White Matter Integrity and Depressive Symptoms in Cerebral Small Vessel Disease: The RUN DMC Study

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Objective: *Depressive symptoms are common in elderly with cerebral small vessel disease (SVD). As not every individual with SVD experiences depressive symptoms, other factors might play a role. We therefore investigated the white matter (WM) integrity of the white matter tracts in elderly with depressive symptoms, independent of global cognitive function, by applying the tract-based spatial statistics (TBSS).* **Design:** *Prospective cohort study with cross-sectional baseline data.* **Setting:** *Radboud University Nijmegen Medical Centre, The Netherlands.* **Participants:** *438 individuals aged between 50–85 years, with SVD without dementia.* **Measurements:** *Diffusion tensor imaging parameters and depressive symptoms, assessed with the Center for Epidemiologic Studies Depression Scale.* **Results:** *Compared with non-depressed participants (N = 287), those with depressive symptoms (N = 151) had lower fractional anisotropy in the genu and body of the corpus callosum, bilateral inferior fronto-occipital fasciculus, uncinate fasciculus, and corona radiata. These differences disappeared after adjustment for white matter hyperintensities (WMH) and lacunar infarcts. Mean-, axial- and radial diffusivity were higher in these areas in participants with depressive symptoms. After additional adjustment for WMH and lacunar infarcts, the changes observed in radial diffusivity also disappeared. Adding global cognition as confounding variable altered the diffusion parameters only slightly.* **Conclusion:** *This study indicates that elderly with depressive symptoms show a lower WM integrity, independent of global cognitive function, and that the presence of SVD is mostly responsible, affecting the fronto-subcortical regions and hereby disrupting the neural circuitry involved in mood regulation.* (Am J Geriatr Psychiatry 2015; 23:525–535)

Key Words: Small vessel disease, DTI, TBSS, depressive symptoms, elderly

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http://dx.doi.org/10.1016/j.jagp.2014.07.002

Small vessel disease (SVD), which includes white matter hyperintensities (WMHs) and lacunar infarcts, is commonly seen in the elderly.[1] Cognitive and motor impairment are known consequences of SVD. The relation between SVD and depressive symptoms is less known, however.[2–4] Depressive symptoms are also common in the elderly, with a prevalence ranging from 1% to 35%.[3–5] SVD might cause disruption of the fronto-striatal white matter tracts of the neural circuit mediating emotion perception and mood regulation, and thereby increase the risk of developing depressive symptoms in an older individual.[6,7] Because not every individual with SVD experiences depressive symptoms, however, other factors apart from SVD-related lesions seen on conventional magnetic resonance imaging (MRI) might be related to depressive symptoms at older age. One of these factors could be damage to the structural integrity of the normal-appearing white matter (NAWM) surrounding the WMH, which cannot be assessed by conventional MRI.

This microstructural organization of the WM, including the NAWM, can now be assessed by diffusion tensor imaging (DTI), an MRI technique that provides valuable information on the microstructural organization of the WM and the NAWM by measuring the molecular motion (diffusion) of water in biological tissue.[8] Several common DTI-derived indices can be measured indexing global characteristics of WM integrity, such as fractional anisotropy; mean, radial, and axial diffusivity; and mode of anisotropy.

To date, relatively few DTI studies have examined the microstructural integrity of WM in patients with depressive symptoms later in life.[9–12] These studies reported compromised integrity of the WM in regions involved in emotional processing. These studies, however, did not have large sample size ($N < 48$), only used the fractional anisotropy as a global measure, and did not adjust for the possible confounders such as WM lesions and cognitive performance.[9,13,14] Tract-based spatial statistics (TBSS) can be used to investigate the structural integrity, by projecting the DTI indices on a virtual skeleton that is located at the center of the white matter tracts. So far, few studies have performed TBSS in patients with depressive symptoms.[15,16] Although they found a lower fractional anisotropy in bilateral frontal, right temporal and midbrain in depressed participants, these studies also have limitations, such as relative small sample sizes and not adjusting for possible confounders such as cognition.

Our aim was to investigate the regional differences in microstructural integrity of the white matter tracts in a large sample of elderly people with SVD with or without depressive symptoms. We investigated the full spectrum of DTI-derived indices using TBSS. We hypothesized that participants with depressive symptoms have a compromised microstructural integrity (low fractional anisotropy and high mean diffusivity) of the WM compared with participants without depressive symptoms, located in critical regions for emotional processing, compared with participants without depressive symptoms. Additionally, we hypothesized that these compromised regions are partially explained by the presence of SVD and independent of global cognition.

