Microinfarcts in the Deep Gray Matter on 7T MRI: Risk Factors, MRI Correlates, and Relation to Cognitive Functioning—The SMART-MR Study

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ABSTRACT

BACKGROUND AND PURPOSE: The clinical relevance of cortical microinfarcts has recently been established; however, studies on microinfarcts in the deep gray matter are lacking. We examined the risk factors and MR imaging correlates of microinfarcts in the deep gray matter on 7T MR imaging and their relation to cognitive functioning.

MATERIALS AND METHODS: Within the Second Manifestations of ARTerial disease–Magnetic Resonance (SMART-MR) study, 213 patients (mean age, 68 [SD, 8] years) had a risk-factor assessment, 7T and 1.5T brain MR imaging, and a cognitive examination. Microinfarcts on 7T MR imaging were defined as lesions of <5 mm. Regression models were used to examine the age-adjusted associations among risk factors, MR imaging markers, and microinfarcts. Cognitive function was summarized as composite and domain-specific *z* scores.

RESULTS: A total of 47 microinfarcts were found in 28 patients (13%), most commonly in the thalamus. Older age, history of stroke, hypertension, and intima-media thickness were associated with microinfarcts. On 1.5T MR imaging, cerebellar infarcts (relative risk = 2.75; 95% CI, 1.4–5.33) and lacunes in the white (relative risk = 3.28; 95% CI, 3.28–6.04) and deep gray matter (relative risk = 3.06; 95% CI, 1.75–5.35) were associated with microinfarcts, and on 7T MR imaging cortical microinfarcts (relative risk = 2.33; 95% CI, 1.32–4.13). Microinfarcts were also associated with poorer global cognitive functioning (mean difference in the global *z* score between patients with multiple microinfarcts versus none = −0.97; 95% CI, −1.66 to −0.28, $P = .006$) and across all cognitive domains.

CONCLUSIONS: Microinfarcts in the deep gray matter on 7T MR imaging were associated with worse cognitive functioning and risk factors and MR imaging markers of small-vessel and large-vessel disease. Our findings suggest that microinfarcts in the deep gray matter may represent a novel imaging marker of vascular brain injury.

ABBREVIATIONS: RR = relative risk; STRIVE = STandards for ReportIng Vascular changes on nEuroimaging; WMH = white matter hyperintensity

Cerebral microinfarcts are a common neuropathologic finding in older individuals.[1-3] Conventionally, they are defined as small, ischemic lesions that are not visible to the naked eye on gross pathology and can range from 100 μm to a few millimeters.[2] Although small, microinfarcts often occur in large numbers, and their effect is thought to extend well beyond their lesion boundaries.[2,4] Associations with cognitive impairment and dementia have been reported, and microinfarcts may play an important role in silent cerebrovascular disease.[4]

Recently, cortical microinfarcts have been identified in vivo using 7T MR imaging.[2] Subsequent neuroimaging studies reported that the causes of cortical microinfarcts are heterogeneous, and their occurrence has been associated with both small-vessel and large-vessel disease, microemboli, and hypoperfusion.[5-8] The clinical importance of cortical microinfarcts has been demonstrated by their association with worse cognitive functioning.[9] In vivo data on the prevalence and risk factors of microinfarcts in the deep gray matter, however, are lacking. Moreover, it is not known to what extent microinfarcts in the deep gray matter are related to cognitive functioning. Previous histopathologic studies reported that microinfarcts as well as lacunes in the deep gray matter were associated

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with worse antemortem cognitive performance.[10-12] Identifying the risk factors and MR imaging markers associated with microinfarcts in the deep gray matter is important because these may provide clues to their underlying etiology and potential targets for intervention. Examining the association with cognitive functioning is important because it will provide evidence on whether microinfarcts in the deep gray matter are structural correlates of impaired cognitive performance.

In the current study, we examined the frequency and distribution of microinfarcts in the caudate nucleus, lentiform nucleus, and thalamus on 7T MR imaging in a large sample of older individuals with a history of arterial disease. In addition, we examined whether microinfarcts in the deep gray matter were associated with risk factors, MR imaging markers of cerebrovascular disease, and cognitive functioning.

