Blood pressure and neuropsychiatric symptoms in old age

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Chapter 8

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

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Abstract

Background

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

Methods

The study included 195 participants (aged ≥75 years) who 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 were used to assess symptoms of depression and apathy, respectively. The association between DTI measures and neurocognitive function was analysed using linear regression models.

Results

In grey matter, a lower FA and higher MD, AxD and RD were associated with worse executive function, psychomotor speed and overall cognition and, in white matter, also with memory. Findings were independent of WMH, lacunar infarcts and cerebral microbleeds. However, 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 scores on the GDS-15 or Apathy Scale.

Conclusion

Microstructural integrity was associated with cognitive, but not psychological dysfunction. Associations were independent of the 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 cognitive[3] and, possibly, of psychological dysfunction.[4] Nevertheless, the relationship between these overt signs of SVD and cognitive and psychological dysfunction is modest and inter-individual variability is high. It is suggested that these visible lesions represent only the tip of an iceberg and that SVD may also cause more subtle and 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 connect brain regions involved in cognitive functions.

DTI measures of WM microstructural integrity may have additional value in explaining the variance in cognitive function beyond conventional MRI features of SVD.[9] It has also been shown 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, irrespective 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 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]

Currently, no data are available for determining the role of microstructural integrity as an independent predictor in the oldest old, in whom overt features of SVD and, in particular, atrophy are more prevalent. Therefore, this cross-sectional study investigated whether microstructural integrity is independently associated with cognitive and psychological dysfunction in an older 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. Excluded from the present study were participants with a clinical diagnosis of dementia, current angina pectoris, cardiac arrhythmia, heart failure, myocardial infarction or a coronary reperfusion procedure ≤3 years ago, and a history of stroke or transient ischemic attack. A detailed description of the 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). After an additional 25 were excluded due to DTI images of insufficient quality, 195 participants were available for the present analyses.

Data acquisition

Demographic and clinical characteristics

Demographic characteristics were assessed at baseline using a standardized interview 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) 3DT1 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 x 175 x 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 x 180 x 144 mm, matrix size 448 x 320, 40 slices, 3.6 mm thick). Symmetric hypointensities in the basal ganglia, likely to represent non-hemorrhagic iron deposits were disregarded. MRI acquisition, image processing and analysis of WMH volume, brain volume and lacunar infarcts have been described previously.[19;20]

Cognitive and psychological function

Global cognitive function was assessed with the MMSE: scores range from 0-30 points with higher scores indicating better performance.[21] 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 by the difference between the time to complete the Trail Making Test part A and B (TMT delta).[23] Memory was measured using 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] Psychomotor speed was evaluated with the Letter-Digit Substitution Test (LDST).[25] All these six tests were combined in the overall cognition compound score. The Geriatric Depression Scale (GDS)-15[26] was used to measure symptoms of depression (range 0-15 points, with higher scores indicating more symptoms) and the Apathy Scale[27] to measure symptoms of apathy (range 0-42 points, with higher scores indicating more symptoms).

Statistical analyses

Characteristics of the 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 in which 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, were entered as dependent variables. In model 1 these analyses were adjusted for age, gender and education; model 2 included these same variables, plus the number of lacunar infarcts/microbleeds and WMH volume; and in model 3, normalized brain volume was also added. The F-test was used to compare the fit (the R-squared; explained variance) of the different models.

Voxelwise statistical analysis of the FA, MD, RD and AxD data was performed using Tract-Based Spatial Statistics (TBSS)[28] part of FSL. TBSS projects the FA data of all subjects onto a mean FA tract skeleton, before applying voxelwise cross-subject statistics.

