AJNR

Influence of Small Vessel Disease and Microstructural Integrity on Neurocognitive Functioning in Older Individuals: The DANTE Study Leiden

J.E.F. Moonen, J.C. Foster-Dingley, A.A. van den Berg-Huijsmans, W. de Ruijter, A.J.M. de Craen, J. van der Grond and R.C. van der Mast

AJNR Am J Neuroradiol 2017, 38 (1) 25-30
doi: https://doi.org/10.3174/ajnr.A4934
http://www.ajnr.org/content/38/1/25

Influence of Small Vessel Disease and Microstructural Integrity on Neurocognitive Functioning in Older Individuals: The DANTE Study Leiden

J.E.F. Moonen, J.C. Foster-Dingley, A.A. van den Berg-Huijsmans, W. de Ruijter, A.J.M. de Craen, J. van der Grond, and R.C. van der Mast

ABSTRACT

BACKGROUND AND PURPOSE: Small vessel disease is a major cause of neurocognitive dysfunction in the elderly. Small vessel disease may manifest as white matter hyperintensities, lacunar infarcts, cerebral microbleeds, and atrophy, all of which are visible on conventional MR imaging or as microstructural changes determined by diffusion tensor imaging. This study investigated whether microstructural integrity is associated with neurocognitive dysfunction in older individuals, irrespective of the conventional features of small vessel disease.

MATERIALS AND METHODS: The study included 195 participants (75 years of age or older) who underwent conventional 3T MR imaging with DTI to assess fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. Cognitive tests were administered to assess cognitive domains, and the Geriatric Depression Scale-15 and Apathy Scale of Starkstein were used to assess symptoms of depression and apathy, respectively. The association between DTI measures and neurocognitive function was analyzed by using linear regression models.

RESULTS: In gray matter, a lower fractional anisotropy and higher mean diffusivity, axial diffusivity, and radial diffusivity were associated with worse executive function, psychomotor speed, and overall cognition and, in white matter, also with memory. Findings were independent of white matter hyperintensities, lacunar infarcts, and cerebral microbleeds. However, after additional adjustment for normalized brain volume, only lower fractional anisotropy in white and gray matter and higher gray matter radial diffusivity remained associated with executive functioning. DTI measures were not associated with scores on the Geriatric Depression Scale-15 or the Apathy Scale of Starkstein.

CONCLUSIONS: Microstructural integrity was associated with cognitive but not psychological dysfunction. Associations were independent of the conventional features of small vessel disease but attenuated after adjusting for brain volume.

ABBREVIATIONS: AD = axial diffusivity; GDS = Geriatric Depression Scale; FA = fractional anisotropy; MD = mean diffusivity; RD = radial diffusivity; SVD = small vessel disease; WMH = white matter hyperintensity

The occurrence of small vessel disease (SVD), seen on conventional MR imaging as white matter hyperintensities (WMHs), lacunar infarcts, cerebral microbleeds, and brain atrophy,[1] increases with advancing age.[2] SVD is a major cause of cognitive[3] and possibly psychological dysfunction.[4] Nevertheless, the relationship between these overt signs of SVD and cognitive and psychological dysfunction is modest, and interindividual variability is high. It is suggested that these visible lesions represent only the tip of the 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, which measures the diffusion of cerebral water molecules. Diffusion changes have been observed not only in lesions visible on standard MR imaging but also in the surrounding normal-appearing brain tissue.[5-7] The pathologic processes underlying changes in DTI measures include axonal degeneration and

Received December 23, 2015; accepted after revision July 20, 2016.

From the Departments of Psychiatry (J.E.F.M., J.C.F.-D., R.C.v.d.M.), Radiology (A.A.v.d.B.-H., J.v.d.G.), Public Health and Primary Care (W.d.R.), and Gerontology and Geriatrics (A.J.M.d.C.), Leiden University Medical Center, Leiden, the Netherlands; and Department of Psychiatry (R.C.v.d.M.), Collaborative Antwerp Psychiatric Research Institute, University of Antwerp, Antwerp, Belgium.

J.E.F. Moonen and J.C. Foster-Dingley contributed equally.

The authors take full responsibility for the integrity of the data and analyses.

