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The relationship of subcortical MRI hyperintensities and brain volume to cognitive function in vascular dementia

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Abstract

The relationship between MRI findings (i.e., subcortical hyperintensities; SH, whole brain volume) and the cognitive dysfunction of vascular dementia (VaD) was examined. Participants included 24 persons that met NINDS-AIREN criteria for VaD (MMSE = 19.9 ± 4.2) and underwent comprehensive neuropsychological assessment and MRI brain imaging. The volume of subcortical hyperintensities (SH) was strongly associated with executive–psychomotor performance, but not with performance across other cognitive domains or global cognitive functional level. Conversely, WBV was strongly associated with global cognitive functioning and performance across most cognitive domains (memory, language, visual integration), but not with executive–psychomotor functioning. The failure of SH to account for either the global dementia evident in these VaD patients or impairments across most cognitive domains suggests that deep subcortical white matter disease may only indirectly contribute to the global cognitive dysfunction of VaD. That WBV emerged as a stronger correlate of dementia raises further questions regarding the cerebral mechanisms that contribute to the development of VaD. (*JINS*, 2002, *8*, 743–752.)

Keywords: Vascular dementia, Neurocognitive functioning, Subcortical hyperintensities, Whole brain volume

INTRODUCTION

Vascular dementia (VaD) accounts for 15 to 20% of dementia cases in reported series (Leys et al., 1999; Mirsen & Hachinski, 1988; Roman, 1991; Tatemichi et al., 1994). Yet, its etiology is still not well understood and differential diagnosis of VaD and Alzheimer's disease (AD) is often fraught with difficulties. Functionally, the cognitive presentation of VaD differs qualitatively from that of AD, with attention, executive and psychomotor functions disproportionately impaired in VaD, and memory and other core cognitive functions frequently less affected (Looi & Sachdev, 1999; Padovani et al., 1995; Roman, 1999), unlike AD which usually causes profound impairments of memory and intellectual functions (Matsuda et al., 1998a, 1998b).

Various cerebrovascular conditions give rise to VaD and produce clinical heterogeneity. VaD may result from (1) multiple infarctions, (2) strategic single-infarction, (3) microvascular disease, (4) cerebral hypoperfusion, (5) hemorrhage, or (6) combinations of these etiologies (Roman et al., 1993). The etiology of dementia in cases of cortical infarction is often evident, as the severity and type of resulting cognitive impairment usually corresponds to the extent of cortical damage and whether strategic areas are affected (Mielke et al., 1992; Tatemichi et al., 1994). The cause of dementia among patients with microvascular disease affecting deep subcortical and periventricular white matter with relative sparing of cortex is less well understood, and is the focus of this study.

Deep subcortical and periventricular white matter ischemia associated with microvascular disease is often clinically determined by interpretation of hyperintensities on brain magnetic resonance imaging (MRI). The presence of a large number of subcortical hyperintensities (SH) on MRI usually is taken as indication of subcortical white matter damage and microvascular disease among patients who have clinical findings consistent with cerebrovascular disease. Yet SH is also quite common among patients with AD

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(Barber et al., 1999; Doddy et al., 1998). Furthermore, small quantities of SH are often evident in healthy elderly people without clinical evidence of stroke or dementia (Erkinjuntti et al., 1994; Inzitari et al., 1987; Liu et al., 1992; Mirsen et al., 1991). While SH volume has been associated with severity of cognitive impairments, particularly in the areas of attention, executive and psychomotor functioning (Breteler et al., 1994a, 1994b; Cahn et al., 1996; Liu et al., 1992; Sultzer et al., 1995), this finding is not consistent among investigations (Rao et al., 1989; Schmidt et al., 1993; Sultzer et al., 1995; Tupler et al., 1992). Ultimately, whether or not cognitive impairments are evident depends on the extent, multiplicity, and location of SH. A threshold seems to exist, above which cognitive impairments and functional problems in daily living are most likely (Boone et al., 1992; Pantoni et al., 1995).

We previously found that SH volume was associated with impairments of attention, executive and psychomotor functioning in VaD (Cohen et al., 2000; Moser et al., 2001). This finding is consistent with the results of other investigations of SH among both neurological patients and healthy elderly persons. The fact that these functions tend to be more impaired in VaD than AD suggests that deep subcortical/periventricular white matter lesions caused by microvascular disease play an important role in VaD. Yet impairments of executive, attention, and psychomotor functions are not the only manifestations of VaD. In fact, severe VaD can be very difficult to distinguish from AD, as many patients with VaD experience a complete loss of cognitive capacity. Such global dementia is difficult to account for. One might posit that deep white matter damage contributes to frontal–subcortical dysfunction, which in turn accounts for VaD. Unfortunately, there is little data actually demonstrating this relationship in VaD, and most studies that have examined this issue have methodological limitations, such as small sample sizes or dichotomization of patients into groups based on the presence or absence of SH (Boone et al., 1992; Inzitari et al., 1987; Liu et al., 1992; Schmidt et al., 1993; Sultzer et al., 1995; Tupler et al., 1992). Therefore, the etiology of dementia associated with severe SH remains unresolved. The current study was conducted to examine the relationship between brain MRI indices of brain pathology and the cognitive impairments contributing to dementia among patients with VaD.