Exploratory local DTI analyses were performed in the hippocampus[29;30], thalamus[31], putamen[20;32;33] and pre- and postcentral gyrus[31;33], because previous studies associated these areas with cognitive dysfunction. To explore the associations between DTI measures in white and grey matter and the features of SVD, linear or logistic regression models were used adjusted for age and gender. 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

Demographic and clinical characteristics

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

TABLE 1. Characteristics of the study population (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^	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^^	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)

TABLE 1. Characteristics of the study population (n=195) (*continued*)

Microstructural integrity in white and grey matter	
Fractional anisotropy	
White	0.24 (0.02)
Grey	0.17 (0.01)
Mean diffusivity, $x10^{-3}$ mm^2/s	
White	1.01 (0.06)
Grey matter	1.15 (0.07)
Axial diffusivity, $x10^{-3}$ mm^2/s	
White	1.24 (0.05)
Grey	1.34 (0.07)
Radial diffusivity, $x10^{-3}$ 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†	
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†	1.0 (0-3.0)
Apathy Scale†	10.7 (4.4)

Data are presented as mean ± standard deviation, median (interquartile range) or as number (percentage) where appropriate.
^Comprises myocardial infarction or coronary intervention procedure ≥3 years ago, or peripheral arterial disease;
^^missing for n=4 participants;
† Higher scores indicate worse functioning.
cc = cubic centiliters.
Delta Trial Making Test (TMT) = difference between TMT-B and TMT-A.
WMH = white matter hyperintensities.

DTI measures and SVD

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

DTI measures and neurocognitive function

Table 2 presents the associations between DTI measures in white matter, and 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 on our findings, these covariates were added separately to model 1; however, the results remained unchanged (data not shown). In model 2, additional adjustment for conventional features of SVD yielded similar effect estimates. In model 3, after further adjustment for brain volume 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 an asterisk (*) in Table 2 and supplementary Table 2.

TBSS showed no associations between microstructural integrity and cognitive and psychological functioning. Supplementary Table 4 shows several associations between DTI measures in local brain regions and various cognitive domains. In both white and grey matter, global or local DTI measures were not associated with scores on the GDS-15 or Apathy Scale.

TABLE 2. Associations between DTI measures in white matter and cognitive and psychological functioning (n=195)

