PAPER

Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia

N L Graham, T Emery, J R Hodges

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Background: There are inconsistencies in published reports regarding the profile of cognitive impairments in vascular dementia, and its differentiation from Alzheimer's disease.

Objectives: To identify the overall profile of cognitive impairment in subcortical vascular dementia as compared with Alzheimer's disease; and the tests which best discriminate between these groups.

Methods: 57 subjects participated: 19 with subcortical vascular dementia, 19 with Alzheimer's disease, and 19 controls. The dementia groups were matched for age, education, and general levels of cognitive and everyday functioning. Subcortical vascular dementia was defined by clinical features (prominent vascular risk factors plus a previous history of transient ischaemic events or focal neurological signs) and substantial white matter pathology on magnetic resonance imaging. All subjects were given a battery of 33 tests assessing episodic and semantic memory, executive/attentional functioning, and visuospatial and perceptual skills.

Results: Despite a minimal degree of overall dementia, both patient groups had impairments in all cognitive domains. The Alzheimer patients were more impaired than those with vascular dementia on episodic memory, while the patients with vascular dementia were more impaired on semantic memory, executive/attentional functioning, and visuospatial and perceptual skills. Logistic regression analyses showed that the two groups could be discriminated with 89% accuracy on the basis of two tests, the WAIS logical memory – delayed recall test and a silhouette naming test.

Conclusions: Subcortical vascular dementia and Alzheimer's disease produce distinctive profiles of cognitive impairment which can act as an adjunct to diagnosis. Many of the neuropsychological deficits thought to characterise Alzheimer's disease are also found in subcortical vascular dementia.

See end of article for authors' affiliations

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Correspondence to:
Professor John R Hodges,
MRC-CBU, 15 Chaucer
Road, Cambridge CB2
2EF, UK;
john.hodges@mrc-cbu.
cam.ac.uk

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The cognitive profile of Alzheimer's disease has been extensively studied over the last decade with an emerging consensus regarding the profile which typifies this disease. Although cerebrovascular disease is the second commonest cause of dementia in later life,[1–3] neuropsychological studies have produced inconsistent results and no clear profile of the cognitive deficits has been identified. These reports will now be reviewed, highlighting possible reasons for the lack of consistency.

In the domain of episodic memory, studies comparing vascular dementia and Alzheimer's disease have typically found either no difference,[4–6] or more severe impairment in patients with Alzheimer's disease.[7–11] Only occasionally have patients with vascular dementia been found to be more impaired than those with Alzheimer's disease on tests of episodic memory.[12] Looi and Sachdev[13] reviewed 18 studies which assessed verbal learning and memory in vascular dementia and Alzheimer's disease, and found that in most of these there appeared to be less impairment in vascular dementia—for example, patients with Alzheimer's disease performed relatively less well on word list learning,[9 10 14–17] and on immediate and delayed recall of stories.[7 14 18–20] Non-verbal episodic memory has been less extensively studied, but the most common finding is of no difference between the two forms of dementia.[13] It is important to note that the finding of episodic memory impairment in vascular dementia is to some extent a self fulfilling prophecy, as most diagnostic criteria for vascular dementia—having been influenced by criteria developed to identify Alzheimer's disease—require episodic memory impairment.[21–23]

Given that semantic memory impairment is a well established feature in Alzheimer's disease, remarkably few studies have examined this area in vascular dementia. A small study by Bentham *et al* suggested that semantic memory impairment is a feature of vascular dementia.[24] They found that patients with vascular dementia and Alzheimer's disease were equally impaired on a range of semantic memory tests, including word–picture matching, category fluency, picture naming, picture sorting, and generation of verbal definitions. The most commonly reported tests of semantic memory in vascular dementia are naming and category fluency. Laine *et al*[25] and Lukatela *et al*[26] found no differences in the impaired naming performance of patients with vascular dementia and Alzheimer's disease in either accuracy or the general pattern of errors made, and other studies have confirmed the lack of difference in accuracy.[4 27] In contrast, some investigations have found that the naming impairment in vascular dementia is less severe than in Alzheimer's disease,[7 28 29] and the converse has also been reported.[19] Category fluency has been found to be equally impaired in the two conditions.[7 29 30]

In the domain of executive function, various studies have shown relatively more impaired performance in vascular dementia than in Alzheimer's disease. The most often used task has been the Wisconsin card sorting test, and most studies have shown greater impairment in vascular dementia on this test.[14 31] Inevitably, a lack of difference between dementia groups has also been documented.[32] Attention may

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also be more compromised in vascular dementia,[18] [33] but the tests used to evaluate this area are often non-specific (for example, trail making, digit cancellation).

Visuospatial skills in patients with vascular dementia are often assessed using constructional tasks. Looi and Sachdev[13] reviewed 11 studies which compared the performance of vascular and Alzheimer patients in this area, using tests such as block design from the WAIS-R (Wechsler adult intelligence scale – revised), clock drawing, or copying the Rey complex figure. Eight of the studies showed no difference between the two groups, while in three it was found that the Alzheimer patients were less impaired. Similarly, tests of visuo-perceptual ability in which the potentially confounding effects of praxic deficits were avoided have also failed to show any consistent difference between vascular dementia and Alzheimer's disease.

To summarise, there is a general consensus that episodic memory is more impaired in Alzheimer's disease, and that executive/attentional processing is more impaired in vascular dementia. However, in other key cognitive domains such as semantic memory and visuospatial function, the evidence is more controversial. In all domains, but particularly the latter two, there are studies with results going each way. Thus no reliable profile of cognitive deficits in vascular dementia has been identified, and reliable differentiation of vascular dementia and Alzheimer's disease on the basis of neuropsychological tests remains at issue.

The inconsistencies in the literature on vascular dementia may arise for several reasons. For example, numerous investigations have failed to match groups on demographic variables,[4] [13] [26] [28] although there has been an attempt to overcome this in more recent studies.[13] Another possible reason for the variability in results from comparison of vascular dementia and Alzheimer's disease is that matching of disease severity across groups is not always attempted.[34] [35] This is a more difficult problem to resolve because the ideal way to match the groups is not obvious. The most often used method is to match patients on the mini-mental state examination (MMSE), but this test is more heavily weighted towards episodic memory—which is more likely to be impaired in Alzheimer's disease—than towards frontal executive function, which is more likely to be impaired in vascular dementia.[23] As a result, this is not an ideal test on which to match these groups. The use of more extensive tests covering a larger range of abilities and without such emphasis on memory would help with this problem. In addition, Looi and Sachdev[13] suggested that a helpful approach would be to use measures of functional ability rather than mental status scales.

A third cause of variability in the results of studies of neuropsychological functioning is the lack of consensus regarding diagnostic criteria for vascular dementia. Several sets of research guidelines have been published,[36] [37] but many patients with vascular aetiology may not meet these stringent criteria, particularly the requirement to have sustained an acute cerebrovascular event.[23] Furthermore, comparison of various criteria has shown that they are not equivalent as they lead to different frequencies of diagnosis of vascular dementia.[38] [39] An additional problem arises from the heterogeneity of pathologies included under the rubric of vascular dementia and cerebrovascular disease, including large cortical infarcts, multiple lacunar infarcts, strategic infarcts, and diffuse white matter ischaemia.

In the present study we investigated the cognitive profile in subcortical vascular dementia, but attempted to overcome the problems highlighted above. In particular, we used fairly large groups which were closely matched both demographically and in terms of disease severity. To match the latter characteristic, we used the MMSE (to enable comparison with published work) as well as a recently developed bedside test, the Addenbrooke's cognitive examination (ACE[40]) which assess a broad range of cognitive abilities, and two measures of everyday functional ability, the clinical dementia rating scale (CDR[41]), and the Cambridge behavioural inventory (CBI[42]).

