Original Article

Brain Magnetic Resonance Imaging Correlates of Impaired Cognition in Patients With Type 2 Diabetes

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The structural correlates of impaired cognition in type 2 diabetes are unclear. The present study compared cognition and brain magnetic resonance imaging (MRI) between type 2 diabetic patients and nondiabetic control subjects and assessed the relationship between cognition and MRI findings and blood pressure and metabolic control. The study included 113 patients and 51 control subjects. Brain MRI scans were rated for white matter lesions (WMLs), cortical and subcortical atrophy, and infarcts. Neuropsychological test scores were divided into five cognitive domains and expressed as standardized *Z* values. Type 2 diabetes was associated with deep WMLs ($P = 0.02$), cortical ($P < 0.001$) and subcortical ($P < 0.05$) atrophy, (silent) infarcts ($P = 0.06$), and impaired cognitive performance (attention and executive function, information-processing speed, and memory, all $P < 0.05$). Adjustment for hypertension did not affect the results. Within the type 2 diabetic group, cognitive function was inversely related with WMLs, atrophy, and the presence of infarcts (adjusted for age, sex, and estimated IQ), and there was a modest association with HbA_{1c} and diabetes duration. This association was strongest for age, even more so than in control subjects. We conclude that cognitive impairments in patients with type 2 diabetes are not only associated with subcortical ischemic changes in the brain, but also with increased brain atrophy. *Diabetes* 55:1106–1113, 2006

Type 2 diabetes can affect the central nervous system (1). Neuropsychological studies reported moderate degrees of cognitive impairment, particularly in tasks involving verbal memory or complex information processing (2,3). Epidemiological studies demonstrated an association between diabetes and dementia (4,5). It is not clear which factors mediate accelerated cognitive decline in patients with type 2 diabetes. Both comorbid conditions (e.g., hypertension and depression) and diabetes-specific factors (e.g., glycemic control) have been implicated (2,6). Some investigators have suggested that hypertension is an important mediator (2,7,8), but this was not supported by others (9,10).

The structural correlates and pathophysiological mechanisms underlying these cognitive impairments are still uncertain. Previous studies report that modest cortical and subcortical atrophy and symptomatic or asymptomatic infarcts are more common in type 2 diabetic patients than in control subjects (11–15). Findings from studies on so-called WMLs are less consistent; some report an association with type 2 diabetes (16), but others report no statistically significant effects (11,17). To the best of our knowledge, there are no published studies that combine detailed assessment of cognitive functioning and magnetic resonance imaging (MRI) of the brain in patients with type 2 diabetes.

The present study aimed to compare cognition and brain MRI in type 2 diabetic patients and nondiabetic control subjects and to relate cognitive functioning in the type 2 diabetic patients to MRI findings, as well as to blood pressure and metabolic control.

RESEARCH DESIGN AND METHODS

The UDES (Utrecht Diabetic Encephalopathy Study) is a cross-sectional population-based study on determinants of impaired cognition in type 2 diabetes. Because the study aimed to identify potential risk factors for cognitive impairment in type 2 diabetes, patients were not selected for the presence or absence of diabetes complications, comorbid conditions (e.g., hypertension), or exposure to other risk factors (e.g., smoking). For inclusion, type 2 diabetic patients had to be 55–80 years of age, have a diabetes duration of at least 1 year, be functionally independent, and speak Dutch. Exclusion criteria for all participants included a psychiatric or neurological disorder (unrelated to diabetes) that could influence cognitive functioning, history of alcohol or substance abuse, or history of dementia, and for control subjects, fasting blood glucose ≥7.0 (18). Subjects with a history of noninvalidating stroke were included. Twice as many diabetic patients as control subjects were included in order to increase statistical power for within-group analyses in the type 2 diabetic group.

In the UDES, 122 patients with type 2 diabetes (aged 56–80 years), 40 patients with type 1 diabetes (aged 52–77 years), and 61 control subjects (aged 53–78 years) were included between September 2002 and November 2004. General practitioners in the area (ACKNOWLEDGMENTS) were asked to participate in the project and to invite all eligible type 2 diabetic patients from their practice. Control subjects were recruited among the spouses or acquaintances of the diabetic patients. The study was approved by the medical ethics committee of the University Medical Center Utrecht, and each participant signed an informed consent form. Participants attended the clinic on 2

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BCR, bicaudate ratio; BFR, bifrontal ratio; DWML, deep WML; FFR, frontal interhemispheric fissure ratio; FLAIR, fluid-attenuating inverse recovery; MRI, magnetic resonance imaging; PWML, periventricular WML; SFR, Sylvian fissure ratio; WML, white matter lesion.

consecutive days and underwent MRI of the brain and neuropsychological and neurological examinations. Medical history and medication use were recorded. Fasting blood samples were collected, blood pressure was recorded, and urine was collected overnight. The study protocol for the type 1 diabetic patients was slightly different and reported separately.

