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Cognitive dysfunction in patients with cerebral microbleeds on T2*-weighted gradient-echo MRI

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Summary

Gradient echo T2*-weighted MRI has high sensitivity in detecting cerebral microbleeds, which appear as small dot-like hypointense lesions. Microbleeds are strongly associated with intracerebral haemorrhage, hypertension, lacunar stroke and ischaemic small vessel disease, and have generated interest as a marker of bleeding-prone microangiopathy. Microbleeds have generally been considered to be clinically silent; however, since they are located in widespread cortical and basal ganglia regions and are histologically characterized by tissue damage, we hypothesized that they would cause cognitive dysfunction. We therefore studied patients with microbleeds (n = 25) and a non-microbleed control group (n = 30) matched for age, gender and intelligence quotient. To avoid the confounding effects of coexisting cerebrovascular disease, the groups were also matched for the extent of MRI-visible white matter changes of presumed ischaemic origin, location of cortical strokes, and for the proportion of patients with different stroke subtypes (including lacunar stroke). A battery of neuropsychological tests was used to assess current intellectual function, verbal and visual memory, naming and perceptual skills, speed and attention and executive function. Microbleeds were most common in the basal ganglia but were also found in frontal, parieto-occipital, temporal and infratentorial regions. There was a striking difference between the groups in the prevalence of executive dysfunction, which was present in 60% of microbleed patients compared with 30% of non-microbleed patients (P = 0.03). Logistic regression confirmed that microbleeds (but not white matter changes) were an independent predictor of executive impairment (adjusted odds ratio = 1.32, 95% confidence interval 1.01–1.70, P = 0.04). Patients with executive dysfunction had more microbleeds in the frontal region (mean count 1.54 versus 0.03; P = 0.002) and in the basal ganglia (mean 1.17 versus 0.32; P = 0.048). There was a modest correlation between the number of microbleeds and the number of cognitive domains impaired (r = 0.44, P = 0.03). This study provides novel evidence that microbleeds are associated with cognitive dysfunction, independent of the extent of white matter changes of presumed ischaemic origin, or the presence of ischaemic stroke. The striking effect of microbleeds on executive dysfunction is likely to result from associated tissue damage in the frontal lobes and basal ganglia. These findings have implications for the diagnosis of stroke patients with cognitive impairment, and for the appropriate use of antihypertensive and antiplatelet treatments in these patients.

Keywords: stroke; microbleeds; MRI; cognitive impairment; frontal lobe; executive function

Abbreviations: FSE = fast spin echo; FLAIR = fluid-attenuated inversion recovery

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Early histopathological studies of patients with small vessel damage related to hypertension described small, focal areas of previous bleeding close to damaged arterioles, sometimes associated with small outpouchings of the vessel wall (Cole and Yates, 1967; Fisher, 1971). Until recently it has been difficult to detect these types of lesion during life. In the last few years, gradient echo T2*-weighted MRI sequences have revealed small, dot-like lesions of low signal intensity

within the brains of patients with haemorrhagic and ischaemic stroke, patients with hypertension, and a smaller proportion of healthy elderly subjects (Chan *et al*., 1996; Offenbacher *et al*., 1996; Kwa *et al*., 1998; Roob *et al*., 1999). These focal hypointensities result from local magnetic field inhomogeneities caused by the paramagnetic properties of haemosiderin, a product of lysed erythrocytes, and have been termed 'microbleeds' or 'microhaemorrhages'. Microbleeds are not usually seen on CT and are difficult to detect on standard T2-weighted MRI sequences. Histological correlation studies confirm that microbleeds represent focal leakage of haemosiderin from abnormal small blood vessels affected by lipofibrohyalinosis or amyloid angiopathy (Fazekas *et al*., 1999). Microbleeds are therefore likely to result either from minor areas of blood leakage through abnormally fragile vascular walls, or tiny areas of self-limiting frank haemorrhage, and the imaging abnormalities persist for many years after bleeding occurs.

Previous work on microbleeds has focused on their detection in patients with previous symptomatic intracranial haemorrhage; they are found in approximately 50% of such patients and appear to predict the future risk of bleeding (Roob *et al*., 2000; Nighoghossian *et al*., 2002). Microbleeds have not been as widely studied in ischaemic stroke, but reports suggest their presence in about 25% of patients (Kwa *et al*., 1998). It has also been suggested that the presence of microbleeds may predict the risk of spontaneous haemorrhagic transformation after acute cerebral infarction or after thrombolytic and antithrombotic treatments (Kidwell *et al*., 2002; Nighossian *et al*., 2002). Microbleeds are particularly associated with lacunar stroke, cerebral white matter lesions and hypertension (Kwa *et al*., 1998; Kato *et al*., 2002), suggesting that they are a manifestation of pathology affecting cerebral small vessels.

Ischaemic small vessel disease is characterized by thickening and hyaline degeneration with lipid deposition (lipofibrohyalinosis) in the small penetrating arteries supplying the cerebral white matter, and is well known to be associated with white matter changes on MRI and neurological (including cognitive) impairments. Typical neurological deficits associated with ischaemic small vessel disease include acute lacunar stroke syndromes, attributed to occlusion of a single deep perforating artery, as well as more progressive deterioration (for example, in gait or cognition) that may be related to diffuse hypoperfusion of white matter, with concomitant confluent radiological changes of leukoaraiosis on MRI. Cognitive impairments associated with ischaemic small vessel disease have been characterized as involving reduced speed of information processing (Ylikoski *et al*., 1993; de Groot *et al*., 2000), memory (Kramer-Ginsberg *et al*., 1999; de Groot *et al*., 2000); global cognitive ability (Gunning-Dixon *et al*., 2000) and executive functions (Kramer-Ginsberg *et al*., 1999). White matter pathology in frontal–basal ganglia circuits has frequently been invoked as an important cause of executive dysfunction. For example, recent studies have shown impairments on standard neuropsychological tests sensitive to executive dysfunction in non-demented patients with subcortical ischaemic vascular disease (Mungus *et al*., 2001; Kramer *et al*., 2002), patients with vascular dementia (Carew *et al*., 1997; Doddy *et al*., 1998; Cannata *et al*., 2002; Kramer *et al*., 2002; O'Brien *et al*., 2003; Graham *et al*., 2004), and in neurologically healthy elderly adults (O'Brien *et al*., 2002; Pugh and Lipsitz, 2002).