METHODS

Clinical Sample

Thirty-nine patients from the Memory and Cognitive Disorders Clinic of the Miriam Hospital in Providence, Rhode Island and from physicians' offices in the surrounding area were invited to participate in a prospective study of VaD. The sample consisted of men and women at least 55 years of age who were undergoing baseline evaluation as part of an experimental drug protocol to examine the effects of Citicoline for the treatment of VaD (#IP302-012). For purposes of current study, we report data from 24 participants for whom complete neuroradiological data were available. Some but not all of these patients were included in previous published reports of analyses of SH and executive functioning (Moser et al., 2001). All participants met NINDS–ARENS criteria for VaD (Roman et al., 1993) determined by a board-certified neurologist (W.S.) from the Memory Disorders Clinic using information obtained from clinical examination, medical history involving interview of the patient and their family, and neuroimaging. NINDS-ARENS criteria require (1) history of cerebrovascular disease, (2) evidence of dementia, and (3) a presumed relationship between these two factors (e.g., temporal relationship, stepwise progression, fluctuating course). Diagnosis of VaD also required evidence of deep subcortical or periventricular white matter lesions and/or cortical infarctions on brain MRI.

All participants were required to have an MMSE in the range of 9 to 24. An upper limit of 24 on MMSE was selected to insure that patients were in fact demented, while the lower limit of 9 was selected to insure that all participants had the cognitive capacity to participate in the study and complete the necessary tests. Furthermore, this range was selected to insure that all VaD patients were in the mild to moderate stages of dementia, a necessary requirement for the drug trial for which these participants were enrolled.

Participants were excluded for (1) co-existing neurological diseases (e.g., AD, seizures, clinically significant closed head injury) affecting the brain; (2) schizophrenia, bipolar illness, current substance abuse problems or other coexisting severe intractable psychiatric disorders; (3) certain systemic diseases, including renal failure and cancer; (4) any illness limiting life expectancy to less than 1 year; (5) contraindications to MRI (i.e., ferrous implants, cardiac pacemakers).

Considerable effort was directed at excluding patients with possible or probable AD from the sample. A clinical diagnosis was made based on all available data by the clinic neurologist in accordance with NINCDS-ADRDA criteria (McKhann et al., 1984). Patients with insidious onset of cognitive symptoms, with gradual progressive worsening of symptoms, and no evidence of an obvious relationship between their dementia and cerebrovascular disease were assumed to have possible AD, and were excluded. Patients with visual evidence of hippocampal atrophy on MRI were excluded from the study on similar grounds. The use of these exclusion criteria partially accounts for the large number of patients (more than 1000) screened to obtain the final sample.

Patients were excluded if they met DSM–IV criteria for major depression at the time of the assessment. Determination of current psychiatric status was made by a geriatric psychiatrist affiliated with the memory disorder clinic. Patients were also excluded if they had a prior head injury involving a loss of consciousness for greater than one hour and/or had been neurologically diagnosed as having brain dysfunction secondary to this trauma. Patients with cancer

were excluded because of concerns about possible adverse affects of Citicoline on cancer growth. Patients with prior neurological disease involving only stroke or other cerebrovascular disease were not excluded. Age- and education-matched elderly men and women were assessed on the same cognitive tests ($n = 25$), and their data served as a control sample for comparison of the cognitive performance of the VaD group. Controls consisting of hospital volunteers, were invited to participate if they had a MMSE ≥ 25, and met other inclusion/exclusion criteria set forth for the VaD patients. They were excluded if they had reported prior or current history of neurological brain disease, major intractable psychiatric illness, including the presence of major depression or current substance abuse problems. Demographic and clinical characteristics of the VaD and control samples are provided in Table 1.

Procedure

A comprehensive neurological and complete physical examination of approximately one-hour duration was conducted on each potential participant to confirm the diagnosis of probable VaD, insure that medical status did not necessitate exclusion, and to obtain clinical neurological measures and medical history. Informed consent was obtained from those patients meeting inclusion and exclusion criteria who wished to participate. Participants were then administered the neuropsychological test battery of approximately 4 hr duration. This was followed by brain MRI, usually performed on the day after the neuropsychological assessment (all MRIs were conducted within 36 hr of the cognitive assessment).

