The neuropsychological profile of vascular cognitive impairment in stroke and TIA patients

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Abstract—*Objective:* To characterize the neuropsychological profile of vascular cognitive impairment (VCI) and vascular dementia (VaD). *Methods:* The authors examined 170 patients with stroke or TIA at 3 to 6 months after the vascular event, and 96 age-matched healthy controls, with detailed neuropsychological and medical-psychiatric assessments, with a majority (66.7%) undergoing MRI brain scans. The subjects were diagnosed as having VaD, VCI, or no cognitive impairment by consensus. The neuropsychological tests were classified into cognitive domains, and composite z-scores adjusted for age and education. *Results:* VaD subjects had disturbance in all cognitive domains, with verbal memory, especially retention, being less affected. VCI subjects had similar but less severe disturbance. The domains that best discriminated cognitively impaired from unimpaired patients were abstraction, mental flexibility, information processing speed, and working memory. Cognitive impairment had a significant correlation with deep white matter hyperintensities, but not with volume and number of infarctions, even though the VaD subjects had larger infarct volumes than VCI subjects. The MRI variables did not provide additional discrimination between subgroups. *Conclusions:* The cognitive deficits in VaD and VCI are characterized by disturbance of frontal functions, with less verbal memory impairment. VaD and VCI differ in severity but not pattern of disturbance. The brain lesions that best account for these deficits are noninfarct subcortical white matter and gray matter changes due to ischemia. The picture of VaD/VCI presented shows subcortical deficits embellished by cognitive deficits from cortical infarctions.

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The neuropathologic basis of vascular dementia (VaD) comprises a variable combination of multiple infarcts, single strategic infarcts, noninfarct ischemic lesions affecting the white matter and basal ganglia, chronic hypoperfusion, and hemorrhage.[1] The neuropsychological profile of VaD is therefore likely to be heterogeneous.[2] Stated simply, the cognitive deficits in multi-infarct dementia (MID) will depend upon the number, size, and location of the infarcts. The syndrome of strategic infarct dementia (SID)[3] will present a different pattern of as yet insufficiently explored cognitive symptoms. VaD that results from multiple lacunar infarcts and noninfarct white matter disease, the so-called subcortical ischemic vascular dementia (SIVD), will present a clinical picture resembling a subcortical dementia.[4]

The above seemingly logical approach to the neuropsychology of VaD does not appear to have passed the empirical test. We recently reviewed a large number of studies of the neuropsychology of VaD[5] and identified many limitations in the published data: the diagnostic criteria used for VaD have been diverse; the definition of dementia itself has imposed constraints on that of VaD, leading to what has been called the Alzheimerization of the concept[6]; concepts such as MID, SID, and SIVD aim to describe more homogeneous subsyndromes, and most patients with VaD have a complex combination of pathologies, which makes such subclassification impossible; and there is considerable overlap of VaD with Alzheimer disease (AD).[7] Furthermore, as has been previously argued,[8] the diagnosis of VaD may occur at too late a stage of cognitive impairment, when the preventive strategies may no longer be potent.

We report the findings of the Sydney Stroke Study, which attempted to address some of the deficiencies in the literature in relation to the neuropsychological profile of vascular cognitive impairment (VCI).

Method. *Sample.* Subjects were consecutive patients admitted to two large teaching hospitals affiliated with the University of New South Wales who had recently had an ischemic stroke as

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diagnosed by two neurologists independently. An ischemic stroke was defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer, with no apparent cause other than of vascular origin" in which a brain CT or MRI scan does not show intracranial hemorrhage.[9] Subjects were recruited over a 38-month period between May 1997 and June 2000. Midway through the study (from May 1998), consecutive inpatients with transient ischemic attacks (TIA), defined as sudden focal neurologic deficits lasting less than 24 hours and not associated with cerebral infarction on CT scan,[10] were also included. The reason for the inclusion of TIA patients was to have a subsample of subjects with noninfarction ischemic cerebrovascular disease, and thereby increase the range of pathology in the sample. Subjects were aged 49 to 87 years, did not have a diagnosis of dementia or other neurologic disorder prior to the stroke/TIA, did not have severe aphasia as a significant limiting factor for assessment (a score of <3 on the Aphasia Severity Rating Scale of the Boston Diagnostic Aphasia Examination),[11] and were well enough to consent to participate. Subjects had had a decline of <5 points on the 16-item IQCODE[12] over the 5 years preceding the stroke/TIA, as rated by an informant who had a minimum of once weekly contact with the subject in this period. Healthy control subjects were unpaid volunteers, recruited from the same neighborhood as the stroke/TIA subjects, matched for age, and who had no history of stroke, TIA, or other neurologic or psychiatric disorder. An attempt was made to match the subjects on sex and years of education, but this was not completely successful, the discrepancy being then taken into account in the analysis.