This study was supported by a grant from the Netherlands Organization for Health Research and Development (ZonMW) and Program Priority Medicines for the Elderly (No. 40-41600-98-9014).

The funding organization played no role in the design, conduct, or analysis of the study.

Please address correspondence to Justine E.F. Moonen, MD, Department of Psychiatry, Leiden University Medical Center, PO Box 10392, 2300 WB, Leiden, the Netherlands; e-mail: j.e.f.moonen@lumc.nl

Indicates open access to non-subscribers at www.ajnr.org

Indicates article with supplemental on-line tables.

http://dx.doi.org/10.3174/ajnr.A4934

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 MR imaging 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 individuals (mean age, 60–70 years) found that diffusion signal abnormality in WMHs, 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 individuals (mean age, 74 years) demonstrated that diffusion signal abnormalities in normal-appearing gray or white brain tissue, rather than in WMHs, 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 with controls, older individuals with psychological dysfunction had diffusion signal abnormalities, even after the exclusion of WMHs from the DTI measurements.[14]

Currently, no data are available for determining the role of microstructural integrity as an independent predictor of neurocognitive function in the oldest elderly individuals, 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.

MATERIALS AND METHODS

Participants

Participants for this cross-sectional study were included from the MR imaging substudy of the Discontinuation of Antihypertensive Treatment in Elderly People on Cognitive Functioning (DANTE) Study Leiden.[15] Between June 2011 and August 2013, community-dwelling persons were included when they were 75 years of age or older, had a Mini Mental State Examination score between 21 and 27, were on antihypertensive medication, and had a current systolic blood pressure of ≤160 mm Hg. 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 MR imaging of the brain, of whom 16 were excluded due to incidental MR imaging 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 of insufficient quality, 195 participants were available for the present analyses.

Data Acquisition

Demographic and Clinical Characteristics. Demographic characteristics were assessed at baseline by using a standardized interview, and blood pressure was measured.[15] General practitioners used structured questionnaires to obtain medical history and medication use.

MR Imaging Acquisition and Processing. All MR images were acquired on a whole-body Achieva MR imaging system operating at a field strength of 3T (Philips Healthcare, Best, the Netherlands), equipped with a 32-channel head coil. DTI was acquired with TR/TE = 9592/56 ms, flip angle = 90°, FOV = 220 × 220 × 128 mm, matrix size = 112 × 110, voxel dimension = 2 mm (isotropic), 64 sections, 32 measurement directions, b=1000. MR images were analyzed with the FMRIB Software Library, Version 5.0.1. (FSL (http://www.fmrib.ox.ac.uk/fsl). With the Diffusion Toolbox in FMRIB (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT), individual fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) images were created.[16] Using the FMRIB Linear Image Registration Tool (FLIRT; http://www.fmrib.ox.ac.uk/) as a non-diffusion-weighted reference volume, we correlated original images for the 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, AD, and RD images. For global quantification of brain tissue FA, MD, AD, and RD in white or gray brain tissue (which included WMH and other features of SVD), we skull-stripped,[17] segmented,[18] and aligned 3D T1 images into the Montreal Neurological Institute 152 standard space by using FLIRT. Lower FA and higher MD, AD, and RD indicated poorer microstructural integrity.

Microbleeds were assessed by using T2*-weighted MR imaging (TR/TE = 45/31 ms, flip angle = 13°, FOV = 250 × 175 × 112 mm, voxel dimension = 0.8 mm, isotropic) and were defined as focal areas of signal void (on T2-MR imaging), which increased in size on T2*-weighted images (blooming effect) compared with the corresponding T2-weighted images (TR/TE = 4200/80 ms, flip angle = 90°, FOV = 224 × 180 × 144 mm, matrix size = 448 × 320, 40 sections, 3.6 mm thick). Symmetric hypointensities in the basal ganglia, likely representing nonhemorrhagic iron deposits, were disregarded. MR imaging 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 Mini-Mental State Examination. Scores range from 0 to 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 Color and Word Test[22] and by the difference between the time to complete the Trail-Making Test A and B.[23] Memory was measured by using the immediate (3 trials) and delayed recall (1 trial) on the 15-Word Verbal Learning Test and the Visual Association Test.[24] Psychomotor speed was evaluated with the Letter Digit Substitution Test.[25] These 6 tests were combined in the overall cognition com-

pound 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 of Starkstein,[27] to measure symptoms of apathy (range, 0–42 points, with higher scores indicating more symptoms).