Table 1. Clinical and demographic characteristics of VaD patients and elderly controls

Variable	VaD patients	Elderly controls
Age (years)	78.2 ± 5.9	76.5 ± 8.9
Education (years)	11.9 ± 4.0	12.4 ± 3.6
Gender (men:women)	12:12	11:14
Hachinski score	7.4 ± 2.4	1.3 ± 0.8
Cognitive indices*		
MMSE score	19.9 ± 4.2	28.2 ± 1.3
VIQ (WAIS–R)	82.8 ± 11.9	104.3 ± 12.5
PIQ (WAIS–R)	85.8 ± 14.1	101.5 ± 11.9
FSIQ (WAIS–R)	77.9 ± 15.5	102.9 ± 13.8
MRI indices		
SH volume (voxels)	6054.5 ± 3980	—
Corrected SH volume (%)	3.6 ± 2.2	—
Whole brain volume (voxels)	174,418 ± 21,794	—
Infarction type (N)**		
SH only	12	—
Cortical involvement	8	—
Thalamic involvement	3	—
Basal ganglia involvement	4	—

*The VaD and control groups differed significantly on the MMSE and WAIS–R IQ indices.
**Fifteen of the VaD patients had subcortical disease with no evidence of cortical infarction. Of this group, only 3 had either basal ganglia or thalamic involvement in addition to having large quantities of SH. A majority of the patients with cortical infarctions, also had either thalamic or basal ganglia infarctions as well. Therefore, the number of patients with basal ganglia and thalamic involvement includes both patients with cortical infarctions and subcortical involvement only.

Cognitive Assessment

Prior to randomization in the Citicoline trial, all participants completed a battery of neuropsychological tests to assess overall cognitive status (MMSE; Folstein et al., 1975); intellectual functioning (WAIS–R subtests; Wechsler, 1981); language (Boston Naming Test: BNT; Kaplan et al. 1983; Controlled Oral Word Association Test: COWAT–Category Fluency–Animals); visual functions (Hooper Visual Organization Test: HVOT; Hooper, 1983; Complex Figure Test: CFT; Lezak, 1995; Block Design; Wechsler, 1981); motor functions (Grooved Pegboard; GPB); memory (Logical Memory, Visual Reproductions; Wechsler Memory Scale–Revised; WMS–R; Wechsler, 1987; California Verbal Learning Test: CVLT; Delis et al., 1987; and CFT); and attention–executive functioning (Digit Span; Wechsler, 1981; Stroop Color–Word Test; Golden, 1978; Trail Making Test; Reitan, 1958; and Digit Symbol subtest; Wechsler, 1981). All tests were administered by a trained clinician using standard procedures.

Brain MRI and SH Quantification

Brain MRI was obtained with a Siemen's Magnatom Vision unit. A standard imaging protocol consisting of both sagittal T1- (TR 500 ms, TE 30 ms) and T2- (TR/TE = 2500/80) weighted conventional spin-echo localizer images as well as axial T1-, T2-, and Flair-weighted (TR/TE = 6000/105) images was used. The slice thickness for all images was 5 mm with a 2-mm intersection gap. The field of view for the T1- and Flair images was 240 × 240 mm with a 192 × 256 matrix and one excitation. To position the structural scan, "scout" images were obtained and slice orientations determined. The T1- and T2- weighted images were used to ensure that patients included in the study did not have other brain disorders that would confound interpretation of results, and for identification of cortical infarctions associated with large vessel stroke. These scans along with the Flair-weighted images were qualitatively examined independently by a neuroradiologist and a neurologist (B.R.O.) for purposes of obtaining a clinical rating of the extent of SH and the presence of discrete infarctions involving the cortex, thalamus, and/or basal ganglia.

The Flair images were used to quantify subcortical and periventricular SH and WBV. The method used to quantify SH and WBV has been used previously by our group and other investigators with strong reliability and validity (Greenwald et al., 1998; Jenkins et al., 1998). SH was quantified

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by calculating lesions in the subcortical and periventricular areas, including thalamus, basal ganglia, and white matter tracts. The extent of SH was quantified using semi-automated thresholding methods to select pixel values representing abnormal brain tissue and ventricular space on Flair. The semi-automatic thresholding method involved a series of processing steps, by which certain bandwidths of light, corresponding to black, white, and gray areas of the scan were selected based on an intensity histogram for each participant. This histogram typically produced three peaks from brain parenchyma, SH, and CSF. Once a threshold was set to reflect the pixel intensity range representing SH, this threshold was applied to all slices in a given patient's scan. The regions identified as SH by this process were then verified visually by a trained rater. When questions concerning whether or not selected areas were to be considered SH, a neurologist reviewed the scan to make a determination. Volume summations were calculated for SH, which were expressed as a ratio of total hyperintense signal (subcortical and periventricular areas) over WBV (excluding ventricular space) on the MRI images sampled.