Assessment. Stroke/TIA subjects had a baseline assessment within 1 week of admission to hospital, which included a detailed medical history and examination, history of risk factors for cerebrovascular disease and dementia, a functional assessment, and the Mini-Mental State Examination.[13] Between 3 and 6 months after the index stroke or TIA, a detailed neuropsychological assessment and medical and psychiatric examination were performed, and the majority of subjects (66.7%) had a brain MRI scan. The comparison group had a similar assessment performed in one stage.

Neuropsychological assessment. The battery comprised the following tests pertaining to various cognitive domains: verbal memory (Logical Memory [LM] I and II subtests from Wechsler Memory Scale–Revised [WMS-R])[14]; visual memory (Visual Reproduction [VR] I & II from WMS-R)[14]; working memory (Digit Span backwards, Arithmetic from Wechsler Adult Intelligence Scale Revised [WAIS-R])[15]; attention (Digit Span forwards [WAIS-R])[15]; mental control (WMS-R)[14]; language (15-item Boston Naming Test)[16]; information processing speed (Trail Making Test Part A,[17] Symbol Digit Modalities Test [SDMT][18]); visuoconstruction (Block Design [WAIS-R][15] and copying simple figures); praxis-gnosis (Western Aphasia Battery ideomotor apraxia subtest items,[19] finger gnosis and stereognosis[20,21]); abstract reasoning (Similarities, Picture Completion [WAIS-R])[15]; mental flexibility (Color Form Sorting Text,[22] Trail Making Test Part B[17]); verbal fluency (phonemic [FAS][23] and semantic [animals][24]). Mental flexibility and verbal fluency were together characterized as executive function. Premorbid ability was estimated using the National Adult Reading Test–Revised (NART-R),[25] and handedness was determined with a modified version of Annett's Test.[26] Trained clinical psychologists performed assessments. Subjects were given breaks where appropriate to minimize the effects of fatigue on performance. Subjects judged to be clinically depressed were not tested until their depression had been satisfactorily treated as judged by a total score on the Global Depression Scale of <5, a reduction in self-reported symptoms of depression, informant report, or further psychiatric assessment.

Medical and psychiatric assessment. Medical and psychiatric assessment comprised the following: medical history; functional assessment (Social and Occupational Functioning Scale [SOFAS],[27] Activities of Daily Living [ADL],[28] and Instrumental ADL [IADL])[29]; a standard neurologic examination (European Stroke Scale)[30]; and detailed psychiatric assessment (past psychiatric history, Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders–IV,[31] 28-item General Health Questionnaire,[32] 15-item Geriatric Depression Scale,[33] Hamilton Depression Rating Scale,[34] and Neuropsychiatric Inventory).[35]

MRI scans. MRI was performed on a 1.5 T Signa GE scanner (GE Systems, Milwaukee, WI) using the following protocol: a scout midsagittal cut (two-dimensional, repetition time [TR] 300 msec, echo time [TE] 14 msec, 5 mm thick, number of excitations 1.5); 1.5-mm-thick T1-weighted contiguous coronal sections through whole brain using a FSPGR sequence and three-dimensional acquisition (TR 14.3 msec, TE 5.4 msec); 4-mm-thick (0 skip) T2-weighted fluid-attenuated inversion recovery coronal slices through whole brain (TR 8900, TE 145, inversion time 2200, field of view 25, 256 × 192).

Analysis of data. Neuropsychological tests. Z-scores were derived using the control group mean and SD. For the purposes of diagnosis and the classification of performance of each subject on each test, age-scaled scores were derived from published norms.[16,36-41] Where no published norms were available, impairment criteria were based on clinical judgment and discussed in the consensus meeting. The tests were grouped into the cognitive domains described above. Verbal and visual memory were further divided into episodic verbal memory—learning (LMI) and retention (1-LMII/LMI), episodic nonverbal memory—learning (VRI) and retention (1-VRII/VRI) in an attempt to differentiate between the processes of encoding and storage. Years of education and performance on the NART-R were used as estimates of premorbid intellectual abilities. To determine an individual's performance on a test, a z-score was computed, and the composite z-score for all tests assigned to a domain was the measure of performance in that domain. The scores from individual tests were used in the exploratory analyses. In a further effort to reduce the number of variables, a principal components analysis was performed on the z-scores on the various tests.