In contrast to the above, the neurological (including cognitive) effects of microbleeds are largely unknown. Despite considerable interest in microbleeds as a marker of bleeding-prone small vessel angiopathy, they have generally been considered to be clinically silent (Kwa *et al*., 1998; Roob *et al*., 2000; Kato *et al*., 2002; Tsushima *et al*., 2003). Only one study has addressed the issue of whether microbleeds are associated with focal neurological symptoms (Kwa *et al*., 1998). This study concluded that of 31 patients with microbleeds, at least 75% did not show motor or sensory symptoms that could have been attributed to microbleeds; no data were reported regarding cognitive functioning in this study. As far as we are aware there have been no previous systematic studies of cognitive impairment in patients with microbleeds. The paucity of studies in this field is perhaps surprising, since histopathological data on microbleeds show not only haemosiderin deposition but also surrounding gliosis, and sometimes frank necrosis or infarction (Tanaka *et al*., 1999). We therefore hypothesized that if microbleeds are multiple, of sufficient size and located in strategic brain areas, they would be expected to have a cumulative effect on cognition. Since microbleeds are particularly common in the basal ganglia, as well as widespread cerebral white matter regions (Roob *et al*., 2000), we hypothesized that executive functions would be most affected, due to disruption of frontal–basal ganglia connections.

To test these hypotheses, we systematically investigated cognitive function in patients with cerebral microbleeds using a battery of neuropsychological tests. Because microbleeds often coexist with other types of cerebrovascular disease that are known to cause cognitive impairment, we compared patients with microbleeds with a non-microbleed control group that was closely matched for the extent of white matter changes on MRI, ischaemic stroke subtype and prevalence and location of cortical infarction.

Methods

Subjects

We retrospectively analysed data from 214 patients who were referred to the one-stop neurovascular clinic at the National Hospital for Neurology and Neurosurgery with suspected stroke or transient ischaemic attack. All patients had a detailed diagnostic assessment, including neurological and neuropsychological investigations, blood pressure measurement, blood tests, including fasting lipids and glucose, MRI (unless contraindicated), echocardiography and carotid ultrasound. This was followed on the same day by diagnosis (by a consultant stroke neurologist [MMB or NAL]). The mechanism of stroke was classified according to the Trial of Org 10172 in Acute

Stroke treatment criteria (Adams *et al*., 1993). On the basis of the results from T2*-weighted gradient echo MRI (see below for details) patients were divided into those with cerebral microbleeds ($n = 29$) and those without ($n = 185$). Four patients with non-cerebrovascular conditions known to influence cognitive function were excluded; two of these patients had probable frontotemporal dementia, one had idiopathic cerebellar degeneration and one patient had probable neurosarcoidosis. Patients with primary intracerebral haemorrhage were excluded. There were no other exclusion criteria with respect to other conditions including hypertension, diabetes or cardiovascular disease. Thus a final microbleed cohort of 25 patients was studied.

After selecting the microbleed patients, a control group of 30 patients without microbleeds were selected from the remaining patient cohort, on the basis of their group similarity to the 25 patients with microbleeds on the following criteria: distribution of age, gender, years of education, total and regional severity of white matter changes evident on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI; diagnosis of stroke or non-stroke; cortical infarct location (anterior or posterior circulation and laterality); and stroke subtype. We set out to select at least as many patients without microbleeds as the number with microbleeds, and needed 30 such patients in order to satisfactorily match for the many different factors we selected ($P > 0.5$ for all comparisons). Matching was done blinded to knowledge of the neuropsychology results and patient identity.

Imaging procedure

All MRI was carried out on a 1.5T Signa Echospeed system (General Electric, Milwaukee, WI, USA). All subjects had an axial T2-weighted fast spin echo (FSE) sequence (TR/TE = 6000/102 ms), an axial T2*-weighted gradient echo sequence (TR/TE = 300/40 ms) and a coronal FLAIR sequence (TR/TI/TE = 9895/2473/140 ms). Coronal FLAIR images were also acquired to assist the identification of ischaemic changes. Hard copies were made for subsequent analysis. T1-weighted imaging was not included in the vascular MRI protocol.

Image analysis

Images were analysed by two observers, who were blinded to the clinical details. One observer was a consultant neuroradiologist with a specialist interest in cerebrovascular disease (HRJ); the other was a trainee in vascular neurology who had received training in the interpretation of T2-weighted, FLAIR and T2*-weighted images (DJW or LJC). Microbleeds were defined as well-defined focal areas of low signal on T2* of less than 10 mm in diameter, and were counted throughout the brain. Symmetrical hypointensities in the globi pallidi (likely to represent calcification or iron deposition) and flow voids from cortical vessels were disregarded. White matter hyperintensities were graded throughout the brain using a method based on the rating scale recommended by the European task force on age-related white matter changes (Wahlund *et al*., 2001). The severity of white matter changes was assessed in frontal, parieto-occipital, temporal, basal ganglia and infratentorial brain regions. A four-point grading scale was used as follows: 0 (no lesions); 1 (focal lesions >5 mm); 2 (early confluent lesions); and 3 (diffuse involvement of an entire brain region). For each patient, mean scores were derived for each region, and a sum score was computed for all regions combined. The volume of cortical infarcts was measured on coronal FLAIR images in each patient using a semi-automated contouring technique (Dispimage; D. Plummer, UCL).

Neuropsychological investigation

A retrospective analysis of the neuropsychological data available on the patient sample was carried out. Not all patients were administered identical sets of tests; however, all of the following areas of cognition were evaluated in all patients using standard neuropsychological tests. Current general intellectual functioning was assessed using either the Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981) or, in a small minority of patients, Coloured Progressive Matrices (two microbleed and three non-microbleed patients) (Raven, 1956). Premorbid intellectual functioning was assessed using the National Adult Reading Test (Nelson, 1991).

Verbal and visual memory functions were assessed with the Recognition Memory Test (Warrington, 1984) and naming skills were examined either with the Graded Naming Test (McKenna, 1983) or the Oldfield Naming Test (Oldfield, 1965). Perceptual functions were assessed using the Visual Object and Space Perception Battery (Warrington and James, 1991). Speed and attention function were examined using one or more of the following tests: 'O' Cancellation, Digit Copy (Willison and Warrington, 1992), Symbol Digit Modalities Test (Smith, 1982) or the Trail Making Test (Part A). Executive functions were examined using two or more of the following tests: Stroop Test (Trennary *et al*., 1989); Word fluency (Spreen and Benton, 1969); Trail Making Test Part B (Army Individual Test Battery, 1944), Weigl Colour Form Sorting Task (Weigl, 1941) and Modified Card Sorting Test (Nelson, 1976).