	Executive function		Memory		Psychomotor speed		Overall cognition		GDS		Apathy Scale	
	ß (95% CI)	P	ß (95% CI)	P	ß (95% CI)	P	ß (95% CI)	P	ß (95% CI)	P	ß (95% CI)	P
FA												
Model 1	0.28 (0.13 to 0.42)	**<0.001**	0.12 (-0.03 to 0.26)	0.12	0.14 (-0.003 to 0.28)	0.06	0.22 (0.08 to 0.36)	**0.003**	0.15 (-0.16 to 0.46)	0.34	0.32 (-0.33 to 0.97)	0.33
Model 2	0.28 (0.11 to 0.44)	**0.002**	0.13 (-0.04 to 0.30)	0.14	0.16 (-0.01 to 0.32)	0.06	0.23 (0.06 to 0.39)	**0.007**	0.15 (-0.22 to 0.52)	0.43	0.48 (-0.27 to 1.22)	0.21*
Model 3	0.22 (0.05 to 0.39)	**0.01***	0.09 (-0.09 to 0.26)	0.34	0.08 (-0.08 to 0.25)	0.33*	0.16 (-0.01 to 0.32)	0.06*	0.18 (-0.21 to 0.56)	0.36	0.55 (-0.23 to 1.32)	0.17
MD												
Model 1	-0.28 (-0.43 to -0.12)	**0.001**	-0.19 (-0.35 to -0.03)	**0.02**	-0.23 (-0.38 to -0.08)	**0.003**	-0.29 (-0.45 to -0.14)	**<0.001**	-0.08 (-0.42 to 0.27)	0.66	-0.08 (-0.80 to 0.63)	0.82
Model 2	-0.27 (-0.44 to -0.10)	**0.002**	-0.19 (-0.37 to -0.02)	**0.03**	-0.26 (-0.43 to -0.09)	**0.002**	-0.30 (-0.46 to -0.13)	**0.001**	-0.07 (-0.45 to 0.32)	0.74	-0.29 (-1.08 to 0.49)	0.47
Model 3	-0.16 (-0.36 to 0.04)	0.12	-0.12 (-0.34 to 0.09)	0.26	-0.13 (-0.33 to 0.07)	0.19*	-0.18 (-0.38 to 0.02)	0.08*	-0.15 (-0.61 to 0.32)	0.54	-0.52 (-1.46 to 0.42)	0.27
AxD												
Model 1	-0.24 (-0.39 to -0.08)	**0.004**	-0.18 (-0.34 to -0.02)	**0.03**	-0.23 (-0.38 to -0.07)	**0.004**	-0.28 (-0.43 to -0.12)	**0.001**	-0.03 (-0.38 to 0.32)	0.87	0.04 (-0.69 to 0.76)	0.92
Model 2	-0.22 (-0.39 to -0.05)	**0.01**	-0.18 (-0.36 to -0.01)	0.04	-0.24 (-0.40 to -0.08)	**0.004**	-0.26 (-0.43 to -0.10)	**0.002**	-0.02 (-0.40 to 0.37)	0.94	-0.18 (-0.95 to 0.60)	0.66
Model 3	-0.09 (-0.29 to 0.11)	0.37*	-0.10 (-0.31 to 0.11)	0.34	-0.11 (-0.30 to 0.09)	0.28*	-0.13 (-0.33 to 0.06)	0.18*	-0.07 (-0.53 to 0.38)	0.76	-0.36 (-1.29 to 0.57)	0.45
RD												
Model 1	-0.29 (-0.44 to -0.13)	**<0.001**	-0.18 (-0.34 to -0.03)	**0.02**	-0.23 (-0.38 to -0.08)	**0.003**	-0.30 (-0.45 to -0.14)	**<0.001**	-0.09 (-0.43 to 0.25)	0.59	-0.12 (-0.83 to 0.59)	0.73
Model 2	-0.28 (-0.45 to -0.11)	**0.001**	-0.20 (-0.38 to -0.02)	**0.03**	-0.26 (-0.43 to -0.10)	**0.002**	-0.30 (-0.47 to -0.14)	**<0.001**	-0.09 (-0.47 to 0.30)	0.66	-0.33 (-1.12 to 0.45)	0.41
Model 3	-0.18 (-0.38 to -0.02)	0.07	-0.13 (-0.34 to 0.09)	0.24	-0.14 (-0.33 to 0.06)	0.17*	-0.19 (-0.39 to 0.01)	0.06*	-0.17 (-0.63 to 0.29)	0.47	-0.57 (-1.50 to 0.36)	0.23

Beta values represent mean change in cognitive domain z-scores, or scores on the Geriatric Depression Scale or Apathy Scale per standard deviation increase in DTI measures.

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

Model 1 = adjusted for gender, age and education

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

Model 3 = same as model 2 + normalized brain volume

* F-test <0.05: indicating significant improved fit of the model compared to the previous model

Discussion

This study shows 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, in addition, 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, in contrast to our findings, a 3-year follow-up study in older persons (mean age 74 years) showed 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] In addition, a large cross-sectional study in older persons (mean age 67 years) showed that diffusion signal abnormalities were associated with several cognitive domains irrespective of brain volume and other conventional features of SVD.[12] A possible explanation for the differences between these latter study findings and ours, is that we used different cognitive tests to assess cognitive function and included older participants all of whom were using antihypertensive medication. Also, adjusting for brain volume in populations with different ages (and a different prevalence for brain atrophy) is likely to yield different results.