No MRI could be obtained for nine diabetic patients due to MRI contraindications, such as claustrophobia or a pacemaker. The present study includes all type 2 diabetic patients with an MRI (n = 113, aged 56–80 years) and all control subjects with an MRI that were at least 56 years of age (n = 51, aged 57–78 years).

MRI scanning protocol. The MRI investigation (1.5 Tesla; Philips Medical Systems, Best, the Netherlands) consisted of an axial T1 weighted scan and an axial T2 and T2 fluid-attenuating inverse recovery (FLAIR) scan (TR/TE/TI: 6000/100/2000, FOV 230 mm, matrix 180 × 256, slice thickness 4.0 mm, contiguous slices, 38 slices). The images were printed on hard copy with a reduction factor of 2.9. WMLs, atrophy, and number and location of infarcts were rated on hard copies or on digital images on a personal computer.

WMLs. WMLs were considered present if they were hyperintense on FLAIR images and not hypointense on T1 weighted images. WMLs were distinguished into periventricular and deep (subcortical) lesions and rated according to the Scheltens rating scale (19). Periventricular WMLs (PWMLs) were rated semiquantitatively per region, adjacent to the frontal horns (frontal capping), the lateral wall of the lateral ventricles (bands), and the occipital horns (occipital capping) on a scale ranging from 0 to 2, with 0 = no PWMLs, 1 = PWMLs ≤5 mm (real size), and 2 = PWMLs >5 mm. The overall degree of PWMLs was calculated by adding up the scores for the three separate categories on the left and right (range 0–12). This is a slight modification of the original scale, which only counts the side with the highest score (range 0–6).

For the rating of deep WMLs (DWMLs), the brain was divided into six regions: frontal, parietal, occipital, temporal, basal ganglia, and infratentorial. This is a slight modification of the original scale, which divides the basal ganglia and infratentorial regions into 5 and 4 different smaller subregions, respectively (19). The different brain regions were determined according to anatomical landmarks, namely the central sulcus, the Sylvian fissure, and the parieto-occipital sulcus, and were shown on templates during the rating. The size and number of the DWMLs were rated per region, on a scale ranging from 0 to 6, with 0 = no DWMLs, 1 = DWMLs ≤3 mm (real size) ($n \leq 5$), 2 = DWMLs ≤3 mm ($n \geq 6$), 3 = DWMLs 4–10 mm ($n \leq 5$), 4 = DWMLs 4–10 mm ($n \geq 6$), 5 = DWMLs ≥11 mm ($n \geq 1$), and 6 = confluent. The overall degree of DWMLs was calculated by adding the scores of all the regions (range 0–36).

Furthermore, brain infarcts were scored by location (cortical and subcortical), type (lacunar or large), and number. A lesion was considered a lacunar infarct if its score was hypointense on T1 and FLAIR images and if its appearance was unlike a perivascular space.

Atrophy rating scales. Cortical atrophy was evaluated quantitatively by the frontal interhemispheric fissure ratio (FFR), i.e., the maximal width of the interhemispheric fissure from any of the cuts demonstrating the frontal lobes divided by the transpineal coronal inner table diameter (20), and by the Sylvian fissure ratio (SFR), i.e., the average of the maximal Sylvian fissure widths taken from the cut showing the widest Sylvian fissure divided by the transpineal coronal inner table diameter (20). Subcortical atrophy was evaluated by the bicaudate ratio (BCR) on the cut best showing the caudate nuclei and by the bifrontal ratio (BFR) measured on the same cut as the BCR. BCR and BFR are defined, respectively, as the minimal distance between the caudate indentations of the frontal horn (20) and the distance between the tips of the frontal horns divided by the distance between the inner tables of the skull along the same line (20). To relate cerebral atrophy to cognitive functioning, the raw data were converted into a cortical atrophy Z score (mean Z FFR and Z SFR) and subcortical atrophy Z score (mean Z BCR and Z BFR), based on the pooled mean of the whole study population.

All MRI scans were independently rated by two raters blinded to diabetes status (S.M.M. and G.J.B.). In the case of disagreements of more than one point on the WML scales in a particular region or >5 mm (actual size) on any of the atrophy measurements (2 mm for fissure widths), consensus readings were held (involving no PWML, 4% DWML, and 4% of atrophy ratio readings). In all other cases the readings of both readers were averaged.