Five derived scores were calculated based on published normative data collected from a sample of individuals of comparable age. (i) The intellectual functioning score was the difference between the NART and the full-scale intelligence quotient (calculated using either the Wechsler Adult Intelligence Scale—Revised or Coloured Progressive Matrices). A difference equal to or greater than 10 was taken as evidence of intellectual decline. (ii) Memory and naming scores were derived by converting the standardized test performance into percentile scores. Scores at or below the fifth percentile were taken to indicate memory or naming impairment. (iii) The perceptual scores could not be converted into percentile scores, because they were not normally distributed. Thus, scores at or below the 5% cut-off were taken to indicate a perceptual impairment. (iv) Speed and attention scores were the mean time (in s) for patients to complete the tasks. A score of more than one standard deviation above (Digit Copy, '0' Cancellation, Trails A) or below (Symbol Digit Modalities Test) the mean of the published normative data were taken as an impaired performance on speed and attention tasks. (v) Three different procedures were adopted to analyse the executive function test scores. (i) Word fluency, Stroop and Trail Making Test scores were derived by converting the standardized test performance into percentile scores. Scores at or below the fifth percentile were taken to indicate impairment. (ii) The responses on the Wisconsin Card Sorting Test were analysed in terms of percentage of total perseverative errors (Nelson, 1976). (iii) A pass or fail procedure was adopted for the Weigl Sorting Task. Failure was defined as a patient achieving only one or neither of the solutions to this task. Patients were classed as having executive dysfunction if their performance was impaired on at least two tests of executive functioning.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 10.0 (SPSS, Chicago, IL, USA). Comparisons between groups for continuous variables used the Mann–Whitney *U* test, and for categorical variables Fisher's exact test was used. The correlation between two variables was assessed using Spearman's correlation coefficient. Binary logistic regression was used to determine the effect of multiple clinical and imaging variables on cognitive measures. Significance was declared at $P < 0.05$ (two-sided).

Results

Clinical data

The clinical and demographic characteristics of the microbleed and control groups are shown in Table 1. The overall and regional severity of white matter changes on MRI and the proportion of patients with different stroke subtypes were similar between the two groups ($P > 0.5$ in all cases). The groups were well matched for the number, arterial territory and lateralization of cortical infarcts, and for general intellectual functioning based on the Wechsler Adult Intelligence Scale—Revised full-scale intelligence quotient scores (Table 1). There were no significant differences between the groups in the prevalence of diabetes or hypertension or in mean blood pressure (Table 1). Similar proportions of patients in each group were receiving antihypertensive medication (19/25 versus 19/30; $P = 0.36$); furthermore, there were no significant between-group differences in the proportion taking each class of antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium channel blockers or diuretics).

The patients who did not have stroke or transient ischaemic attack were also closely matched for diagnosis between the two groups: in the microbleed group the diagnoses were asymptomatic carotid stenosis ($n = 1$), vertigo ($n = 1$) and transient global amnesia ($n = 1$), whilst in the non-microbleed group the non-stroke diagnoses were asymptomatic carotid stenosis ($n = 1$), vertigo ($n = 1$) transient global amnesia ($n = 1$) and migraine ($n = 1$).

Table 1 *Characteristics of the patients*

	Patients with microbleeds ($n = 25$)	Patients without microbleeds ($n = 30$)	P[a]
Gender (% female)	28	33	NS[b]
Age: years (SD)	67.6 (11.9)	67.2 (10.4)	NS
Number of years in education (%)			
<10	1 (4)	2 (6)	NS
10–12	13 (52)	18 (60)	NS
>12	11 (44)	10 (33)	NS
Diagnosis of hypertension: number (%)	20 (80)	18 (60)	0.15
Systolic blood pressure: mmHg (SD)	150 (24)	138 (27)	0.13
Diastolic blood pressure: mmHg (SD)	83 (11)	78 (26)	NS
Diabetes: no. (%)	6 (23)	7 (23)	NS[b]
Mean total WMC score (SD)	4.80 (4.4)	4.40 (4.9)	NS
Mean frontal WMC score (SD)	0.96 (0.91)	0.83 (0.85)	NS
Mean parieto-occipital WMC score (SD)	0.80 (0.89)	0.77 (0.89)	NS
Mean temporal WMC score (SD)	0.12 (0.26)	0.12 (0.39)	NS
Mean basal ganglia WMC score (SD)	0.30 (0.54)	0.35 (0.73)	NS
Mean infratentorial WMC score (SD)	0.44 (0.77)	0.33 (0.71)	NS
Diffuse WMC: no. (%)	3 (12)	3 (10)	NS[b]
Index stroke subtype			
Atherothrombotic	5 (20)	3 (10)	NS
Cardioembolic	1 (4)	2 (6.7)	NS
Lacunar	7 (28)	9 (30)	NS
TIA	1 (4)	3 (10)	NS
Undetermined	9 (30)	8 (27)	NS
Non-stroke diagnosis: no. (%)	3 (12.0)	4 (13.3)	NS[b]
Previous stroke: no. (%)	5 (20)	3 (10)	NS[b]
Anterior circulation stroke: no. (%)	6 (22.2) (3 right-sided)	6 (20.0) (3 right-sided)	NS[b]
Posterior circulation stroke: no. (%)	3 (11.1) (1 right-sided)	3 (10.0) (1 right-sided)	NS[b]
Mean cortical infarct volume: arbitrary units (SD)	10229 (10524)	14839 (12549)	NS

[a]Mann–Whitney *U* test; [b]Fisher's exact test (two-sided).
NS = not significant ($P > 0.50$); WMC = white matter changes.

Imaging data

In the microbleed group ($n = 25$), microbleeds were multiple in 76% of cases. Microbleeds were most commonly located in the basal ganglia (68.0% of cases) followed by the parieto-occipital (40.0%), frontal (36.0%), temporal (36.0%) and infratentorial regions (32.0%). The mean microbleed count was 6.4; the range was 1–32 (SD 7.6). Examples of axial T2- and T2*-weighted gradient echo MRI scans from patients with and without executive dysfunction are shown in Fig. 1A–D and Fig. 2A and B, respectively.

Neuropsychological data

The tests used to evaluate the above areas of cognition varied for naming skills, perception, executive functions and speed/attention. However, there was a similar degree of variability in tests administered to both groups (Table 2). The proportions of patients with impairment of each neuropsychological domain for the microbleed and non-microbleed groups are shown in Fig. 3. Neuropsychological assessment showed one or more areas of clear-cut cognitive impairment in similar numbers of microbleed [20/25 (80%)] and non-microbleed patients [22/30 (73%)]. Deficits in general intellectual functioning did not differ significantly between groups [6/25 (24%) of microbleed patients versus 4/30 (13%) of non-microbleed patients]. Executive dysfunction was the most common abnormality; strikingly, this domain of cognition