Our present study also differs from earlier studies which have tended either to focus on a particular domain or to assess in a cursory manner performance across various domains of cognitive functioning. These approaches make it difficult to get a full picture of the cognitive profile in vascular dementia. We attempted to resolve controversy in the literature by using a comprehensive battery which included a range of tasks with different sensitivity in each of the following domains: episodic memory, semantic memory, executive/attentional functioning, and visuospatial and perceptual skills. Because of the heterogeneity in pathologies underlying vascular cognitive impairment we focused on patients with diffuse subcortical ischaemic leucoencephalopathy which, in many clinicians' experience, including our own, constitutes the commonest subgroup of patients referred to a memory clinic.[43] [44]

Thus the main aim of this study was to identify the profile of cognitive impairment in subcortical vascular dementia. A subsidiary goal was to identify a short neuropsychological battery to discriminate between vascular dementia and Alzheimer's disease.

METHODS
Subjects
Three groups participated in the study: 19 patients with subcortical vascular dementia (five female, 14 male), 19 patients with Alzheimer's disease (10 female, nine male), and 19 age and education matched normal control subjects (10 female, nine male). Informed consent was obtained from the subjects, or from their caregivers where appropriate. In all groups, subjects were excluded if they had a known or suspected history of alcohol abuse, head injury, depression, or other major medical illness. Subjects in the patient groups were seen in a memory clinic and were assessed by a senior neurologist (JRH), a psychiatrist, and a neuropsychologist, and all had MRI scans. The demographic details of each of the groups included in the study are reported in table 1.

Patients with vascular dementia
This group comprised an unselected consecutive series of patients presenting to the memory disorders clinic in Cambridge between 1999 and 2000 who were willing to be enrolled into the study. To avoid the pervasive problem of heterogeneity across patients with vascular dementia we selected those who had substantial subcortical white matter pathology on T2 weighted magnetic resonance imaging (MRI), together with vascular risk factors plus a history of transient ischaemic attacks (TIA) (10 of 19) or focal neurological signs on examination (12 of 19). Focal signs included mild facial paresis, clumsiness of fine finger movements, reflex asymmetry, extensor plantar responses, and cortical sensory signs. None of the patients had visual field defects on clinical testing. Formal perimetry was not done. We did not apply the NINDS-AIREN (National Institute for Neurological Diseases and Stroke Association – Association International pour la Recherché et l'Enseignement en Neurosciences) criteria for probable vascular dementia as these require a chronological relation between a major vascular event and cognitive impairment, and the presence of focal neurological signs.[37] We also excluded patients who had had major cortical strokes or strategic thalamic infarcts. The extent of white matter pathology was rated as severe (confluent areas of high signal

Table 1 Demographic data and measures of general level of cognitive and everyday functioning for vascular and Alzheimer groups and controls

| | Patients | | Controls | | |
	VaD	DAT	Main control group	Doors and people test	Camel and cactus test
n	19	19	19	24	13
Age (years)	71.2 (7.8)	68.9 (8.6)	68.1 (6.3)	67.8 (8.9)	67.2 (7.8)
Years of full time education	11.6 (3.1)	13.1 (3.4)	11.3 (1.1)	11.3 (3.1)	–
Mini-mental state examination (30)	25.3 (3.8)	24.2 (3.7)	28.7 (1.0)	29.5 (0.7)	–
Addenbrooke's cognitive examination (100)	75.7 (13.8)	75.4 (10.9)	93.3 (3.0)	–	–
Clinical dementia rating scale (3)	1.0 (0.8)	0.8 (0.8)	–	–	–
Cambridge behavioural inventory (324)	52.9 (39.6)	60.9 (36.1)	–	–	–

Values are mean (SD). Maximum scores are given in brackets following the name of each test. Descriptions of the tests and control groups are included in the text. Note that higher scores on the clinical dementia rating scale and the Cambridge behavioural inventory indicate greater impairment.
DAT, dementia of Alzheimer type; VaD, vascular dementia.

on T2 weighted MRI images involving >75% of deep white matter; n = 4), moderate (50–75%; n = 8), or mild (25–50%; n = 7). Representative MRI scans from three patients are illustrated in fig 1.

Patients with probable Alzheimer's disease

These patients were selected from a larger cohort who presented to the memory disorders clinic in Cambridge between 1996 and 2001, and who were participating in a longitudinal study of neuropsychological functioning. Using pairwise matching, the Alzheimer patients who matched most closely with the vascular patients on age, education, and general levels of cognitive functioning and everyday impairment were chosen retrospectively for inclusion in the present study. The general level of cognitive functioning was assessed with both the MMSE[45] and ACE,[40] a longer and more detailed test that assesses orientation, attention, anterograde and retrograde memory, verbal fluency, naming, language comprehension, repetition, reading, writing, and visuospatial/constructional skills. The level of everyday impairment was assessed using the CDR[41] and the CBI, an 81 item questionnaire which was adapted from Bozeat *et al*.[42] The CBI was completed by each patient's carer and covers numerous aspects of everyday functioning, including memory, orientation and attention, everyday skills, self care, mood, beliefs, challenging behaviour, disinhibition, eating habits, sleep, sterotypic behaviours, motivation, and insight/awareness. Statistical tests comparing the patient groups on

the MMSE, ACE, CDR, and CBI indicated no significant differences (*t* values <1, p values >0.1).

The diagnosis of probable Alzheimer's disease was made according to the criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA).[46] All patients with Alzheimer's disease presented with progressive cognitive deterioration, with early and predominant episodic memory impairment. They had all undergone brain MRI, which revealed a mild degree of cerebral atrophy, including the medial temporal lobe. A proportion of cases (eight of 19) showed a degree of white matter abnormality on T2 weighted images which in no instance exceeded 25% of the deep white matter. Patients presenting with a history typical of Alzheimer's disease but with substantial white matter pathology (>25%) in the absence of a history of TIA/stroke and focal neurological signs were not included in the study.

Control subjects

Performance of the patient groups was compared with that of 19 normal control subjects who were members of the MRC Cognition and Brain Sciences Unit subject panel, and who were matched to both patient groups on the basis of age and education. One way analyses of variance revealed no significant difference between the vascular dementia, Alzheimer, and control groups for age or years of education (both F values <2.5, p values >0.1).
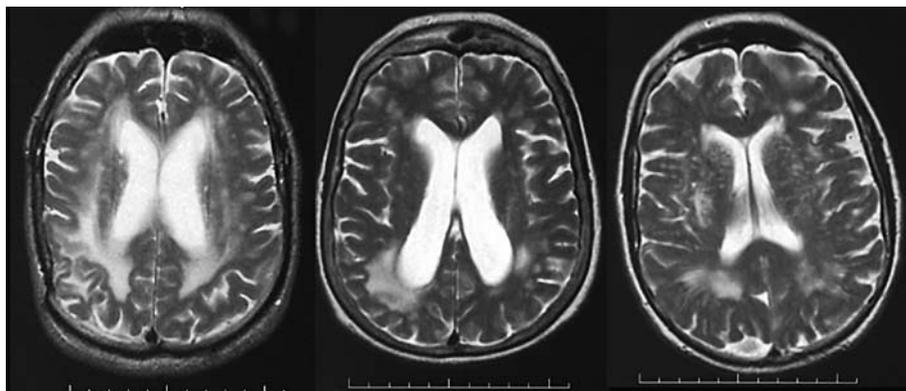

Figure 1 T2 weighted magnetic resonance imaging of the brain of three patients illustrating different degrees of severity of periventricular white matter lesions (left to right: severe, moderate, mild).

Two additional (but similar) groups of control subjects were assessed on tasks that were added to our test battery subsequent to the testing of the main control group: 24 controls undertook the doors and people test,[47] while a different group of 13 controls undertook the camel and cactus test.[48] As was the case with the main control group, the additional control groups were well matched to the patient groups on age (F values <2, p values >0.1) and for the former test on education (F = 1.0, p >0.1); unfortunately we do not have the educational details of the controls who performed the camel and cactus test.