Neuropsychological tests. All participants performed an extensive neuropsychological examination tapping the major cognitive domains in both a verbal and nonverbal manner. Eleven tasks were administered in a fixed order that took ~90 min to complete. These tasks were divided into five cognitive domains to reduce the amount of neuropsychological variables and for clinical clarity. This division was made a priori, according to standard neuropsychological practice and cognitive theory, as described in detail in Lezak's *Neuropsychological Assessment* (21). The domain "abstract reasoning" was assessed by Raven Advanced Progressive Matrices (12-item short form). The domain "memory," included four subdomains, "working memory," assessed by the forward and backward digit span of the WAIS-III (Wechsler Adult Intelligence Scale-III) and the Corsi Block-Tapping Task; "immediate memory and learning rate," including verbal memory assessed by the Rey Auditory Verbal Learning Test and visual memory assessed by the Location Learning Test; "forgetting rate," assessed by the delayed task of the Rey Auditory Verbal Learning Test and of the Location Learning Test; and "incidental memory," assessed by the delayed trial of the Rey-Osterrieth Complex Figure. The domain "information processing speed" was assessed by the Trail Making Test Part A, the Stroop Color-Word Test (Part I and II), and the subtest Digit Symbol of the WAIS-III. The domain "attention and executive function" was assessed by the Trail Making Test Part B, the Stroop Color-Word Test (Part III), the Brixton Spatial Anticipation Test, a verbal fluency test using the N and A, and category fluency using animal names. The domain of visuoconstruction was assessed by the Rey-Osterrieth Complex Figure (copy trial). A premorbid IQ was tested with the Dutch version of the National Adult Reading Test.

Since depression is more common in patients with type 2 diabetes than in control subjects (22) and depression may influence cognitive functioning, mood was assessed with a Beck Depression Inventory (23). Both the total score on this self-rated depressive symptoms inventory and the percentage of people scoring above the cutoffcriterion of 15 were recorded.

To compare the five different cognitive domains between the two groups and to perform regression analysis within the type 2 diabetic group, the raw scores were standardized into Z scores per domain. These Z scores were calculated on the pooled mean of the whole study population.

Medical history, blood pressure, blood samples, and vascular disease. In a standardized interview, participants were asked about diabetes duration, height and weight, history of hypertension, stroke or cardiovascular disease, and smoking. Furthermore, all participants measured their blood pressure at home at nine different time points during the day (Omron MX3; Omron, Mannheim, Germany). Fasting glucose, HbA_{1c} (A1C), fasting triglycerides, and fasting cholesterol were determined. BMI was calculated as weight divided by the square of height. Hypertension was defined as an average systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥95 mmHg or self-reported use of blood pressure–lowering drugs. Hypercholesterolemia was defined as a fasting cholesterol >6.2 mmol/l or self-reported use of cholesterol-lowering drugs (24).

Microvascular and macrovascular complications were also assessed. Fundus photographs were rated according to the Wisconsin Epidemiologic Study of Diabetic Retinopathy scale (25). A score ≥1.5 was defined as retinopathy. Albuminuria was defined as microalbuminuria (albumin 30–250 mg/l) or macroalbuminuria (albumin 250 mg/l or positive protein dip-stick test) in the overnight urine sample. Neuropathy was defined as a score ≥6 on the Toronto Clinical Neuropathy Scoring System (26). "Any microvascular disease" was defined as retinopathy, albuminuria, or neuropathy. "Any macrovascular event" was defined as a history of myocardial infarction, stroke, or surgery or endovascular treatment for coronary, carotid, or peripheral (legs, abdominal aorta) artery disease. More detailed data on these complications in relation to cognition and brain MRI will be reported separately.

Statistical analysis. For the population characteristics and cognition and brain MRI findings, between-group differences were analyzed with t test for means, Mann-Whitney U test for nonparametric data, and χ^2 test for proportions. Between-group differences on cognition and brain MRI were also assessed by regression analyses and expressed as estimated between-group difference with 95% CI. The primary analyses were adjusted for age, sex, and estimated IQ and in additional analyses, also for blood pressure and the depression inventory score.

Within the type 2 diabetic population, associations between cognition, brain MRI findings, and disease variables were assessed by linear or logistic regression analysis, adjusting for age, sex, and estimated IQ. For the between-group comparisons, $P < 0.05$ was considered statistically significant. For the within group analyses in the type 2 diabetic patients, a significance level of $P < 0.01$ was used to accommodate the effects of repeated testing.

RESULTS

Clinical data. The groups were well balanced for age, sex, level of education (seven categories) (27), and estimated IQ (Table 1). Of the 113 type 2 diabetic participants, 11 (10%) subjects had no treatment or only dietary treatment, 68 (60%) received oral antidiabetic drugs, and 34 (30%) received insulin. Patients with type 2 diabetes had more hypertension, whereas their lipid profile was better than that of control subjects.