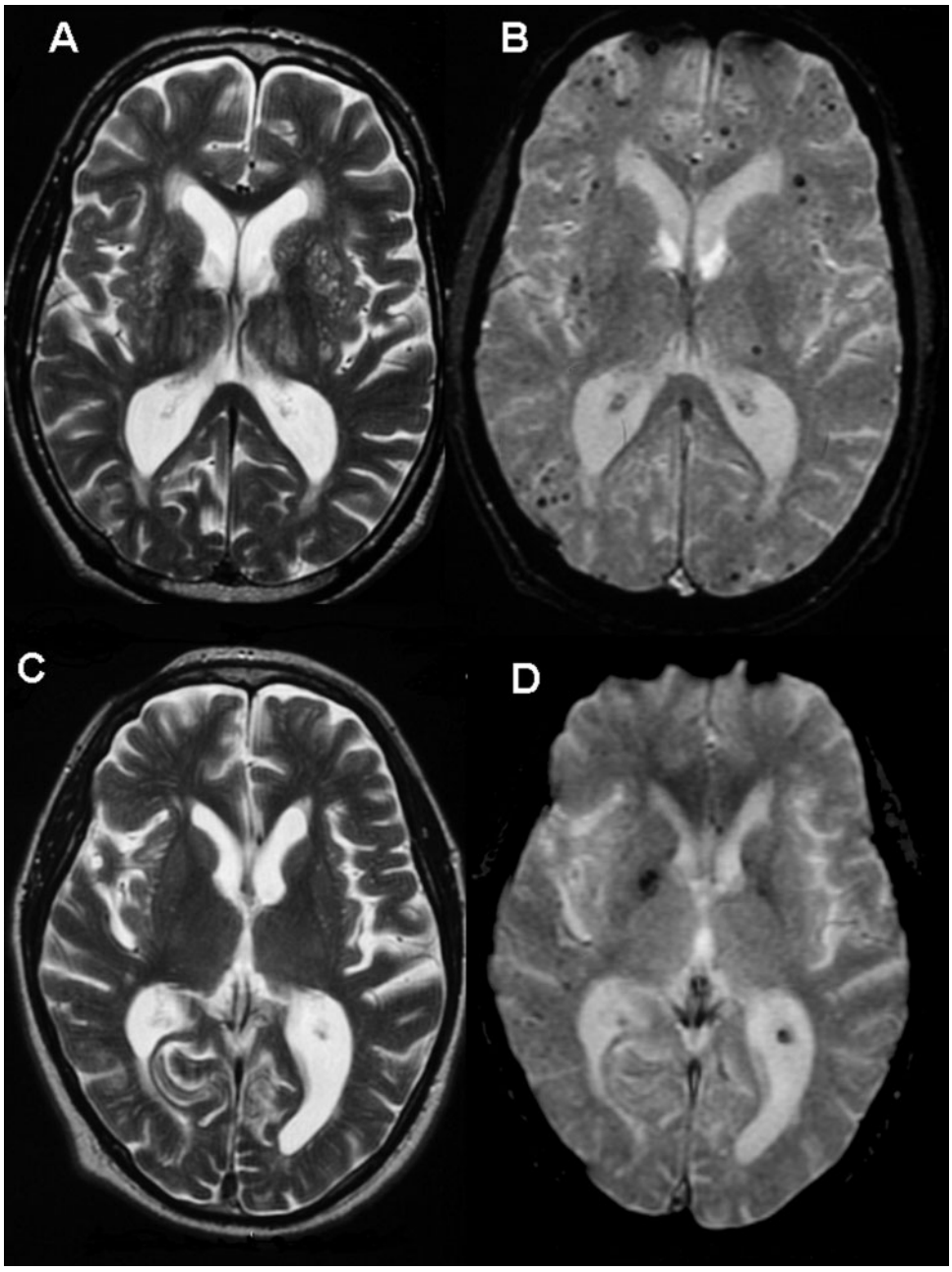

Fig. 1 In images **A–D** the right of the brain is on the left side of the panel. (**A**) Axial T2-weighted FSE and (**B**) T2*-weighted gradient-echo MRI of a 63-year-old male patient with executive dysfunction. The T2*-weighted gradient echo (**B**) shows numerous microbleeds (low-signal intensity foci), particularly in the frontal regions but also in the parieto-occipital regions; these are not visible on the standard T2-weighted FSE. (**C**) Axial T2-weighted FSE and (**D**) T2*-weighted gradient-echo MRI of an 81-year-old male patient with executive dysfunction. Two microbleeds are visible in the basal ganglia on the right on the T2*-weighted gradient echo (**D**), but not the T2-weighted FSE (**C**).

was twice as often impaired in the microbleed group [15/25 (60%) versus 9/30 (30%); $P = 0.03$, Fisher's exact test]. Speed and attention functions were also frequently impaired, but with similar numbers affected in each group [10/24 (42%) of microbleed patients; 13/29 (45%) of non-microbleed patients]. Naming deficits were less common, and were noted in a similar proportion of patients in both groups [3/25 (12%) microbleed versus 6/30 (20%) non-microbleed patients]. Memory impairments were less common still, with no statistically significant difference in prevalence between groups. Perceptual functions were virtually intact in both groups and not significantly different.

Executive impairment

In view of the observed association between executive dysfunction and cerebral microbleeds, binary logistic regression

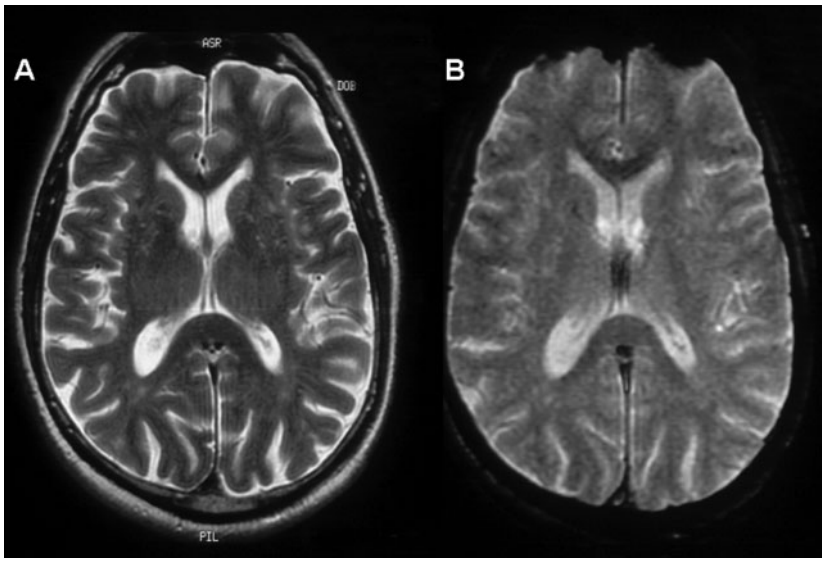

Fig. 2 (**A**) Axial T2-weighted FSE and (**B**) T2*-weighted gradient-echo MRI of a 73-year-old male patient with normal executive function. Note the absence of well-defined low signal foci on gradient-echo MRI.

Table 2 *Proportion of each patient group receiving each neuropsychological test*

Number (%) administered each neuropsychological test	Patients with microbleeds (n = 25)	Patients without microbleeds (n = 30)
Naming		
Graded Naming Test (remainder were administered the Oldfield naming test)	19 (76)	24 (80)
Visual perception		
Object Decision Test (remainder were administered the Incomplete Letters Test)	15 (60)	19 (63)
Speed and attention		
'O' cancellation task	11 (44)	10 (33)
Trail Making Test part A	10 (40)	16 (53)
Symbol Digit Modalities test	5 (20)	13 (43)
Digit Copy task	5 (20)	4 (13)
Executive function		
Word fluency	18 (72)	26 (87)
Stroop task	12 (48)	12 (40)
Weigl Sorting task	13 (52)	10 (33)
Trail Making Test part B	9 (36)	15 (50)
Wisconsin Card Sorting Test	6 (24)	5 (17)

Note that for naming and visual perception patients received one test; for speed and attention one or more tests; and for executive function two or more tests. No differences were statistically significant [$P > 0.05$, Fisher's exact test (two-sided)].

was used to determine whether microbleeds have an effect independent of the potentially confounding factors of MRI white matter changes, diagnosis of stroke and diagnosis of hypertension. When these variables were included in the model, only the number of microbleeds was a significant predictor of executive dysfunction (odds ratio adjusted for other factors 1.32, 95% confidence interval 1.01–1.70, P = 0.04; Table 3). When unadjusted odds ratios were determined, the number of microbleeds remained the only significant predictor of executive dysfunction (unadjusted odds ratio 1.34, 95% confidence interval 1.05–1.68, P = 0.02; Table 3).