MATERIALS AND METHODS

Study Population

Data were used from the Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study, a prospective cohort study at the University Medical Center Utrecht with the aim of investigating risk factors and consequences of brain changes on MR imaging in patients with symptomatic atherosclerotic disease.[13] In brief, between 2001 and 2005, thirteen hundred nine middle-aged and older adults newly referred to the University Medical Center Utrecht for treatment of symptomatic atherosclerotic disease (coronary artery disease, cerebrovascular disease, peripheral arterial disease, or abdominal aortic aneurysm) were included for baseline measurements. During a 1-day visit to our medical center, a physical examination, ultrasonography of the carotid arteries to measure the intima-media thickness (millimeters), blood and urine sampling, neuropsychological assessment, and 1.5T brain MR imaging were performed. Height and weight were measured, and the body mass index (kilograms/square meter) was calculated. Questionnaires were used for the assessment of demographics, risk factors, medical history, medication use, and cognitive and physical functioning.

Of the 1309 individuals included, 754 had follow-up measurements after an average of 4 years between January 2006 and May 2009. From November 2013, all patients alive were invited for a second follow-up, including a 7T brain MR imaging. Of the 329 individuals included between November 2013 and October 2017, two hundred thirteen had 7T MR imaging, and these patients formed the current study sample. A participation flow chart of the SMART-MR study is shown in the Online Supplemental Data.

In the present study, we used the 1.5T brain MR imaging, cognitive functioning, and vascular risk factor data obtained during follow-up. Due to logistical reasons, however, the 1.5T brain MR imaging and cognitive function measurements were obtained before the 7T brain MR imaging in 97 patients (median, 1.5 years; range, 0.6–2.7 years), whereas in 116 patients, these examinations were obtained on the same day. Also, vascular risk factor assessment was performed before the 7T brain MR imaging in 163 patients (median, 2.3 years; range, 0.6–9.4 years), whereas in 50 patients, vascular risk factors were obtained concurrently with the 7T brain MR imaging.

The SMART-MR study was approved by the medical ethics committee of the University Medical Center Utrecht according to the guidelines of the Declaration of Helsinki of 1975, and written informed consent was obtained from all patients.

Vascular Risk Factors

Methods of measuring vascular risk factors are described in the Online Supplemental Data.

MR Imaging Protocol

High-field imaging of the brain was performed on a whole-body 7T MR system (Philips Healthcare) with a volume transmit and 32-channel receive head coil (Nova Medical). Conventional MR imaging of the brain was performed on a 1.5T whole-body system (Gyroscan ACS-NT; Philips Healthcare). The 7T and 1.5T scan protocols are described in the Online Supplemental Data.

Assessment of MR Imaging Markers of Cerebrovascular Disease

Brain infarcts (cortical, cerebellar, or brainstem), lacunes of presumed vascular origin, and white matter hyperintensity (WMH) and brain volumes were determined using 1.5T MR imaging data. Cortical microinfarcts and cerebral microbleeds were rated on 7T MR imaging data due to the enhanced conspicuity of these lesions at higher field strengths.[14,15] All ratings were performed blinded to patient characteristics.

Brain infarcts (cortical, cerebellar, or brainstem) and lacunes were visually rated by an experienced rater (M.H.T.Z.) with 6 years of experience in neuroradiology on the T1-weighted, T2-weighted, and FLAIR sequences of the 1.5T MR images. Lacunes were rated according to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) criteria as round or ovoid, subcortical, fluid-filled cavities (signal similar to CSF) of 3–15 mm in diameter in the territory of 1 perforating arteriole.[16] Uncertain lesions were discussed during a consensus meeting (M.H.T.Z.) to reach agreement.

WMH and brain volumes were obtained using an automated segmentation program on the T1-weighted, FLAIR, and T1-weighted inversion recovery sequences of the 1.5T MR images. A probabilistic segmentation technique was performed with k-nearest neighbor classification, distinguishing gray matter, white matter, CSF, and lesions.[17] Brain infarcts, including lacunes and their hyperintense rim, were manually segmented. All WMH segmentations were visually checked by an investigator (R.G.) using an image-processing framework (MeVisLab 2.7.1.; MeVis Medical Solutions) to ensure that brain infarcts were correctly removed from the WMH segmentations.

Periventricular WMH were defined as adjacent to or within 1 cm of the lateral ventricles, and deep WMHs were defined as located in the deep white matter tracts that may or may not have adjoined the periventricular WMH. Total brain volume was calculated by summing the volumes of gray matter, white matter, total WMH, and, if present, the volumes of brain infarcts. Total intracranial volume was calculated by summing the CSF volume and total brain volume.