MRI scans. These were rated by a trained rater with good inter-rater (intraclass correlations from 0.7 to 0.86 on various measures on 10 scans) and intrarater (intraclass correlations from 0.8 to 0.92 on 20 scans) reliability. All ratings were carried out on a computer console using ANALYZE (Mayo Foundation, Rochester, MI) software. Brain infarctions were identified on T1-weighted images and each infarction delineated manually to obtain its area, which multiplied by thickness gave the total stroke volume. Periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH) were rated on a 0 to 3 scale.[42] For PVH, ratings were performed for the lining of the lateral ventricles (rims) and the frontal and occipital horns (caps), the sum of which on either side gave the total PVH score (max score = 18). For DWMH rating, the frontal, temporoparietal, and occipital white matter and the internal capsules were rated separately, and the scores for both sides added to give a total DWMH score (max score = 24). As a measure of atrophy, two ventricle-brain ratios (anterior and midsection) (VBR) were obtained.[43]

Consensus diagnosis. The diagnosis was assigned to each subject in a case conference at which all medical, psychiatric, neuropsychological, and neuroimaging data were presented, and a consensus was reached. A neuropsychiatrist, a psychogeriatrician, a neurologist, and one or more research psychologists attended the meeting. Guidelines were drawn up for a diagnosis of dementia, VaD, and VCI. For dementia (VaD) diagnosis, a subject must have definite impairment in two or more cognitive domains (impairment in memory was not necessary), demonstrate evidence of functional decline because of the cognitive deficits, and have evidence of CVD on MRI or CT scan judged to be sufficient to account for cognitive impairment. Definite impairment was defined as performance below the 5th percentile relative to age-adjusted published normative data, and functional decline was a decline in SOFAS score of ≥20 from the premorbid estimate or failure on one item of ADL or two items of IADL due to cognitive deficits as judged by consensus. For a diagnosis of VCI, the subject must have definite impairment in one domain or marginal impairment in two domains or, if there was impairment in more domains, the functional decline criterion for VaD was not met. Marginal impairment was performance at 5th to 10th percentiles of age-matched normative data.

Statistical analysis. The two groups were compared on sociodemographic, neuropsychological, and brain imaging variables. The comparisons of the neuropsychological test scores were corrected for age, NART, and years of education. Because the z-scores already took age and education into account, no further correction was applied to their comparisons. We examined the cognitive profile of VaD and VCI by determining the percentage of subjects

with definite or marginal impairment in each domain. The MRI measures were correlated with performance on relevant cognitive domains and with the loadings on the first principal component of the neuropsychological data. A discriminant function analysis was performed to determine which cognitive domains best discriminated between stroke/TIA group subjects with no cognitive impairment and those with VCI or VaD, and further between VCI and VaD. Using the sum of ADL and IADL scores (max 14) as an index of functional level, a discriminant function analysis was performed to determine which cognitive domains best related to functional impairment.

Results. *Subject characteristics.* During the duration of recruitment, 1,050 patients with possible stroke or TIA were screened for suitability and 252 who met inclusion and exclusion criteria entered into the study. The major reasons for exclusion, in order of frequency, were as follows: 1) refusal by subject or family member (n = 550); 2) lack of confirmation of diagnosis (n = 66); 3) critical medical condition (n = 53); 4) lack of English (n = 44); 5) aphasia (n = 36); 6) pre-existing dementia clinically or based on IQCODE score (n = 27); and 7) age >85 years (n = 22). By the time of detailed assessment at 3 to 6 months following the cerebrovascular event, 42 were lost to follow-up (33 due to withdrawal, 3 had deceased, 4 relocated outside Sydney, 1 was not contactable), and 1 was excluded for baseline dementia missed earlier. Of the 210 patients in the study (176 stroke and 34 TIA patients), 170 completed a detailed neuropsychological assessment. Of the 160 who volunteered as potential control subjects, 130 were found to meet inclusion criteria; 109 of these were assessed, but data were incomplete for 6. Because 7 control subjects were noted to have an incidental brain infarct on MRI, 96 are included in this report. Patients included (n = 210) were compared with potential subjects excluded (n = 840) on age and sex and there were no significant differences. The patients with (n = 170) and without (n = 40) complete assessment were compared on age, sex, and years of education, with no significant differences noted, but those with complete assessment were nonsignificantly higher functioning on ADL and IADL.

The patients and controls were well matched on age but not on education or NART-IQ. The latter were therefore used as covariates in the analyses, wherever appropriate. There were more men in the stroke/TIA group, but a comparison by sex did not yield any significant differences in cognitive function after taking age and education into consideration. The results are presented in table 1.