The present study shows that most of the associations between DTI measures and cognitive dysfunction attenuated after adjusting for brain volume. It is possible that the observed associations were, at least in part, mediated by atrophy. In support of this hypothesis, a longitudinal study reported 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, irrespective of brain volume and overt features of SVD. FA in white and grey matter, and RD in grey matter, 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 might be explained by the fact that microstructural damage to myelin/axons/neurons[37] (undetectable on conventional MRI) may lead to disruption of neuronal circuits. These microstructural changes are thought to be secondary to SVD and related to vascular risk factors, in particular to hypertension.[38] Executive function is known to be the cognitive domain most sensitive to subtle and diffuse deterioration of microstructural integrity of vascular origin.[9;39]

To investigate to what extent hypertension contributed to our findings, blood pressure was included as an additional covariate. In model 1, adding blood pressure did not

affect any of the associations, suggesting that hypertension is an unlikely etiology for DTI abnormalities and cognitive dysfunction in our population. However, 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 a different pathophysiology. FA reflects a normalized ratio of diffusion directionality, whereas MD reflects the overall magnitude of water diffusion. Although 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 no causal inference can be made 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 null hypothesis). The Bonferroni correction was not applied, as this method is considered too conservative 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, irrespective 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 between DTI measures in white and grey matter and features of SVD (n=195)

	WMH^		Presence of lacunar infarcts		Presence of microbleeds		Normalised brain volume	
	Beta (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	Beta (95% CI)	P
White matter								
FA	-0.55 (-0.72 to -0.39)	**<0.001**	0.49 (0.34 to 0.72)	**<0.001**	0.59 (0.41 to 0.86)	**0.006**	13.01 (4.95 to 21.07)	**0.002**
MD	0.40 (0.21 to 0.60)	**<0.001**	1.91 (1.29 to 2.83)	**0.001**	2.19 (1.45 to 3.31)	**<0.001**	-33.81 (-41.52 to -26.11)	**<0.001**
AxD	0.33 (0.13 to 0.53)	**0.001**	1.77 (1.20 to 2.61)	**0.004**	2.18 (1.44 to 3.29)	**<0.001**	-35.31 (-42.98 to -27.64)	**<0.001**
RD	0.43 (0.23 to 0.62)	**<0.001**	1.96 (1.33 to 2.90)	**0.001**	2.16 (1.44 to 3.26)	**<0.001**	-32.40 (-40.13 to -24.66)	**<0.001**
Grey matter								
FA	-0.25 (-0.43 to -0.07)	**0.006**	0.55 (0.37 to 0.80)	**0.002**	0.91 (0.64 to 1.29)	0.60	5.62 (-2.49 to 13.74)	0.17
MD	0.01 (-0.20 to 0.22)	0.92	1.61 (1.08 to 2.40)	**0.02**	1.82 (1.20 to 2.74)	**0.005**	-41.95 (-49.10 to -34.79)	**<0.001**
AxD	0.01 (-0.20 to 0.22)	0.90	1.55 (1.04 to 2.29)	**0.03**	1.84 (1.22 to 2.77)	**0.004**	-42.28 (-49.37 to -35.19)	**<0.001**
RD	0.01 (-0.20 to 0.22)	0.95	1.65 (1.10 to 2.46)	**0.01**	1.79 (1.18 to 2.70)	**0.006**	-41.29 (-48.52 to -34.07)	**<0.001**

Adjusted for gender and age.

^white matter hyperintensities were log transformed

Beta values represent mean change in white matter hyperintensities volume or in normalised brian 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 between DTI measures in grey matter and cognitive and psychological functioning (n=195)