Data Analyses

Descriptive statistics were derived for all cognitive and MRI indices. SH and WBV indices were subjected to *z*-score transformation and the resulting *z* scores used in subsequent analyses. The MMSE, and WAIS–R summary indices (VIQ, PIQ, FSIQ) were analyzed initially. All subsequent analyses were conducted by domain, with neuropsychological measures grouped into one of four domains: (1) language–verbal functions, (2) visual functions, (3) learning–memory, and (4) attention–executive-psychomotor functions. Neuropsychological measures were included in each domain as follows: (1) *language–verbal*: Information (WAIS–R), Vocabulary (WAIS–R), Comprehension (WAIS–R), Boston Naming Test (BNT), Category "Animal" Naming; (2) *visual*: Picture Completion (WAIS–R), Block Design (WAIS–R), Hooper Visual Organization Test, Complex Figure Test–Copy; (3) *learning–memory*: Logical Memory–Immediate Recall (WMS–R), Visual Reproductions–Immediate Recall (WMS–R), CFT–Immediate Recall, CFT–Recognition, CVLT–Total Recall; (4) *attention–executive–psychomotor*: Digit Symbol (WAIS–R), Digit Span (WAIS–R), Trail Making B, Grooved Pegboard–Dominant Hand, FAS–Total, Stroop Color Word Test–Interference trial. Raw scores were used in analyses testing these domains. The cognitive performance of the entire VaD sample was contrasted with data from a group of elderly normal control subjects without neurological disease by multivariate analysis of variance (MANOVA). Separate multivariate analysis of variance (MANOVA) procedures were conducted to contrast the cognitive performance of patients with and without cortical and/or subcortical gray matter infarctions across measures for each of the four domains.

Stepwise multiple regression analysis was performed to test the relationships between neuropsychological performance and SH and WBV. Four separate regression analyses were conducted using neuropsychological measures obtained from the four domains of (1) language–verbal functions, (2) visual functions, (3) learning and memory, and (4) attention and executive functions and each of the two MRI indices as dependent measures for all VaD patients in the sample. Subsequent stepwise regression analyses were conducted using the same independent and dependent measures for those patients without cortical infarctions ($n = 15$), and then on a subset of this group of patients with only SH ($n = 12$).

RESULTS

Clinical and Demographic Characteristics

Table 1 provides descriptive statistics of the demographic and clinical characteristics for the VaD and control groups. The groups did not differ in age, education level or sex distribution. The VaD patients had elevated Hachinski scores compared to the elderly controls [$t(48) = 6.82$, $p < .01$].

Neuroradiological Findings

While all VaD patients had a history of cerebrovascular disease and evidence of cerebral infarctions on MRI, the exact distribution and type of lesions varied. The qualitative interpretations of the MRI by the neuroradiologist were validated by interpretation of an independent neurologist who was unaware of the neuroradiological reading and 100% agreement was achieved with respect to the presence of SH. All VaD had well defined quantities of deep subcortical and/or periventricular SH on MRI. A minority of the VaD patients also had a history of prior large vessel stroke and evidence of cortical infarction on MRI, including 8.3% with multiple cortical infarctions. Thalamic infarctions were evident in 8.3% of the sample, while basal ganglia infarctions were apparent in 12.5% (see Table 1). SH volume was significantly correlated with WBV ($r = -.42$, $p = .04$).

Cognitive Functioning

The VaD patients had severe impairments across cognitive domains compared to both our control sample and also normative data. They were moderately demented with severe overall cognitive impairment as measured by their MMSE score compared to intact performance for the controls [$t(63) = 32.5$, $p < .001$].

VaD patients were impaired relative to controls across each of the four cognitive domains examined, including: (1) learning/memory [Wilks's Lambda = .45; $F(1,62) = 15.4$, $p < .001$]; (2) verbal/language memory [Wilks's Lambda = .62; $F(1,63) = 10.3$, $p < .01$]; (3) visual/construction memory [Wilks's Lambda = .38, $F(1,64) = 18.1$, $p < .001$], and (4) attention/executive [Wilks's

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Lambda = .23, $F(1,60) = 21.3$, $p < .001$]. Table 2 provides a breakdown of performance for the VaD and control groups for individual measures within each of these domains.

Relationship Between MRI Findings and Cognitive Functioning in VaD

A significant relationship was observed between these MRI indices and MMSE score [$R = .64$; $F(1,24) = 15.33$, $p < .01$], though only WBV accounted for the variance in this relationship (Beta = .64). Furthermore, overall cognitive ability as measured by the WAIS–R indices (VIQ, PIQ, FSIQ) was not associated with SH volume.