To further investigate the relationship between microbleeds and executive dysfunction, we compared the number of microbleeds (both regional and total counts) in patients with and without executive dysfunction. Compared with patients with normal executive function (n = 31), patients with executive dysfunction (n = 24) had a significantly greater number of frontal microbleeds [mean 1.54 (SD 2.99) versus 0.03 (0.18); P = 0.002, Mann–Whitney test]; a significantly greater number of basal ganglia microbleeds [mean 1.17 (SD 1.63) versus 0.32 (SD 0.79); P = 0.048, Mann–Whitney test]; and a significantly greater total number of microbleeds [mean 5.46 (SD 8.15) versus 0.90 (SD 1.96); P = 0.004, Mann–Whitney test] (Fig. 4A–C). There were no significant differences between these two groups in microbleed counts in the other cerebral regions.

Effects of microbleeds on the extent of cognitive impairment

We also investigated whether microbleeds are associated with more widespread cognitive dysfunction, defined as multiple (two or more) impaired domains. Patients with multiple domains of cognition impaired had significantly more microbleeds [mean 5.43 (SD 8.4) versus 1.06 (SD 2.0); P = 0.027].

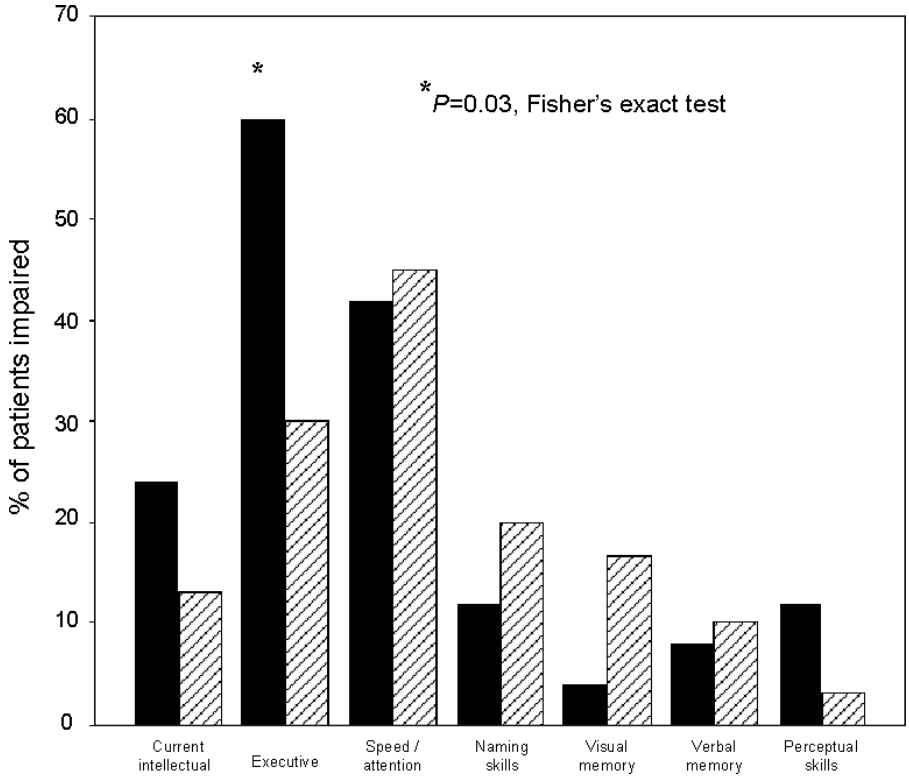

Fig. 3 Proportion of patients with impairment of each neuropsychological domain for microbleed and non-microbleed groups. Solid bars, patients with microbleeds; hatched bars, patients without microbleeds.

Table 3 *Odds ratios of factors predicting executive dysfunction derived from binary logistic regression analysis*

Variable	Odds ratio (95% confidence interval) adjusted for other factors in this table	Significance	Odds ratio (95% confidence interval) unadjusted for other factors in this table	Significance
Number of microbleeds	1.32 (1.01–1.70)	0.04*	1.34 (1.05–1.68)	0.02*
Total WMC score	1.06 (0.92–1.21)	0.21	1.12 (0.99–1.28)	0.08
Diagnosis of stroke	0.50 (0.11–2.26)	0.53	0.30 (0.07–1.25)	0.10
Diagnosis of hypertension	1.65 (0.45–6.02)	0.45	0.87 (0.27–2.75)	0.81

*$P < 0.05$. WMC = white matter changes.

To investigate whether this association is independent of the effect of white matter changes of presumed ischaemic origin, diagnosis of stroke or diagnosis of hypertension, we used binary logistic regression. Only the number of microbleeds was significantly associated with multiple domain impairment (odds ratio adjusted for other factors 1.28, 95% confidence interval 1.02–1.61, $P = 0.034$).

Within the microbleed group, there was a modest but significant correlation between microbleed count and number of domains impaired (Spearman's $r = 0.44$, $P = 0.03$) (Fig. 5). Thus, an increased microbleed count was related to more widespread cognitive impairment.

Discussion

To the best of our knowledge, this is the first study to examine the cognitive impact of cerebral microbleeds. Our results provide strong evidence that microbleeds are associated with executive dysfunction; furthermore, the effect of microbleeds on cognition appears to be independent of coexisting ischaemic cerebrovascular disease, and in particular is independent of the severity of ischaemic small vessel disease as assessed by MRI white matter changes. These observations challenge the current prevailing view that microbleeds are clinically silent (Kwa *et al*., 1998; Roob *et al*., 2000; Kato *et al*., 2002; Tsushima *et al*., 2003).