	Executive function		Memory		Psychomotor speed		Overall cognition		GDS		Apathy Scale	
	ß (95% CI)	P	ß (95% CI)	P	ß (95% CI)	P	ß (95% CI)	P	ß (95% CI)	P	ß (95% CI)	P
FA												
Model 1	0.20 (0.05 to 0.35)	**0.008**	0.03 (-0.12 to 0.17)	0.73	0.05 (-0.09 to 0.19)	0.49	0.11 (-0.04 to 0.25)	0.14	0.30 (-0.01 to 0.60)	0.06	0.53 (-0.11 to 1.17)	0.10
Model 2	0.18 (0.03 to 0.34)	**0.02**	0.02 (-0.13 to 0.18)	0.77	0.05 (-0.10 to 0.20)	0.49	0.10 (-0.05 to 0.25)	0.18	0.31 (-0.02 to 0.64)	0.06	0.60 (-0.06 to 1.26)	0.07
Model 3	0.16 (0.01 to 0.31)	**0.04***	<0.001 (-0.15 to 0.16)	0.96*	0.02 (-0.12 to 0.17)	0.74*	0.07 (-0.07 to 0.22)	0.32*	0.32 (-0.01 to 0.65)	0.06	0.62 (-0.04 to 1.28)	0.07
MD												
Model 1	-0.28 (-0.44 to -0.11)	**0.001**	-0.14 (-0.31 to 0.02)	0.09	-0.23 (-0.38 to -0.07)	**0.004**	-0.27 (-0.42 to -0.11)	**0.001**	-0.01 (-0.36 to 0.34)	0.95	0.12 (-0.62 to 0.86)	0.75
Model 2	-0.29 (-0.45 to -0.13)	**0.001***	-0.14 (-0.31 to 0.02)	0.10	-0.24 (-0.40 to -0.09)	**0.003**	-0.27 (-0.43 to -0.11)	**0.001**	-0.06 (-0.43 to 0.31)	0.76	-0.17 (-0.92 to 0.59)	0.67
Model 3	-0.20 (-0.41 to <0.01)	0.05	-0.04 (-0.25 to 0.18)	0.73	-0.11 (-0.31 to 0.09)	0.29*	-0.14 (-0.34 to 0.06)	0.17*	-0.15 (-0.62 to 0.32)	0.52	-0.39 (-1.35 to 0.56)	0.42
AxD												
Model 1	-0.26 (-0.43 to -0.10)	**0.001**	-0.15 (-0.31 to 0.02)	0.08	-0.22 (-0.38 to -0.07)	**0.005**	-0.26 (-0.42 to -0.10)	**0.001**	0.03 (-0.32 to 0.39)	0.86	0.21 (-0.53 to 0.94)	0.58
Model 2	-0.28 (-0.44 to -0.12)	**0.001***	-0.15 (-0.32 to 0.02)	0.09	-0.24 (-0.39 to -0.08)	**0.003**	-0.26 (-0.42 to -0.10)	**0.001**	-0.01 (-0.37 to 0.36)	0.97	-0.07 (-0.83 to 0.68)	0.85
Model 3	-0.18 (-0.39 to 0.03)	0.09	-0.04 (-0.26 to 0.17)	0.70	-0.10 (-0.29 to 0.10)	0.33*	-0.13 (-0.33 to 0.07)	0.20*	-0.07 (-0.54 to 0.40)	0.76	-0.25 (-1.21 to 0.71)	0.61
RD												
Model 1	-0.28 (-0.44 to -0.12)	**0.001**	-0.14 (-0.30 to 0.02)	0.09	-0.23 (-0.38 to -0.07)	**0.004**	-0.27 (-0.42 to -0.11)	**0.001**	-0.04 (-0.39 to 0.32)	0.84	0.07 (-0.67 to 0.81)	0.85
Model 2	-0.30 (-0.46 to -0.14)	**<0.001***	-0.14 (-0.31 to 0.03)	0.11	-0.24 (-0.40 to -0.09)	**0.003***	-0.27 (-0.43 to -0.11)	**0.001**	-0.09 (-0.46 to 0.28)	0.65	-0.21 (-0.97 to 0.54)	0.58
Model 3	-0.21 (-0.42 to -0.01)	**0.04**	-0.03 (-0.25 to 0.18)	0.75	-0.11 (-0.30 to 0.09)	0.28*	-0.14 (-0.34 to 0.06)	0.16*	-0.20 (-0.66 to 0.27)	0.41	-0.46 (-1.41 to 0.49)	0.34

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

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

Model 1 = adjusted for gender, age and education

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

Model 3 = same as model 2 + normalized brain volume

* F-test <0.05: indicating significant improved fit of the model compared to the previous model

SUPPLEMENTARY TABLE 3. Beta coefficients for each co-variate in the fully adjusted model for FA in white matter and overall cognitive function

	Overall cognitive function	
	ß (95% CI)	**P**
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**

FA= fractional anisotropy, WMH= white matter hyperintensity

Beta values represent mean change in overall cognitive z-score per standard deviation increase in co-variates.