Neuropsychological assessment

Four cognitive domains were assessed: episodic memory, semantic memory, executive/attentional functioning, and visuospatial skills. The tests used to evaluate performance in each domain are described below.

Assessments of episodic memory

Logical memory subtest of the Wechsler memory scale – revised[49]

Subjects listened to two short passages and were then asked to recall each one, both immediately and after a delay of 30 minutes. Each passage contains 25 elements of information, and the score used is the mean of the two stories.

Rey complex figure test[50]

Subjects were asked to copy this figure freehand, and without time restriction. After an interval of 45 minutes, subjects were asked (without warning) to reproduce from memory the figure which they had copied. Both copy and recall were scored out of a maximum of 36.

Short recognition memory test (RMT) for words and for faces[51]

There are two versions of this test involving forced choice recognition for words or faces. Each test is scored out of 25.

The doors and people test[47]

This test consists of several subtests which assess recognition and recall of visual and verbal material. The visual recognition subtest, called the *doors test*, is a forced choice recognition test for pictures of doors which is done in two sets of 12 items, resulting in a maximum score of 24. The visual recall subtest, called the *shapes test*, involves copying four drawings of crosses and then recalling them. The crosses are drawn from memory three times in succession immediately following the copy, and then once again following a 10 minute delay. The maximum score on the shapes test is 36 on immediate recall, and 12 on delayed recall. The verbal recognition subtest, called the *names test*, is a forced choice recognition test for names of people, which is done in two sets of 12 items, resulting in a maximum score of 24. The verbal recall subtest, called the *people test*, involves learning four names which consist of a forename and surname. There are three trials which are undertaken following stimulus presentation (immediate recall), and which are scored out of 36, while delayed recall is performed about 10 minutes later, and is scored out of 12.

Assessments of semantic memory

Semantic memory test battery

The tests in this battery[52–54] include the same 64 concrete concepts in each task. Half the test items are living things, while half are man-made items, and the pictures are taken from the Snodgrass and Vanderwart corpus.[55] The tests included in the present study are:

- *Category fluency*: Subjects were asked to produce as many different category exemplars as possible in one minute, for

four categories of living things (animals, fruit, birds, and breeds of dog), and four categories of man-made things (household items, tools, vehicles, and types of boat).
- *Naming*: Subjects were shown 64 line drawings and asked to name each one.
- *Word-picture matching*: Subjects were given a spoken word and were asked to pick the picture which matches it from within-category arrays of 10 items.

Camel and cactus test[48]

Subjects were asked to pick which of four pictures matches conceptually with a target picture (for example, tree, sunflower, rose, or cactus, with a camel). There are 64 items in this test.

Concrete and abstract word synonym test[56]

Subjects were required to choose which of two words is more similar in meaning to a target word (for example, *marquee* should be matched with *tent* rather than *palace*). This test is scored out of 50.

Graded naming test[57]

Subjects were shown 30 line drawings, and asked to name each one. This is a more difficult naming test than the one described above because it includes lower frequency items.

Executive and attentional tasks

Letter fluency

For the letters F, A, and S, subjects were asked to produce as many words as possible in one minute which start with the given letter.

Della Sala et al's dual task performance[58]

This consists of two tasks, repeating digit spans at the subject's own span length, and putting crosses into a trail of boxes on a sheet of paper. The tasks are initially undertaken on their own, each for two minutes, and are then done simultaneously for two minutes. The score reported is the dual task decrement. This is a measure of divided attention, and was calculated according to the following formula: dual task decrement = [120 seconds/number of boxes crossed on dual task]/[proportion of digit span strings correct on dual task] − [120 seconds/number of boxes crossed on single task]/[proportion of digit span strings correct on single task].

Stroop[59]

This task measures the interference that the automatic process of reading has on a more effortful process. Subjects were initially required to read aloud a list of 112 colour words (red, green, blue, tan); in the interference task, they were given another list of 112 colour words, but this time were required to name the colour of the ink in which each word was printed. The colour of the ink always differs from the word, so for example, if the word *red* is written in green ink the subject should say ''green.'' The score is the speed of naming the colour of the ink in the interference condition, and is given in words per minute.

Wisconsin card sorting test, short version[60]

This is a test of attentional set shifting in which subjects were required to sort 64 cards according to different concepts, which change during the course of the test. The score is the number of categories correct out of a maximum of 6.

Test of everyday attention (TEA)[61]

Three subtests from this battery were used:

- *Elevator counting*: This is a test of sustained attention. Subjects listened to a recording of seven strings of tones,

which range in length from three to 14, and were asked to count the number of tones. The maximum score is 7.

- *Elevator counting with distraction*: This is a test of selective attention. Subjects listened to a recording of 10 series of tones, and were asked count the high tones while ignoring the low tones. The maximum score is 10.
- *Map search task*: This is a timed task of selective attention. Subjects were given two minutes to locate target symbols (for example, a petrol pump) on a map which contains numerous irrelevant (distractor) symbols. The maximum score is 80.

Digit span
Forward and reverse digit spans were assessed using the standard method from the Wechsler memory scale – revised.[49]

Visuospatial tasks
Copy of the Rey complex figure[50]
In this task, which was described above because its recall component is a test of episodic memory, subjects were asked to copy a complicated line drawing free hand and without time restriction. The copy was scored out of a maximum of 36.

Visual object and space perception battery (VOSP)[52]
Six subtests from this battery were used:

- *Incomplete letters*: Subjects were asked to name 20 capital letters in which the clarity has been degraded, rendering identification more difficult.
- *Silhouette naming*: Subjects were required to name silhouette drawings of common animals and objects which have been rotated to varying degrees. The rotation increases demand on perceptual skills, but it should be noted that there is also a semantic component to this test since accurate performance relies on naming/identification. The maximum score is 30.
- *Object decision*: Subjects were shown arrays of four silhouette drawings, including a rotated real object, and three object-like distractors, and were asked to point to the real object. There are 20 items in this test.
- *Dot counting*: Subjects were shown arrays of between five and nine black dots, and were asked to count them. There are 10 items in this test.
- *Number location*: Subjects were shown two squares, one of which contains randomly placed numbers and one of which contains a black dot which is positioned in the same location within its square as one of the numbers is in the other square. The task is to name the number which is in the same position as the dot. The maximum score is 10.
- *Cube analysis*: Subjects were asked to count the number of cubes represented in two dimensional drawings of arrangements of between five and 12 cubes. The maximum score is 10.

Analyses
The differences between the groups were analysed using one way analysis of variance (ANOVA). Post hoc comparisons using Tukey-Cramer tests were applied to explore significant group effects; this test corrects for multiple comparisons and unequal group variances.[63] In order to look at individual patients' performance in each domain, we used the control data to calculate z scores for each patient on each test, and averaged each patient's z scores on the two most sensitive tasks in each domain. Patients were considered to be impaired on a test/domain if their z scores were below -2.

Backward stepwise logistic regression analyses were undertaken to identify the tests which best discriminate between the patient groups.

RESULTS
Comparison of performance across the groups in each cognitive domain
The scores of the two patient groups and the controls on each of the neuropsychological tests are shown in table 2. The performance of individual patients in each cognitive domain is shown in table 3.

Episodic memory
One way ANOVA showed a significant effect of group on all 11 tests of episodic memory (all F values >10, all p values <0.001). Post hoc comparisons indicated that both patient groups were impaired on every test. The Alzheimer patients were significantly more impaired than the vascular dementia patients on the delayed recall portion of the logical memory test, delayed recall of the Rey figure, and on most of the subtests from the doors and people test, including immediate and delayed recall of shapes (crosses), immediate recall of names, and recognition memory for names. The two patient groups were equally impaired on the immediate recall portion of the logical memory test, as well as recognition memory for words, faces, and doors, and delayed recall of names. The test battery included tests of both verbal and non-verbal episodic memory, but there was no systematic difference in the performance of the patient groups in these two areas: they were equally impaired on three of six verbally based tests, and two of five non-verbal tests, while on the remaining tests the Alzheimer patients were significantly more impaired than the vascular dementia patients.