Microbleeds are much more apparent on T2*-weighted gradient echo sequences than standard spin echo sequences; they are characterized histologically by haemosiderin around abnormal small vessels, with necrosis or infarction of the surrounding tissue (Tanaka *et al*., 1999). Microbleeds would therefore be expected to cause cognitive impairment if they disrupt strategically important white matter tracts or

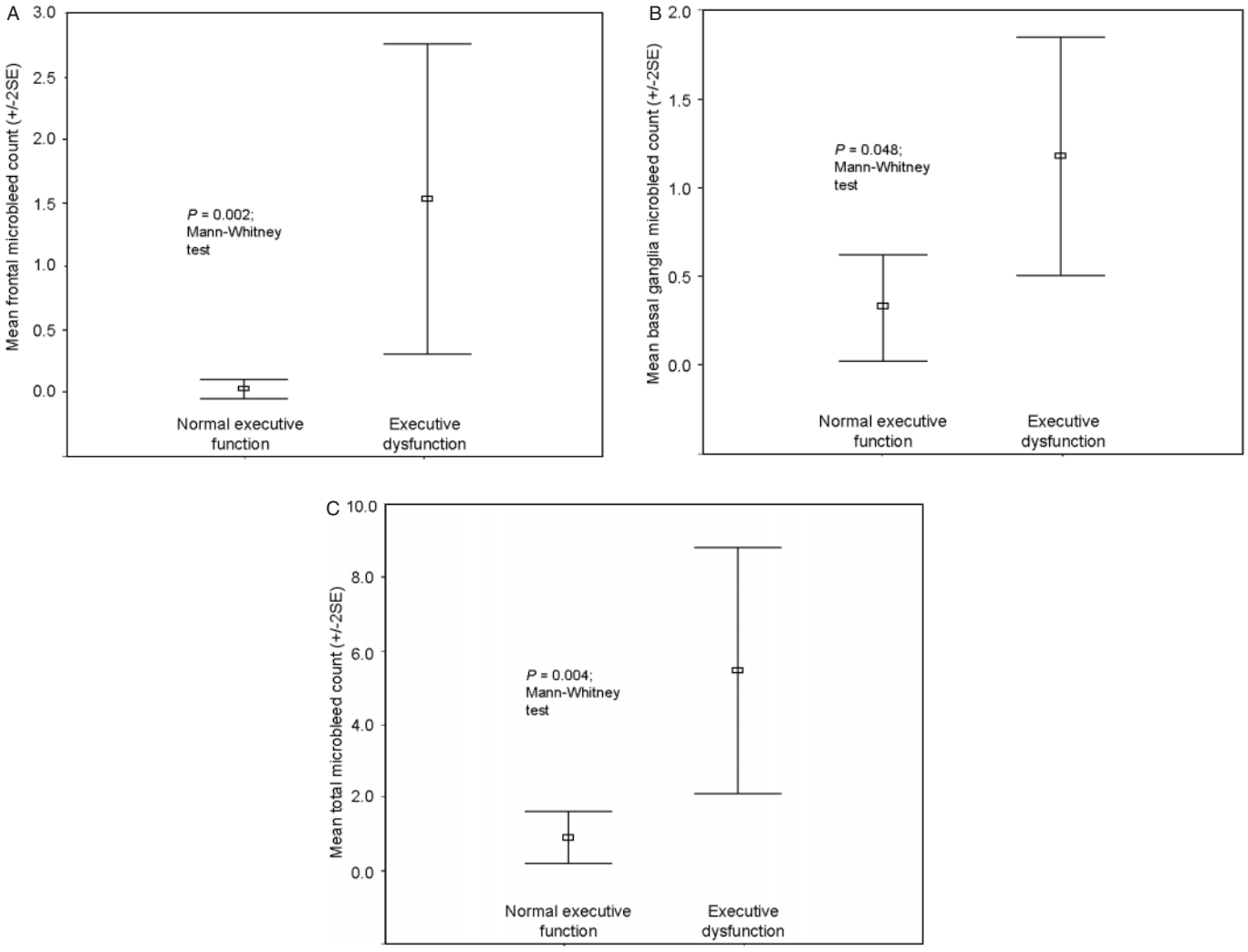

Fig. 4 (**A**) Mean frontal microbleed count (± 2 SEM) for patients with and without executive dysfunction. (**B**) Mean basal ganglia microbleed count (± 2 SEM) for patients with and without executive dysfunction. (**C**) Mean total microbleed count (± 2 SEM) for patients with and without executive dysfunction.

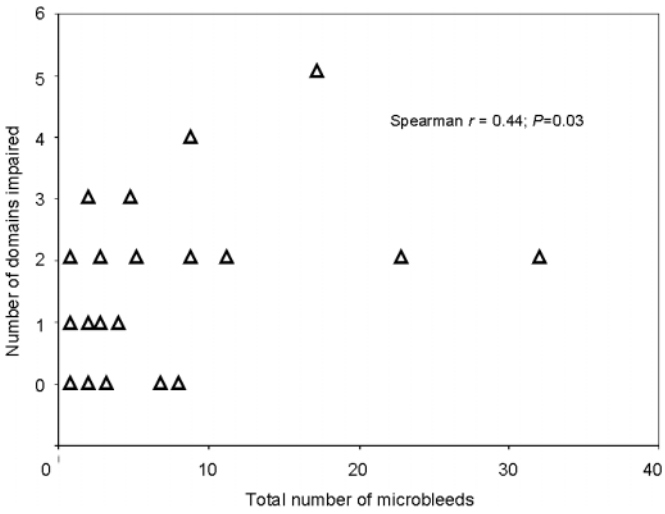

Fig. 5 For each patient with microbleeds (n = 25) the number of cognitive domains impaired is shown on the y axis, with the total number of microbleeds on the x axis.

eloquent cortical areas. In common with previous studies, we observed microbleeds most frequently in the basal ganglia (68% of microbleed cases), though they were also common in the frontal, parieto-occipital and temporal regions. This anatomical distribution of microbleeds is relevant in analysing the possible mechanisms of increased executive dysfunction. We found more microbleeds in the frontal lobes and basal ganglia in patients with executive impairment, suggesting that the executive dysfunction may result from the effects of damage in these regions. This explanation is in keeping with recent concepts of the neurobiology of executive functions, which emphasize the importance of frontal–subcortical circuits (Alexander and Crutcher, 1990; Cummings, 1993, 1995; Tekin and Cummings, 2002). Cummings (1993) reviewed reports of patients with degenerative disorders or focal lesions involving frontal lobe or linked subcortical structures, and postulated that the clinical dysexecutive syndromes observed with frontal lobe injury may also result from strategic lesions in subcortical components of specific

frontal-subcortical circuits. In addition, executive functions are affected in pathologies that target the basal ganglia, for example Parkinson's disease (Brown and Marsden, 1990) and basal ganglia calcification (Lopez-Villegas *et al*., 1996). Furthermore, a conceptual reasoning task has been shown to induce basal ganglia activation in functional imaging studies (Rao *et al*., 1997). Thus, the model of frontal–subcortical circuits provides a plausible mechanism by which microbleeds in frontal and basal ganglia regions may cause executive dysfunction.

It is of interest that speed and attention was impaired to a similar extent in the microbleed and non-microbleed groups, in contrast to the different extents of executive dysfunction. Speed and attention reflect widely distributed cognitive skills, and, although they are related to the integrity of frontal–subcortical circuits, often occur in the context of diffuse cerebral damage for example that following head injury (Levin *et al*., 1990). Speed and attention deficits have also been reported in the context of widespread ischaemic small vessel disease (Ylikoski *et al*., 1993). It is therefore not surprising that the extent of speed and attention dysfunction is similar between the microbleed and non-microbleed groups, which were closely matched for the extent and anatomical disribution of white matter changes reflecting ischaemic small vessel disease. The additional impairment of executive functions in the microbleed group could be explained by focal bleeding in critical frontal and basal ganglia structures; because microbleeds are small, they may selectively target executive functions without affecting speed and attention.