Subjects with and without MRI scans were compared on age, years of education, and sex, and no significant differences were noted. When the MRI scans were carefully analyzed, 74.3% of patients had brain infarcts, which were large infarcts in 31.7% (right-sided 23, left-sided 9), and lacunar infarcts in 42.6%. Incidentally, 7 (9.1%) control subjects had MRI evidence of infarction, lacunar in 6 and large infarct in 1. In the patients with lacunar infarcts, the mean number was 2 (range 1 to 6), and in those with large infarcts, the mean was 1.8 (range 1 to 5). The mean volume of lacunar infarcts was 0.59 mL and that of large infarcts was 6.4 mL. The stroke/TIA subjects had more cortical atrophy, greater VBR, and more extensive DWMH and PVH, but the hyperintensities in subcortical gray matter were not significantly different in the two groups. These data are summarized in table 2.

Table 1 *The sociodemographic and functional characteristics of the subjects*

Characteristics	Control, mean (SD), n = 96	Stroke/TIA, mean (SD), n = 170	t-Test *p* value
Age, y	71.32 (6.6)	72.15 (9.0)	0.389
% Women	50.5	39.4	0.001*
Education, y	11.80 (3.3)	10.11 (2.6)	<0.001
NART-IQ	114.34 (7.14)	104.93 (10.5)	<0.001
MMSE	28.75 (1.4)	27.83 (2.6)	<0.001
ADL	5.93 (0.3)	5.22 (1.4)	<0.001
IADL	7.07 (1.4)	6.74 (2.0)	0.065
IQCODE	49.18 (1.9)	49.31 (6.8)	0.883
SOFAS	90.17 (5.3)	79.78 (13.1)	<0.001
Risk factors	**Frequency %**	**Frequency %**	**χ^2 *p* value**
Hypertension	37.5 (39/104)	58.7 (71/121)	0.0015†
Hyperhomocysteinemia‡	49.1 (26/53)	83.0 (73/88)	<0.0001†
Hypercholesterolemia	25.3 (25/99)	37.8 (45/119)	0.0479
Smoking	41.3 (43/104)	61.2 (74/121)	0.0846
Diabetes mellitus	5.8 (6/104)	17.8 (21/118)	0.0062
Previous TIA	0 (0/103)	24.1 (29/120)	<0.0001†
Previous stroke	0 (0/103)	17.6 (21/119)	<0.0001†
Previous AMI	8.8 (9/102)	17.8 (21/118)	0.0531
Previous angina	10.7 (11/103)	20.8 (25/120)	0.1483
Atrial fibrillation	2.0 (2/102)	25.9 (30/116)	<0.0001†

TIA = transient ischemic attack; NART-IQ = National Adult Reading Test-Intelligence Quotient[25]; MMSE = Mini-Mental State Examination[13]; ADL = Activities of Daily Living[28]; IADL = Instrumental Activities of Daily Living[29]; IQCODE = Informant Questionnaire for Cognitive Decline in Elderly[12]; SOFAS = Social and Occupational Functioning Assessment Scale[31]; AMI = acute myocardial infarction.

* Chi-square *p* value.

† Given the number of risk factors, only those below 0.01 should be considered significant.

‡ Only 53 controls and 88 patients had homocysteine measurement.

Comparison of neuropsychological test scores. The two groups, after excluding the control subjects with incidental infarcts (n = 7), were compared initially on the individual test scores, correcting for age, education, and NART scores. These comparisons are presented in table 3. While the performance of the stroke/TIA subjects was poorer on all the tests, the differences after correction were significant for performance on VR, Block Design, Similarities, Trails B, Verbal fluency (animals), SDMT, and gnosis function. When the composite z-scores on the different cognitive domains were compared, the differences were significant for the domains executive function, information processing speed, visual memory, abstraction, and visuoconstruction, with the stroke/TIA subjects performing worse. The patients also performed worse on abstract reasoning, working memory, language, and praxis-gnosis by over 0.5 SD, but the differences were not significant. Scores on verbal memory did not differ between the groups (table 4).