SUPPLEMENTARY TABLE 4. Associations between DTI measures in local brain regions and cognitive and psychological functioning (n=195)

	Executive function		Memory		Psychomotor speed		Overall cognition		GDS		Apathy Scale	
	ß (95% CI)	P	ß (95% CI)	P	ß (95% CI)	P	ß (95% CI)	P	ß (95% CI)	P	ß (95% CI)	P
Hippocampus												
FA	0.12 (-0.03 to 0.26)	0.12	0.03 (-0.11 to 0.18)	0.66	0.13 (-0.01 to 0.26)	0.07	0.11 (-0.03 to 0.25)	0.12	0.10 (-0.21 to 0.41)	0.52	0.03 (-0.60 to 0.67)	0.92
MD	-0.12 (-0.26 to 0.03)	0.13	-0.28 (-0.42 to -0.14)	**<0.001***	-0.13 (-0.27 to 0.01)	0.06	-0.25 (-0.38 to -0.12)	**<0.001^**	-0.24 (-0.54 to 0.06)	0.12	-0.39 (-1.01 to 0.23)	0.22
AxD	-0.07 (-0.22 to 0.07)	0.33	-0.29 (-0.43 to -0.15)	**<0.001***	-0.12 (-0.26 to 0.01)	0.07	-0.23 (-0.37 to -0.10)	**0.001^**	-0.21 (-0.51 to 0.09)	0.17	-0.27 (-0.90 to 0.36)	0.40
RD	-0.12 (-0.27 to 0.03)	0.10	-0.27 (-0.41 to -0.13)	**<0.001***	-0.13 (-0.27 to <0.01)	0.05	-0.25 (-0.38 to -0.11)	**<0.001^**	-0.25 (-0.55 to 0.05)	0.11	-0.40 (-1.02 to 0.22)	0.21
Thalamus												
FA	0.23 (0.08 to 0.37)	**0.002^**	0.04 (-0.11 to 0.18)	0.62	0.10 (-0.04 to 0.24)	0.16	0.14 (-0.004 to 0.28)	0.06	0.001 (-0.31 to 0.31)	0.99	0.37 (-0.26 to 1.01)	0.25
MD	-0.12 (-0.26 to 0.03)	0.11	-0.10 (-0.24 to 0.05)	0.18	-0.14 (-0.27 to <-0.01)	0.05	-0.12 (-0.26 to 0.02)	0.08	0.02 (-0.28 to 0.32)	0.90	-0.24 (-0.86 to 0.38)	0.45
AxD	-0.10 (-0.25 to 0.04)	0.16	-0.10 (-0.24 to 0.05)	0.18	-0.14 (-0.27 to <-0.01)	**0.04^**	-0.12 (-0.25 to 0.02)	0.09	0.02 (-0.28 to 0.32)	0.90	-0.23 (-0.85 to 0.40)	0.48
RD	-0.12 (-0.27 to 0.02)	0.09	-0.09 (-0.24 to 0.05)	0.19	-0.13 (-0.27 to <0.01)	0.05	-0.12 (-0.26 to 0.02)	0.08	0.02 (-0.28 to 0.32)	0.90	-0.25 (-0.87 to 0.37)	0.43
Putamen												
FA	0.25 (0.10 to 0.40)	**0.001***	-0.01 (-0.16 to 0.15)	0.95	0.06 (-0.08 to 0.21)	0.38	0.15 (0.01 to 0.29)	**0.04^**	0.15 (-0.16 to 0.46)	0.35	0.63 (-0.02 to 1.27)	0.06
MD	-0.17 (-0.31 to -0.02)	**0.03^**	0.10 (-0.14 to 0.16)	0.90	-0.07 (-0.20 to 0.07)	0.36	-0.09 (-0.23 to 0.05)	0.22	-0.05 (-0.37 to 0.26)	0.74	-0.29 (-0.94 to 0.35)	0.37