Statistical Analysis

Characteristics of the participants are presented as mean ± SD, median (interquartile 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 a natural logarithm. Linear models were used in which DTI measures in white and gray matter (standardized FA, MD, AD, and RD) were entered as independent variables; and standardized cognitive domain scores or GDS-15 and Apathy Scale of Starkstein scores were entered as dependent variables. In model 1, these analyses were adjusted for age, sex, and education; model 2 included these same variables plus the number of lacunar infarcts and number of microbleeds and WMH volume; and in model 3, normalized brain volume was added.

The *F* test was used to compare the fit (the R^2; explained variance) of the different models. Voxelwise statistical analyses of the FA, MD, RD, and AD data were performed by using Tract-Based Spatial Statistics (TBSS; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/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 gray matter and the features of SVD, we adjusted linear or logistic regression models for age and sex.

The SPSS software for Windows (Version 20.0.0.1; IBM, Armonk, New York) was used for statistical analyses. A *P* value $< .05$ was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

The Table presents the characteristics of the study population; the mean age was 80.7 ± 4.1 years, and 41.5% were men.

Characteristics of the study population ($n = 195$)[a]

Characteristics	
Demographic and clinical	
Age (yr)	80.7 (4.1)
Male	81 (41.5%)
Education (>6 yr)	137 (70.3%)
Current smoking	13 (6.7%)
Diabetes mellitus	39 (20.0%)
Cardiovascular disease[b]	17 (8.7%)
Systolic blood pressure (mm Hg)	147.5 (20.5)
Diastolic blood pressure (mm Hg)	81.2 (10.5)
Cerebrovascular pathology and brain volumes	
WMH volume (mL)	22.5 (8.1–56.3)
Lacunar infarcts present[c]	52 (26.7%)
Cerebral microbleeds present	50 (26.2%)
Brain volume total (mL)	1000.0 (92.7)
Gray matter volume (mL)	497.2 (48.1)
White matter volume (mL)	502.8 (52.5)
Microstructural integrity in white and gray matter	
Fractional anisotropy	
White matter	0.24 (0.02)
Gray matter	0.17 (0.01)
Mean diffusivity ($\times 10^{-3}$ mm^2/s)	
White matter	1.01 (0.06)
Gray matter	1.15 (0.07)
Axial diffusivity ($\times 10^{-3}$ mm^2/s)	
White matter	1.24 (0.05)
Gray matter	1.34 (0.07)
Radial diffusivity ($\times 10^{-3}$ mm^2/s)	
White matter	0.89 (0.06)
Gray matter	1.05 (0.07)
Cognitive and psychological measures	
Mini-Mental State Examination	26.0 (25.0–27.0)
Executive[d]	
Δ Trail-Making Test (sec)[e]	130.8 (66.6)
Stroop interference score (sec)	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[d]	1.0 (0–3.0)
Apathy Scale of Starkstein[d]	10.7 (4.4)

[a] Data are presented as mean ± SD, median (interquartile range), or as number (percentage) where appropriate.
[b] Comprises myocardial infarction or a coronary intervention procedure ≥3 years ago or peripheral artery disease.
[c] Missing for $n = 4$ participants.
[d] Higher scores indicate worse functioning.
[e] Δ Trail-Making Test denotes difference between Trail-Making Test-B and Trail-Making Test-A.

DTI Measures and SVD

In white matter, the FA, MD, AD, and RD were all related to WMHs, lacunar infarcts, cerebral microbleeds, and normalized brain volume (all $P < .01$) (On-line Table 1). In gray matter, a higher FA was associated with a lower volume of WMH and fewer lacunar infarcts. In addition, in gray matter, higher MD, AD, and RD were associated with the presence of lacunar infarcts and microbleeds and, most strongly, with a lower normalized brain volume.

DTI Measures and Cognitive and Psychological Function

On-line Table 2 presents the associations between DTI measures in white matter and cognitive and psychological function. In model 1, MD, AD, and RD in white matter were associated with worse executive function, memory, psychomotor speed, and overall cognition (all, $P < .05$). FA was associated with executive function and overall cognition. To assess the impact of diabetes mellitus and hypertension on our findings, we added these covariates 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 gray matter (On-line Table 3) followed a pattern similar to that of white matter, with the exception of the lack of any association with memory. After adjustment for normalized brain volume, only FA and RD in gray matter remained associated with executive functioning.