TABLE 1
Participant characteristics

	Type 2 diabetic patients	Control subjects
n (male/female)	113 (56/57)	51 (22/29)
Mean age (years)	66.1 ± 5.6	65.1 ± 5.3
Education level	4 (3–5)	4 (3–5)
Estimated IQ	99 ± 15	100 ± 14
Depressive symptoms (%)*	7	2
Diabetes duration (years)	8.8 ± 6.2	—
History of severe hypoglycemia (%)	6	—
A1C (%)	6.9 ± 1.2†	5.5 ± 0.3
Fasting serum glucose (mmol/l)	8.6 ± 3.0†	5.5 ± 0.6
Use of insulin (%)	30	—
BMI (kg/m^2)	28.0 ± 4.3	27.2 ± 4.9
Hypercholesterolemia (%)	63	49
Fasting serum cholesterol (mmol/l)	5.0 ± 0.9†	5.7 ± 0.9
Fasting triglycerides (mmol/l)	1.9 ± 1.0‡	1.5 ± 0.9
Use of lipid-lowering drugs (%)	53†	22
Hypertension (%)	73†	33
Use of antihypertensive drugs (%)	70†	33
Systolic blood pressure (mmHg)	147 ± 19†	137 ± 19
Diastolic blood pressure (mmHg)	81 ± 10	78 ± 9
Any microvascular disease (%)	58†	18
Any macrovascular event (%)	29†	6

Data are means ± SD and median (interquartile range) unless otherwise indicated. *Beck Depression Inventory score ≥16. †$P < 0.01$, ‡$P < 0.05$.

Differences between type 2 diabetic patients and control subjects on brain MRI and cognitive domains. Patients with type 2 diabetes had more cortical and subcortical atrophy than control subjects (FFR $P < 0.001$, SFR $P < 0.001$, BCR $P = 0.003$, and BFR $P = 0.14$.) (Table 2). Patients with type 2 diabetes had a higher DWML score than control subjects ($P = 0.02$) (Fig. 1), but PWMLs were not different between the groups ($P = 0.13$). Furthermore, patients with type 2 diabetes had more (silent) cerebral infarcts than control subjects (type 2 diabetes 22 of 113 and control subjects 4 of 54, $P = 0.06$). From the 22 patients with infarcts, 12 had lacunar infarcts, 6 had other infarcts (e.g., cortical or large subcortical), and 4 had both lacunar and other infarcts. Of the 22 patients with a visible infarct on their MRI, 6 reported a history of stroke. One control subject had a lacunar infarct, and three control subjects showed other infarcts on their MRI, but none of them reported a history of stroke. The effect of diabetes on cortical atrophy persisted after adjusting for the presence of WML and infarcts.

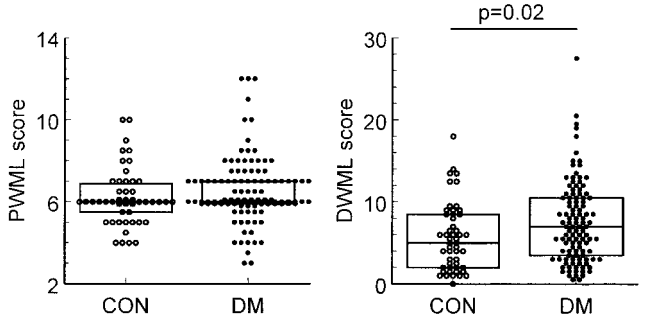

FIG. 1. MRI findings in control subjects (CON) and type 2 diabetic patients (DM) for PWML (Scheltens scale 0–12) and DWML (Scheltens scale: 0–36). Box represents median with interquartile range (ref. 19).

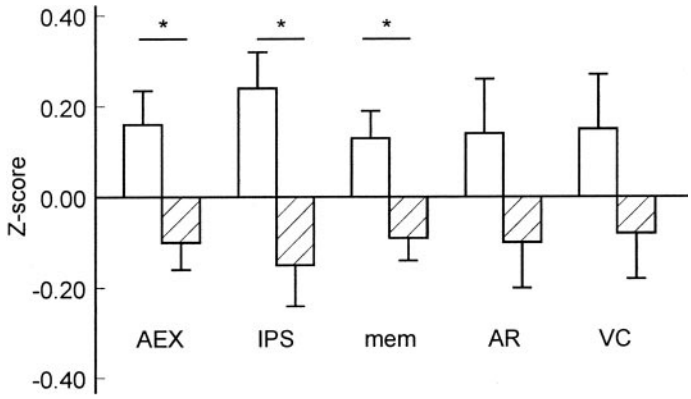

FIG. 2. Cognitive domains in control subjects (□) and type 2 diabetic patients (▨). Raw scores were standardized into *Z* scores per domain. Data are means ± SE. AEX, attention and executive functioning; AR, abstract reasoning; IPS, information processing speed; mem, memory; VC, visuoconstruction. $P = 0.01$.