MATERIALS AND METHODS

Study Sample

This study sample is embedded within the Radboud University Nijmegen Diffusion Tensor and MRI Cohort (RUN DMC) study that prospectively investigates risk factors and cognitive, motor, and mood consequences of brain changes, as assessed by MRI in elderly with SVD.[17] On the basis of established research criteria SVD was defined as the presence of lacunar infarcts and/or WMH on neuroimaging.[18] The presence of any of these manifestations of cerebral SVD qualified for the cutoff for presence of SVD. The selection procedure of the participants and the study rationale and protocol were described previously in detail.[17] In short, in 2006, consecutive patients referred to the Department of Neurology between October 2002 and November 2006 were selected for participation. Inclusion criteria were: 1) age between 50 and 85 years; 2) cerebral SVD on neuroimaging (WMH and/or lacunar infarcts). Exclusion criteria were: 1) dementia[19]; 2) Parkinson(-ism)[20]; 3) life expectancy of less than six months; 4) intracranial space occupying lesion; 5) current (psychiatric) disease interfering with cognitive testing or follow-up, serious mental illness in their history,

or a current depression; 6) recent/current use of acetylcholine-esterase inhibitors, neuroleptic agents, L-dopa or dopa-a(nta)gonists; 7) WMH or SVD mimics (e.g., multiple sclerosis and irradiation-induced gliosis); 8) prominent visual or hearing impairment; 9) language barrier; and 10) MRI contraindications or known claustrophobia. This study comprises 503 elderly without dementia or parkinsonism, aged between 50 and 85 years with cerebral SVD. For the present study, 65 participants were additionally excluded because of the presence of territorial infarcts (N = 55), inadequate quality of the MR image (N = 4), and incomplete data on neuropsychological tests (N = 6). This study was approved by the medical review ethics committee of the Arnhem-Nijmegen region and all participants gave written informed consent prior to inclusion.

Assessment of Depressive Symptoms

Depressive symptoms were assessed with the Centre for Epidemiologic Studies Depression Scale (CES-D).[21] Depressive symptoms were considered present in patients with a CES-D score 16 or higher and/or current use of antidepressive medication, taken for depression, irrespective of their actual CES-D score, because depressive symptoms were considered to be the indication for the medication prescription. Those who mentioned psychiatric diagnoses during medical history taking and/or when this became apparent when retrieving the information from medical records, were excluded from participation, apart from those with a diagnosis of depression in their history. A total of 53 participants used antidepressants: 30 participants had a CES-D score of 16 or higher, and the other participants had a CES-D score lower than 16. All participants were taking antidepressants for depression (and not for other reasons such as anxiety, insomnia, or neuropathic pain). All other participants in the RUN DMC study sample were considered as the comparison non-depressed group.

MRI Acquisition

MRI scans of all participants were acquired on a single 1.5-Tesla MRI (Magnetom Sonata, Siemens Medical Solutions, Erlangen, Germany). The protocol included, among other sequences, 3-D T1 MPRAGE (TR/TE/TI 2250/3.68/850 msec; flip angle 15°; voxel size 1.0 × 1.0 × 1.0 mm), a FLAIR pulse sequence (TR/TE/TI 9000/84/2200 msec; voxel size 1.0 × 1.2 × 5.0 mm, interslice gap 1mm) and a DTI sequence (TR/TE 10100/93 msec; voxel size 2.5 × 2.5 × 2.5 mm, 4 unweighted scans, 30 diffusion weighted scans with b-value of 900 s/mm^2).[17]

Conventional MRI Analysis

WMHs were manually segmented on FLAIR images by two trained raters and the total WMH volume was calculated by summing the segmented areas multiplied by slice thickness.[17] WMHs were defined as hyperintense lesions on FLAIR MRI without corresponding cerebrospinal fluid−like hypo-intense lesions on the T1 weighted image. Gliosis surrounding lancunar and territorial infarcts are not considered to be WMHs.[22] Inter-rater variability (assessed by intra-class correlation coefficient) for total WMH volume was 0.99. Lacunar infarcts are defined as hypo-intense areas greater than 2 mm and less than or equal to 15 mm on FLAIR and T1, ruling out enlarged perivascular spaces (≤2 mm, except around the anterior commissure, where perivascular spaces can be large) and infraputaminal pseudolacunes.[22] The intra- and inter-rater reliability for the lacunar infarcts yielded a weighted kappa of 0.80 and 0.88.[17]

To obtain the gray matter (GM), WM, and cerebrospinal spinal fluid (CSF) volume, the T1 MPRAGE images were segmented using Statistical Parametric Mapping 5 unified segmentation routines. Total GM, WM, and CSF volumes were subsequently calculated by summing all voxel volumes that had a p value less than 0.5 for belonging to that tissue class. The sum of GM and WM volume was considered as total brain volume (TBV). The intracranial volume was a summation of all tissue classes. To normalize for the head size, TBV was expressed as percentage of total intracranial volume.