Phase-contrast MR angiography was used to measure total CBF because this method has been demonstrated to be a fast,

Table 1: Frequency of patients with microinfarcts and with infarcts of ≥5 mm in the deep gray matter on 7T MR imaging

	Infarct ≥5 mm		
Microinfarct (<5 mm)	No	Yes	Total
No	171	14	185
Yes	16	12	28
Total	187	26	213

reproducible, and noninvasive method to measure total CBF in large cohorts.[18] Previous studies established that phase-contrast MR angiography correlates well with arterial spin-labeling perfusion MR imaging, though estimates tend to be somewhat higher and more variable than arterial spin-labeling perfusion MR imaging.[19] Postprocessing of the CBF measurements was performed by 1 investigator (M.H.T.Z.). The flow through the basilar artery and the left and right internal carotid arteries was summed to calculate the total CBF (milliliters/minute). Total CBF was expressed per 100 mL of brain parenchymal volume to obtain parenchymal CBF. Cortical microinfarcts were visually rated by a rater (M.H.T.Z.) on the 3D T1-weighted, 3D T2-weighted, and 3D FLAIR sequences of the 7T MR imaging scans according to criteria previously described.[2] Cerebral microbleeds were rated by a rater (M.H.T.Z.) using the minimum-intensity-projection images and source images of the 7T SWI sequence. Microbleeds were labeled as lobar or deep using the Microbleed Anatomical Rating Scale.[20]

We considered cortical, cerebellar, and brainstem infarcts rated on 1.5T MR imaging as markers of large-vessel disease,[21] whereas lacunes of presumed vascular origin, WMH, and microbleeds were considered markers of small-vessel disease, consistent with the STRIVE criteria.[16]

Assessment of Cognitive Functioning

All patients underwent neuropsychological assessment for memory, executive functioning, information processing speed, and working memory. The tests used to assess each of these cognitive domains are described in the Online Supplemental Data. Domain-specific z scores were calculated by converting raw test scores to standardized z scores and averaging these for each domain prior to the final z transformation. A global cognitive functioning composite z score was calculated by standardizing the averaged domain-specific z scores.

Assessment of Microinfarcts in the Deep Gray Matter

First, all available 7T MR imaging scans were screened by an experienced neuroradiologist. All lesions hypointense on T1-weighted images, hyperintense on T2-weighted images, and either hyperintense or hypointense with a hyperintense rim on FLAIR images consistent with the imaging criteria set forth in our previous work[14] were rated as possible microinfarcts. The lesions were restricted to the caudate nucleus, lentiform nucleus, or thalamus and not appearing as a perivascular space, artery, vein, or microbleed on the SWI sequence. In addition, the lesion had to be detectable in the axial, coronal, and sagittal views. Uncertain lesions were discussed during a consensus meeting to reach agreement. Next, all identified possible microinfarcts were inspected by an investigator (R.G.) using MR imaging software, and the largest diameter of each lesion was determined on the FLAIR sequence. Lesions of <5 mm in their largest diameter were accepted as microinfarcts because this value has been suggested by previous studies on cortical microinfarcts.[6,22-26] The presence and number of lesions of ≥ 5 mm in the deep gray matter were also recorded because these may act as potential confounders in the relation between microinfarcts and cognitive functioning.

Statistical Analysis

First, vascular risk factors and MR imaging markers of cerebrovascular disease were calculated in patients with and without microinfarcts in the deep gray matter on 7T MR imaging and in the entire study sample. Second, relative risks (RRs) for the presence of microinfarcts in the deep gray matter were estimated for vascular risk factors and MR imaging markers of cerebrovascular disease using log-binomial regression, adjusted for age. For continuous variables, a relative risk of the presence of microinfarcts was estimated for a 1 SD increase. For dichotomous variables, a relative risk for microinfarcts was calculated for the presence of a vascular risk factor or MR imaging marker. Third, to examine the association between microinfarcts in the deep gray matter and cognitive functioning, ANCOVA was used to estimate age- and education level–adjusted cognitive functioning z scores for patients without microinfarcts, with a single microinfarct, and with multiple microinfarcts. Age and education level were entered as covariates because these represent the most important potential confounders in the relation between microinfarcts and cognitive functioning.

We repeated the abovementioned analyses with additional adjustment for the number of infarcts of ≥5 mm in the deep gray matter on 7T MR imaging. Statistical significance was set at a $P < .05$.

RESULTS

A total of 47 deep gray matter microinfarcts (caudate nucleus, $n = 17$; lentiform nucleus, $n = 9$; thalamus, $n = 21$) were identified in 28 patients on 7T MR imaging (range, 1–6 microinfarcts). A single microinfarct was seen in 19 patients (68%), while multiple microinfarcts were seen in 9 patients (32%). The size of the microinfarcts ranged from 2.1 to 4.8 mm (caudate nucleus, 2.1–4.7 mm; lentiform nucleus, 2.7–4.1 mm; thalamus, 2.4–4.8 mm). Of patients with microinfarcts ($n = 28$), 12 patients (42%) also showed infarcts of ≥5 mm in the deep gray matter on 7T MR imaging (Table 1). Examples of deep gray matter microinfarcts are shown in Fig 1.

