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5 structure can be divided into the area just beneath the neocortex and the area  
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7 surrounding the ventricles. The periventricular region contains many long  
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9 association fibers that connect the cerebral cortex with subcortical nuclei such  
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11 as found in the striatum and with more distant cortical areas. On the other hand,  
12  
13 the subcortical region close to the neocortex features a high density of short  
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15 looped U-fibers connecting adjacent cortical areas (39). Periventricular WMHs  
16  
17 damage the long-tract white matter pathways connecting many cortical areas,  
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19 which might explain their effects on multiple domains of cognition.  
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22  
23 Impaired cognitive function in elderly diabetics was correlated with subcortical  
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25 WMHs in parietal lobe as well as hyperintensities in the thalamus in this study.  
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27 Thalamus is recognized to be associated with cognitive function such as  
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29 learning, memory and executive function (32, 40). Parietal lobe constitutes  
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31 association areas that are the site of cortical integration for all behaviour such  
32  
33 as vision, body awareness and spatial orientation and for abstract and complex  
34  
35 cognitive functions. Recent neuroradiological studies have demonstrated  
36  
37 reduced regional cerebral blood flow and metabolism in Alzheimer's diseases  
38  
39 especially in the parieto-temporal cortical areas and correlated with the  
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41 distribution of Alzheimer pathological features, while the primary sensori-motor  
42  
43 and visual cortical areas were relatively preserved (41, 42). Symptoms of early  
44  
45 stage Alzheimer's disease originate from the impaired temporal and parietal  
46  
47 lobe functions. Incidental onset of Alzheimer's disease in elderly diabetics can  
48  
49 be expected to exacerbate the functional loss and clinical symptoms related to  
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51 temporal and parietal lobes, as also observed in the case of diabetic cognitive  
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53 dysfunction.  
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The pathophysiological origins of WMHs are still unclear, with vascular and nonvascular contributions likely to be causative factors. Subcortical WMHs on T2-weighted MR imaging correlate with several pathological changes such as myelin pallor, dilatation of the perivascular space, myelin or axonal loss, scattered cystic infarcts and angioneclerosis. Periventricular hyperintensities on MR scans are associated with partial break down of the ependymal cell lining and subependymal gliosis in addition to the pathological changes of subcortical WMHs (43, 44). Although characteristic pathological features of the diabetic brain have yet not been identified, vascular compromise is common in the elderly and is accompanied by damage to white matter pathways (12, 45). Age and hypertension have been the most consistent predictors of WMHs (32, 33, 46, 47), while some other studies have indicated that diabetes increases the risk of WMHs (13, 36, 48). The increased WMHs in elderly diabetics, presumably accompanied by as yet unidentified clinical variables, may account, at least in part, for diabetic cognitive dysfunction.

To reduce the rate of dementia in elderly diabetics, it is crucial to identify the factors responsible for the progression towards severe cognitive decline. Degenerative changes in cerebral small vessels may affect diabetic cognitive dysfunction, while it seems likely that it is also influenced by diabetic metabolic abnormalities and complications with or without unidentified genetic susceptibility. However, the results of our study do not support the notion of any relationship between cognitive dysfunction and diabetic clinical characteristics. Whether variations in glucose homeostasis influence cognitive function remains controversial (49-51), although it has been found that the cognitive function of

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6 diabetic and nondiabetic subjects fluctuates in accordance with the serum  
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8 glucose levels (50, 51). At the same time, increased insulin resistance is  
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10 associated with atrophy of medial temporal lobe structures in elderly diabetics  
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12 (52). For these reasons, new surrogate markers that reflect chronic  
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14 hyperglycemia in the diabetic brain are needed. Hyperglycemia causes  
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16 oxidative stress via the polyol pathway, enhances advanced glycation end-  
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18 products (AGE), and increases lipid peroxidation and imbalances in the  
19  
20 generation of reactive oxygen species and their scavengers (53, 54). N<sup>ε</sup>-  
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22 Carboxymethyllysine (CML), the most prominent AGE product, is crucially  
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24 involved in the development of diabetic microangiopathy (55), and the level of  
25  
26 CML expression is high in the blood vessels and brain of diabetics, but low in  
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28 aging controls (56). Oxidative stress has also been implicated in the  
29  
30 pathophysiology of Alzheimer's disease and hypoxic brain insults (57-59).  
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32 Progression of diabetic retinopathy strongly correlates with the total sum of  
33  
34 blood glucose control, and may constitute a predictor for cerebral small vessel  
35  
36 disease (60, 61).