In general, there was a tendency for the Alzheimer patients to do worse than the vascular dementia patients on tests involving delayed recall (this was true on three of four tests), while performance of the patient groups was equally impaired on tests of recognition (three of four tests). Episodic memory impairment was, however, pervasive in both groups, and was somewhat worse in the Alzheimer patients, whose scores were either equally poor (on five of 11 tasks) or worse (on six of 11 tasks) than those of the vascular dementia patients.

Table 3 shows the performance of individual patients on episodic memory. Most patients in both groups were impaired on episodic memory, which is in keeping with the finding from the group analyses that both groups were impaired on all tasks in this domain.

Semantic memory
On the two easiest tests of semantic memory, the word–picture matching and naming tests from the semantic battery, both patient groups showed normal performance (both F values <2, p values >0.1), while on the remaining four semantic tests (category fluency, the camel and cactus test, the concrete and abstract word synonym test, and the graded naming test), there was a significant effect of group (F values >7, p values <0.01); post hoc comparisons showed that the vascular patients were impaired on each of these. By contrast, the Alzheimer patients were impaired only on category fluency and the graded naming test, and the degree of impairment was similar to that of the vascular dementia patients. The concrete and abstract word synonym test results were analysed with a 3 (groups) × 2 (concreteness: concrete v abstract words) ANOVA, but results showed no significant main effect or interaction involving concreteness (F values <1, p values >0.1).

Table 2 Performance of the vascular and Alzheimer patient groups and of the controls on the neuropsychological test battery

Test	Vascular	DAT	Controls	p Value	Post hoc comparisons
Episodic memory tasks					
Logical memory – immediate recall (25)	6.0 (2.4)	4.2 (1.9)	9.5 (2.4)	<0.001	Controls>VaD = AD
Logical memory – delayed recall (25)	3.9 (2.5)	0.4 (1.0)	7.6 (2.7)	<0.001	Controls>VaD>AD
Rey figure – delayed recall (36)	7.1 (6.5)	2.4 (3.6)	18.3 (5.7)	<0.001	Controls>VaD>AD
RMT words (25)	19.1 (3.7)	18.9 (3.3)	24.5 (1.0)	<0.001	Controls>VaD = AD
RMT faces (25)	20.5 (3.7)	21.3 (3.5)	24.6 (0.5)	<0.001	Controls>VaD = AD
Doors and people visual – recognition (24)	13.0 (2.6)	11.7 (4.4)	16.7 (3.1)	<0.001	Controls>VaD = AD
Doors and people visual – immediate recall (36)	17.5 (8.6)	11.4 (6.6)	29.0 (7.1)	<0.001	Controls>VaD>AD
Doors and people visual – delayed recall (12)	6.0 (3.7)	2.9 (2.9)	10.3 (1.9)	<0.001	Controls>VaD>AD
Doors and people verbal – recognition (24)	14.3 (3.9)	11.2 (3.0)	17.7 (2.3)	<0.001	Controls>VaD>AD
Doors and people verbal – immediate recall (36)	14.5 (8.3)	7.2 (7.5)	21.3 (7.2)	<0.001	Controls>VaD>AD
Doors and people verbal – delayed recall (12)	4.1 (3.7)	2.2 (3.0)	8.2 (3.2)	<0.001	Controls>VaD = AD
Semantic memory tasks					
Category fluency (8 categories)	65.8 (24.9)	75.8 (25.3)	119.1 (19.0)	<0.001	Controls>VaD = AD
Semantic battery naming (64)	60.2 (4.3)	60.1 (7.1)	62.3 (1.8)	NS	–
Word–picture matching (64)	62.4 (1.6)	62.4 (4.0)	63.8 (0.4)	NS	–
Camel and cactus test (64)	47.0 (10.6)	53.5 (10.5)	58.9 (3.2)	<0.01	Controls>VaD†
Concrete and abstract word synonym test (50)	41.1 (6.6)	44.4 (4.0)	46.9 (3.1)	<0.01	Controls>VaD†
Graded naming test (30)	17.6 (5.4)	19.6 (5.8)	24.7 (2.9)	<0.001	Controls>VaD = AD
Executive and attentional tasks					
Letter fluency (FAS)	23.4 (14.9)	36.2 (12.1)	40.9 (8.8)	<0.001	Controls = AD>VaD*
Della Sala dual task – decrement	8.3 (12.5)	1.6 (2.6)	0.5 (1.2)	<0.01	Controls = AD<VaD*
Stroop – words per minute	22.9 (12.6)	28.0 (19.1)	52.0 (12.8)	<0.001	Controls>VaD = AD
Wisconsin card sorting (6)	2.8 (1.9)	3.8 (2.2)	5.8 (0.5)	<0.001	Controls>VaD = AD
TEA elevator counting (7)	5.5 (1.9)	6.4 (1.5)	6.8 (0.4)	0.01	Controls = AD>VaD
TEA elevator counting with distraction (10)	5.0 (3.6)	6.8 (3.0)	8.7 (1.8)	<0.01	Controls>VaD†
TEA map search (80)	22.3 (10.9)	37.2 (17.7)	58.9 (15.4)	<0.001	Controls>AD>VaD
Forward digit span	5.9 (1.5)	6.5 (1.3)	7.0 (1.0)	<0.05	Controls>VaD†
Reverse digit span	3.9 (1.3)	4.2 (1.5)	5.2 (1.4)	<0.05	Controls>VaD†
Visuospatial tasks					
Rey copy (36)	22.0 (10.6)	27.5 (11.0)	33.9 (1.6)	<0.001	Controls>VaD = AD
VOSP incomplete letters (20)	17.1 (2.8)	17.7 (5.1)	19.2 (0.8)	NS	–
VOSP silhouette naming (30)	15.6 (4.5)	19.8 (5.7)	21.5 (2.7)	<0.001	Controls = AD>VaD
VOSP object decision (20)	15.6 (3.3)	17.6 (3.0)	17.2 (2.4)	NS	–
VOSP dot counting (10)	8.8 (2.0)	9.7 (0.6)	9.9 (0.3)	<0.05	Controls = AD>VaD
VOSP number location (10)	7.3 (2.2)	8.1 (3.0)	8.7 (3.4)	NS	–
VOSP cube analysis (10)	6.8 (3.1)	7.8 (2.7)	10.2 (2.6)	<0.01	Controls>VaD = AD

Values are mean (SD). Maximum scores are given in brackets following the name of each test. The p values are from the one way analyses of variance comparing the groups.
†All other comparisons not significant.
DAT, dementia of Alzheimer type; RMT, recognition memory test; TEA, test of everyday attention; VOSP, visual object and space perception battery.

Overall, the vascular dementia patients showed a greater degree of semantic memory impairment than the Alzheimer patients in that they were impaired on more tests. This is consistent with the findings from individual patients which show that more patients with vascular dementia had semantic memory impairment (table 3).

Executive and attentional function
There were significant group effects on all nine tests of executive/attentional function (F values >3, p values <0.05). Post hoc analyses showed that the patients with vascular dementia were significantly impaired on every test in this domain, while the Alzheimer patients were impaired on the Stroop, Wisconsin card sorting, and TEA map search only.

The degree of impairment was equal for the two patient groups on the Stroop and Wisconsin, while the vascular dementia patients were significantly more impaired than the Alzheimer patients on the TEA map search.

Taken together these results indicate that the patients with vascular dementia had greater impairment in executive/attentional function. This finding is supported by examination of the results of individual patients in this domain (table 3) in that a greater proportion of the vascular dementia group showed impairment.