DTI Analysis

The in-house developed algorithm named 'PATCH' (www.ru.nl/neuroimaging/diffusion)[23] was applied to the raw diffusion data to detect and correct head and cardiac motion artefacts using an iteratively re-weighted-least-squares algorithm. Corrections of eddy current and motion artefacts from affine misalignment, which were based on

TABLE 1. Baseline Characteristics of the Participants with and Without Depressive Symptoms

	All Participants (N = 438)	Participants Without Depressive Symptoms (N = 287)	Participants With Depressive Symptoms (N = 151)	Significance
Characteristics				
Demographic and clinical characteristics				
Age (SD)	65.1 (8.8)	64.8 (8.9)	65.6 (8.6)	p = 0.377 (a)
Men, no. (%)	239 (54,6)	169 (58.9)	70 (46.4)	p = 0.012 (b)
CES-D (SD)	11.1 (9.4)	5.9 (4.5)	21.0 (8.3)	p < 0.001 (a)
Antidepressive medication, no.	53	0	53	N.A.
Only primary education, no. (%)	41 (9.4)	19 (6.6)	22 (14.6)	p = 0.007 (b)
MMSE (SD)	28.2 (1.6)	28.4 (1.5)	27.8 (1.7)	p < 0.001 (c)
Cognitive index (SD)[a]	0.00 (0.45)	0.04 (0.43)	−0.08 (0.47)	p = 0.006 (a)
Vascular risk factors				
Hypertension no. (%)	314 (71.7)	202 (70.4)	112 (74.2)	p = 0.403 (b)
Diabetes no. (%)	60 (13.7)	35 (12.2)	25 (16.6)	p = 0.207 (b)
Hypercholesterolemia no. (%)	192 (43.8)	118 (41.1)	74 (49.0)	p = 0.114 (b)
Smoking status no. (%) ∞	305 (69.7)	205 (71.4)	100 (66.2)	p = 0.351 (b)

Notes: Data represent number of participants, mean (standard deviation). MMSE: Mini Mental State Examination; CES-D: Center for Epidemiologic Studies on Depression; N.A. = not applicable. Smoking status defined as current and former smoking. Univariate analysis: (a) Independent t test; df = 436. (b) χ^2 test; df = 1, ∞ df = 2. (c) Mann-Whitney U test.

[a]Six were additionally excluded because of incomplete neuropsychological data.

minimization of the residual diffusion tensor error, were performed simultaneously. Next, fractional anisotropy, mean diffusivity, axial and radial diffusivity, and mode of anisotropy images were calculated using DTIFit within the FSL toolbox, which were fed into the TBSS pipeline.[24] The thinning procedure was conducted on the mean fractional anisotropy image to create a common skeleton using a threshold value 0.3 for the fractional anisotropy, which represents the core-structure of the white matter tract. The threshold value 0.3 was chosen to include major white matter tracts and to reduce intersubject variability. These skeleton projection vectors were then applied to the mean, radial, and axial diffusivity, and mode of anisotropy.

Fractional anisotropy represents a normalized ratio of diffusion directionality and can be used as a measurement of structural integrity of the WM. Mean diffusivity, which measures the averaged diffusion in all directions, can be used as a marker for fibre density. A low fractional anisotropy and/or a high mean diffusivity is typically inferred to the loss of microstructural integrity of the WM, due to various underlying pathophysiological mechanisms. Axial diffusivity reflects the diffusivity parallel to the white matter tracts, and radial diffusivity measures the diffusivity perpendicular to these tracts. Changes in axial diffusivity may implicate axonal damage, whereas changes in radial diffusivity indicates loss of myelin integrity.[25] Mode of anisotropy denotes the shape of the diffusion tensor ranging from planar to linear anisotropy,[26] and can reflect selective degeneration of fibers and/or reorganization of these fibers. The investigation of these diffusivities and mode of anisotropy[26] may yield important information about these underlying mechanisms. Studies showed that DTI can be used to assess the SVD-induced changes in the WM and that areas with WMH could have quite different DTI characteristics. To this end, a comprehensive analysis of the full spectrum of DTI-derived indices is necessary.