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38 Certain limitations of our study need to be considered. The first limitation is that  
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40 this analysis was a cross-sectional study. The second is the possibility that  
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42 participants with some other cognitive dysfunction could be involved in this  
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44 study. The mean MMSE score of our diabetic patients was  $26.2 \pm 0.3$ , which  
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46 means that most of the subjects did not attain the full MMSE score. In particular,  
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48 we could not completely exclude the patients with mild cognitive impairment.  
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50 The third limitation is the method for measuring brain atrophy. We used linear  
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52 measurements to evaluate subcortical atrophy adjacent to the lateral ventricles,  
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6 and this procedure is outdated and less accurate than the recently developed  
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8 volumetric analysis of MR images (62). However, volumetric MR analyses of a  
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10 number of diabetic patients from the different institutes and hospitals could not  
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12 be performed. Finally, we did not estimate the effects of treatment per se for  
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14 diabetes, hypertension, and lipid abnormalities on diabetic cognitive domains.  
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16 The Rotterdam study has suggested that use of oral medication and insulin  
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18 treatment for diabetes increases the association with dementia. While MR  
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20 imaging has demonstrated that hypertension is associated with cognitive  
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22 dysfunction and WMHs (63, 64). Recent prospective intervention studies have  
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24 indicated that appropriate blood pressure control delays the progression of  
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26 cognitive decline (65). Furthermore, there are indications that impaired  
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28 cholesterol transport may have a pathophysiological roles in Alzheimer's  
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30 disease and that HMG-CoA reductase inhibitors (statin) may have a protective  
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32 effects on cognitive dysfunction in the elderly (66-68). Most of the diabetic  
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34 subjects enrolled in this study were successfully treated for their blood pressure  
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36 and lipid abnormalities, which could diminish the impacts of hypertension and  
37  
38 lipid abnormalities on diabetic cognitive impairment and brain structural  
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40 changes. The effects of these limitations of our study will be analyzed in the  
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42 prospective intervention J-EDIT study.  
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50 In summary, WMHs and subcortical brain atrophy observed on MRI scans of  
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52 elderly diabetics without symptomatic brain infarctions were found to be  
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54 associated with impaired speed of mental processes and memory, while WMHs  
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56 are thought to be responsible for degenerative changes of cerebral small  
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58 vessels and to be implicated in the pathogenesis of cognitive impairment. These  
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5 findings suggest that hyperintensities in the parietal lobe and thalamus and  
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7 subcortical atrophy in particular constitute predictors of the rate of cognitive  
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9 dysfunction in elderly diabetics and may underlie procession towards severe  
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11 cognitive impairment. Our prospective J-EDIT study should help to determine  
12  
13 the factors that can prevent cognitive dysfunction in elderly diabetics.  
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**Table 1** Clinical Characteristics of elderly patients with diabetes mellitus

