (-49.10 to -34.79)	<.001
AxD	0.01 (-0.20 to 0.22)	.90	1.55 (1.04 to 2.29)	.03	1.84 (1.22 to 2.77)	.004	-42.28 (-49.37 to -35.19)	<.001
RD	0.01 (-0.20 to 0.22)	.95	1.65 (1.10 to 2.46)	.01	1.79 (1.18 to 2.70)	.006	-41.29 (-48.52 to -34.07)	<.001

Adjusted for gender and age. ^aWhite matter hyperintensities were log transformed. Beta's represent mean change in white matter hyperintensities volume or in normalised brain volume per standard deviation increase in DTI measures. Odds Ratio's represent the change in the log of the odds of presence of lacunar infarcts or microbleeds per standard deviation increase in DTI measures. FA=Fractional Anisotropy, MD=Mean Diffusivity, AxD=Axial Diffusivity, RD=Radial Diffusivity, OR=Odds Ratio

Supplementary table 2. Associations for DTI measures in grey matter and cognitive and psychological functioning (n=195)

	Executive function		Memory		Psychomotor speed		Overall cognition		GDS		Apathy Scale	
	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P
FA												
Model 1	0.20 (0.05 to 0.35)	.008	0.03 (-0.12 to 0.17)	.73	0.05 (-0.09 to 0.19)	.49	0.11 (-0.04 to 0.25)	.14	0.30 (-0.01 to 0.60)	.06	0.53 (-0.11 to 1.17)	.10
Model 2	0.18 (0.03 to 0.34)	.02	0.02 (-0.13 to 0.18)	.77	0.05 (-0.10 to 0.20)	.49	0.10 (-0.05 to 0.25)	.18	0.31 (-0.02 to 0.64)	.06	0.60 (-0.06 to 1.26)	.07
Model 3	0.16 (0.01 to 0.31)	.04*	<0.001 (-0.15 to 0.16)	.96*	0.02 (-0.12 to 0.17)	.74*	0.07 (-0.07 to 0.22)	.32*	0.32 (-0.01 to 0.65)	.06	0.62 (-0.04 to 1.28)	.07
MD												
Model 1	-0.28 (-0.44 to -0.11)	.001	-0.14 (-0.31 to 0.02)	.09	-0.23 (-0.38 to -0.07)	.004	-0.27 (-0.42 to -0.11)	.001	-0.01 (-0.36 to 0.34)	.95	0.12 (-0.62 to 0.86)	.75
Model 2	-0.29 (-0.45 to -0.13)	.001*	-0.14 (-0.31 to 0.02)	.10	-0.24 (-0.40 to -0.09)	.003	-0.27 (-0.43 to -0.11)	.001	-0.06 (-0.43 to 0.31)	.76	-0.17 (-0.92 to 0.59)	.67
Model 3	-0.20 (-0.41 to <0.01)	.05	-0.04 (-0.25 to 0.18)	.73	-0.11 (-0.31 to 0.09)	.29*	-0.14 (-0.34 to 0.06)	.17*	-0.15 (-0.62 to 0.32)	.52	-0.39 (-1.35 to 0.56)	.42
AxD												
Model 1	-0.26 (-0.43 to -0.10)	.001	-0.15 (-0.31 to 0.02)	.08	-0.22 (-0.38 to -0.07)	.005	-0.26 (-0.42 to -0.10)	.001	0.03 (-0.32 to 0.39)	.86	0.21 (-0.53 to 0.94)	.58
Model 2	-0.28 (-0.44 to -0.12)	.001*	-0.15 (-0.32 to 0.02)	.09	-0.24 (-0.39 to -0.08)	.003	-0.26 (-0.42 to -0.10)	.001	-0.01 (-0.37 to 0.36)	.97	-0.07 (-0.83 to 0.68)	.85
Model 3	-0.18 (-0.39 to 0.03)	.09	-0.04 (-0.26 to 0.17)	.70	-0.10 (-0.29 to 0.10)	.33*	-0.13 (-0.33 to 0.07)	.20*	-0.07 (-0.54 to 0.40)	.76	-0.25 (-1.21 to 0.71)	.61
RD												
Model 1	-0.28 (-0.44 to -0.12)	.001	-0.14 (-0.30 to 0.02)	.09	-0.23 (-0.38 to -0.07)	.004	-0.27 (-0.42 to -0.11)	.001	-0.04 (-0.39 to 0.32)	.84	0.07 (-0.67 to 0.81)	.85
Model 2	-0.30 (-0.46 to -0.14)	<.001*	-0.14 (-0.31 to 0.03)	.11	-0.24 (-0.40 to -0.09)	.003*	-0.27 (-0.43 to -0.11)	.001	-0.09 (-0.46 to 0.28)	.65	-0.21 (-0.97 to 0.54)	.58
Model 3	-0.21 (-0.42 to -0.01)	.04	-0.03 (-0.25 to 0.18)	.75	-0.11 (-0.30 to 0.09)	.28*	-0.14 (-0.34 to 0.06)	.16*	-0.20 (-0.66 to 0.27)	.41	-0.46 (-1.41 to 0.49)	.34