We found a modest but significant graded relationship between the number of cerebral microbleeds and the number of cognitive domains impaired, suggesting that an increasing microbleeds load may have a more general effect on cognitive function. The effect on general cognitive function is likely to reflect the cumulative effects of microbleeds that are widely anatomically distributed in the brain.

A potentially serious confound in the investigation of the cognitive effects of microbleeds is the coexistence of other types of ischaemic cerebrovascular disease. Since microbleeds are considered to be a manifestation of pathology affecting small vessels, it is especially important to avoid erroneously attributing cognitive effects of ischaemic small vessel disease to the presence of microbleeds. Our study has several methodological strengths designed to minimize this problem. Firstly, we selected a non-microbleed cohort that was well matched for ischaemic small vessel disease as assessed by MRI-visible white matter change severity (both globally and regionally); for the prevalence, vascular territory and lateralization of cortical ischaemic stroke; and for the subtype of ischaemic stroke. To further minimize the potential confounding effect of white matter changes, we used binary logistic regression and included this potential confounding factor in the model, in order to seek evidence for an independent effect of microbleeds on cognition.

How could microbleeds cause cognitive effects that are independent of ischaemic small vessel disease? Ischaemic small vessel disease is considered to cause cognitive impairment by mechanisms of reduced perfusion and impaired autoregulation due to a widespread microangiopathy affecting cerebral small vessels. Chronic, widespread ischaemia is thought to result in the radiological changes of leukoaraiosis (Pantene and Garcia, 1997). By contrast, microbleeds are likely to influence cognitive function by the effects of small focal destructive lesions accumulating in strategic subcortical and cortical structures, or important connection fibres. The different mechanisms that may operate for ischaemic small vessel disease and microbleeds may explain why they appear to have at least partially independent effects on cognition. We cannot exclude the possibility that a difference in the number of lacunar infarcts associated with microbleeds could have contributed to our results. In this study we did not perform T1-weighted imaging and were therefore not able to make a definitive count of lacunes, which are defined in MRI terms as being hyperintense on T2-weighted sequences and low signal intensity on T1-weighted sequences. However, a significant difference in the number of lacunes is unlikely because they will have been included in our assessment of grade 1 focal T2-hyperintense lesions, which were well matched in the two groups.

The finding that microbleeds are associated with cognitive deficits has potential diagnostic and therapeutic implications. CT and MRI are important for evaluating the causes of cognitive impairment in cerebrovascular disease, and T2-weighted MRI is particularly sensitive to the changes of ischaemic small vessel disease. Although ischaemic small vessel disease and microbleeds share a common pathogenesis of small vessel abnormalities, including lipofibrohyalinosis, their association is not invariable. Thus, in patients with cerebrovascular risk factors and cognitive impairment, T2*-weighted gradient echo MRI may be a helpful adjunct to standard MRI in clarifying the mechanism of cognitive impairment.

From our results, it is reasonable to hypothesize that the accumulation of multiple microbleeds over time could cause deterioration in executive functions. Further follow-up studies are required to test this hypothesis. Hypertension is a strong risk factor for microbleeds, and improved hypertensive control may reduce the rate of accumulation of microbleeds and thus cognitive deterioration. Indeed, there is some evidence that reduction in blood pressure after stroke reduces the endpoint of cognitive decline (though only when associated with recurrent stroke events) (Tzourio *et al*., 2003). Thus, the detection of cerebral microbleeds further emphasizes the need for rigorous control of hypertension in patients with cerebrovascular disease.

Microbleeds may predict the risk of haemorrhagic transformation after ischaemic stroke (Nighoghossian *et al*., 2002), and have recently been reported to be a predictor of aspirin-associated intracerebral haemorrhage (Wong *et al*., 2003). Thus, patients with microbleeds may be at increased risk of recurrent intracerebral haemorrhage microbleeding when treated with antiplatelet agents. There is interest in

the use of antiplatelet agents in preventing the development of cognitive dysfunction related to cerebrovascular disease (Richards *et al*., 1997), but no consistent evidence for therapeutic efficacy. The role of microbleeds should be considered in future studies investigating the effect of antiplatelet treatments on cognition.

Conclusion

This study provides novel evidence that microbleeds have an impact on cognitive function that is independent of the extent of associated white matter changes and ischaemic stroke. Our data show the most marked effect on executive functions, which is likely to result from tissue damage associated with microbleeds in the frontal lobes and basal ganglia, disrupting frontal-subcortical circuits. These findings have implications for the diagnosis of stroke patients with cognitive impairment, and for the appropriate use of antihypertensive and antiplatelet treatments in these patients.

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References

Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial: TOAST: Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993; 24: 35–41.

Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 1990; 13: 266–71.

Army Individual Test Battery. Manual and directions for scoring. Washington (DC): War Department, Adjunct General's Office; 1944.

Brown RG, Marsden CD. Cognitive function in Parkinson's disease: from description to theory. Trends Neurosci 1990; 13: 21–9.

Cannata AP, Alberoni M, Franceschi M, Mariani C. Frontal impairment in subcortical ischemic vascular dementia comparison to Alzheimer's disease. Dement Geriatr Cogn Disord 2002; 13: 101–11.

Carew TG, Lamar M, Cloud BS, Grossman M, Libon DJ. Impairment in category fluency in ischemic vascular dementia. Neuropsychology 1997; 11: 400–12.

Chan S, Kartha K, Yoon SS, Desmond DW, Hilal SK. Multifocal hypointense cerebral lesions on gradient-echo MR are associated with chronic hypertension. AJNR Am J Neuroradiol 1996; 17: 1821–7.

Cole FM, Yates P. Intracerebral microaneurysms and small cerebrovascular lesions. Brain 1967; 90: 759–68.

Cummings JL. Frontal–subcortical circuits and human behaviour. Arch Neurol 1993; 50: 873–80.

Cummings JL. Anatomic and behavioral aspects of frontal–subcortical circuits. Ann NY Academic Sci 1995; 769: 1–13.

de Groot JC, de Leeuw FE, Oudkerk M, van Gijn J, Hofman A, Jolles J, et al. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. Ann Neurol 2000; 47: 145–51.

Doddy RS, Massman PJ, Mawad M, Nance M. Cognitive consequences of subcortical magnetic resonance imaging changes in Alzheimer's disease: comparison to small vessel ischemic vascular dementia. Neuropsychiatry Neuropsychol Behav Neurol 1998; 11: 191–9.

Fazekas F, Kleinert R, Roob G, Kleinert G, Kapeller P, Schmidt R, et al. Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. AJNR Am J Neuroradiol 1999; 20: 637–42.