	N	Mean±SEM
<i>Clinical character</i>		
Age (years)	95	72.8±0.5
Male: Female	38 : 57	
Education (years)	77	10.7±0.3
Duration of diabetes mellitus (years)	92	18.4±1.2
Body mass index (kg/m <sup>2</sup> )	92	23.2±0.4
Waist/hip ratio	92	0.92±0.0
Systolic blood pressure (mmHg)	95	135.4±1.2
Diastolic blood pressure (mmHg)	95	75.5±0.9
Cardiovascular complication	95	0.16±0.0
Retinopathy	88	0.70±0.1
Nephropathy	87	0.59±0.1
Neuropathy	87	0.66±0.1
Fasting blood glucose (mg/dl)	82	164.2±5.1
HbA1c (%)	95	7.9±0.1
Insulin	77	9.3±1.3
Total cholesterol (mg/dl)	95	203.4±3.2
Triglyceride (mg/dl)	95	150.1±12.8
HDL cholesterol (mg/dl)	94	65.0±2.7
<i>Cognitive function</i>		
Mini-mental state examination	80	26.2±0.3
Immediate word-list recall	81	8.2±0.2
Delayed word-list recall	80	6.8±0.3
Immediate paragraph recall	80	7.5±0.3
Delayed paragraph recall	80	5.8±0.3
Stroop test (B)	80	40.2±1.6
Digit symbol substitution test	77	35.8±1.2
<i>MRI</i>		
White matter hyperintensities (WMHs)		
Frontal lobe (ml)	95	1.8±0.2
Parietal lobe (ml)	95	1.0±0.1
Temporal lobe (ml)	95	0.8±0.1
Occipital lobe (ml)	95	0.3±0.1
Thalamus (ml)	95	0.1±0.0
Basal ganglia (ml)	95	0.3±0.0
Total (ml)	95	4.3±0.4
Periventricular hyperintensity	86	9.7±0.31
Evans ratio	95	26.0±0.34
Caudate head index	95	13.5±0.25
inverse Cella media index	95	26.3±0.40
Basal cistern index	95	19.6±0.27

**Table 2** Canonical correlation between cognitive function and WMHs

Canonical correlation coefficient; 0.64			P=0.004
Immediate word-list recall	0.33	WMHs of frontal lobe	-0.07
Delayed word-list recall	0.47	WMHs of parietal lobe	-0.33
Immediate paragraph recall	0.14	WMHs of temporal lobe	-0.31
Delayed paragraph recall	0.29	WMHs of occipital lobe	0.33
MMSE	0.65	Thalamus	-0.39
Stroop test (B)	-0.41	Basal ganglia	-0.23
Digit symbol substitution test	0.76	Total WMHs	-0.34
		Periventricular hyperintensity	-0.45

Each value represents correlation of canonical variables.

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**Table 3** Canonical correlation between cognitive function and subcortical brain atrophy

Canonical correlation coefficient; 0.61		p=0.004	
Immediate word-list recall	-0.79	Evans ratio	0.83
Delayed word-list recall	-0.61	Caudate head index	0.79
Immediate paragraph recall	-0.28	inverse Cella media index	0.92
Delayed paragraph recall	-0.55	Basal cistern index	0.35
MMSE	-0.32		
Stroop test (B)	0.30		
Digit symbol substitution test	-0.71		

Each value represents correlation of canonical valuables.