Other Measurements

Age, sex, level of education,[27] normalized TBV, and global cognitive function were considered as possible confounders. Global cognitive function was evaluated by the Mini-Mental State Exam (MMSE)[28] and the cognitive index. The cognitive index is a compound score that was calculated as the mean of the z-scores of the one-letter subtask of the Paper-Pencil Memory Scanning Task, the mean of the Reading Subtask of the Stroop test, the mean of the Symbol-Digit Substitution Task, and the mean of the added score on the three learning trials of the RAVLT and the delayed recall of this last test.[29] For assessment of vascular risk factors,

TABLE 2. Neuroimaging Characteristics of the Participants With and Without Depressive Symptoms

	Participants Without Depressive Symptoms (N = 287)	Participants With Depressive Symptoms (N = 151)	Significance
Neuroimaging			
WMH volume, mL[a] (IQR)	6.0 (3.2–15.3)	7.7 (3.3–20.7)	p = 0.127 (a)
Lacunar infarcts, presence, no. (%)	82 (28.6)	52 (34.4)	p = 0.205 (b)
Normalized TBV (SD)	1105.7 (87.0)	1097.2 (85.6)	p = 0.332 (c)
Mean FA skeleton (SD)	0.423 (0.0292)	0.417 (0.0297)	p = 0.037 (c)
Mean MD skeleton (SD)	8.14×10^{-4} (4.57×10^{-5})	8.23×10^{-4} (4.19×10^{-5})	p = 0.038 (c)
Mean AD skeleton (SD)	1.20×10^{-3} (4.16×10^{-5})	1.20×10^{-3} (3.54×10^{-5})	p = 0.051 (c)
Mean RD skeleton (SD)	6.16×10^{-4} (5.14×10^{-5})	6.26×10^{-4} (4.86×10^{-5})	p = 0.049 (c)

Notes: Data represent mean (standard deviation). TBV: total brain volume; WMH: white matter hypertintensities. TBV is normalized to the intracranial volume. (a) Independent t test; df 436. (b) χ^2 test; df = 1. (c) Independent t test.
[a]represents median, IQR: inter quartile range.

structured questionnaires were used together with measurements of blood pressure taken on separate occasions. The risk factors included presence of hypertension (mean blood pressure ≥140/90 mm Hg and/or use of anti-hypertensive medications), diabetes (treatment with antidiabetic medications), hypercholesterolemia (treatment with lipid-lowering drugs), and smoking status.

Statistical Analyses

Demographic and neuro-imaging characteristics in Tables 1 and 2 were tested through univariate analysis, and by an independent t test, a χ^2 test, or a Mann-Whitney U test. When the Levene's test for equality of variances was significant, the significance of the difference between the groups was computed using Welch's t test (equal variances not assumed). To compare the DTI parameters (fractional anisotropy; mean, radial, and axial diffusivity; and mode of anisotropy) between those with or without depressive symptoms, we performed a two-sample t test using a permutation-based statistical interference as a part of FSL toolbox ('randomise'), with a standard number of permutation tests set to 5,000. Significant clusters were identified using the threshold-free cluster enhancement with a p value less than 0.05, family-wise error corrected to control for multiple comparisons. A stepwise analysis was performed. First, age, sex, educational level, and normalized TBV were added as nuisance covariates when performing the group comparisons to keep comparability with other studies. Second, the same analyses were done with additional adjustments for WMH volume and number of lacunar infarcts. Finally, we executed the analysis additionally adjusted for MMSE and cognitive index, to adjust for the possible confounding effect global cognition may have on the relation between microstructural integrity and depressive symptoms.