Table 2 *Mean (SD) brain MRI characteristics of the sample*

MRI variables	Controls, n = 67	Stroke/TIA, n = 97	NCI, n = 39	VCI, n = 37	VaD, n = 18	ANOVA* *p* value	VCI vs VaD	(VCI + VaD) vs NCI	NCI vs Con
Total cortical atrophy	1.03 (1.2)	1.60 (1.8)	1.41 (1.6)	1.51 (1.8)	1.83 (1.25)	0.007	0.598	0.856	0.107
VBR	0.216 (0.04)	0.233 (0.05)	0.23 (0.04)	0.24 (0.03)	0.211	0.025	0.211	0.548	0.362
Stroke volume	—	2318.9 (7886.5)	1809.5 (8722.3)	913.4 (1683.3)	6896.0 (12412.2)	N/A	0.01	0.541	—
Total brain WMH (FLAIR)	5.15 (2.6)	7.60 (3.80)	6.19 (2.7)	8.08 (4.1)	9.58 (3.9)	0.000	0.176	0.004	0.03
Deep WMH	1.80 (1.7)	3.48 (2.29)	2.70 (1.9)	3.66 (2.3)	4.61 (2.5)	0.000	0.168	0.015	0.006
Periventricular WMH	3.26 (1.02)	3.89 (1.30)	3.43 (1.05)	4.00 (1.46)	4.29 (1.25)	0.005	0.414	0.01	0.407
Internal capsule WMH	1.63 (1.5)	3.20 (2.01)	2.56 (1.8)	3.32 (2.0)	4.13 (2.1)	0.000	0.186	0.027	0.003
Subcortical GMH	0.36 (0.83)	0.61 (1.16)	0.13 (0.32)	0.44 (1.04)	0.54 (0.78)	0.165	0.664	0.025	0.606

The scores on visual ratings are presented. NCI + VCI + VaD = 94. The remaining three stroke subjects had non-VaD dementia/cognitive impairment.

* Analysis of variance (ANOVA) controlling for age and multiple comparisons (with Bonferroni correction).

TIA = transient ischemic attack; NCI = no cognitive impairment; VCI = vascular cognitive impairment; VaD = vascular dementia; Con = controls; VBR = ventricle to brain ratio; N/A =not applicable; WMH = white matter hyperintensities; FLAIR = fluid-attenuated inversion recovery; GMH = gray matter hyperintensities.

The frequency of definite impairment on the various cognitive domains in the patients with VaD, VCI, and NCI is presented in table 5. The VaD subjects had a high frequency of disturbance in all cognitive domains except verbal memory. The decreasing order of the frequency of disturbance in various domains was as follows: information processing speed, praxis-gnosis, visual memory (learning), mental flexibility and abstraction, attention, and visuoconstruction. The pattern was similar in VCI. In the latter, while visual memory was frequently abnormal, verbal memory impairment was not more prevalent than in the control group. The NCI group did not differ from the control group. While learning of visual material was abnormal in 63.9% of VaD patients, memory retention was definitely abnormal in a much smaller proportion (27.8%), a pattern different from that seen in AD.[5] The proportion of VaD patients with language impairment is probably biased by the exclusion of subjects with severe aphasia from the study. The VaD and VCI groups were qualitatively similar in the pattern of neuropsychological impairment, but they did differ quantitatively, the differences being significant at $p < 0.01$ for information processing speed, attention, working memory, and praxis-gnosis function. Of note was the absence of significantly increased disturbance in verbal memory acquisition and retention in the VCI group compared to the control group. Seven stroke/TIA subjects were above the cutoff for depression at the time of testing. The analysis was repeated after excluding them, and the results were unchanged.

Discriminant analyses. A discriminant function analysis was performed using the composite z-scores on the cognitive domains as the predictor variables. The variables that predicted the discrimination between vascular impairment (VaD and VCI) and no impairment (NCI) in the stroke/TIA group, with a discriminant value >0.6, were abstraction, mental flexibility, information processing speed, and working memory. Overall, 83.6% of subjects were correctly classified using this model. The accuracy of classification was 84.3% with the top two neuropsychological variables (abstraction and mental flexibility), and this did not improve by the addition of more variables. The analysis was repeated for the discrimination between VaD and VCI, and 76.6% of cases were correctly classified, but with only attention and concentration having a discriminant value >0.6.

MRI and cognitive function. The VaD, VCI, NCI, and control groups were contrasted on the MRI variables. Subjects with cognitive impairment (VaD + VCI) had greater WMH scores than those without (NCI). The NCI had more WMH than the control group. The VCI and VaD did not differ significantly on WMH scores, but the VaD group had greater stroke volumes. To further examine the relationship between cognitive function and neuropsychological variables, we subjected the latter to a principal components analysis. A four factor solution accounted for 62.7% of variance, with Factor I accounting for 43.5% of variance. The tests with the highest loading on Factor I, with their coefficients, were as follows: Trails B (−0.81), SDMT (0.81), Trails A (−0.79), VRI (0.76), Block Design (0.75), and VRII (0.75). This factor had a correlation, after correction for age, with total brain hyperintensity scores ($r = -0.32$, $p = 0.002$), DWMH scores ($r = -0.29$, $p = 0.04$), as well as subcortical gray matter hyperintensity scores ($r = -0.21$, $p = 0.04$). The correlation of Factor I with stroke volume was −0.19 ($p = 0.07$). Cortical atrophy had a correlation with the first factor ($r = -0.25$, $p = 0.01$), but not with VBR.