SH and Cognitive Performance

As we previously reported (Cohen et al., 2000; Moser et al., 2001), a strong relationship was observed between performance on measures of attention–executive–psychomotor functioning and corrected SH volume [$R = .69$; $F(3,20) = 4.81$, $p < .01$]. Digit Symbol accounted for most of the variance (22.8%) associated with SH volume, while Trail Making Test–Part B accounted for 10.5%, and Digit Span performance accounted 6.5% of this association. A significant relationship was also found between only one measure of learning and memory and corrected SH volume [$R = .74$; $F(1,22) = 23.43$, $p < .01$], as CFT–Recognition accounted for 53.5% of the variance associated with SH (Beta = −.54). A significant relationship was also found between performance on one visual–construction task and SH [$R = .54$; $F(1,21) = 8.5$, $p < .01$], as CFT–Copy accounted for 28.8% of the variance associated with SH among the visual–construction measures examined. None of the measures of language and verbal functioning were significantly associated with SH volume.

WBV and Cognitive Performance

Regression analyses of the relationship between cognitive performance and WBV revealed a dissociation from the results with regard to SH. The attention–executive–psychomotor domain was not found to be associated with WBV, as none of the individual measures in this domain significantly correlated with WBV. In contrast, a statistically significant relationship between the verbal–language domain and WBV was observed [$R = .57$; $F(1,21) = 10.26$, $p < .01$], with performance on the BNT accounting for 32.5% of the variance in WBV. Visual–construction performance was also significantly associated with WBV [$R = .42$; $F(1,21) = 4.53$, $p < .05$]. Picture completion performance accounted for the majority of variance associated with this relationship (17.6%). Learning and memory per-

Table 2. Cognitive performance of VaD patients and elderly controls

Measure	VaD patients	Elderly controls
Memory measures		
Logical Memory–Immediate Recall	7.5 ± 4.7	16.6 ± 5.4
Visual Reproductions–Immediate Recall	13.7 ± 7.4	24.3 ± 6.8
CVLT–Total Recall	15.7 ± 7.1	50.1 ± 9.6
CVLT–Discrimination	.63 ± .17	.93 ± .08
CFT–Immediate Recall	3.6 ± 4.4	15.3 ± 7.5
CFT–Discrimination	.66 ± .13	.89 ± .09
Language measures		
Information	6.5 ± 3.4	10.7 ± 1.6
Vocabulary	7.8 ± 3.4	10.9 ± 2.2
Comprehension	7.9 ± 3.1	11.0 ± 2.0
Boston Naming	32.6 ± 12.9	52.7 ± 4.5
Animal Naming	7.3 ± 3.8	17.8 ± 6.2
Visual measures		
Picture Completion	7.4 ± 3.0	10.8 ± 1.5
Block Design	4.8 ± 3.0	9.9 ± 1.7
Hooper Visual Organization Test	15.2 ± 5.4	22.6 ± 3.3
CFT–Copy	17.6 ± 10.0	32.1 ± 3.6
Attention–executive–psychomotor		
Digit Symbol	16.7 ± 12.2	34.2 ± 10.9
Digit Span	7.0 ± 3.2	9.8 ± 1.8
FAS	16.5 ± 11.3	29.4 ± 8.4
Stroop Test–Interference	10.8 ± 07.7	28.4 ± 14.7
Grooved Pegboard–Dominant	161.6 ± 81.4	78.7 ± 10.3
Trail B (s)	269.9 ± 61.7	90.8 ± 33.5

Note. Data from the Digit Span, Information, Vocabulary, Comprehension, Picture Completion, and Block Design subtests are reported as scaled scores. All other data are raw scores.

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formance was strongly associated with WBV as well [R = .85; $F(3,19) = 8.721$, $p < .01$]. Performance on the CVLT–Total score accounted for most of the variance in this relationship (25.4%), though CFT–Recognition (18.9%), and Logical Memory–Immediate Recall (Beta = 7.8%), also contributed to this association.

Findings Among Patients Without Cortical Infarctions)

Regression analyses were next conducted to examine the relationship between cognitive performance and the MRI indices for VaD patients without cortical infarctions (n = 15) (see Table 3). This group consisted of 12 persons with SH only, and 3 persons with SH and other subcortical damage (thalamic = 1, basal ganglia = 2). Again only WBV was found to be significantly associated with MMSE score [R = .55; $F(1,14) = 6.12$, $p < .01$], with WBV accounting for 30.0% of the variance associated with MMSE. SH was not significantly associated with MMSE.

A strong relationship between attention–executive–psychomotor domain and SH was again observed [R = .79; $F(4,10) = 6.32$, $p < .01$]. Time for completion of the GPB accounted for the majority of variance in this relationship (23.3%), though Digit Symbol (19.7%), Trail Making–B (13.4%), and Digit Span (8.8%) also accounted for the variance associated with SH.