Twenty-six patients showed a total of 33 infarcts of ≥5 mm in the deep gray matter on 7T MR imaging, ranging from 6.7 to 15.7 mm (Table 1). Of these 33 lesions, 18 (55%) were rated as lacunes in the deep gray matter on the corresponding 1.5T MR imaging.

Baseline characteristics and MR imaging markers of patients with microinfarcts in the deep gray matter ($n = 28$), in those without microinfarcts ($n = 185$), and in the total study sample ($n = 213$) are shown in Tables 2 and 3, respectively.

Compared with the baseline (2001–2005) characteristics of patients without a 7T brain MR imaging, patients in the study sample with a 7T brain MR imaging were younger, more often had current alcohol intake, often had less diabetes mellitus, and

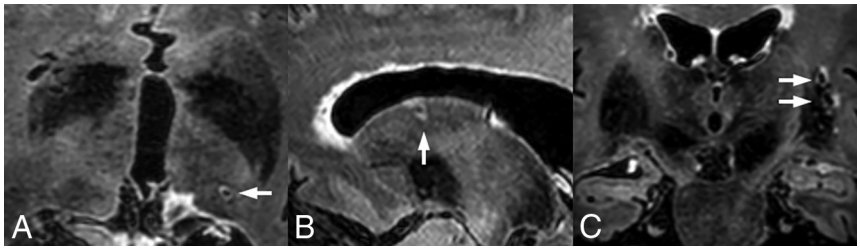

FIG 1. Examples of microinfarcts in the deep gray matter on 7T MR imaging. *A*, Microinfarct with a diameter of 2.3 mm (*arrow*) in the left thalamus of a 73-year-old woman on transversal 7T FLAIR. *B*, Microinfarct with a diameter of 2.9 mm (*arrow*) in the left caudate nucleus of a 64-year-old man on sagittal 7T FLAIR. *C*, Two microinfarcts with diameters of 3.0 and 3.2 mm (*arrows*) in the left putamen of a 65-year-old man on coronal 7T FLAIR. Note that the gliotic rim extends into the adjacent external capsule.

showed a slightly lower intima-media thickness and a slightly higher ankle brachial index (Online Supplemental Data).

Vascular Risk Factors

Higher age was associated with the presence of microinfarcts in the deep gray matter (RR per year increase = 1.05; 95% CI, 1.02–1.08; $P = .001$). In addition, after adjusting for age, a history of stroke (RR = 2.88; 95% CI, 1.24–6.67; $P = .01$), hypertension (RR = 3.16; 95% CI, 1.30–7.65; $P = .01$), and a higher intima-media thickness (RR per 1 SD increase = 1.29; 95% CI, 1.04–1.61; $P = .02$) were associated with microinfarcts. The number of smoking pack years (RR per SD increase = 1.11; 95% CI, 0.87–1.42; $P = .40$), carotid artery stenosis ≥50% (RR = 1.39; 95% CI, 0.70–2.75; $P = .34$), and the presence of metabolic syndrome (RR = 1.47; 95% CI, 0.74–2.91; $P = .27$) were not significantly associated with the presence of microinfarcts in the deep gray matter after adjusting for age (Table 2).

After additionally adjusting for the number of infarcts of ≥5 mm in the deep gray matter on 7T MR imaging, older age (RR per year increase = 1.04; 95% CI, 1.01–1.07; $P = .01$) and hypertension (RR = 5.25; 95% CI, 1.43–19.28; $P = .01$) remained associated with microinfarcts, whereas a history of stroke (RR = 2.37; 95% CI, 0.94–5.79; $P = .07$) and a higher intima-media thickness (RR per 1 SD increase = 1.25; 95% CI, 0.98–1.57; $P = .07$) lost statistical significance.