MRI and discrimination between subgroups. We used the neuropsychological domain scores and summary MRI variables (total WMH, cortical atrophy, VBR, stroke volume, and number of strokes) in two different analyses: 1) discriminant analysis to predict diagnostic category of vascular impairment (VaD and VCI) and NCI, and 2) multiple regression to predict overall cognition (PCA1). Both analy-

Table 3 *Neuropsychological summary scores by groups*

Test	Control, mean, n = 96	SD	Stroke/TIA, mean, n = 163	SD	F-statistic	ANOVA* *p* value
Mental control	5.39	1.0	4.73	1.4	0.47	0.495
Logical Memory 1	23.51	7.2	22.02	7.4	1.98	0.161
Logical Memory 2	18.28	8.2	16.17	8.7	0.35	0.552
Visual Reproduction 1	31.60	6.1	26.24	8.8	6.41	0.012
Visual Reproduction 2	23.74	10.1	16.78	10.7	8.56	0.004
Digit Span age	15.04	3.9	12.59	3.8	1.08	0.300
Picture Completion	13.39	3.7	10.40	4.7	4.68	0.032
Block Design	23.99	9.4	17.15	10.0	8.20	0.005
Arithmetic	12.14	3.8	9.94	3.7	0.55	0.458
Similarities	18.16	4.7	12.50	6.7	5.42	0.021
Trails A (s)	43.49	15.1	66.33	41.6	3.80	0.053
Trails B (s)	107.00	44.9	177.93	120.9	9.29	0.003
COWAT	38.27	13.1	27.42	12.5	3.14	0.078
Verbal Fluency (animals)	17.55	4.7	14.31	4.7	8.32	0.004
BNT	13.61	1.4	12.76	2.2	0.46	0.500
Symbol Digit Modalities Test	42.74	9.6	34.13	12.9	7.90	0.005
Ideomotor apraxia (maximum = 18)	17.24	1.1	16.94	1.5	1.22	0.270
Gnosis† (maximum = 30)	29.34	1.5	27.99	2.6	5.78	0.017
Draw‡ (maximum = 8)	7.05	1.0	6.37	1.9	1.13	0.289
Colour Form Sort Test	3.95	0.3	3.32	1.1	3.21	0.075

All comparisons controlled for age, NART, education, depression (HAM-D score >10 were excluded, n = 7 patients), and multiple comparisons (with Bonferroni correction).

* Analysis of variance (ANOVA) controlling for age and multiple comparisons (Bonferroni correction).
† Sum stereognosis (/6) and finger gnosis (/24).
‡ Sum copy figure 1 (/4) and copy figure 2 (/4).

NART = National Adult Reading Test; HAM-D = Hamilton Depression Rating Scale; COWAT = Controlled Oral Word Association Test; BNT = Boston Naming Test.

ses showed that the MRI variable did not add significant predictor information, and a discrete number of cognitive domains were able to explain a majority of the variance.

Functional correlates of cognitive impairment. The VaD group was, by definition, functionally impaired. The VCI group also showed impairment in comparison with the NCI subjects, after controlling for physical deficits related to stroke, suggesting a contribution by cognitive impairment on performance in these subjects. To determine which cognitive domains had the most impact on function, we performed a discriminant function analysis between subjects with impairment (combined score on ADL and IADL <10) and those without (score ≥ 10). Cognitive predictors were able to correctly classify subjects as impaired or unimpaired at 92.2% accuracy. The variables that best discriminated between the two groups (discriminant function score >0.4) were praxis-gnosis function, information processing speed, mental flexibility, and visuoconstruction.

Discussion. Defining VaD poses a challenge, as the definition must accommodate its heterogeneity and yet be specific and operational. To base it on the better-defined disorder of AD may be acceptable when cognitive deficits are severe, but not when the purpose is to define early impairment. There is another reason for a concerted effort to identify the early and perhaps core neuropsychological abnormalities in VaD. We know that the cognitive deficits in other dementias, such as AD and frontotemporal dementia, follow a pattern that reflects the nature and development of the pathology in these disorders. If we accept that VaD is more than a simple aggregation of infarcted brain regions, and that the involvement of specific brain regions may be necessary for the dementia syndrome to manifest, we must identify the central neuropsychological deficits that characterize VCI. It is likely that there are critical brain areas that are central to the dementia caused by vascular factors, and other brain areas when disrupted superimpose diversity on this central dysfunction. These critical regions have been proposed to be the limbic and paralimbic areas, the diencephalon, the basal forebrain, the striatum, frontal lobes, and the surrounding white matter that provides connections to and from these areas.[44] The question our study addresses is whether the salient neuropsychological deficits reflect this pattern of dysfunction.