The verbal–language domain was not associated with SH, as none of the measures in this domain significantly correlated with SH. Yet verbal–language performance was again found to be strongly associated with WBV [R = .815; $F(3,11) = 6.59$, $p < .01$]. BNT had the strongest association with WBV, accounting for 29.2% of the variance of this relationship, though both Information (WAIS–R) and Category Fluency also contributed to this relationship. A similar finding was found with respect to the measures of visual function, as most visual measures were significantly associated with WBV on simple correlation. Furthermore, regression analysis indicated a strong relationship between the visual measures and WBV [R = .59; $F(1,14)$ = 7.34, $p < .02$], with Picture Completion score best accounting for this association (34.8%). While an association was found between the visual measures and SH [R = .40; $F(1,14) = 4.13$, $p < .05$], only CFT–Copy was correlated with SH.

Several of the memory indices were correlated with WBV and a highly significant overall relationship was observed [R = .88; $F(4,11) = 8.42$, $p < .01$], with CVLT–Total (Beta = .93), Logical Memory–Immediate Recall (Beta = −.91, CVLT–Recall (Beta = −.72), and CFT–Recognition (Beta = .81) contributing to this association. A significant association was also observed between memory performance and SH [R = .55; $F(1,14) = 5.55$, $p < .05$], though again only CFT–Recognition accounted for much of this relationship (Beta = .55).

Table 3. Cognitive performance of patients with cortical + subcortical infarctions *vs.* subcortical infarctions only

Measure	Cortical + subcortical	Subcortical only
Memory measures		
LM1–Immediate Recall	7.0 ± 4.4	7.7 ± 4.9
VR1–Immediate Recall	15.1 ± 8.0	14.0 ± 7.4
CVLT–Total	13.0 ± 6.4	16.4 ± 7.3
CVLT–Discrimination	.60 ± .19	.65 ± .12
CFT–Immediate Recall	3.9 ± 5.2	3.3 ± 4.2
CFT–Discrimination	.65 ± .10	.69 ± .10
Language measures		
Information	6.3 ± 3.4	6.4 ± 3.5
Vocabulary	5.1 ± 3.0	8.3 ± 2.9
Comprehension	7.0 ± 2.7	8.4 ± 3.3
Boston Naming	30.7 ± 15.6	34.0 ± 12.2
Animal Naming	6.3 ± 3.1	7.3 ± 3.8
Visual measures		
Picture Completion	7.4 ± 3.1	7.8 ± 2.9
Block Design	3.0 ± 1.7	5.8 ± 3.1
Hooper Visual Organization Test	14.8 ± 8.1	15.7 ± 4.3
CFT–Copy	16.8 ± 10.2	19.2 ± 9.7
Attention–executive		
Digit Span	6.1 ± 2.8	7.7 ± 3.1
Digit Symbol	12.0 ± 11.7	20.3 ± 11.3
FAS	11.1 ± 9.3	19.7 ± 11.4
Grooved Pegboard–Dominant	202.6 ± 92.7	152.2 ± 72.5
Stroop–Interference (s)	10.6 ± 6.6	11.6 ± 8.2
Trail B (s)	247.9 ± 89.3	272.4 ± 56.2

Note. Data from the Digit Span, Information, Vocabulary, Comprehension, Picture Completion, and Block Design subtests are reported as scaled scores. All other data are raw scores.

Findings Among Patients With Only SH

The analysis of VaD without cortical infarctions was repeated excluding the 3 patients who had subcortical abnormalities involving the basal ganglia and/or thalamus. A significant relationship was observed between the attention–executive–psychomotor domain and SH [R = .86; $F(2,9)$ = 5.65, $p < .05$]. Digit Symbol and GPB performance accounted for the majority of variance in this relationship. A significant relationship between the attention–executive–psychomotor domain and WBV was not observed.

The verbal–language, visual, and learning–memory domains were not significantly associated with SH volume for this patient subgroup. In contrast, WBV was significantly correlated with the visual domain [R = .57; $F(1,10) = 6.56$, $p < .05$]. Picture Completion accounted for 32.4% of this relationship. Verbal–language performance also was associated with WBV [R = .67, $F(1,10) = 5.47$, $p < .05$], with performance on the BNT accounting for this relationship. Among this group of patients with SH only, total recall on the CVLT approached a statistically significant relationship with WBV [R = .65; $F(1,10) = 3.85$, p = .07].

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DISCUSSION

The present findings provide general support for the hypothesis that a relationship exists between SH volume and performance on measures of attention, executive, and psychomotor functioning among persons with VaD. Several of the measures from this domain were significantly correlated with SH volume. Digit Symbol performance was among the variables most strongly associated with SH volume. Performance on this task requires focused attention, working memory, rapid information processing and fine motor skills, functions that are strongly associated with attention and executive capacity.