MR Imaging Markers of Cerebrovascular Disease

For cerebrovascular markers on 1.5T MR imaging, cerebellar infarcts (RR = 2.18; 95% CI, 1.23–3.87; $P = .008$), lacunes in the white matter (RR = 3.28; 95% CI, 1.79–6.04; $P < .001$), and lacunes in the deep gray matter (RR = 3.93; 95% CI, 1.99–7.78; $P < .001$) were associated with the presence of microinfarcts in the deep gray matter, after adjusting for age. For cerebrovascular markers on 7T MR imaging, cortical microinfarcts (RR = 2.33; 95% CI, 1.32–4.13; $P = .004$) were associated with microinfarcts in the deep gray matter after adjusting for age. Although the RR was increased, cortical infarcts (RR = 1.64; 95% CI, 0.76–3.51; $P = .21$), brainstem infarcts (RR = 3.37; 95% CI, 0.95–12.0; $P = .07$), and periventricular WMH volume (RR per SD increase = 1.14; 95% CI, 0.95–1.37; $P = .16$) on 1.5T MR imaging were not significantly associated with the presence of microinfarcts in the deep gray matter after adjusting for age. Deep microbleeds (RR = 1.60; 95% CI, 0.70–3.68; $P = .27$) and lobar microbleeds (RR = 1.27; 95% CI, 0.59–2.72; $P = .54$) on 7T MR imaging were also not significantly associated with microinfarcts in the deep gray matter after adjusting for age (Table 3).

After additionally adjusting for the number of infarcts of ≥5 mm in the deep gray matter on 7T MR imaging, lacunes in the white matter on 1.5T MR imaging (RR = 2.76; 95% CI, 1.45–5.27; $P = .002$), cerebellar infarcts on 1.5T MR imaging (RR = 2.05; 95% CI, 1.13–3.73; $P = .02$), and cortical microinfarcts on 7T MR imaging (RR = 2.16; 95% CI, 1.20–3.90; $P = .01$) remained associated with microinfarcts.

Cognitive Functioning

Global cognitive functioning z scores differed significantly between patients without ($n = 185$), with a single ($n = 19$), and with multiple microinfarcts ($n = 9$) in the deep gray matter (ANCOVA $P = .007$), adjusted for age and education level. Specifically, the presence of multiple microinfarcts in the deep gray matter was associated with worse global cognitive functioning compared with the absence of microinfarcts or the presence of a single microinfarct (mean difference in z score = −0.92; 95% CI, −1.53 to −0.31; $P = .003$; −1.10; 95% CI, −1.81 to −0.39; $P = .002$, respectively). This pattern was observed for each cognitive domain. The mean estimates of domain-specific z scores were lower for patients with multiple microinfarcts compared with patients with none or a single microinfarct, for memory, executive functioning, information processing speed, and working memory (Fig 2).

After additionally adjusting for the number of infarcts of ≥5 mm in the deep gray matter on 7T MR imaging, the association between microinfarcts and global cognitive functioning persisted (ANCOVA $P = .01$; mean difference in z scores between patients with multiple microinfarcts versus none: −0.97; 95% CI, −1.66 to −0.28; $P = .006$; versus a single microinfarct: −1.13; 95% CI, −1.88 to −0.39; $P = .003$).

DISCUSSION

In this cohort of patients with a history of arterial disease, microinfarcts in the deep gray matter on 7T MR imaging were detected in 13% of patients. These lesions were associated with older age, a history of stroke, hypertension, and a higher intima-media thickness. With regard to MR imaging markers, microinfarcts were associated with lacunes and cerebellar infarcts on 1.5T MR imaging and with cortical microinfarcts on 7T MR imaging. The presence of multiple microinfarcts in the deep gray matter was associated with worse global cognitive functioning independent of age, education level, and the number of infarcts of ≥5 mm.

We previously reported that small infarcts in the caudate nucleus on 7T MR imaging can be detected with excellent intrarater and interrater agreement and that the imaging characteristics of

Table 2: Association of vascular risk factors and the presence of microinfarcts in the deep gray matter on 7T MR imaging[a]