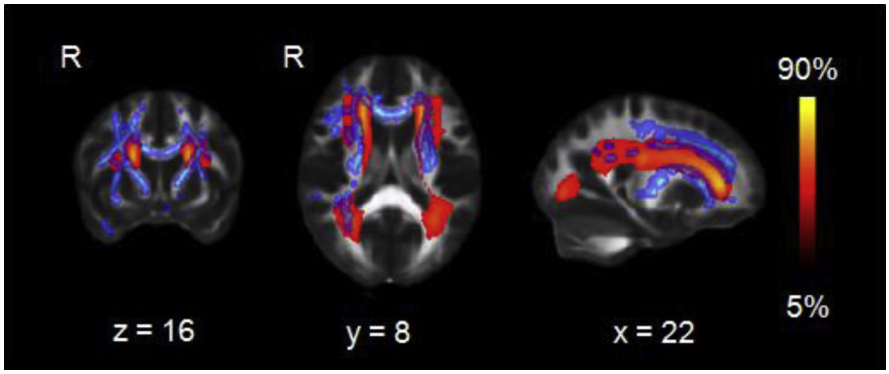
RESULTS

Demographic, clinical, and neuroimaging characteristics are shown in Table 1. Mean age did not significantly differ between participants with (mean: 65.6 years, standard deviation [SD]: 8.6) or without depressive symptoms (64.8 years, SD: 8.9). There were no significant differences for total WMHs volume, lacunar infarcts, and normalized total brain volume between the groups. In both groups, WMHs were predominately periventricular located—especially in the frontal regions—as shown in Figure 1.

A lower overall fractional anisotropy and a higher overall mean and radial diffusivity within the white matter skeleton was seen in participants with depressive symptoms compared with those without (see Table 2). Axial diffusivity did not differ significantly between the groups.

The regions of the significant differences between the groups for each DTI parameters are shown in Figure 2. Participants with depressive symptoms exhibited lower fractional anisotropy in the genu and the body of the corpus callosum, bilateral inferior fronto-occipital fasciculus, uncinate fasciculus, and corona radiata than those without. Figure 3

FIGURE 1. The probability distribution of the white matter hyperintensities.



Notes: WMHs are in red and color-coded in percent (color bar), thresholded from 5 to 90%. These images are projected onto the spatially normalized (Montreal Neurological Institute stereotactic space) and averaged (n = 438) structural map. The statistical map (mean diffusivity) of the group comparisons adjusted for age, sex, education level, is presented in blue.

displays the location of these white matter tracts. These differences disappeared after adjustment for WMHs and lacunar infarcts. The mean, axial, and radial diffusivity were significantly higher in participants with depressive symptoms in the genu and body of the corpus callosum, bilateral inferior fronto-occipital fasciculus, uncinate fasciculus, and corona radiata than in participants without depressive symptoms. This was also seen for fractional anisotropy (Fig. 2). In addition to these regions, the spatial patterns of these diffusivity changes also include bilateral anterior cingulum bundle, internal and external capsule, and right inferior longitudinal fasciculus and parietal lobe. The mean diffusivity remained significantly higher in the genu and body of corpus callosum, right anterior cingulum bundle, and bilateral superior corona radiata after adjustment for WMH's and lacunar infarcts, as was the axial diffusivity in the right superior corona radiata and right superior longitudinal fasciculus. There were no regions with a higher mean, axial, and radial diffusivity in patients without depressive symptoms. The changes observed for radial diffusivity disappeared after additional adjustment for WMH and lacunar infarcts. We observed a trend for lower mode of anisotropy in the body of corpus callosum, right superior corona radiata, and right inferior fronto-occipital fasciculus not surpassing the p value less than 0.05 family-wise error-corrected (data not shown). Among those with depressive symptoms, there was no relationship between severity of depressive symptoms (measured by CES-D score) and the DTI measures (fractional anisotropy and mean diffusivity).

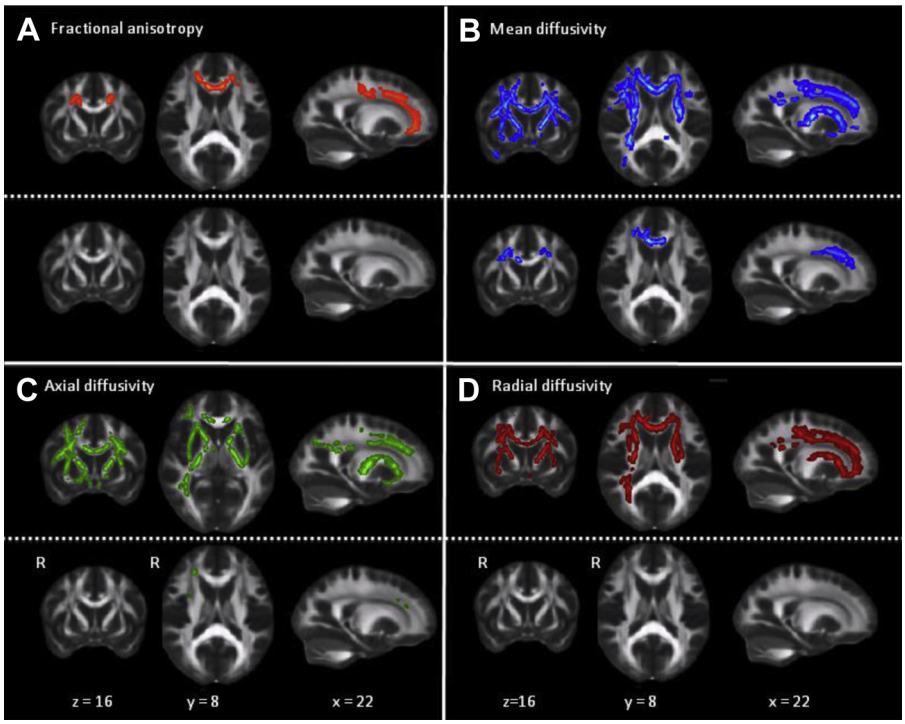
As antidepressant medication in itself can have effects on the structural integrity of the white matter, we repeated the analyses while controlling for current use of antidepressant medication. These analyses did not alter our findings.