AxD	-0.15 (-0.30 to <-0.01)	**0.045^**	-0.03 (-0.18 to 0.11)	0.66	-0.07 (-0.21 to 0.07)	0.33	-0.10 (-0.25 to 0.04)	0.15	0.04 (-0.28 to 0.35)	0.82	-0.14 (-0.79 to 0.52)	0.68
RD	-0.18 (-0.33 to -0.04)	**0.02^**	0.01 (-0.14 to 0.15)	0.94	-0.13 (-0.27 to 0.01)	0.08	-0.12 (-0.26 to 0.02)	0.09	-0.04 (-0.36 to 0.28)	0.81	-0.41 (-1.05 to 0.24)	0.21
Precentral gyrus												
FA	0.15 (<0.01 to 0.29)	**0.047^**	0.01 (-0.13 to 0.16)	0.84	0.09 (-0.05 to 0.23)	0.21	0.09 (-0.05 to 0.23)	0.21	0.17 (-0.14 to 0.47)	0.28	0.35 (-0.28 to 0.98)	0.27
MD	-0.14 (-0.28 to 0.01)	0.06	0.06 (-0.08 to 0.21)	0.38	-0.06 (-0.20 to 0.07)	0.36	-0.05 (-0.19 to 0.09)	0.50	0.01 (-0.21 to 0.40)	0.53	0.01 (-0.62 to 0.65)	0.98
AxD	-0.10 (-0.25 to 0.05)	0.19	0.05 (-0.09 to 0.20)	0.48	-0.07 (-0.20 to 0.07)	0.35	-0.04 (-0.18 to 0.10)	0.56	0.11 (-0.19 to 0.42)	0.46	0.02 (-0.62 to 0.66)	0.95
RD	-0.13 (-0.28 to 0.01)	0.08	0.06 (-0.09 to 0.20)	0.45	-0.07 (-0.20 to 0.07)	0.33	-0.05 (-0.19 to 0.09)	0.46	0.09 (-0.22 to 0.39)	0.57	-0.04 (-0.67 to 0.59)	0.90
Postcentral gyrus												
FA	0.16 (0.02 to 0.31)	**0.03^**	0.05 (-0.09 to 0.20)	0.47	0.08 (-0.06 to 0.22)	0.26	0.12 (-0.02 to 0.26)	0.09	0.09 (-0.22 to 0.39)	0.58	0.16 (-0.48 to 0.79)	0.62
MD	-0.17 (-0.31 to -0.02)	**0.02***	0.02 (-0.13 to 0.16)	0.83	-0.08 (-0.22 to 0.06)	0.25	-0.10 (-0.24 to 0.04)	0.16	-0.01 (-0.31 to 0.28)	0.93	-0.02 (-0.66 to 0.61)	0.94
AxD	-0.17 (-0.32 to -0.03)	**0.02***	0.02 (-0.12 to 0.17)	0.76	-0.08 (-0.21 to 0.06)	0.28	-0.10 (-0.24 to 0.04)	0.18	-0.02 (-0.31 to 0.28)	0.91	<0.01 (-0.63 to 0.64)	0.99
RD	-0.17 (-0.31 to -0.02)	**0.03***	0.01 (-0.14 to 0.16)	0.88	-0.08 (-0.22 to 0.06)	0.24	-0.10 (-0.24 to 0.04)	0.15	-0.01 (-0.30 to 0.29)	0.95	-0.04 (-0.68 to 0.60)	0.90

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

DTI=Diffusion Tensor Imaging, FA=Fractional Anisotropy, MD=Mean Diffusivity, AxD=Axial Diffusivity, RD=Radial Diffusivity, GDS=Geriatric Depression Scale. WMH= white matter hyperintensity. 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