Visuospatial function
On three of the seven tests in this domain—incomplete letters, object decision, and number location—there was no

Table 3 Performance of individual patients with either vascular dementia or probable Alzheimer's disease on all cognitive domains, using impairment on the two most sensitive tasks in each domain as a measure of impairment in that domain

Group	Subject	MMSE	Episodic memory	Semantic memory	Executive/attentional function	Visuospatial function
VaD	SE	30	−	+	+	+
VaD	RB	29	+	−	+	+
VaD	RD	29	+	+	+	+
VaD	KE	29	−	−	−	−
VaD	VP	29	−	−	−	−
VaD	DB	28	−	−	−	−
VaD	EJ	27	+	+	+	+
VaD	PR	27	+	+	+	−
VaD	LW	27	+	+	+	+
VaD	PH	26	+	+	−	+
VaD	SM	26	+	+	+	+
VaD	RY	26	+	+	+	−
VaD	CG	24	+	+	+	+
VaD	HP	24	+	+	−	+
VaD	HG	22	+	+	+	+
VaD	IB	20	+	+	+	+
VaD	MW	20	+	+	+	+
VaD	RS	19	+	+	+	+
VaD	HK	18	+	+	+	+
% VaD patients impaired:			78.9	78.9	73.7	73.7
DAT	PS	30	−	−	−	−
DAT	AA	29	−	+	+	−
DAT	IHe	28	−	−	+	−
DAT	DJ	27	+	−	−	−
DAT	MR	27	+	−	−	−
DAT	BK	26	+	−	−	−
DAT	EL	26	+	−	−	−
DAT	JP	26	+	−	−	+
DAT	JS	26	+	−	−	−
DAT	MU	25	+	+	+	+
DAT	AD	24	+	−	+	+
DAT	JW	24	+	+	+	+
DAT	BC	23	+	−	+	+
DAT	RG	22	+	−	+	+
DAT	IW	21	+	−	+	−
DAT	PB	20	+	−	+	−
DAT	IHu	20	+	+	−	+
DAT	JA	18	+	+	+	−
DAT	VM	17	+	+	+	+
% DAT patients impaired:			84.2	31.6	57.9	42.1

The tasks used are as follows: episodic memory – Rey delayed recall, recognition memory test for words; semantic memory – category fluency, camel and cactus test; executive/attentional function – Wisconsin card sorting, STROOP; visuospatial function – Rey copy, dot counting.
Although the table seems to show that three VaD patients (KE, VP, DB) and one DAT patient (PS) had no impairment in any cognitive domain, all four patients showed deficits on other tasks not included in the table.
DAT, dementia of Alzheimer type; VaD, vascular dementia; +, impaired.

significant effect of group (F values <2.5, p values >0.1), indicating that both vascular dementia and Alzheimer patients were unimpaired. On the remaining four tests—copy of the Rey figure, silhouette naming, dot counting, and cube analysis—investigation of the significant group effects (F values ≥4, p values <0.05) through post hoc comparisons indicated that the patients with vascular dementia were significantly impaired on all four tests, while the Alzheimer patients showed normal performance on silhouette naming and dot counting, but were as impaired as the vascular dementia group on the Rey copy and cube analysis. Note that both patient groups showed impairment on tests of both constructional and visuo-perceptual ability.

Overall, these results suggest that the degree of visuospatial impairment is somewhat worse in the patients with vascular dementia, as they were more impaired than the Alzheimer group on two of the tests in this domain. A difference between the groups is more obvious if one looks at the performance of individual patients (table 3), as a much larger percentage of patients with vascular dementia than with Alzheimer's disease showed impairment in visuospatial function.

Profile of neuropsychological impairment in vascular dementia and Alzheimer's disease

To explore the pattern of impairment in the two patient groups across cognitive domains, we calculated or averaged z scores for, first, the most sensitive task in each domain (Rey delayed recall for episodic memory, category fluency for semantic memory, Wisconsin card sorting for executive/attentional function, and Rey copy for visuospatial function); second, the average of the two most sensitive tasks in each domain (see table 3); and third, the average across all tasks in each domain. The pattern of performance across domains did not differ in the three analyses, so we will report only the results using z scores on the two most sensitive tasks in each domain.

The percentage of patients in each group showing normal performance on the different cognitive modules is shown in table 3. In three of the four domains more vascular dementia patients than Alzheimer patients were impaired. The exception to this occurred with episodic memory, although the vast majority of patients in both groups showed impairment in this domain. This is not surprising given that the diagnostic criteria used require episodic memory impairment.

The largest difference between the groups was observed in the domain of semantic memory. Although semantic memory impairment is pervasive in Alzheimer's disease,[53][64][65] the patients included in this study had only minimal to mild dementia and may not yet have developed significant semantic impairment. This confirms previous findings that the degree of semantic memory impairment in Alzheimer's disease is variable in the early stages.[53][66][67] In contrast, nearly 80% of the patients with vascular dementia were semantically impaired.

In the domains of executive/attentional and visuospatial function more patients with vascular dementia than with Alzheimer's disease were impaired. The evidence to date regarding visuospatial function in vascular dementia is limited, but it seems that impairment in this domain is common in mild vascular dementia, and is more prevalent than in Alzheimer's disease.

In summary, although the patient groups were carefully matched in terms of their general level of cognitive impairment as well as on everyday functioning, it was still possible to detect differences between the groups. Both the group analyses and examination of the data from individual patients indicated that the patients with Alzheimer's disease were more impaired in episodic memory, while the patients with vascular dementia were more impaired in semantic memory, executive/attentional function, and visuospatial function. Although all of the patients in this study had only minimal to mild dementia, most showed a range of cognitive impairments.

Neuropsychological tests which distinguish between vascular dementia and Alzheimer's disease

The results described above indicate that subcortical vascular dementia and Alzheimer's disease have relatively distinct profiles of neuropsychological impairment, even in the earliest stages of the illnesses. One of the goals of our study was to identify the tests which best differentiate between the patient groups. To this end, we performed binary logistic regression and used a backward stepwise technique. The domains were analysed separately to keep an acceptably large ratio of observations to predictors.

In the domain of episodic memory, the only significant predictor of group membership was logical memory – delayed recall (Wald's $\chi^2(1) = 8.90$, $p<0.01$, odds ratio = 0.334). As scores increase, patients are more likely to have vascular dementia than Alzheimer's disease. On the basis of logical memory – delayed recall, 80.6% of the patients were classified into the correct groups, while only three additional patients (a total of 88.9%) were classified correctly on the basis of all 11 episodic memory tasks.

In the next logistic regression analysis, the semantic tasks were used as predictor variables. Results showed that the semantic battery naming test (Wald's $\chi^2(1) = 2.72$, $p<0.1$, odds ratio = 0.86) and the camel and cactus test (Wald's $\chi^2(1) = 4.41$, $p<0.05$, odds ratio = 1.14) together classified 73.7% of the cases correctly, while on their own these tests did not predict group membership. As naming scores increase, patients were more likely to have vascular dementia, while they were more likely to have Alzheimer's disease as camel and cactus scores go up.

In the domain of executive/attentional function, we had to omit the Della Sala dual task test from the analysis because of missing data. Although all subjects completed this task, five patients with vascular dementia and two with Alzheimer's disease showed such impaired performance that it was not possible to calculate a value for dual task decrement, as these patients scored 0 on crossing boxes in the dual task section of the test. Logistic regression analysis on the remaining eight executive/attentional tests indicated that only the TEA map search significantly discriminated between the groups (Wald's $\chi^2(1) = 5.32$, $p<0.05$, odds ratio = 1.07). Higher scores on this task indicate that a patient is more likely to have Alzheimer's disease than vascular dementia. Interestingly, this test alone discriminated between the groups (75.0% of patients correctly classified) better than all of the executive/attentional tasks together (72.0% correctly classified).

Logistic regression using the visuospatial tasks as predictor variables showed that the VOSP silhouette naming test was the only significant predictor of group membership (Wald's $\chi^2(1) = 4.58$, $p<0.05$, odds ratio = 1.18), with higher scores being more suggestive of Alzheimer's disease than vascular dementia. This test correctly classified 77.1% of the patients, and discriminated slightly better than all of the visuospatial tasks together, which correctly classified 68.6% of the patients.