Fisher CM. Pathological observations in hypertensive cerebral hemorrhage. J Neuropathol Exp Neurol 1971; 30: 536–50.

Graham NL, Emery T, Hodges JR. Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia. J Neurol Neurosurg Psychiatry 2004; 75: 61–71.

Gunning-Dixon FM, Raz N. The cognitive correlates of white matter abnormalities in normal aging: a quantitative review. Neuropsychology 2000; 14: 224–32.

Kato H, Izumiyama M, Izumiyama K, Takahashi A, Itoyama Y. Silent cerebral microbleeds on T2*-weighted MRI. Correlation with stroke subtype, stroke recurrence, and leukoaraiosis. Stroke 2002; 33: 1536–40.

Kidwell CS, Saver JL, Villablanca P, Duckwiler G, Fredieu A, Gough K, et al. Magnetic resonance imaging detection of microbleeds before thrombolysis: an emerging application. Stroke 2002; 33: 95–8.

Kramer JH, Reed BR, Mungus D, Weiner MW, Chui HC. Executive dysfunction in subcortical ischaemic vascular disease. J Neurol Neurosurg Psychiatry 2002; 72: 217–20.

Kramer-Ginsberg E, Greenwald BS, Krishnan KR, Christiansen B, Hu J, Ashtari M, et al. Neuropsychological functioning and MRI signal hyperintensities in geriatric depression. Am J Psychiatry 1999; 156: 438–44.

Kwa VI, Franke CL, Verbeeten B Jr, Stam J. Silent intracerebral microhemorrhages in patients with ischemic stroke. Ann Neurol 1998; 44: 372–7.

Levin HS, Gary HE Jr, Eisenberg HM, Ruff RM, Barth JT, Kreutzer J, et al. Neurobehavioral outcome 1 year after severe head injury. Experience of the Traumatic Coma Data Bank. J Neurosurg 1990; 73: 699–709.

Lopez-Villegas D, Kulisevsky J, Deus J, Junque C, Pujol J, Guardia E, et al. Neuropsychological alterations in patients with computed tomography-detected basal ganglia calcification. Arch Neurol 1996; 53: 251–6.

McKenna P, Warrington EK. Graded Naming Test. Windsor (UK): NFER-Nelson; 1983.

Mungus D, Jasut WJ, Reed BR, Kramer JH, Weiner MW, Schuff N, et al. MRI predictors of cognition in subcortical ischemic vascular disease and Alzheimer's disease. Neurology 2001; 57: 2229–35.

Nelson HE. A modified card sorting test sensitive to frontal lobe defects. Cortex 1976; 12: 313–24.

Nelson HE. The National Adult Reading Test (NART): for the assessment of premorbid intelligence in patients with dementia. 2nd ed. Windsor (UK): NFER-Nelson; 1991.

Nighoghossian N, Hermier M, Adeleine P, Blanc-Lasserre K, Derex L, Honnorat J, et al. Old microbleeds are a potential risk factor for cerebral bleeding after ischemic stroke: a gradient-echo T2*-weighted brain MRI study. Stroke 2002; 33: 735–42.

O'Brien JT, Wiseman R, Burton EJ, Barber B, Wesnes K, Saxby B, et al. Cognitive associations of subcortical white matter lesions in older people. Ann N Y Acad Sci 2002; 977: 436–44.

O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, et al. Vascular cognitive impairment. Lancet Neurol 2003; 2; 89–98.

Offenbacher H, Fazekas F, Schmidt R, Koch M, Fazekas G, Kapeller P. MR of cerebral abnormalities concomitant with primary intracerebral hematomas. AJNR Am J Neuroradiol 1996; 17: 573–8.

Oldfield RC, Wingfield A. Response latencies in naming objects. Q J Exp Psychol 1965; 17: 273–81.

Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. Stroke 1997; 28: 652–9.

Pugh KG, Lipsitz LA. The microvascular frontal-subcortical syndrome of aging. Neurobiol Aging 2002; 23: 421–31.

Rao SM, Bobholz JA, Hammeke TA, Rosen AC, Woodley SJ, Cunningham JM, et al. Functional MRI evidence for subcortical participation in conceptual reasoning skills. Neuroreport 1997; 8: 1987–93.

Raven JC. Coloured progressive matrices. London: H. K. Lewis; 1956.

Richards M, Meade TW, Peart S, Brennan PJ, Mann AH. Is there any evidence for a protective effect of antithrombotic medication on cognitive function in men at risk of cardiovascular disease? Some preliminary findings. J Neurol Neurosurg Psychiatry 1997; 62: 269–72.

Roob G, Schmidt R, Kapeller P, Lechner A, Hartung HP, Fazekas F. MRI evidence of past cerebral microbleeds in a healthy elderly population. Neurology 1999; 52: 991–4.

Roob G, Lechner A, Schmidt R, Flooh E, Hartung H-P, Fazekas F. Frequency and location of microbleeds in patients with primary intracerebral hemorrhage. Stroke 2000; 31: 2665–9.

Smith A. Symbol Digit Modalities Test (SDMT) Manual (Revised). Los Angeles: Western Psychological Services; 1982.

Spreen O, Benton AL. Neurosensory Center Comprehensive Examination for Aphasia. Victoria (BC): Neuropsychology Laboratory, University of Victoria; 1969.

Tanaka A, Ueno Y, Nakayama Y, Takano K, Takebayashi S. Small chronic hemorrhages and ischemic lesions in association with spontaneous intracerebral hematomas. Stroke 1999; 30: 1637–42.

Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. J Psychosom Res 2002; 53: 647–54.

Trennary MR, Crossen B, DeBoe J, Leber WR. Stroop Neuropsychological Screening Test (SNST). Odessa (FL): Psychological Assessment Resources; 1989.

Tsushima Y, Aoki J, Endo K. Brain microhemorrhages detected on T2*-weighted gradient-echo MR images. AJNR Am J Neuroradiol 2003; 24: 88–96.

Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 2003; 163: 1069–75.

Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjogren M, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001; 32: 1318–22.

Warrington EK. Recognition Memory Test. Windsor (UK): NFER-Nelson, 1984.

Warrington EK, James M. Visual Object and Space Perception Battery. Bury St. Edmunds (UK): Thames Valley Test Company; 1991.

Wechsler D. Wechsler Adult Intelligence Scale—Revised. New York: Psychological Corporation; 1981.

Weigl E. On the psychology of so-called processes of abstraction. J Abnormal Soc Psychol 1941; 36: 3–33.

Willison JR, Warrington EK. Cognitive retardation in a patient with preservation of psychomotor speed. Behav Neurol 1992; 5: 113–6.

Wong KS, Chan YL, Liu JY, Gao S, Lam WWM. Asymptomatic microbleeds as a risk factor for aspirin-associated intracerebral hemorrhage. Neurology 2003; 60: 511–3.

Ylikoski R, Ylikoski A, Erkinjuntti T, Sulkava R, Raininko R, Tilvis R. White matter changes in elderly persons correlate with attention and speed of mental processing. Arch Neurol 1993; 50: 818–24.