To assess the individual contribution of each covariate to overall cognitive functioning, we present the standardized β coefficients for each variable in the fully adjusted model for 1 DTI measure (FA in white matter) in On-line Table 4. The largest effect estimates were found for education and normalized brain volume. Model 3 fit significantly better (F test <0.05) than model 2 for executive function, psychomotor speed, and overall cognition as indicated by footnote *c* in On-line Tables 2 and 3.

TBSS showed no associations between microstructural integrity and cognitive and psychological functioning. On-line Table 5 shows several associations between DTI measures in local brain regions and various cognitive domains. In both white and gray matter, global or local DTI measures were not associated with scores on the GDS-15 or the Apathy Scale of Starkstein.

DISCUSSION

This study shows that in older individuals with mild cognitive deficits, DTI abnormalities in the gray 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 WMHs, lacunar infarcts, or cerebral microbleeds, but strongly attenuated after adjusting for brain volume.

In contrast to other studies,[34,35] no global or local associations between microstructural integrity and symptoms of depression or apathy were found. Also, in contrast to our findings, a 3-year follow-up study in older individuals (mean age, 74 years) showed that DTI abnormalities in normal-appearing brain tissue predicted worse executive function, memory, and psychomotor speed, independent of WMHs, lacunar infarcts, and total brain volume.[13] In addition, a large cross-sectional study in older individuals (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. In addition, 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 gray matter and RD in gray matter remained associated with executive functioning. Furthermore, FA in the putamen and MD, AD, and RD in the postcentral gyrus remained associated with executive functioning; and MD, AD, and RD in the hippocampus remained associated with memory. These findings might be because microstructural damage to myelin/axons/neurons[37] (undetectable on conventional MR imaging) 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, we included blood pressure as an additional covariate in model 1, which did not affect any of the associations. This finding suggests that hypertension is an unlikely etiology for DTI abnormalities and cognitive dysfunction in our population. However, these findings should be interpreted with caution because only participants with a blood pressure of $\leq$160 mm Hg were included, and all participants used antihypertensive treatment, following the strict inclusion criteria from the DANTE study.

Compared with 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 pathologic 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 because 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 individuals 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 because 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 by using FA, MD, AD, and RD in both white and gray matter. Moreover, in the analyses of 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, to our knowledge.

CONCLUSIONS

DTI measures in white and gray matter were associated with worse functioning on several cognitive domains. Associations were independent of WMHs, lacunar infarcts, and cerebral microbleeds but strongly attenuated after adjusting for brain volume. Only white and gray matter fractional anisotropy and gray 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.

ACKNOWLEDGMENTS

The authors thank all the DANTE participants and the coinvestigators.

Disclosures: Justine E.F. Moonen—*RELATED*: *Grant*: Netherlands Organization for Health Research and Development (ZonMW),* *Comments*: program Priority Medicines for the Elderly, No. 40-41600-98-9014. The funding organization played no role in the design, conduct, or analysis of the study. Wouter de Ruijter—*RELATED*: *Grant*: Netherlands Organization for Health Research and Development (ZonMW),* *Comments*: reference No. 11-31010-03 (ZonMW acts on behalf of the Dutch Ministry of Health, Welfare and Sports). A.J.M. de Craen—*RELATED*: *Grant*: Netherlands Organization for Health Research and Development (ZonMW).* *Money paid to the institution.