A relationship between time for completion of Trail Making B and SH was also found. In a previous analysis of the data, we reported that SH volume was most associated with Trail Making A performance (Moser et al., 2001). Trail Making B was not included in the analysis, because a number of the VaD patients were unable to complete the task in the required time limit. In the current analysis, we included Trail Making B, and found that while many patients showed a floor effect, inability to perform this task was strongly associated with SH volume. While executive control, specifically cognitive flexibility and the ability to switch response set, is required for Trail Making B, successful completion of this task is also strongly dependent on information processing speed. The fact that SH was found to be strongly associated with Trail Making A in separate analyses reinforces the conclusion that reduced processing speed is a major consequence of SH.

With respect to specific effects on attention and executive functioning, the results suggest that executive control may be less effected by SH than is attention. Both the Digit Symbol and Digit Span tasks were associated with quantity of SH. These tasks measure different aspects of attention capacity (Cohen, 1993). Performance on the Digit Symbol subtest is strongly influenced by capacity for focused attention. The Digit Span task is sensitive to attention span and focus as well. While performance on Trail Making was associated with SH, performance on other measures of executive control, such as the Stroop test and controlled word generation (FAS) was not. In sum, these results provide further evidence that subcortical and periventricular lesions among patients with VaD cause cognitive impairments that relate primarily to diminished speed of information processing, with secondary effects on attention and to a lesser extent executive functioning.

Performance on the Digit Symbol and Trail Making tasks is known to be susceptible to frontal–subcortical dysfunction (Cohen, 1993; Lezak, 1995). Accordingly the observed relationship between performance on these measures and SH is consistent with expectations given the effects of subcortical white matter damage. The structural consequence of white matter disease involves the breakdown of communication between cortical and subcortical brain systems (Cummings, 1993; McPherson et al., 1996; Roman et al., 1993). Disruption of information processing across cortical and subcortical systems is known to affect attention and executive functioning. In VaD, this is thought to cause cognitive deficits in executive function, including decreased attention, speed of processing, retrieval of information, and response generation (Padovani et al., 1995; Roman, 1999). In contrast, general intelligence, language functions, and recognition memory remain relatively intact (Caine et al., 1986; Rao, 1995, 1996).

Performance across the other cognitive domains was not associated with SH volume. For example, no relationship was found between language–verbal functions (e.g., Boston Naming Test, Animal Naming, Vocabulary, Comprehension) and SH volume. Similarly, most measures of learning-memory and visual-integrative functioning were not significantly correlated with SH volume. While copy, recall, and recognition of the CFT were significantly correlated with SH, these deficits were probably not linked to major memory or visual impairments. The CFT requires considerable planning and organizational capacity, and has been shown to be sensitive to impairments of executive functioning (Klicpera, 1983; Schreiber et al., 1999). Therefore, it is likely that the observed relationship between CFT deficits and SH volume was more strongly associated with the executive demands of this task than with memory or visual demands.

In contrast, WBV was associated with overall cognitive performance, including MMSE and the WAIS–R intellectual measures. In fact, performance across most cognitive domains was found to be strongly associated with WBV, including verbal performance on the Boston Naming Test and Similarities, visual inference ability on Picture Completion, and memory performance on the DRS and CVLT. Yet, WBV did not correlate with performance on the measures of attention-executive functioning found to be strongly associated with SH. Furthermore, SH was found to only weakly correlate with WBV. This finding is consistent with results from several other recent studies that have suggested a link between brain atrophy and VaD (Lis et al., 1997; Pantel et al., 1998; Rushton et al., 1995).

A double dissociation is evident. SH was strongly associated with attention-executive impairments among VaD patients, but largely was not associated with other cognitive impairments observed among these patients. Conversely, WBV was strongly associated with overall cognitive ability, including verbal and nonverbal reasoning and memory capacity, but did not account for the executive–attention impairments common among these patients. While this dissociation is relatively straightforward, it poses a paradox in light of the diagnoses and presumed neuropathology of this clinical sample with VaD. The most ubiquitous characteristic of this VaD sample was that all patients had significant quantities of SH. Approximately, one-third of the group also had cortical infarctions, which in principal might have accounted for reduced cortical function. Yet, cortical infarctions would not have directly reduced WBV, as areas of infarction were included in the WBV measurement. Moreover, when we examined those VaD

patients without cortical infarctions, WBV was still more strongly associated than SH with MMSE score, verbal–language, visual, and learning–memory functioning. Therefore, the presence of cortical infarctions *per se* was not the basis for the observed relationship between WBV and dementia.