The performance of type 2 diabetic patients on all five cognitive domains was worse compared with that of control subjects, but statistically significant changes were observed only for the domains "attention and executive functioning" ($P = 0.01$), "information processing speed" ($P = 0.01$), and "memory" ($P = 0.01$) (Fig. 2). Effect sizes were in the small to moderate range (0.2–0.4).

Adjustment for the possible effects of blood pressure (mean arterial pressure) did not affect the difference between the type 2 diabetic and control groups on the MRI measures or cognition (Table 3). Adjustment for the presence or absence of hypertension gave similar results (data not shown). Moreover, when the findings in hypertensive and nonhypertensive subjects were analyzed separately, the magnitude of the effect of diabetes remained essentially the same (Table 3). The exclusion of control subjects ($n = 10$) with impaired fasting glucose (>6.0 mmol/l) (28) did not have an apparent effect on between-group differences on cognition or brain MRI.

One control subject and eight type 2 diabetic patients scored above the cutoffcriterion of 15 for the depression inventory score. Exclusion of these participants from the analyses, or adjustment for the depression score, did not affect the between-group differences on cognition (data not shown).

Relation between cognition, MRI, and disease variables in the patients with type 2 diabetes. Within the type 2 diabetic group, statistically significant associations between MRI abnormalities and cognition were noted, even after adjustment for age, sex, and IQ (Table 4). DWMLs, cortical atrophy, and infarcts were related to information processing speed ($P < 0.01$). PWMLs and subcortical atrophy also tended to be related to information processing speed ($P < 0.05$). Subcortical atrophy was

TABLE 2
Cerebral atrophy: sulci-to-brain and ventricle-to-brain ratios

	Type 2 diabetic patients	Control subjects
FFR $\times 10^2$	4.3 ± 1.5*	3.3 ± 1.3
SFR $\times 10^2$	4.1 ± 1.3*	3.3 ± 0.8
BCR $\times 10^2$	14.9 ± 3.6†	13.1 ± 3.0
BFR $\times 10^2$	33.0 ± 4.8	31.9 ± 4.4

Data are means ± SD. *$P < 0.001$, †$P < 0.01$.

TABLE 3
Adjusted between-group differences in MRI and cognition

	Whole population			
	Model 1	Model 2	No hypertension	Hypertension
n (type 2 diabetic/control)	113/51	113/51	30/33	83/18
PWMLs	0.5 (0–0.5)	0 (−0.5 to 0.5)	0.5 (−0.5 to 1)	0 (−1 to 0.5)
DWMLs	1.5 (0–3)*	1.5 (0–3)*	1.5 (−0.5 to 4)	1.5 (−1 to 4)
FFR $\times 10^3$	7.9 (3.6–12.3)†	7.7 (3.2–12.1)†	9.6 (3.0–16.2)†	7.7 (0.7–14.7)*
SFR $\times 10^3$	6.4 (2.8–10.0)†	5.9 (2.2–9.5)†	5.5 (1.0–9.9)*	6.3 (0–12.6)
BCR $\times 10^3$	13.9 (3.9–24.1)†	14.8 (4.6–25.0)†	12.1 (−0.1 to 24.2)	9.7 (−7.8 to 27.3)
BFR $\times 10^3$	7.0 (−6.8 to 20.9)	8.1 (−6.0 to 22.2)	7.4 (−7.7 to 22.6)	10.0 (−15.1 to 35.1)
Executive function	−0.19 (−0.36 to −0.02)*	−0.19 (−0.37 to −0.02)*	−0.10 (−0.321 to 0.13)	−0.23 (−0.52 to 0.06)
Information processing	−0.30 (−0.55 to −0.04)*	−0.29 (−0.55 to −0.03)*	−0.17 (−0.52 to 0.17)	−0.41 (−0.83 to 0.02)
Memory	−0.16 (−0.30 to −0.02)*	−0.18 (−0.32 to −0.03)*	−0.30 (−0.53 to −0.08)†	−0.13 (−0.34 to 0.09)
Abstract reasoning	−0.13 (−0.41 to 0.14)	−0.10 (−0.38 to 0.18)	0.04 (−0.31 to 0.38)	−0.14 (−0.61 to 0.34)
Visuoconstruction	−0.17 (−0.48 to 0.14)	−0.16 (−0.48 to 0.16)	0.04 (−0.34 to 0.41)	−0.08 (−0.60 to 0.45)

Data are estimated mean differences (95% CI). Model 1 includes adjustment for age, sex, and IQ. Model 2 includes additional adjustment for mean arterial pressure. The last two columns are adjusted for age, sex, and IQ. Estimated mean differences >0 for MRI and <0 for cognition reflect worse scores in the diabetic group relative to the control group. *$P < 0.05$, †$P < 0.01$.

related to attention and executive function ($P < 0.01$) and tended to be related to two other cognitive domains. In a multivariate model with age, sex, IQ, and the different MRI measures as the independent variables and information processing speed as the dependent variable, only the associations with age ($P = 0.001$), IQ ($P < 0.001$), DWMLs ($P < 0.001$), and infarcts ($P < 0.001$) were statistically significant.