**Table 4** Multivariate regression analysis for subcortical WMHs with adjustment for age, education, and blood pressure

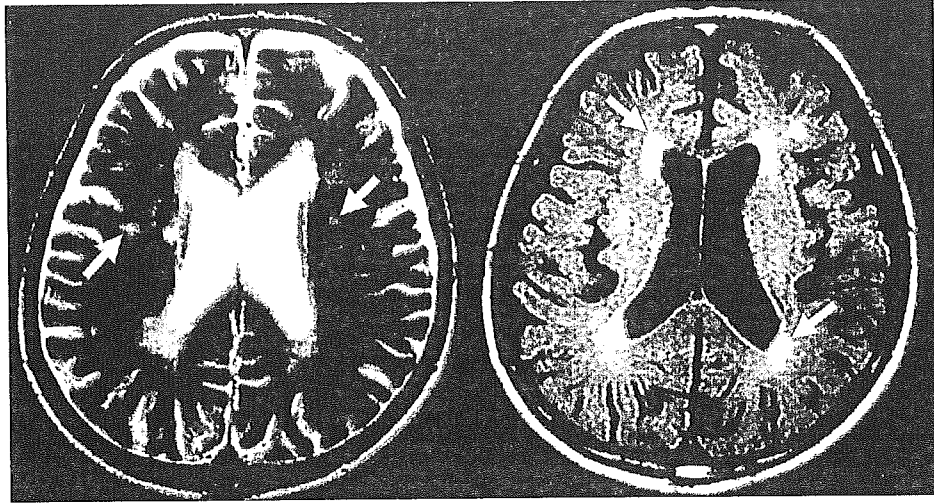
Digit symbol substitution test		
	P value	95% CI
WMHs of frontal lobe	0.13	-0.0004— 0.0033
WMHs of parietal lobe	<.05	-0.0057—-0.0002
WMHs of temporal lobe	0.99	-0.0039— 0.0038
WMHs of occipital lobe	0.56	-0.0048— 0.0087
Thalamus	0.34	-0.0187— 0.0065
Basal ganglia	0.31	-0.0092— 0.0030
Periventricular hyperintensity	0.54	-1.34— 0.70
MMSE		
	P value	95% CI
WMHs of frontal lobe	0.85	-0.0004— 0.0005
WMHs of parietal lobe	0.10	-0.0012— 0.0001
WMHs of temporal lobe	0.47	-0.0006— 0.0012
WMHs of occipital lobe	0.18	-0.0005— 0.0027
Thalamus	<.05	-0.0062—-0.0002
Basal ganglia	0.57	-0.0018— 0.0010
Periventricular hyperintensity	0.93	-0.23— 0.25

Each variable is adjusted for age, education, and systolic blood pressure  
 CI; confidence intervals

**Table 5** Multivariate regression analysis for subcortical atrophy with adjustment for age, education, and blood pressure

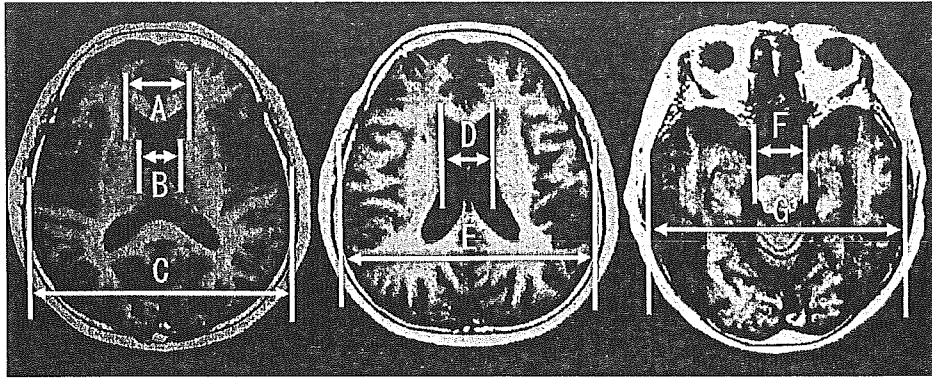
Immediate word-list recall	P value	95% CI
Evans ratio	0.50	-0.24— 0.12
Caudate head index	<.05	-0.33—-0.02
inverse Cella media index	0.28	-0.22— 0.07
Basal cistern index	0.77	-0.14— 0.11
Digit symbol substitution test	P value	95% CI
Evans ratio	0.87	-1.15— 1.35
Caudate head index	1.00	-1.07— 1.08
inverse Cella media index	<.05	-2.07—-0.08
Basal cistern index	0.13	-1.54— 0.20

Each variable is adjusted for age, education, and systolic blood pressure  
 CI; confidence intervals



An example of subcortical (left) and periventricular (right) white matter hyperintensities on brain MR imaging.

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Measured portions on MR imaging. A, the maximum distance between the tips of the anterior horns; B the width between the bilateral heads of the caudate nuclei; C, the maximum transverse inner diameter of the cranial space at the same MR section (left); D, the maximum width of the cella mediae; E, the maximum transverse inner diameter at the same section (center); F, the internal width between the bilateral temporal lobe at the level of basal cistern; G, the maximum transverse inner diameter at the same level (right). Evans ratio=  $A/C$ , Caudate Head Index=  $B/C$ , inverse Cella Media Index=  $D/E$ , Basal Cistern Index=  $F/G$ .