Beta's represent mean change in cognitive domain z-scores, GDS or Apathy Scale scores per standard deviation increase in DTI measures. Abbreviations: DTI, Diffusion Tensor Imaging; FA, Fractional Anisotropy; MD, Mean Diffusivity; AxD, Axial Diffusivity; RD, Radial Diffusivity; GDS, Geriatric Depression Scale; WMH, white matter hyperintensities.

Model 1 = adjusted for gender, age and education

Model 2 = model 1 + number of lacunar infarcts, number of microbleeds and logWMH volume

Model 3 = model 2 + normalized brain volume

* F-test <0.05; indicating significant improved fit of the model compared with the previous model

Supplementary table 3. Beta coefficients for each co-variate in the fully adjusted model for FA in white matter (determinant) and overall cognitive function (outcome).

	Overall cognitive function B (95% CI)	P-value
FA white matter	0.16 (-0.01 to 0.32)	0.06
Gender	0.12 (-0.01 to 0.25)	0.08
Age	-0.06 (-0.21 to 0.09)	0.42
Education	0.32 (0.19 to 0.46)	<0.001
WMH volume log	-0.11 (-0.26 to 0.04)	0.15
Number of microbleeds	-0.06 (-0.21 to 0.09)	0.42
Number of lacunar infarcts	0.16 (0.01 to 0.31)	0.04
Normalized brain volume	0.22 (0.08 to 0.36)	0.002

Beta's represent mean change in overall cognitive z-score per standard deviation in co-variates. Abbreviations: FA, fractional anisotropy; WMH, white matter hyperintensity

Supplementary table 4. Associations for DTI measures in local brain regions and cognitive and psychological functioning (n=195)