Adjustment for MMSE did not markedly alter our findings. After additional adjustment for cognitive index, the difference in fractional anisotropy between those with or without depressive symptoms disappeared. Higher mean, axial, and radial diffusivity for patients with depressive symptoms compared with those without remained present in the similar regions as in the unadjusted analysis.

DISCUSSION

This study clearly shows regional differences in the microstructural integrity of the WM using TBSS in a large sample of elderly people with or without depressive symptoms. We found that participants with depressive symptoms had a lower microstructural integrity in several WM regions, predominantly located in the prefrontal white matter tracts. These differences were independent of global cognition and might, at least in part, be explained by the presence of

FIGURE 2. Spatially distributed differences in DTI parameters between participants with depressive symptoms and without depressive symptoms.

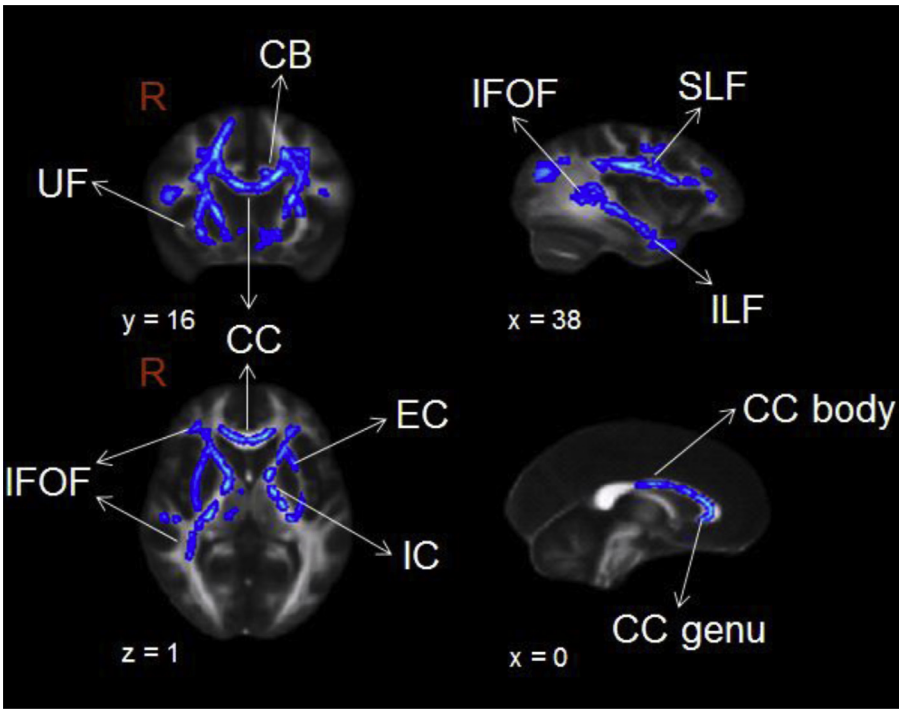


Notes: Voxel-wise analysis of the DTI parameters, A) fractional anisotropy, B) mean diffusivity, C) axial diffusivity and D) radial diffusivity. Fractional anisotropy is reduced in frontal regions in participants with depressive symptoms, while the mean, axial and radial diffusivity is increased in mainly the frontal regions ($p < 0.05$, family-wise error corrected for multiple comparisons). The upper panels within each box display the statistical maps of the group comparisons adjusted for age, sex, educational level and normalized total brain volume. The lower panels within each box displays the statistical maps additionally adjusted for white matter hyperintensity volume and lacunar infarcts.

SVD. To the best of our knowledge, this is the first study conducting TBSS in a large group of participants while controlling for multiple possible confounders, including global cognitive function.