	Patients with Microinfarcts in the Deep Gray Matter (*n* = 28)	Patients without Microinfarcts in the Deep Gray Matter (*n* = 185)	All Patients (*n* = 213)	Microinfarct (Presence vs Absence) RR (95% CI)[b]
Age (yr)	70 (SD, 7)	64 (SD, 9)	64 (SD, 9)	1.05 (1.02–1.08)[c,d]
Sex (% men)	85.7	82.2	82.6	0.78 (0.30–2.02)[e]
History of stroke (%)	50.0	23.2	26.8	2.88 (1.24–6.67)[d]
BMI (kg/m^2)	28 (SD, 4)	27 (SD, 4)	27 (SD, 4)	1.20 (0.87–1.65)
Smoking (pack-years)[f]	27 (0, 56)	20 (0, 47)	22 (0, 49)	1.11 (0.87–1.42)
Alcohol intake				
No or <1 U/week (%)	22.2	26.5	25.9	1 (reference)
1–10 U/week (%)	59.3	41.1	43.4	1.55 (0.67–3.61)
≥11 U/week (%)	18.5	32.4	30.7	0.65 (0.22–1.98)
Hypertension (%)	96.4	72.4	75.6	3.16 (1.30–7.65)[d]
Diabetes mellitus (%)	14.3	16.2	16.0	0.85 (0.32–2.21)
Carotid stenosis ≥50% (%)	17.9	7.6	8.9	1.39 (0.70–2.75)
Hypercholesterolemia (%)	77.8	86.4	85.3	1.33 (0.86–2.05)
IMT (mm)	1.0 (SD, 0.3)	0.8 (SD, 0.2)	0.9 (SD, 0.2)	1.29 (1.04–1.61)[d]
ABI	1.1 (SD, 0.2)	1.1 (SD, 0.1)	1.1 (SD, 0.2)	0.86 (0.67–1.11)
Homocysteine (μmol/l)	13.0 (SD, 5.2)	12.5 (SD, 4.3)	12.5 (SD, 4.4)	1.07 (0.40–2.82)
APOB (g/L)	0.8 (SD, 0.2)	0.8 (SD, 0.2)	0.8 (SD, 0.2)	0.84 (0.58–1.23)
Metabolic syndrome	60.7	51.4	52.6	1.47 (0.74–2.91)
≥1 *APOE ε4* allele (%)	35.7	28.1	29.1	1.58 (0.79–3.20)

Note:—BMI indicates body mass index; IMT, intima-media thickness; ABI, ankle brachial index; *APOB*, *apolipoprotein B*; *APOE*, *apolipoprotein E*

[a] Characteristics are presented as mean (SD) or percentage. RR represents the relative risk for microinfarcts in the presence of a risk factor (in case of a dichotomous variable) or for 1 SD increase in the risk factor (in case of a continuous variable).

[b] Log-binomial regression with adjustment for age.

[c] Per year increase.

[d] $P < .05$.

[e] Men versus women.

[f] Median (10th percentile, 90th percentile). Natural log-transformed due to a non-normal distribution in the analysis.

these lesions are similar to those in the cerebral cortex.[14] The present study extends our previous findings and emphasizes the potential clinical importance of these lesions, which is in accordance with postmortem studies that reported associations between microinfarcts in the deep gray matter and antemortem cognitive impairment.[10,12] In addition, we found that most patients with microinfarcts in the deep gray matter did not show larger infarcts in the deep gray matter on 7T MR imaging and, most important, that the relationship between microinfarcts and worse global cognitive functioning was independent of infarcts of ≥5 mm. These findings suggest that microinfarcts in the deep gray matter are structural correlates of impaired cognitive functioning that are largely undetected on conventional MR imaging.[1]

The association between microinfarcts and worse cognitive functioning may be explained by the important role that the basal ganglia play in cognition through receiving and processing cortical information in the caudate and lentiform nuclei and sending information back to the cerebral cortex through the thalamus.[27,28] Damage to this neuronal network may compromise cognition.[29] However, we did not find differences in cognition between patients without microinfarcts and patients with a single microinfarct, suggesting that the impact of a single microinfarct on cognition may be weak, contrary to the presence of multiple lesions. A possible explanation is that the damage associated with a single microinfarct is insufficient to affect neural network integrity and therefore result in lower cognitive performance, whereas this may be the case for multiple microinfarcts. Alternatively, it may be that patients with multiple microinfarcts are also more likely to have smaller lesions that are not discernible on 7T MR imaging.[30]

The associations of microinfarcts in the deep gray matter with older age, hypertension, a higher intima-media thickness, lacunes, and cerebellar infarcts suggest that small-vessel and large-vessel disease may be involved in the pathogenesis of these lesions. Support for this notion is provided by a large postmortem study in which atherosclerosis and arteriolosclerosis were associated with subcortical microinfarcts.[31] However, because the in vivo associations presented in this study are novel, further studies in different populations are needed to identify risk factors of microinfarcts that may pose potential targets for intervention.

Strengths of our study include the large sample size for a 7T MR imaging study and the detailed information available on vascular risk factors, MR imaging markers of cerebrovascular disease, and cognitive functioning that enabled us to examine these relationships in 1 study. A limitation of this study is that microinfarcts in the deep gray matter, cortical microinfarcts, and microbleeds were rated on 7T MR imaging data, whereas other MR imaging markers were evaluated on 1.5T MR imaging data. Several remarks have to be made with respect to this matter. First, we obtained brain volumes from 1.5T MR imaging data due to a lack of robust and validated brain-segmentation software for 7T MR imaging data. Second, CBF measurements were obtained from 1.5T MR imaging data because our standardized 7T MR imaging protocol did not contain phase-contrast sequences. Third, the greatest added value of ultra-high-field 7T MR imaging lies in its ability to visualize the smallest cerebrovascular