The general pattern of results did not change when the data from patients with only SH on MRI were analyzed. Again SH correlated with performance on tasks sensitive to processing speed, but not with other cognitive functions. Furthermore, WBV correlated with measures of verbal–language and visual functioning, but not the attention–executive–psychomotor measures. The only difference in the results was that only a trend in the direction of an association between learning–memory and WBV was found for this subgroup. Overall these results suggest that WBV was more strongly associated with most aspects of cognition than SH even among those VaD patients who only had SH abnormalities on MRI.

There are several possible explanations for reduced WBV in VaD and how reduced WBV might relate to the development of dementia: (1) tissue loss associated with cortical and/or subcortical infarctions resulting from microvascular or large vessel disease; (2) atrophy associated with cerebral ischemia not directly attributable to discrete infarctions; (3) atrophy of other unknown origin, such as a progressive degenerative disease; or (4) premorbid differences in brain volumes among certain patients. The least likely explanation is that premorbid differences in brain volume are responsible for greater dementia among certain patients with VaD. It is well known that adults in the general population differ with respect to their brain volumes and that a relationship between brain volume and cognitive ability exists (Kalaria, 2000; Rushton et al., 1995). Yet, there is little reason to believe that variation in premorbid brain volume accounts for differences in how VaD patients respond to cerebrovascular disease or for the development of dementia. That some VaD patients in our sample may have had a progressive neuronal degenerative disease (e.g., AD) that caused reduced WBV also seems unlikely, as extreme efforts taken to exclude patients with probable AD based on clinical course and presentation. On the other hand, cerebrovascular disease is known to be a risk factor for the development of AD (Breteler, 2000), and clinical differentiation of the two disorders is difficult.

Given that subcortical infarctions involving deep white matter were presumed to underlie dementia in this VaD cohort, the most obvious explanation for the association between WBV and cognitive impairment is that it occurred as an indirect effect of SH volume. Impaired white matter and subcortical function may have affected cortical functions by diaschisis. This explanation has parsimony, and is partially supported by the results, as SH volume was moderately correlated with WBV, a finding that is consistent with recent reports from other investigators (Fein et al., 2000). Yet, SH accounted for less than 20% of the variance in WBV, suggesting that diminished WBV probably can not be attributed to SH alone. Furthermore, SH and WBV were independently correlated with different cognitive functions. Therefore, even if they are etiologically related, they seem to have different functional consequences in VaD.

Alternatively, cortical atrophy in this VaD sample may have occurred as a secondary byproduct of cerebrovascular disease. As reviewed by Loeb and Meyer (1996), atrophy is a frequent developmental change in normal individuals, especially after the age of 60. In individuals with cardiovascular illness, the severity of atrophy may be exacerbated, due to chronic ischemia. How cerebrovascular disease contributes to the development of atrophy in VaD remains an important area of future study, especially considering the strong relationships between WBV and overall dementia identified in the current investigation.

A discussion of limitations of the present study is warranted. The present findings were based on a relatively small sample of VaD patients. This is particularly true for the analyses involving patients with SH only, as there were only 12 participants included in this analysis. The small sample for this analysis may account for why only a trend on the regression of WBV and the learning-memory measures was found. Validation of these findings will ultimately require a larger sample size. The VaD patients had slightly less than 12 years of education on average. While this level of educational attainment is consistent with expectations from an elderly cohort, these results might not generalize to more highly educated people with VaD. Another limitation of the present study arises from the fact that AD can not be completely ruled out in anyone without neuropathological analysis. Extreme efforts were made to exclude patients with possible AD based on clinical presentation, symptom course, and the presence of hippocampal atrophy on MRI. Furthermore, all patients had evidence of cerebrovascular disease with associated cognitive changes. However, since neuropathological data was unavailable on these patients, a definitive rule out of AD was not possible. As discussed earlier, it is likely that some VaD patients would eventually develop pathological changes associated with AD secondary to their cerebrovascular disease, even though they did not meet AD criteria at baseline. These issues point to the complex relationship between cerebrovascular disease, VaD, and AD. Future studies aimed at examining the development of AD in patients with cerebrovascular disease and probable VaD are needed.

In summary, the present findings indicate that SH volume, a proxy for subcortical white matter disease, is associated with diminished information processing among patients with VaD. Slowed processing speed contributed to weak performance on measures of attention and executive functioning. Yet the presence of SH does not fully account for dementia in VaD, as WBV, a proxy for brain atrophy, was more strongly associated than SH with dementia severity and impairments across most other cognitive domains. The apparent relationship between WBV and cognitive dysfunction in VaD is intriguing given the presumed cerebrovascular etiology of this disorder. Ultimately, the findings

of this study confirm the relationship between SH and processing speed, and also raise question as to the cause of reduced brain volume in VaD, and its impact on functional status.

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