Executive function	Memory		Psychomotor speed		Overall cognition		GDS		Apathy Scale	
	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P	B (95% CI)	P
Hippocampus										
FA	0.12 (-0.03 to 0.26)	.12	0.03 (-0.11 to 0.18)	.66	0.13 (-0.01 to 0.26)	.07	0.11 (-0.03 to 0.25)	.12	0.10 (-0.21 to 0.41)	.52
MD	-0.12 (-0.26 to 0.03)	.13	-0.28 (-0.42 to -0.14)	<.001*	-0.13 (-0.27 to 0.01)	.06	-0.25 (-0.38 to -0.12)	<.001^	-0.24 (-0.54 to 0.06)	.12
AxD	-0.07 (-0.22 to 0.07)	.33	-0.29 (-0.43 to -0.15)	<.001*	-0.12 (-0.26 to 0.01)	.07	-0.23 (-0.37 to -0.10)	.001^	-0.21 (-0.51 to 0.09)	.17
RD	-0.12 (-0.27 to 0.03)	.10	-0.27 (-0.41 to -0.13)	<.001*	-0.13 (-0.27 to <0.01)	.05	-0.25 (-0.38 to -0.11)	<.001^	-0.25 (-0.55 to 0.05)	.11
Thalamus										
FA	0.23 (0.08 to 0.37)	.002^	0.04 (-0.11 to 0.18)	.62	0.10 (-0.04 to 0.24)	.16	0.14 (-0.004 to 0.28)	.06	0.001 (-0.31 to 0.31)	.99
MD	-0.12 (-0.26 to 0.03)	.11	-0.10 (-0.24 to 0.05)	.18	-0.14 (-0.27 to <0.01)	.05	-0.12 (-0.26 to 0.02)	.08	0.02 (-0.28 to 0.32)	.90
AxD	-0.10 (-0.25 to 0.04)	.16	-0.10 (-0.24 to 0.05)	.18	-0.14 (-0.27 to <0.01)	.04^	-0.12 (-0.25 to 0.02)	.09	0.02 (-0.28 to 0.32)	.90
RD	-0.12 (-0.27 to 0.02)	.09	-0.09 (-0.24 to 0.05)	.19	-0.13 (-0.27 to <0.01)	.05	-0.12 (-0.26 to 0.02)	.08	0.02 (-0.28 to 0.32)	.90
Putamen										
FA	0.25 (0.10 to 0.40)	.001*	-0.01 (-0.16 to 0.15)	.95	0.06 (-0.08 to 0.21)	.38	0.15 (0.01 to 0.29)	.04^	0.15 (-0.16 to 0.46)	.35
MD	-0.17 (-0.31 to -0.02)	.03^	0.10 (-0.14 to 0.16)	.90	-0.07 (-0.20 to 0.07)	.36	-0.09 (-0.23 to 0.05)	.22	-0.05 (-0.37 to 0.26)	.74
AxD	-0.15 (-0.30 to <0.01)	.045^	-0.03 (-0.18 to 0.11)	.66	-0.07 (-0.21 to 0.07)	.33	-0.10 (-0.25 to 0.04)	.15	0.04 (-0.28 to 0.35)	.82
RD	-0.18 (-0.33 to -0.04)	.02^	0.01 (-0.14 to 0.15)	.94	-0.13 (-0.27 to 0.01)	.08	-0.12 (-0.26 to 0.02)	.09	-0.04 (-0.36 to 0.28)	.81
Precentral gyrus										
FA	0.15 (<0.01 to 0.29)	.047^	0.01 (-0.13 to 0.16)	.84	0.09 (-0.05 to 0.23)	.21	0.09 (-0.05 to 0.23)	.21	0.17 (-0.14 to 0.47)	.28
MD	-0.14 (-0.28 to 0.01)	.06	0.06 (-0.08 to 0.21)	.38	-0.06 (-0.20 to 0.07)	.36	-0.05 (-0.19 to 0.09)	.50	0.01 (-0.21 to 0.40)	.53
AxD	-0.10 (-0.25 to 0.05)	.19	0.05 (-0.09 to 0.20)	.48	-0.07 (-0.20 to 0.07)	.35	-0.04 (-0.18 to 0.10)	.56	0.11 (-0.19 to 0.42)	.46
RD	-0.13 (-0.28 to 0.01)	.08	0.06 (-0.09 to 0.20)	.45	-0.07 (-0.20 to 0.07)	.33	-0.05 (-0.19 to 0.09)	.46	0.09 (-0.22 to 0.39)	.57
Postcentral gyrus										
FA	0.16 (0.02 to 0.31)	.03^	0.05 (-0.09 to 0.20)	.47	0.08 (-0.06 to 0.22)	.26	0.12 (-0.02 to 0.26)	.09	0.09 (-0.22 to 0.39)	.58
MD	-0.17 (-0.31 to -0.02)	.02*	0.02 (-0.13 to 0.16)	.83	-0.08 (-0.22 to 0.06)	.25	-0.10 (-0.24 to 0.04)	.16	-0.01 (-0.31 to 0.28)	.93
AxD	-0.17 (-0.32 to -0.03)	.02*	0.02 (-0.12 to 0.17)	.76	-0.08 (-0.21 to 0.06)	.28	-0.10 (-0.24 to 0.04)	.18	-0.02 (-0.31 to 0.28)	.91
RD	-0.17 (-0.31 to -0.02)	.03*	0.01 (-0.14 to 0.16)	.88	-0.08 (-0.22 to 0.06)	.24	-0.10 (-0.24 to 0.04)	.15	-0.01 (-0.30 to 0.29)	.95

Beta's represent mean change in cognitive domain z-scores, GDS or Apathy Scale scores per standard deviation increase in DTI measures.

Abbreviations: DTI, Diffusion Tensor Imaging; FA, Fractional Anisotropy; MD, Mean Diffusivity; AxD, Axial Diffusivity; RD, Radial Diffusivity; GDS, Geriatric Depression Scale.

Adjusted for gender, age and education.

* remained significant after further adjustment for number of lacunar infarcts, number of microbleeds, log WMH volume and normalized brain volume

^ no longer significant after further adjustment for number of lacunar infarcts, number of microbleeds, log WMH volume and normalized brain volume