In the final logistic regression analysis, we included the significant predictors from each of the four cognitive domains, as identified in the analyses just described. Results showed that two tests significantly predicted group membership: logical memory – delayed recall (Wald's $\chi^2(1) = 7.95$, $p<0.01$, odds ratio = 0.32), and VOSP silhouette naming (Wald's $\chi^2(1) = 3.56$, $p = 0.06$, odds ratio = 1.23). On the logical memory – delayed recall, higher scores indicate that a patient is more likely to have vascular dementia, while the opposite was true for VOSP silhouette naming. Together these tests predicted group membership for 88.6% of the patients. This was little better than the predictive value of logical memory – delayed recall on its own, which predicted group membership for 81.1%; this difference represents one patient of 38. Thus there is an argument for using only the logical memory – delayed recall to discriminate between vascular dementia and Alzheimer's disease. Examination of the data revealed that 18 of the 19 patients with vascular dementia scored >0.25 on this test, while 16 of 18 patients with Alzheimer's disease scored ⩽0.25, indicating that patients with scores higher than 0.25 have a high chance of having vascular dementia, while patients with lower scores have a high chance of having Alzheimer's disease.

To summarise, logistic regression analyses of the tests in each cognitive domain showed that logical memory – delayed recall, semantic battery naming, camel and cactus, TEA map search and VOSP silhouette naming were significant predictors of group membership. In an analysis which included only these variables, we found that logical memory – delayed recall provided good discrimination between the two patient groups. Although both groups are impaired on this test (see ANOVA results above), the patients with vascular dementia tend to have higher scores than those with Alzheimer's disease. More specifically, scores tend to be above 0.25 for the vascular dementia group. The VOSP silhouette naming test also provided good discrimination between the groups, with the Alzheimer patients tending to have higher scores. Thus a short neuropsychological test battery including either the five tests listed above, or just the logical memory – delayed recall should be helpful in making a differential diagnosis between vascular dementia and Alzheimer's disease.

DISCUSSION

We used a comprehensive battery of neuropsychological tests, with closely matched groups of patients with subcortical vascular dementia or Alzheimer's disease, to resolve controversies in published reports over differences in the cognitive profile. The patient groups showed clear differences, both from each other and from the control group. In keeping with the general trend found in previous studies (see the introduction) we have confirmed that Alzheimer's disease is characterised by greater impairment in episodic

memory, while patients with vascular dementia have greater deficits in executive/attentional abilities. More surprising was the finding that patients with vascular dementia showed greater impairment in both semantic memory and visuospatial/perceptual function than the patients with Alzheimer's disease.

In Alzheimer's disease there is a pervasive deficit in all aspects of anterograde episodic memory which reflects early and severe involvement of the hippocampal complex.[68 69] In cognitive terms, the deficit in Alzheimer's disease is one of encoding new material into long term memory. This produces a rapid decay of memory traces which affects both recall and recognition of verbal and visual material.[69 70] In vascular dementia, the deficit is generally regarded as one of information retrieval, in which case there should be consistently better performance on recognition based rather than recall based tests. To examine this hypothesis we used the doors and people test,[47] which contains subtests assessing both recall and recognition. The results were only partially supportive of this supposition. There was a trend for patients with vascular dementia to be less impaired than patients with Alzheimer's disease on the recall based subtests. Consistent with this finding, recent volumetric MRI studies have shown less atrophy of the hippocampal formation in vascular dementia than in Alzheimer's disease, although this key region is involved in both pathologies.[71]

It should be noted that on several measures of attentional function—letter based verbal fluency (FAS), decrement on a dual task performance test, digit span, and components of the TEA—there was no difference in performance between controls and Alzheimer patients, which reflects the mild stage of our Alzheimer cohort. Many of the tasks used overlapped with those employed by Perry et al,[72] who established that the Stroop test and the Wisconsin card sorting test were among those most sensitive to attentional and executive dysfunction in Alzheimer's disease, respectively. We have corroborated this finding in an independent cohort of early cases of Alzheimer's disease. In addition, our results add to the small body of reports suggesting that executive and attentional functions are more impaired in vascular dementia than in Alzheimer's disease. Interestingly the tasks which revealed the greatest magnitude of deficit in vascular dementia were the FAS task and the Della Sala dual performance test, in which subjects are required to undertake simultaneous cancellation of a box trail and repetition of digit strings after performing each task separately. These findings suggest that not only is attentional dysfunction greater in vascular dementia than in Alzheimer's disease, but the nature and hence underlying neural basis might be quite distinct. In Alzheimer's disease the deficit in selective attention is thought to reflect posterior association cortices with or without cingulate pathology, while in vascular dementia the impact on divided and sustained attention is likely to reflect interruption of dorsolateral cortex–basal ganglia circuits.[73]

Semantic functioning in vascular dementia has received scant attention in published reports. This is the first detailed examination of this area, and our results indicate that semantic impairment is common even in minimal to mild vascular dementia. Impairment in semantic memory is a well established core deficit in Alzheimer's disease, which can be found in the majority of cases from a very early stage of disease and is thought to reflect involvement of the temporal neocortex.[53 69] The finding of greater deficits in vascular dementia than in Alzheimer's disease is thus of considerable theoretical and practical interest. The impairment in category fluency could reflect, in part, the attentional dysfunction, but this would not readily explain the greater anomia found in vascular dementia. In addition, vascular dementia patients were impaired on a pictorial test of associative knowledge, the camel and cactus test, and on a test of synonym judgement, indicating a generalised breakdown in semantic memory. The neural basis of the semantic deficit is presumably identical in vascular dementia and Alzheimer's disease. Convergent findings from studies of patients with semantic dementia and normal subjects undergoing brain activation point to the left temporal neocortex as a key region in semantic processing.[74–76]

It is interesting to note, given the variability in the reported results on naming in patients with vascular dementia, that naming performance was impaired on the graded naming test, but was normal on the semantic battery naming. Thus we documented normal naming on a relatively easy test and impaired naming on a more difficult test within the same group of patients. The issue of test difficulty may go some way to explaining the results on variability in naming results in reports on vascular dementia.

Deficits in visuospatial function were mild in both patient groups but on all tests there was either equivalent or greater impairment in the vascular dementia group. As highlighted in the introduction, previous studies have often used tests that confound praxic and visuospatial ability. To disentangle these contributions we used the VOSP test battery, which eliminates praxic aspects and separates spatial tasks which are more dependent on occipito-parietal (dorsal stream) function from those that stress visuo-perceptual (ventral stream) ability. Interestingly, patients with vascular dementia were impaired on both spatial (dot counting and cube analysis) and perceptual (silhouette naming) subtests. These deficits could not be attributed to gross field defects although it would, in retrospect, have been valuable to quantify visual fields and to examine low level functions such as acuity and contrast sensitivity.

Our patients with vascular dementia were selected on the basis of their substantial white matter pathology as evident on MRI. The presence of such diffuse pathology makes it difficult to draw firm conclusions about structure–function relations. It is also likely that the defect in attentional processing underlies many of their other difficulties, although if the difference were simply a matter of severity then one would expect that all abilities, including episodic memory, would be worse in vascular dementia, which was *not* the case.

One of the goals of this study was to identify neuropsychological tests which are useful in discriminating between subcortical vascular dementia and Alzheimer's disease. Because it may be possible to prevent further vascular damage in patients with cerebrovascular disease, early and accurate diagnosis of vascular dementia is of paramount importance. We found that the WAIS logical memory – delayed recall was the single most useful test to discriminate between the vascular dementia and Alzheimer's disease patients. Although the performance of both groups was impaired, the impairment was more severe in the Alzheimer patients. This test is probably useful to discriminate between vascular dementia and Alzheimer's disease only when the dementia is mild; with increasing severity, the performance of both groups seems likely to reach the floor, rendering discrimination based on this test impossible. We were able to identify four additional tests which provided significant discrimination between the groups: two from the semantic battery (naming, and the camel and cactus test), one attentional (TEA map search), and one perceptual (VOSP silhouette naming). The fact that a combination of logical memory – delayed recall and the VOSP silhouette naming test provided the best discrimination (89% correct classification) is of interest, as correct performance on the VOSP test depends on both perceptual and semantic processes, each of

which are compromised to a greater degree in vascular dementia than in Alzheimer's disease.