The findings of our study are consistent with the published literature[2,5] that frontal-executive dysfunc-

Table 4 *Composite z-scores on different cognitive domains for the two groups*

Cognitive domain	Control, n = 96	Stroke/TIA, n = 163	F-value	ANOVA* p value
Attention and concentration	−0.010	−0.623	0.743	0.390
Global memory				
Learning	0.054	−0.489	0.86	0.355
Recall	0.005	−0.362	3.358	0.068
Total	−0.102	−0.567	2.456	0.119
Visual memory				
Learning	0.048	−0.845	6.492	0.012*
Recall	−0.005	−0.525	5.637	0.019*
Total	−0.246	−0.956	9.503	0.002*
Verbal memory				
Learning	0.061	−0.149	1.947	0.164
Recall	0.015	−0.213	0.510	0.476
Total	0.042	−0.191	0.204	0.652
Executive function	0.021	−1.189	12.130	0.001*
Abstract reasoning	0.012	−0.977	7.139	0.008*
Working memory	0.032	−0.552	1.438	0.232
Language	−0.039	−0.627	0.832	0.363
Visuoconstructive function	0.011	−0.722	4.274	0.040*
Praxis—gnosis function	0.017	−1.925	1.618	0.205
Speed of information processing	0.009	−1.015	7.168	0.008*

All comparisons controlled for age, NART, education, depression (HAM-D score >10 were excluded), and multiple comparisons (with Bonferroni correction).

* $p < 0.05$.

NART = National Adult Reading Test; HAM-D = Hamilton Depression Rating Scale; ANOVA = analysis of variance.

tion and psychomotor slowing are two prominent features of both VCI and VaD. In addition, dominant and nondominant parietal lobe functions were affected. Even though naming was affected in the impaired group, this may be an underestimate of language impairment as patients with severe aphasia were excluded from the study. Frontal-executive dysfunction was a good discriminator not only for the presence of impairment but also between VCI and VaD. The nature of the deficits was similar in VCI and VaD, suggesting VaD was but a more severe form that was not qualitatively different. For frontal-executive abilities, the dysfunction was in the categories of working memory, abstraction, reasoning, mental flexibility, and fluency.

It is interesting that the VCI subjects did not perform poorly on verbal memory tasks. While the stroke/TIA patients had somewhat lower scores on LM, the difference was not significant, and they did not have a higher frequency of definite impairment as defined by performance less than −1.5 SD. While LMI scores were lower in those with cognitive impairment (VaD + VCI), their memory retention scores were not different from controls. VCI subjects did not differ from controls on both verbal memory learning and retention. This pattern is different from what is seen in AD, in which the retention of new information is poorer from an early stage, with increased rates of forgetting.[45] It is likely that deficits in attention, information processing speed, and working memory contributed to the problems in learning a story in the VaD and VCI subjects, but the information that had been acquired was well retained. While the deficits in visual memory in VaD and VCI patients are more pronounced, the pattern is similar to verbal memory, with acquisition being more affected than retention. The findings are consistent with previous literature that emphasizes higher rates of forgetting in AD as compared to VaD.[46-48]

When considering the impairment caused by stroke, neurologists have traditionally looked to physical deficits. This study, along with others,[49,50] emphasizes the contribution of cognitive deficits to functional impairment, evident in deficits in IADL. The functional impairment was present in both VaD and VCI subjects, which by definition differed quantitatively in the degree of disability. As mentioned above, these two syndromes in stroke patients are similar neuropsychologically, again differing in the extent of disturbance rather than its type. This leads to the conclusion that the demarcation between VaD

Table 5 *Frequency (%) of definitive impairment ($z < -1.5$) in cognitive domains by diagnostic grouping*