Age was evidently related to atrophy and WML severity (Table 5). After adjusting age for diabetes duration, these results did not change notably. No significant (at the $P < 0.01$ level) relations between MRI parameters and blood pressure, A1C, and diabetes duration were found, although mean arterial blood pressure tended to be related to PWMLs ($P < 0.05$). Age was also significantly related to cognition in three of the five cognitive domains (Table 5). Adjustment for diabetes duration did not notably change these results. Mean arterial blood pressure tended to be related to improved memory function ($P < 0.05$), whereas hypertension was associated with lower performance on the other four cognitive domains, albeit not statistically significant. A1C level and diabetes duration tended to be related to information processing speed ($P < 0.05$). A history of macrovascular events tended to be related to impaired cognition ($P < 0.05$) and more severe DWMLs ($P < 0.05$). Although microvasular disease was not related to brain MRI findings, there was an association with lower performance on the five cognitive domains, albeit not statistically significant. There was no relation between sex and cognition, but subcortical atrophy was more pronounced in men. For the domains "information processing speed" and "memory," the association with age appeared to be stronger in the type 2 diabetic than in the control group (*B* values per 5 years for control subjects vs. type 2 diabetic patients, respectively: information processing speed −0.09 ($P = 0.19$) vs. −0.32 ($P < 0.001$) and memory −0.06 ($P = 0.25$) vs. −0.21 ($P < 0.001$). For memory, this interaction between age and group was statistically significant ($P = 0.01$).

DISCUSSION

On brain MRI, patients with type 2 diabetes had more cortical and subcortical atrophy and more DWMLs and infarcts than control subjects. The performance of the patients with type 2 diabetes on the neuropsychological examination was worse, particularly affecting the domains "attention," "executive functioning," "information processing speed," and "memory." Adjustment for hypertension did not affect the results. Within the type 2 diabetic group, cognitive function was inversely related to WMLs, atrophy, and the presence of infarcts, and there was a modest association between impaired cognition and A1C and diabetes duration. This association was strongest for age, even more so than in the control group.

Cognitive function of patients with type 2 diabetes has been the subject of several studies (rev. in 2,3), generally reporting deficits in verbal memory and information processing speed and less consistently in executive functioning and nonverbal memory. Our results are in line with these findings. Studies that examined relations between different disease variables and cognitive functioning showed that patients with worse glycemic control were more likely to show cognitive deficits (29). Most of these studies used sample sizes smaller than those used in our study. Moreover, although most studies did not use age as an independent predictor, the largest effect of type 2 diabetes on cognitive function was observed in studies in which patients were older (30). When addressing the relation between hypertension and cognition, the results of previous studies are less consistent. One population-based study found that hypertensive patients with type 2 diabetes were at the greatest risk for poor cognitive performance (31), but other longitudinal studies did not observe an evident relation between hypertension and cognitive performance (9,32,33), in line with the present observations.

Thus far, relatively few studies have specifically addressed brain MRI abnormalities in patients with type 2 diabetes. In line with the present observations, these studies indicate that modest cortical and subcortical atrophy and symptomatic or asymptomatic infarcts are more common in type 2 diabetic patients than in control subjects (11–15). The relation between cerebral atrophy and hypertension in type 2 diabetic patients, however, is less clear. One study reports no effects of adjustment for hypertension (12), which is consistent with our findings, whereas another study indicated that hypertension appeared to be a major determinant of cerebral atrophy in

TABLE 4
Relations between brain MRI abnormalities and cognitive function in type 2 diabetic patients expressed as regression β coefficients (CI)

	Attention and executive function	Information processing speed	Memory	Abstract reasoning	Visuoconstruction
PWMLs	−0.08 (−0.15 to −0.02)*	−0.13 (−0.24 to −0.03)*	−0.03 (−0.08 to 0.03)	−0.04 (−0.16 to 0.07)	0.04 (−0.08 to 0.17)
DWMLs	−0.01 (−0.04 to 0.01)	−0.06 (−0.09 to −0.03)†	−0.01 (−0.03 to 0.01)	−0.02 (−0.05 to 0.02)	0.02 (−0.02 to 0.06)
Cortical atrophy	−0.09 (−0.21 to 0.03)	−0.27 (−0.44 to −0.10)†	−0.03 (−0.12 to 0.07)	−0.17 (−0.36 to 0.02)	−0.01 (−0.25 to 0.23)
Subcortical atrophy	−0.17 (−0.29 to −0.05)†	−0.19 (−0.38 to 0.00)*	−0.06 (−0.16 to 0.04)	−0.25 (−0.45 to −0.06)*	−0.29 (−0.52 to −0.06)*
Infarcts	−0.02 (−0.29 to 0.25)	−0.77 (−1.14 to −0.39)†	−0.10 (−0.31 to 0.10)	−0.41 (−0.82 to 0.01)	0.02 (−0.47 to 0.51)