REFERENCES

1. Wardlaw JM, Smith EE, Biessels GJ, et al; STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1). **Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration.** *Lancet Neurol* 2013;12:822–38 CrossRef Medline
2. Vernooij MW, Ikram MA, Tanghe HL, et al. **Incidental findings on brain MRI in the general population.** *N Engl J Med* 2007;357:1821–28 CrossRef Medline
3. Pantoni L. **Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges.** *Lancet Neurol* 2010;9:689–701 CrossRef Medline
4. Thomas AJ, O'Brien JT, Davis S, et al. **Ischemic basis for deep white matter hyperintensities in major depression: a neuropathological study.** *Arch Gen Psychiatry* 2002;59:785–92 CrossRef Medline
5. Akoudad S, de Groot M, Koudstaal PJ, et al. **Cerebral microbleeds are related to loss of white matter structural integrity.** *Neurology* 2013;81:1930–37 CrossRef Medline
6. Reijmer YD, Freeze WM, Leemans A, et al. **The effect of lacunar infarcts on white matter tract integrity.** *Stroke* 2013;44:2019–21 CrossRef Medline
7. Ropele S, Seewann A, Gouw AA, et al; LADIS study group. **Quantitation of brain tissue changes associated with white matter hyperintensities by diffusion-weighted and magnetization transfer imaging: the LADIS (Leukoaraiosis and Disability in the Elderly) study.** *J Magn Reson Imaging* 2009;29:268–74 CrossRef Medline
8. Schmierer K, Wheeler-Kingshott CA, Boulby PA, et al. **Diffusion tensor imaging of post mortem multiple sclerosis brain.** *Neuroimage* 2007;35:467–77 CrossRef Medline
9. Nitkunan A, Barrick TR, Charlton RA, et al. **Multimodal MRI in cerebral small vessel disease: its relationship with cognition and sensitivity to change over time.** *Stroke* 2008;39:1999–2005 CrossRef Medline
10. Tuladhar AM, van Norden AG, de Laat KF, et al. **White matter integrity in small vessel disease is related to cognition.** *Neuroimage Clin* 2015;7:518–24 CrossRef Medline
11. van Norden AG, de Laat KF, van Dijk EJ, et al. **Diffusion tensor imaging and cognition in cerebral small vessel disease: the RUN DMC study.** *Biochim Biophys Acta* 2012;1822:401–07 CrossRef Medline
12. Vernooij MW, Ikram MA, Vrooman HA, et al. **White matter microstructural integrity and cognitive function in a general elderly population.** *Arch Gen Psychiatry* 2009;66:545–53 CrossRef Medline
13. Jokinen H, Schmidt R, Ropele S, et al; LADIS Study Group. **Diffusion changes predict cognitive and functional outcome: the LADIS study.** *Ann Neurol* 2013;73:576–83 CrossRef Medline
14. Shimony JS, Sheline YI, D'Angelo G, et al. **Diffuse microstructural abnormalities of normal-appearing white matter in late life depression: a diffusion tensor imaging study.** *Biol Psychiatry* 2009;66:245–52 CrossRef Medline
15. Moonen JE, Foster-Dingley JC, de Ruijter W, et al. **Effect of Discontinuation of Antihypertensive Treatment in Elderly People on Cognitive Functioning: the DANTE Study Leiden—a randomized clinical trial.** *JAMA Intern Med* 2015;175:1622–30 CrossRef Medline Medline
16. Behrens TE, Woolrich MW, Jenkinson M, et al. **Characterization and propagation of uncertainty in diffusion-weighted MR imaging.** *Magn Reson Med* 2003;50:1077–88 CrossRef Medline
17. Smith SM. **Fast robust automated brain extraction.** *Hum Brain Mapp* 2002;17:143–55 CrossRef Medline
18. Zhang Y, Brady M, Smith S. **Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm.** *IEEE Trans Med Imaging* 2001;20:45–57 CrossRef Medline
19. Foster-Dingley JC, Moonen JE, van den Berg-Huijsmans AA, et al. **Lower blood pressure and gray matter integrity loss in older persons.** *J Clin Hypertens (Greenwich)* 2015;17:630–37 CrossRef Medline
20. Foster-Dingley JC, van der Grond J, Moonen JE, et al. **Lower blood pressure is associated with smaller subcortical brain volumes in older persons.** *Am J Hypertens* 2015;28:1127–33 CrossRef Medline
21. Folstein MF, Folstein SE, McHugh PR. **"Mini-mental state": a practical method for grading the cognitive state of patients for the clinician.** *J Psychiatr Res* 1975;12:189–98 CrossRef Medline
22. Houx PJ, Jolles J, Vreeling FW. **Stroop interference: aging effects assessed with the Stroop Color-Word Test.** *Exp Aging Res* 1993;19:209–24 CrossRef Medline
23. Arbuthnott K, Frank J. **Trail making test, part B as a measure of executive control: validation using a set-switching paradigm.** *J Clin Exp Neuropsychol* 2000;22:518–28 CrossRef Medline
24. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment.* 4th ed. New York: Oxford University Press; 2004
25. Van der Elst W, van Boxtel MP, Van Breukelen GJ, et al. **The Letter Digit Substitution Test: normative data for 1,858 healthy participants aged 24–81 from the Maastricht Aging Study (MAAS)—influence of age, education, and sex.** *J Clin Exp Neuropsychol* 2006;28:998–1009 CrossRef Medline
26. D'Ath P, Katona P, Mullan E, et al. **Screening, detection and management of depression in elderly primary care attenders, I: the acceptability and performance of the 15 item Geriatric Depression Scale (GDS15) and the development of short versions.** *Fam Pract* 1994;11:260–66 CrossRef Medline
27. Starkstein SE, Mayberg HS, Preziosi TJ, et al. **Reliability, validity, and clinical correlates of apathy in Parkinson's disease.** *J Neuropsychiatry Clin Neurosci* 1992;4:134–39 CrossRef Medline
28. Smith SM, Jenkinson M, Johansen-Berg H, et al. **Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data.** *Neuroimage* 2006;31:1487–505 CrossRef Medline
29. Wessa M, King AV, Meyer P, et al. **Impaired and preserved aspects of feedback learning in aMCI: contributions of structural connectivity.** *Brain Struct Funct* 2016;221:2831–46 CrossRef Medline
30. Brueggen K, Dyrba M, Barkhof F, et al. **Basal forebrain and hippocampus as predictors of conversion to Alzheimer's disease in patients with mild cognitive impairment: a multicenter DTI and volumetry study.** *J Alzheimers Dis* 2015;48:197–204 CrossRef Medline
31. Reginold W, Itorralba J, Tam A, et al. **Correlating quantitative tractography at 3T MRI and cognitive tests in healthy older adults.** *Brain Imaging Behav* 2015 Dec 9. [Epub ahead of print] CrossRef Medline
32. de Jong LW, van der Hiele K, Veer IM, et al. **Strongly reduced volumes of putamen and thalamus in Alzheimer's disease: an MRI study.** *Brain* 2008;131:3277–85 CrossRef Medline
33. Wang Z, Wang J, Zhang H, et al. **Interhemispheric functional and structural disconnection in Alzheimer's disease: a combined resting-state fMRI and DTI study.** *PLoS One* 2015;10:e0126310 CrossRef Medline
34. Ota M, Sato N, Nakata Y, et al. **Relationship between apathy and diffusion tensor imaging metrics of the brain in Alzheimer's disease.** *Int J Geriatr Psychiatry* 2012;27:722–26 CrossRef Medline
35. Reppermund S, Zhuang L, Wen W, et al. **White matter integrity and late-life depression in community-dwelling individuals: diffusion**