Cognitive domain	Control, n = 96	NCI, n = 66	VCI, n = 58	VaD, n = 36	VCI vs VaD,* p value	(VCI + VaD) vs NCI,* p value	NCI vs Con,* p value
Attention	5.3	7.7	10.3	50.0	<0.0001*	0.0067	0.5215
Global memory learning	3.2	3.1	19.0	38.9	0.0378	0.0001	0.9862
Global memory retention	8.5	6.2	15.5	19.4	0.7692	0.0489	0.6054
Global memory total	7.4	7.4	21.4	33.3	0.1980	0.0043	0.9243
Visual memory learning	7.4	10.8	37.9	63.9	0.0219	<0.0001*	0.4423
Visual memory retention	9.6	10.8	22.4	27.8	0.6348	0.0312	0.7717
Visual memory total	10.6	10.8	37.9	63.9	0.0219	<0.0001*	0.9431
Verbal memory learning	8.5	0.0	12.1	25.0	0.1423	0.0005	0.0170
Verbal memory retention	8.5	4.6	10.3	22.2	0.1646	0.0472	0.3589
Verbal memory total	7.4	0.0	12.1	22.2	0.2599	0.0009	0.0260
Executive function	3.2	3.1	34.5	58.3	0.0380	<0.0001*	0.9862
Abstraction	7.4	4.6	39.7	58.3	0.1145	<0.0001*	0.4900
Working memory	0.0	0.0	8.6	38.9	0.0005	0.0001	0.3939
Language	10.6	4.6	31.0	41.7	0.3003	<0.0001*	0.1850
Visuoconstructive function	6.4	6.2	25.9	47.2	0.0329	<0.0001*	0.9802
Praxis—gnosis function	14.9	16.9	43.1	75.0	0.0033	<0.0001*	0.6875
Speed of information processing	3.2	3.1	36.2	69.4	0.0027	<0.0001*	0.9862

Those with HAM-D >10 were excluded from analysis. Total NCI, VCI, or VaD = 160. The remaining three stroke subjects were judged to have non-VaD dementia/cognitive impairment.

* χ^2 Tests.
† $p < 0.01$ Considered significant.

HAM-D = Hamilton Depression Rating Scale; NCI = no cognitive impairment; VCI = vascular cognitive impairment; VaD = vascular dementia; Con = controls.

and VCI is an arbitrary one imposed by the a priori definition of the syndromes. It supports the calls for a rationalization of the concepts.[51]

The neuropathologic basis of cognitive impairment in our subjects was most likely to be lesions visualized on structural MRI, in particular T2-weighted imaging. Stroke patients frequently had lacunar infarcts, which were usually multiple. However, it was not the volume or number of infarctions but the extent of the white matter pathology and hyperintense lesions in the basal ganglia and thalamus that best correlated with cognitive dysfunction. Of the white matter pathology, it was the deep WMH, in particular those in the frontal white matter and the internal capsule, which had significant correlations with neuropsychological function. This suggests that the major abnormalities in VaD and VCI relate to disconnection of the frontal cortex from the striatum, thalamus, and possibly the medial temporal regions. While large cortical strokes do leave a signature on the neuropsychological deficits, they are best regarded as being superimposed on a baseline subcortical pathology. The VaD subjects had greater stroke volumes than the VCI, suggesting that larger infarctions lead to functional decompensation of a vulnerable brain, but it would be inappropriate to conceptualize VaD as a simple accumulation of infarctions. The cognitive impairment was also significantly correlated with a measure of total brain atrophy. The basis of this atrophy is uncertain, but because our stroke/TIA patients had more brain atrophy than control subjects, we consider this to be a consequence of CVD. Further, although we excluded subjects with gradual cognitive decline prior to the stroke/TIA, it is possible that some subjects with early AD may have entered the study. Only neuropathologic verification on follow-up can settle this issue definitely.

The strengths of our study were the relatively large sample size, the detailed neuropsychological assessments, the inclusion of MRI data in a majority, and the wide range of impairment in the subjects, with many being in the mild range. Our study had a number of limitations. First, we studied impairment in a stroke/TIA cohort and did not include VaD subjects from other settings. We expected that this selection process would lead to a profile suggestive of multi-infarct dementia. VaD patients seen in memory clinics, falls clinics, and continence clinics have been suggested to have a picture of subcortical dementia,[52] with emphasis on frontal-executive dysfunction and behavioral and psychiatric syndromes. Our finding of similar neuropsychological disturbance in a stroke/TIA cohort, however, further sup-

ports the view that such dysfunction may be common to all VaD and VCI and may be described as being central to the syndrome. Secondly, this is a cross-sectional design and many aspects of the pathogenesis of VCI are best studied longitudinally. We only had retrospective measures of the subjects' pre-stroke/TIA functioning. In spite of our exclusion of subjects with baseline cognitive impairment prior to stroke/TIA, we cannot be certain that subjects with mild cognitive impairment on the basis of Alzheimer-type pathology did not enter the study. Third, our control subjects were not matched on sex and education with the stroke/TIA group, a limitation we dealt with statistically. Fourth, a large proportion of subjects was excluded for various reasons, but we do not consider this to have introduced a systematic bias in our sample. However, the more severely affected patients were likely to be excluded.

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