Adjusted for age, estimated IQ, and sex. *$P < 0.05$; †$P < 0.01$.

type 2 diabetic patients (11). Results of previous studies on the association between type 2 diabetes and WMLs are inconsistent. The majority of these studies involved selected subgroups of patients with, for example, clinically manifest cardiovascular disease or stroke (16,17) and used relatively insensitive measures to rate WMLs. Some of these studies in patients with vascular disease reported relatively more severe WMLs in patients with type 2 diabetes (16), whereas others reported no statistically significant relation between type 2 diabetes and WMLs (17). The study on WMLs in elderly subjects with diabetes that involved the largest cohort and the most detailed rating method thus far reported no effect of diabetes on PWMLs, although the volume of DWMLs tended to be higher in the diabetic group (11).

There are, to our knowledge, no previous studies that specifically address the relation between brain MRI abnormalities and cognitive functioning in patients with type 2 diabetes. However, previous studies in general populations of elderly subjects that studied brain MRI abnormalities and cognitive function show results that are comparable with ours. A study of 139 healthy adults (50–81 years of age), for example, observed an association between atrophy of the prefrontal cortex and the volume of WMLs in the prefrontal region and age-related impairments of executive functioning but not with memory (34). Another study involving 68 healthy, nondemented individuals tested at ages 50, 60, 70, and 80 years reported that PWMLs were related to decline in information processing speed and visuoconstruction and that DWMLs were related to visuoconstruction (35).

The present study may provide some clues regarding the causes of cognitive deficits in patients with type 2 diabetes, as cognitive impairments were associated with subcortical ischemic MRI abnormalities (silent infarcts and WMLs). However, nonvascular mechanisms could also be involved because more diffuse cerebral changes, like cortical atrophy, were also related to impaired cognition. Blood pressure showed a relation with PWMLs and might thus to some extent be involved in the cognitive deficits. However, as is clearly indicated in Table 3, adjustment for hypertension had no obvious effect on the differences in cognition and MRI ratings between control subjects and patients with type 2 diabetes. Chronic hyperglycemia could also be involved, although the relation between A1C and diabetes duration and changes in cognition was only modest. In the present study, the strongest determinant of changes in cognition and on MRI was age. Age was strongly related to all MRI parameters and to three of the five cognitive domains in patients with type 2 diabetes, and the interaction term of age and group was significant for the domain "memory." This points to an interaction between type 2 diabetes and ageing. In fact, several processes that have been implicated in brain ageing, including oxidative stress, accumulation of so-called advanced glycosylation end products, microvascular dysfunction, and alterations in cerebral glucose and insulin metabolism may be accelerated by diabetes (36), which may explain part of this interaction.

A strength of our study is that we combined a detailed analysis of both cognitive function and brain imaging by means of MRI, thus allowing an accurate assessment of the relation between these parameters. A possible limitation of our study could be selection bias. In general, individuals who participate in research projects that include a detailed work-up at a hospital tend to be less affected than individ-

TABLE 5
Relations between disease variables and MRI abnormalities and cognition in type 2 diabetic patients

	PWMLs	DWMLs	Cortical atrophy	Subcortical atrophy	Infarct
Age (per 5 years)	0.5 (0.2–0.7)*	1.0 (0.2–1.8)†	0.33 (0.18–0.48)*	0.35 (0.21–0.49)*	1.5 (1.0–2.4)
Sex‡	−0.4 (−0.2 to 1.0)	1.1 (−0.7 to 2.9)	−0.20 (−0.53 to 0.14)	−0.58 (−0.90 to −0.27)*	0.6 (0.2–1.6)
MAP (per 10 mmHg)	0.3 (0.0–0.5)†	0.2 (−0.6 to 1.0)	0.06 (−0.09 to 0.21)	−0.05 (−0.19 to 0.10)	1.1 (0.7–1.7)
Hypertension	0.2 (−0.5 to 0.8)	0.5 (−1.5 to 2.6)	0.03 (−0.35 to 0.40)	0.07 (−0.29 to 0.42)	1.4 (0.5–4.4)
Microvascular disease	−0.1 (−0.6 to 0.5)	−1.0 (−2.9 to 0.9)	0.19 (−0.16 to 0.53)	−0.10 (−0.42 to 0.22)	0.9 (0.3–2.4)
Macrovascular events	0.1 (−0.6 to 0.7)	2.0 (0.0–4.1)†	0.11 (−0.27 to 0.50)	0.20 (−0.16 to 0.56)	2.8(1.1–7.9)†
Diabetes duration (per 5 years)	−0.2 (−0.4 to 0.0)	−0.5 (−1.3 to 0.3)	0.10 (−0.05 to 0.24)	0.00 (−0.04 to 0.03)	1.2 (0.8–1.7)
A1C (%)	−0.1 (−0.3 to 0.2)	0.4 (−0.3 to 1.2)	−0.03 (−0.11 to 0.16)	−0.03 (−0.15 to 0.10)	1.1 (0.7–1.6)