Several methodological issues need to be addressed. First, a limitation is the cross-sectional nature of our study, which prevents us from making causal inferences. Second, participants with 16 or more points on CES-D and/or current use of antidepressive medication were considered to be participants with depressive symptoms. Using these criteria, not all participants with depressive symptoms will be diagnosed as major depressive disorder.[30] Third, the CES-D is commonly used as a screening tool and could be considered a screen for general affective distress, including depression and anxiety. However, one has to keep in mind that it is not a specific screening tool for depressive symptoms. In order to exclude other psychiatric disorders that might have proven screen-positive with the CES-D, we excluded participants at baseline with serious mental illness, including an anxiety disorder by medical history-taking and structured screening of medical records and subsequent adjudication of the psychiatric events to be excluded. Fourth, we applied TBSS, which is criticized for problems with the repetitive registration process required and for issues related to constraining analyses to only large and highly organized fiber bundles. Nevertheless, this observer-independent analysis method mitigates several methodological constraints of voxel-based analysis, such as misalignment due to registration procedure and smoothing effects. Finally, the proportion of participants with depressive symptoms in our study is relatively high (34.5%). The high rate of depressive

FIGURE 3. Map of the location of specific white matter tracts, with decreased white matter structural integrity, in participants with depressive symptoms.



Notes: This map shows the mean diffusivity parameters of the group comparisons adjusted for age, sex, educational level and normalized total brain volume. CB: cingulum bundle, UF: uncinate fasciculus, CC: corpus callosum (body and genu), IFOF: inferior frontal occipital fasciculus, ILF: inferior longitudinal fasciculus, SLF: superior longitudinal fasciculus, IC: internal capsule, EC: external capsule.

symptoms is not so much a methodological limitation, but rather a consequence of the fact that we selected participants on the basis of SVD, which is characterized (among other things) by depressive symptoms.

Major strengths of our study include its design of a homogeneous population that covers the whole spectrum of cerebral SVD, its large sample size, the single-center design, the use of a single scanner, and high response rate over 70%. Furthermore, we manually segmented the WMH and the analyses were adjusted for various possible confounders. We intentionally did not adjust for vascular risk factors, such as hypertension or diabetes, as they were considered a part of the causal chain between SVD and depressive symptoms.

In this study, participants with depressive symptoms showed compromised microstructural integrity in several white matter tracts, predominantly located in the prefrontal regions. Especially, frontal-subcortical circuits are thought to play an important role in the pathogenesis of mood, but also cognitive and motor symptoms.[13] The vascular depression hypothesis[31] entails that WMHs, caused by cerebrovascular disease, disrupt white matter tracts within the frontostriatal-subcortical circuit and/or interrupt the connections with limbic structures.[6,32] Disruption of these circuits, which are involved in mood-regulation,[33] may lead to a "disconnection syndrome"[34] and consequently to depressive symptoms. Brain areas that connect the prefrontal cortex with subcortical areas, such as the amygdala and the ventral striatum, are crucially involved in the (patho)physiology of mood. In a recent DTI study,[35] we were able to show that subtle WM changes in the connectivity of the amygdala and medial prefrontal cortex might be key factors in the pathophysiology of major depressive disorder, and this may account for functional changes. Indeed, a recent meta-analysis[36] of patients with major depressive disorder showed

changes in the white matter fascicles connecting the prefrontal cortex within cortical and subcortical areas (amygdala and hippocampus).

We found lower microstructural integrity in the inferior longitudinal fasciculus. This is an associative bundle connecting the occipital and temporal lobes. These long fibres connect the visual areas to the amygdala and hippocampus, which are important components of the limbic system. The corpus callosum is the largest fiber bundle of the human brain and is involved in several perceptual, cognitive and motor functions. The genu (anterior portion) connects the prefrontal and orbitofrontal regions, and the body (central portion) connects the precentral frontal regions and the parietal lobes.[37] Lower microstructural integrity was also evident in the genu and body of the corpus callosum in participants with depressive symptoms, which is consistent with previous findings.[38] We found loss of microstructural integrity in the anterior cingulum bundle in patients with depressive symptoms, unlike a recent TBSS study in which patients with depression showed a lower fractional anisotropy in the middle cingulate cortex.[39] This region is activated during anger and fear and is reported as abnormal in functional and structural imaging studies.[40] Most other areas in which we found lower microstructural integrity are consistent with other findings, such as the loss of structural integrity in the uncinate fasciculus[41] and the superior longitudinal fasciculus.[42] Both have frequently been demonstrated to be involved in mood regulation. Taken together, these findings suggest that the changes in white matter tracts might underlie the occurrence of depressive symptoms in participants with SVD by disrupting the critical white matter tracts involved in emotional circuitry. These findings have implications in the understanding of neurobiological circuit of depression in elderly participants with SVD. Furthermore, the disruption of the frontal-subcortical circuits has been associated with the presence of motivational symptoms. This also could play a role in the underlying pathophysiology of depressive symptoms in elderly with SVD.