tensor imaging study using tract-based spatial statistics. *Br J Psychiatry* 2014;205:315–20 CrossRef Medline
36. Ly M, Canu E, Xu G, et al. **Midlife measurements of white matter microstructure predict subsequent regional white matter atrophy in healthy adults.** *Hum Brain Mapp* 2014;35:2044–54 CrossRef Medline
37. Peters A. **The effects of normal aging on myelin and nerve fibers: a review.** *J Neurocytol* 2002;31:581–93 CrossRef Medline
38. Muñoz Maniega S, Chappell FM, Valdés Hernández MC, et al. **Integrity of normal-appearing white matter: influence of age, visible lesion burden and hypertension in patients with small-vessel disease.** *J Cereb Blood Flow Metab* 2016 Mar 1. [Epub ahead of print] CrossRef Medline
39. O'Sullivan M, Morris RG, Huckstep B, et al. **Diffusion tensor MRI correlates with executive dysfunction in patients with ischaemic leukoaraiosis.** *J Neurol Neurosurg Psychiatry* 2004;75:441–47 CrossRef Medline
40. Kale RA, Gupta RK, Saraswat VA, et al. **Demonstration of interstitial cerebral edema with diffusion tensor MR imaging in type C hepatic encephalopathy.** *Hepatology* 2006;43:698–706 CrossRef Medline