	Attention and executive function	Information processing speed	Memory	Abstract reasoning	Visuoconstruction
Age (per 5 years)	−0.13 (−0.23 to −0.04)*	−0.32 (−0.46 to −0.17)*	−0.21 (−0.28 to −0.14)*	−0.13 (−0.28 to 0.02)	−0.03 (−0.20 to 0.14)
Sex	−0.09 (−0.31 to 0.11)	−0.07 (−0.38 to 0.25)	0.12 (−0.04 to 0.28)	−0.10 (−0.43 to 0.23)	−0.14 (−0.52 to 0.23)
MAP (per 10 mmHg)	0.01 (−0.09 to 0.10)	−0. 03 (−0.17 to 0.12)	0.08 (0.01–0.15)†	−0.16 (−0.21 to 0.09)	−0.01 (−0.16 to 0.18)
Hypertension	−0.15 (−0.38 to 0.09)	−0.21 (−0.57 to 0.14)	0.18 (0.00 to −0.36)	−0.31 (−0.68 to 0.06)	−0.39 (−0.79 to 0.03)
Microvascular disease	−0.09 (−0.03 to 0.13)	−0.09 (−0.42 to 0.24)	−0.13 (−0.29 to 0.04)	−0.32 (−0.66 to 0.01)	−0.29 (−0.67 to 0.09)
Macrovascular events	−0.12 (−0.36 to 0.11)	−0.43 (−0.78 to −0.08)†	−0.21 (−0.40 to −0.03)†	−0.21 (−0.59 to 0.17)	0.04 (−0.39 to 0.46)
Diabetes duration (per 5 years)	0.00 (−0.09 to 0.09)	−0. 15 (−0.28 to −0.02)†	−0.07 (−0.13 to 0.00)	−0.02 (−0.18 to 0.14)	0.15 (−0.02 to 0.31)
A1C (%)	−0.05 (−0.14 to 0.03)	−0.17 (−0.30 to −0.04)†	−0.04 (−0.10 to 0.03)	−0.13 (−0.27 to 0.01)	0.07 (−0.08 to 0.21)

Data are regression β coefficients (CI) for all data except infarct, which are OR (95% CI). Coefficients are adjusted for age, estimated IQ, and sex. An increase in MRI scores reflects more severe MRI abnormalities, whereas a decrease in Z values for cognition reflects more pronounced performance impairments. *$P < 0.01$, †$P < 0.05$. ‡For sex, negative β values reflect relatively worse MRI scores or better cognition in men; for infarcts, ORs were calculated for women relative to men. MAP, mean arterial pressure.

uals who refuse participation. Hence, we do not think this selection bias has a large impact on our results, if any; the strength of the associations would be underestimated because of a healthier study population. We specifically decided not to exclude participants with comorbidity such as hypertension or macrovascular events, as this comorbidity is an integral part of the diabetic condition. If we had excluded subjects with these disorders a priori, our findings would not be generalizable to the general population of type 2 diabetic subjects. The characteristics (i.e., A1C, total cholesterol, triglycerides, blood pressure, and BMI) of the patients with type 2 diabetes that were included in the present study are similar to those reported in large population-based surveys of type 2 diabetic subjects in the Netherlands (37,38). Mean A1C was 6.9% in our type 2 diabetic population, which indicates a moderately well-controlled diabetes. Another limitation of the present study might be its cross-sectional design. This can clearly affect the interpretation of data on the relation between impaired cognition and potential mediators such as blood pressure and glycemic control. In elderly individuals, various factors can affect the outcome measures that were assessed in the present study, of which only a proportion are directly related to type 2 diabetes. A follow-up project involving the present study population has been initiated and may provide more detailed information on the potential role of different metabolic and vascular risk factors.

We conclude that cognitive impairments in patients with type 2 diabetes are related to structural changes in the brain. These changes are indicative of a vascular etiology, although the increased cortical brain atrophy and the relation with age are also suggestive of other mechanisms such as accelerated brain ageing.

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APPENDIX

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