The occurrence of depressive symptoms in elderly might be a psychological reaction to (perceived) lower cognitive function.[43] On the other hand, loss of the structural integrity of the WM in specific regions may increase susceptibility to depression and thereby, loss of motivation and can be expressed clinically as cognitive impairment. These cognitive changes add to the severity of symptoms and disability that older depressed patients experience.[44] To exclude the possibility of the effect of global cognition on the depressive symptoms, additional analyses were performed while adjusting for global cognition. These analyses did not markedly alter the conclusion, though increased the variance explained by global cognitive functioning.

During the last decade, studies have shown higher volume of WMHs in elderly depressed patients compared with age-matched controls.[45] In our study, the significant differences of the DTI parameters between the groups diminished after additional adjustment for the WMHs and lacunar infarcts. This suggests a major role of SVD in the loss of microstructural WM integrity in the participants with depressive symptoms. After adjustment for WMHs and lacunar infarcts, however, these participants exhibit significantly higher mean and axial diffusivity, suggesting the occurrence of mechanisms other than SVD. This is consistent with the concept that different pathological mechanisms often coexist in one participant.[46] It is interesting to note that the few white matter tracts that remained significant, such as genu of the corpus callosum and anterior cingulum bundle, have all been previously related to mood dysregulation, whereas other regions, such as internal/external capsule, which were no longer significant after adjustment for SVD, have not been related to mood dysregulation.

Several pathophysiological mechanisms might have occurred governing the diffusion changes (lower fractional and higher mean, axial, and radial diffusivity) in participants with depressive symptoms. First, the microstructural abnormalities of the WM could be caused by ischemic damage due to SVD, hereby increasing the blood−brain permeability, subsequently leading to reduced myelination, axonal degeneration, and/or gliosis.[47] Second, indirect effects of SVD can lead to decreased microstructural integrity by means of antero- and retrograde degeneration of neuronal fibres surrounding the WMHs (e.g., Wallerian degeneration[48]). Third, other factors might play a role in the etiology of depression, independent of ischaemic disease. The microstructural changes could also partially reflect the disorganization of the white matter tracts, alterations of the intracellular compartment, and glial

changes.[49] This is further corroborated by the findings of the frontal WM infrastructure alterations in participants with major depression in postmortem studies.[50] These changes can lead to water molecule diffusion increases in every direction, which might govern the increase in mean, radial, and axial diffusivity, and to a lesser extent, in the decrease of fractional anisotropy, as seen in our study. Because our study is cross-sectional, the differences in structural integrity between those with or without depressive symptoms can also be a consequence of depressive symptoms rather than a cause.

In conclusion, our study provides evidence for microstructural damage in participants with depressive symptoms, independent of global cognition. This damage is predominantly located at the prefrontal white matter fibers, disrupting the fronto-subcortical circuits that are involved in emotional processing. The loss of microstructural integrity in our participants with depressive symptoms might, at least in part, be related to the presence of SVD. However, other mechanisms might also play a role in the etiology of depression, independent of cerebrovascular disease. The analysis of the full spectrum of DTI-derived parameters is relevant and provides additional insights into the pathophysiological mechanisms that underline the occurrence of the depressive symptoms in elderly with SVD. Both direct and indirect effects of SVD may result in axonal loss (higher axial diffusivity) and demyelization (higher radial diffusivity). It also helps us to refine the imaging endophenotype of patients with depressive symptoms for future studies. Future studies are, however, needed to investigate the influence of SVD on not only the structural connectivity, but also on functional connectivity and the effect of treatment. This information is important in understanding the pathology of depressive symptoms in elderly with SVD and might be of added value to find a more specific medical treatment for elderly with depressive symptoms.

F.E.d.L and E.J.v.D. have received personal fellowships from the Dutch Brain Foundation (H04-12; F2009(1)-16). This study was supported by a clinical fellowship from the Dutch Organization for Scientific Research (40-00703-97-07197), the 'Internationale Stichting Alzheimer Onderzoek' (grant number 08510), and a VIDI innovational grant from Dutch Organization for Scientific Research (grant 016.126.351).

The authors have no disclosures to report.

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