One inevitable shortcoming of this study is the assumption of pathology. For this initial study we attempted to exclude cases with suspected mixed pathology but it is highly likely that some of the patients with vascular dementia have concomitant Alzheimer's disease, and possibly vice versa. In clinical practice many patients present with intermediate states which are not represented here. Our sample is also biased in that patients were recruited through a memory clinic rather than from a stroke or TIA clinic. In addition, we excluded patients with focal cortical infarcts or with strategically placed subcortical lesions involving, for instance, the thalamus. The patients selected represent the commonest form of vascular dementia presenting to memory clinics.[44]

Conclusions

The profile of cognitive impairments shown by mildly demented patients with subcortical vascular dementia includes moderate to severe episodic memory and attentional/executive deficits, in conjunction with milder impairments in semantics and visuospatial skills. Qualitative differences in the patterns of dementia in mild vascular dementia and Alzheimer's disease were documented: the groups were matched on levels of cognitive impairment and everyday functioning, but the patients with vascular dementia were less impaired in episodic memory, and more severely impaired on tests of attentional/executive function, semantic memory, and visuospatial skills. Although differential diagnosis is most difficult when dementia is in the early stages, as with the patients studied here, in future it would be beneficial to extend these findings to a wider range of dementia severities in vascular dementia and Alzheimer's disease.

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Authors' affiliations
N L Graham, T Emery, J R Hodges, University of Cambridge Neurology Unit, Addenbrooke's Hospital, and MRC Cognition and Brain Sciences Unit, 15 Chaucer Rd, Cambridge, UK

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REFERENCES

1 **Aguero-Torres H**, Winblad B, Fratiglioni L. Epidemiology of vascular dementia: some results despite research limitations. *Alzheimer Dis Assoc Disord* 1999;**13**(suppl 3):S15–20.
2 **Rocca WA**, Hofman A, Brayne C, *et al*. The prevalence of vascular dementia in Europe: facts and fragments from 1980–1990 studies. *Ann Neurol* 1991;**30**:817–24.
3 **Erkinjuntti T**. Vascular dementia: challenge of clinical diagnosis. *Int Psychogeriatr* 1997;**9**(suppl 1):51–8.
4 **Almkvist O**, Backman L, Basun H, *et al*. Patterns of neuropsychological performance in Alzheimer's disease and vascular dementia. *Cortex* 1993;**29**:661–73.
5 **Erkinjuntti T**, Laaksonen R, Sulkava R, *et al*. Neuropsychological differentiation between normal aging, Alzheimer's disease and vascular dementia. *Acta Neurol Scand* 1986;**74**:393–403.
6 **Fischer P**, Gatterer G, Marterer A, *et al*. Nonspecificity of semantic impairment in dementia of Alzheimer's type. *Arch Neurol* 1988;**45**:1341–3.
7 **Villardita C**. Alzheimer's disease compared with cerebrovascular dementia: neuropsychological similarities and differences. *Acta Neurol Scand* 1993;**87**:299–308.
8 **Kertesz A**, Clydesdale S. Neuropsychological deficits in vascular dementia vs. Alzheimer's disease. *Arch Neurol* 1994;**51**:1226–31.
9 **Carlesimo GA**, Fadda L, Bonci A, *et al*. Differential rates of forgetting from long-term memory in Alzheimer's and multi-infarct dementia. *Int J Neurosci* 1993;**73**:1–11.
10 **Gainotti G**, Parlato V, Monteleone D, *et al*. Neuropsychological markers of dementia on visuo-spatial tasks: a comparison between Alzheimer's type and vascular forms of dementia. *J Clin Exp Neuropsychol* 1992;**14**:239–52.
11 **Donnelly K**, Grohman K. Can the Mattis dementia rating scale differentiate Alzheimer's disease, vascular dementia, and depression in the elderly? *Brain Cogn* 1999;**39**:60–3.
12 **Libon DJ**, Malamut BL, Swenson R, *et al*. Further analyses of clock-drawing among demented and non-demented older subjects. *Arch Clin Neuropsychol* 1996;**11**:193–205.
13 **Looi JCL**, Sachdev PS. Differentiation of vascular dementia from AD on neuropsychological tests. *Neurology* 1999;**53**:670–8.
14 **Padovani A**, Di Piero V, Bragoni M, *et al*. Patterns of neuropsychological impairment in mild dementia: a comparison between Alzheimer's disease and multi-infarct dementia. *Acta Neurol Scand* 1995;**92**:433–42.
15 **Lamar M**, Carew TG, Resh R, *et al*. Perseverative behavior in Alzheimer's disease and subcortical ischemic vascular dementia. *Neuropsychology* 1997;**11**:523–34.
16 **Mendez MF**, Cherrier MM, Perryman KM. Differences between Alzheimer's disease and vascular dementia on information processing measures. *Brain Cogn* 1997;**43**:301–10.
17 **Libon DJ**, Bogdanoff B, Bonavita J, *et al*. Dementia associated with periventricular deep white matter alterations: a subtype of subcortical dementia. *Arch Clin Neuropsychol* 1997;**12**:239–50.
18 **Doody RC**, Massman PJ, Mawad M, *et al*. 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.
19 **Kontiola P**, Laaksonen R, Sulkava R, *et al*. Pattern of language impairment is different in Alzheimer's disease and multi-infarct dementia. *Brain Lang* 1990;**38**:364–83.
20 **Lafosse JM**, Reed BR, Mungas D, *et al*. Fluency and memory differences between ischemic vascular dementia and Alzheimer's disease. *Neuropsychology* 1997;**11**:514–22.
21 **Bowler JV**, Hachinski V. Criteria for vascular dementia: replacing dogma with data. *Arch Neurol* 2000;**57**:170–1.
22 **Desmond DW**, Erkinjuntti T, Sano M, *et al*. The cognitive syndrome of vascular dementia: implications for clinical trials. *Alzheimer Dis Assoc Disord* 1999;**13**(suppl 3):S21–S9.
23 **Hodges JR**, Graham NL. Vascular dementias. In: Hodges JR, ed. *Early-onset dementia: a multidisciplinary approach*. New York: Oxford University Press, 2001:319–37.
24 **Bentham PW**, Jones S, Hodges JR. A comparison of semantic memory in vascular dementia and dementia of Alzheimer's type. *Int J Geriatr Psychiatry* 1997;**12**:575–80.
25 **Laine M**, Vuorinen E, Rinne JO. Picture naming deficits in vascular dementia and Alzheimer's disease. *J Clin Exp Neuropsychol* 1997;**19**:126–40.
26 **Lukatela K**, Malloy P, Jenkins M, *et al*. The naming deficit in early Alzheimer's and vascular dementia. *Neuropsychology* 1998;**12**:565–72.
27 **Loewenstein DA**, D'Elia L, Guterman A, *et al*. The occurrence of different intrusive errors in patients with Alzheimer's disease, multiple cerebral infarctions, and major depression. *Brain Cogn* 1991;**16**:104–17.
28 **Powell AL**, Cummings JL, Hill MA, *et al*. Speech and language alterations in multi-infarct dementia. *Neurology* 1988;**38**:717–19.
29 **Barr A**, Benedict R, Tune L, *et al*. Neuropsychological differentiation of Alzheimer's disease from vascular dementia. *Int J Geriatr Psychiatry* 1992;**7**:621–7.
30 **Crossley M**, D'Arcy C, Rawson NSB. Letter and category fluency in community-dwelling Canadian seniors: a comparison of normal participants to those with dementia of the Alzheimer or vascular type. *J Clin Exp Neuropsychol* 1997;**19**:52–62.
31 **Tei H**, Miyazaki A, Iwata M, *et al*. Early stage Alzheimer's disease and multiple subcortical infarction with mild cognitive impairment: neuropsychological comparison using an easily applicable test battery. *Dement Geriatr Cogn Disord* 1997;**8**:355–8.
32 **Starkstein SE**, Sabe L, Vazquez S, *et al*. Neuropsychological, psychiatric, and cerebral blood flow findings in vascular dementia and Alzheimer's disease. *Stroke* 1996;**27**:408–14.
33 **Almkvist O**. Neuropsychological deficits in vascular dementia in relation to Alzheimer's disease: reviewing evidence for functional similarity or divergence. *Dementia* 1994;**5**:203–9.
34 **Bowler JV**, Eliasziw M, Steenhuis R, *et al*. Comparative evolution of Alzheimer disease, vascular dementia, and mixed dementia. *Arch Neurol* 1997;**54**:697–703.
35 **Bowler JV**, Hachinski V. Vascular dementia. In: Feinberg TE, Farah MJ, ed. *Behavioural neurology and neuropsychology*. New York: McGraw Hill, 1997:589–603.
36 **Chui HC**, Victoroff JI, Margolin D, *et al*. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer Disease Diagnostic and Treatment Centers (ADDTC). *Neurology* 1992;**42**:473–80.
37 **Roman GC**, Tatemichi TK, Erkinjuntti T, *et al*. Vascular dementia: diagnostic criteria for research studies. *Neurology* 1993;**43**:250–60.
38 **Chui HC**, Mack W, Jackson E, *et al*. Clinical criteria for the diagnosis of vascular dementia. *Arch Neurol* 2000;**57**:191–6.
39 **Erkinjuntti T**, Ostbye T, Steenhuis R, *et al*. The effect of different diagnostic criteria on the prevalence of dementia. *N Engl J Med* 1997;**337**:1667–74.
40 **Mathuranath PS**, Nestor PJ, Berrios GE, *et al*. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology* 2000;**55**:1613–20.
41 **Berg L**. Clinical dementia rating scale (CDR). *Psychopharmacol Bull* 1988;**24**:637–9.
42 **Bozeat S**, Gregory CA, Lambon Ralph MA, *et al*. Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *J Neurol Neurosurg Psychiatry* 2000;**69**:178–86.