Table 3: Association of MR imaging markers of cerebrovascular disease and the presence of microinfarcts in the deep gray matter on 7T MR imaging[a]

	Patients with Microinfarcts in the Deep Gray Matter (*n* = 28)	Patients without Microinfarcts in the Deep Gray Matter (*n* = 185)	All Patients (*n* = 213)	Microinfarct (Presence vs Absence) RR (95% CI)[b]
Infarcts on 1.5T MR imaging (%)				
Cortical	21	11	12	1.64 (0.76–3.51)
Cerebellar	32	9	12	2.18 (1.23–3.87)[c]
Brainstem	7	1	2	3.37 (0.95–12.0)
Lacunes in the white matter on 1.5T MR imaging (%)	32	6	9	3.28 (1.79–6.04)[c]
Lacunes in the deep gray matter on 1.5T MR imaging (%)	43	8	12	3.93 (1.99–7.78)[c]
WMH volumes on 1.5T MR imaging (mL)[d]				
Total	3.3 (0.9–32.5)	2.0 (0.3–9.3)	2.0 (0.4–10.0)	1.13 (0.93–1.38)[e]
Periventricular	2.9 (0.7–31.7)	1.4 (0.2–8.3)	1.4 (0.3–9.0)	1.14 (0.95–1.37)[e]
Deep	0.2 (0.1–0.9)	0.3 (0.0–1.5)	0.2 (0.0–1.4)	0.67 (0.38–1.16)[e]
Total brain volume (mL)	1104.9 (SD, 116.5)	1125.3 (SD, 104.3)	1122.7 (SD, 105.9)	0.84 (0.56–2.72)[f]
Total intracranial volume (mL)	1449.2 (SD, 114.7)	1452.6 (SD, 126.4)	1452.16 (SD, 128.5)	1.21 (0.85–1.73)
Parenchymal CBF (mL/min per 100- mL brain volume)	50.5 (SD, 16.8)	48.2 (SD, 12.0)	48.5 (SD, 12.7)	1.13 (0.93–1.38)
Cortical microinfarcts on 7T MR imaging (%)	32	9	12	2.33 (1.32–4.13)[c]
Deep microbleeds on 7T MR imaging (%)	21	10	12	1.60 (0.70–3.68)
Lobar microbleeds on 7T MR imaging (%)	36	26	27	1.27 (0.59–2.72)

[a] Characteristics are presented as mean (SD) or percentage. RR represents the relative risk for microinfarcts in the presence of an MR imaging marker (in case of a dichotomous variable) or for 1 SD increase in the MR imaging marker (in case of a continuous variable).
[b] Log-binomial regression with adjustment for age.
[c] $P < .05$.
[d] Median (10th percentile, 90th percentile).
[e] Natural log-transformed due to a non-normal distribution and normalized for total intracranial volume.
[f] Adjusted for age and total intracranial volume.

lesions (ie, microinfarcts and microbleeds) due to the higher signal-to-noise ratio compared with conventional 1.5T MR imaging. Although it would be preferable to determine all cerebrovascular lesions on the 7T MR imaging scans for consistency, it is unlikely that 7T MR imaging yields a greater detection rate for larger lesions such as cortical infarcts.

Another limitation is the potential overlap that may occur between microinfarcts and lacunes of presumed vascular origin in the deep gray matter. According to the STRIVE criteria, lacunes of presumed vascular origin are defined as small subcortical infarcts ranging from 3 to 15 mm.[16] Because microinfarcts were previously defined as lesions of <5 mm, it is possible that larger microinfarcts in the range of 4 mm may have been classified as lacunes on 1.5T MR imaging. The potential overlap, however, was limited because most patients with microinfarcts did not show lacunes in the deep gray matter on 1.5T MR imaging. In addition, we controlled for the effects of infarcts of ≥5 mm in the analyses.

Another possible limitation of this study is that the sample consisted of patients who completed 2 follow-up measurements, and these patients represent a slightly healthier subset. This may have led to an underestimation of the association of microinfarcts with vascular risk factors, MR imaging markers of cerebrovascular disease, and cognitive functioning. A further limitation of this study is that in some patients, the 7T brain MR imaging did not coincide with the 1.5T brain MR imaging, cognitive function measurements, and vascular risk factor assessment. Especially for the vascular risk factor assessment, the interval was quite large in some patients. Due to logistical reasons, we were not able to repeat the measurement of vascular risk factors at the time of the brain MR imaging and cognitive assessment in these patients, possibly under- or overestimating the associations. However, in a previous analysis,[32] we did not see major changes in the relationship with 7T MR imaging outcomes when adjusting for the time interval between vascular risk factor assessment and 7T brain MR imaging.