43 **Leys D**, Erkinjuntti T, Desmond DW, *et al.* Vascular dementia: the role of cerebral infarcts. *Alzheimer Dis Assoc Disord* 1999;**13**(suppl 3):S38–48.

44 **Rockwood K**, Wentzel C, Hachinski V, *et al.* Prevalence and outcomes of vascular cognitive impairment. Vascular cognitive impairment investigators of the Canadian Study of Health and Aging. *Neurology* 2000;**54**:447–51.

45 **Folstein MF**, Folstein SE, McHugh PR. ''Mini-mental state''. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**:189–98.

46 **McKhann G**, Drachman D, Folstein M, *et al.* Clinical diagnosis of Alzheimer's disease. *Neurology* 1984;**34**:939–44.

47 **Baddeley AD**, Emslie H, Nimmo-Smith I. *The doors and people test: a test of visual and verbal recall and recognition.* Bury St Edmunds: Thames Valley Test Company, 1994.

48 **Bozeat S**, Lambon Ralph MA, Patterson K, *et al.* Non-verbal semantic impairment in semantic dementia. *Neuropsychologia* 2000;**38**:1207–15.

49 **Wechsler DA**. *Wechsler memory scale - revised.* San Antonio: Psychological Corporation, 1987.

50 **Rey A**. L'examen psychologique dans les cas d'encephalopathie traumatique. *Arch Psychol* 1941;**28**:286–340.

51 **Warrington EK**. *The Camden memory tests.* Hove, East Sussex: Psychology Press, 1996.

52 **Hodges JR**, Salmon DP, Butters N. Semantic memory impairment in Alzheimer's disease: failure of access or degraded knowledge? *Neuropsychologia* 1992;**30**:310–4.

53 **Hodges JR**, Patterson K. Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. *Neuropsychologia* 1995;**33**:441–59.

54 **Hodges JR**, Bozeat S, Lambon Ralph MA, *et al.* The role of conceptual knowledge in object use: evidence from semantic dementia. *Brain* 2000;**123**:1913–25.

55 **Snodgrass JG**, Vanderwart M. A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity and visual complexity. *J Exp Psychol: Hum Learn Mem* 1980;**6**:174–215.

56 **Warrington EK**, McKenna P, Orpwood L. Single word comprehension: a concrete and abstract synonym test. *Neuropsychol Rehabil* 1998;**8**:143–54.

57 **McKenna P**, Warrington EK. *Graded naming test.* Windsor: NFER-Nelson, 1983.

58 **Della Sala S**, Baddeley AD, Papagno C, *et al.* Dual task paradigm: a means to examine the central executive. *Ann NY Acad Sci* 1995;**769**:161–71.

59 **Trenerry MR**, Crosson B, DeBoe J, *et al.* Stroop neuropsychological screening test. Florida: Psychological Assessment Resources, 1989.

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

61 **Robertson IH**, Ward T, Ridgeway V, *et al. Test of everyday attention.* Bury St Edmunds: Thames Valley Test Company, 1994.

62 **Warrington EK**, James M. *The visual object and space perception battery.* Bury St Edmunds: Thames Valley Test Company, 1991.

63 **Howell DC**. *Statistical methods for psychology*, 3rd ed. Belmont, California: Duxbury Press, 1992.

64 **Chertkow H**, Bub D. Semantic memory loss in dementia of Alzheimer's type: what do various measures measure? *Brain* 1990;**113**:397–417.

65 **Hodges JR**, Patterson K, Graham N, *et al.* Naming and knowing in dementia of Alzheimer's type. *Brain Lang* 1996;**54**:302–25.

66 **Hodges JR**, Patterson K, Ward R, *et al.* The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of frontotemporal dementia) from early Alzheimer's disease: a comparative neuropsychological study. *Neuropsychology* 1999;**13**:31–40.

67 **Caine D**, Hodges JR. Heterogeneity of semantic and visuospatial deficits in early Alzheimer's disease. *Neuropsychology* 2001;**15**:155–64.

68 **Braak H**, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol* 1991;**82**:239–59.

69 **Hodges JR**. Memory in the dementias. In: Tulving E, Craik FIM, ed. *Oxford handbook of memory.* Oxford: Oxford University Press, 2000:441–59.

70 **Salmon DP**, Hodges JR. Neuropsychological assessment of early onset dementia. In: Hodges JR, ed. *Early-onset dementia: a multidisciplinary approach.* Oxford: Oxford University Press, 2001:47–73.

71 **Barber R**, Scheltens P, Gholkar A, *et al.* White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. *J Neurol Neurosurg Psychiatry* 1999;**67**:66–72.

72 **Perry RJ**, Watson P, Hodges JR. The nature and staging of attention dysfunction in early (minimal to mild) Alzheimer's disease: relationship to episodic and semantic memory impairment. *Neuropsychologia* 2000;**38**:252–71.

73 **Perry RJ**, Hodges JR. Attentional and executive deficits in Alzheimer's disease: a review. *Brain* 1999;**122**:383–404.

74 **Galton CJ**, Patterson K, Graham K, *et al.* Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology* 2001;**57**:216–25.

75 **Mummery CJ**, Patterson K, Wise RJS, *et al.* Disrupted temporal lobe connections in semantic dementia. *Brain* 1999;**122**:61–73.

76 **Martin A**, Chao LL. Semantic memory and the brain: structure and processes. *Curr Opin Neurobiol* 2001;**11**:194–201.