CONCLUSIONS

Our findings demonstrate that microinfarcts in the deep gray matter on 7T MR imaging are associated with worse cognitive functioning and vascular risk factors and MR imaging markers of small-vessel and large-vessel disease in patients with a history of arterial disease. These results suggest that microinfarcts in the deep gray matter may be relevant imaging markers of vascular brain injury that, together with cortical microinfarcts, could be a potential target for future prevention strategies of vascular cognitive impairment.

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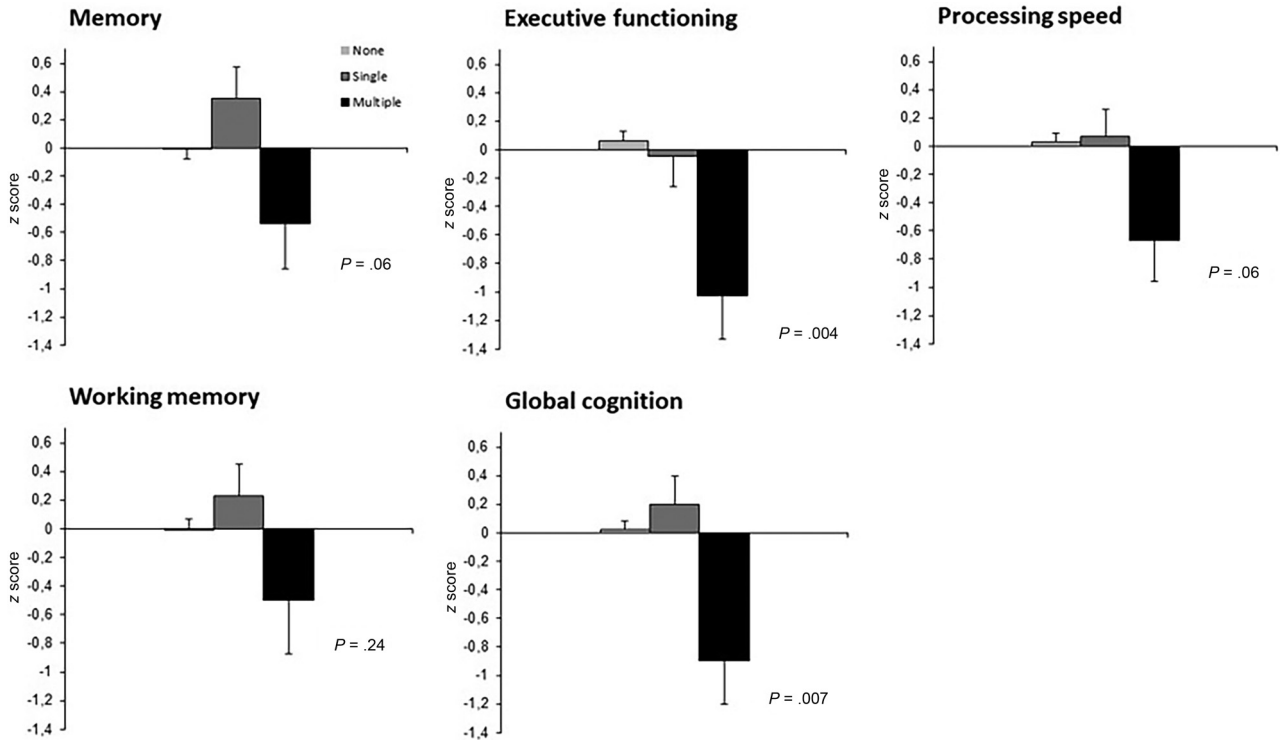

FIG 2. Association between microinfarcts in the deep gray matter and global and domain-specific cognitive functioning *z* scores. Values are mean ± standard error *z* scores, adjusted for age and educational level. Memory: none, −0.01 ± 0.07; single, 0.35 ± 0.22; multiple, −0.54 ± 0.32. Executive functioning: none, 0.05 ± 0.07; single, −0.05 ± 0.21; multiple, −1.02 ± 0.31. Processing speed: none, 0.02 ± 0.06; single, 0.07 ± 0.20; multiple, −0.67 ± 0.29. Working memory: none, −0.01 ± 0.07; single, 0.22 ± 0.22; multiple, −0.50 ± 0.37. Global cognition: none, 0.02 ± 0.06; single, 0.20 ± 0.20; multiple; −0.90 ± 0.30.

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