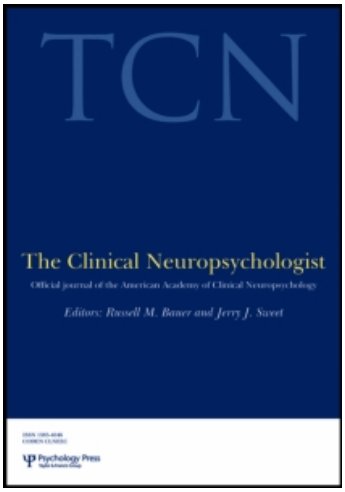

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From Binswanger's Disease to Leuokoaraiosis: What We Have Learned About Subcortical Vascular Dementia

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ABSTRACT

The literature regarding subcortical vascular dementia associated with periventricular and deep white matter alterations is reviewed. Information pertaining to neuropathological, neuropsychological, and neuroradiological studies is emphasized. Based on this review and prior neuropsychological studies associating subcortical vascular pathology with greater deficits on tests of executive dysfunction and with relatively better performance on tests of delayed recognition memory, we conclude that vascular dementia associated with periventricular and deep white matter alterations can and should be regarded as a subcortical dementing illness. Also, we support schemes suggested by Erkinjuntti et al. (2000) and Cosentino et al. (this issue) that attempt to integrate neuropsychological and neuroradiological data into a diagnostic paradigm that describes, as well as diagnoses, dementing disorders. We discuss questions and issues about vascular dementia that deserve further consideration and study.

INTRODUCTION

Cerebrovascular disease was of great interest in the 19th and early 20th centuries (Roman, 1999). From the early French neurologist, Max Durand-Fardel (1843) to Hachinski and colleagues (1974, 1975, 1987) a great deal was learned about vascular pathology and behavior. However, during the mid 20th century this interest waned, perhaps due to the association between gray matter cerebral alterations and dementing illnesses such as Alzheimer's disease (AD) and the misconception that all vascular dementia syndromes were synonymous with a diagnosis of '*multi-infarct dementia*'. Since the 1990's, there has been a resurgence of interest in small vessel vascular disease and its association with a wide range of behavioral disturbances including dementia (Filley, 2001; Lamar, Price, Davis, Kaplan, & Libon, 2002; Lin et al., 2000; Pugh & Lipsitz, 2002; Stuss & Cummings, 1990).

Early French neurological science provided the foundation for understanding the pathological and behavioral alterations of vascular dementia. For example, Max Durand-Fardel (see Hauw, 1995, for a review) made original macroscopic descriptions of vascular lesions including *lacunar infarcts*, *etat crible*, and *atrophe interstitelle du*

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cerveau. His purpose was to separate these phenomena from other vascular lesions such as haemorrhages and large infarcts. For Durand-Fardel (1843, cited in Hauw, 1995), a *lacune* represented a small cavity in the brain "without any change in consistency or color from which it was possible to remove a little cellular tissue containing very small vessels with a thin forceps." Durand-Fardel believed that lacunes were healed infarcts, distinctly separated from other vascular lesions. In contrast, he used the term *etat crible* (translated as 'sieve-like state') to describe sections of the subcortical white matter that "were riddled with a number of little holes, with sharp edges, usually surrounded by a quite normal white matter, without any change in color or consistency" (Durand-Fardel, 1842, cited in Hauw, 1995). The term *Atrophe interstitelle du cerbeau* (translated as interstitial atrophy of the bran) represented, "alterations of the cerebral pulp . . . different from infarctions . . . not due to a change in the consistency of the brain but a rarefaction of the pulp". Interestingly, this description has been described as analogous to Hachinski, Potter and Meresky's (1987) definition of leukoaraiosis – a term to describe the white matter alterations surrounded by normal white matter as seen on modern imaging studies of older adults (Hauw, 1995).

Supplementing Durand-Fardel's work, Pierre Marie (1901) provided precise macroscopic, as well as histological descriptions of lacunes, and clearly stated that lacunes represent very small infarctions (Hauw, 1995). However, Pierre Marie perhaps created some unintentional controversy in suggesting that some lacunes may not be associated with infarction, but may be caused by "microscopic softening or hemorrhage." Subsequent work has tended to blur the distinctions made by Durand-Fardel and Marie regarding lacunes and other vascular states until C.M. Fisher (1965, 1982) confirmed Durand-Fardel's original observations and noted that lacunes were caused by the occlusion of small perforating arteries. C.M. Fisher believed that, in most cases, arterial occlusion was associated with arteriosclerosis and high blood pressure.

Interest in the behavioral alterations associated with vascular pathology is usually traced to the work of Otto Binswanger. Binswanger's papers have been translated, and a number of comprehensive reviews are in the current literature (see Babikian & Ropper, 1987; Blass, Hoyer, & Nitsch, 1991; Caplan, 1995; Fisher, 1989; Libon, Scalon, Swenson, & Coslett, 1990; Pantoni & Garcia, 1995; Roman, 1987, 2002; Schorer & Rodin, 1990). Binswanger introduced the idea that white matter atrophy, caused by vascular insufficiency, can result in mental impairment. In support of this proposal, Binswanger described patients who experienced a slowly progressive course of mental confusion in combination with focal neurologic signs, enlarged ventricles particularly around the temporal and occipital horns, and substantial loss of corresponding white matter with a general sparing of the cortex. Binswanger introduced the term *encephalitis subcorticalis chronica progressiva* to label this disorder and proposed that damage to white matter alone could cause mental impairment (Blass et al., 1991; Filley, 2001). Unfortunately, detailed microscopic information regarding these patients was never published. This has caused no small degree of confusion regarding the classification of subsequent cases.

A few years after Binswanger's 1894 article, Alois Alzheimer (1902, see Roman, 1999) published findings that generally substantiated Binswanger's observations, and also provided detailed pathological observations. Labeling the disorder as *Binswanger's disease*, Alzheimer described the presence of small focal lesions in the internal capsule, lenticular nuclei, and pyramidal areas around the pons. Soon after, in his 1910 *Textbook of Psychiatry*, Emil Kraeplin differentiated dementia associated with a vascular atherosclerosis from dementia involving cortical atrophy (i.e., Alzheimer's disease; Berchtold & Cotman, 1998). More recently, case descriptions by Olszewski (1962) and Caplan and Schoene (1978) have essentially substantiated the clinical and neuropathological observations of Binswanger and Alzheimer regarding Binswanger's disease.

Remarkably, from the time of Kraeplein, dementia associated with vascular arterioscerlosis became synonymous with senile dementia, such that it was believed that widespread cortical

atrophy was associated with decreased perfusion to the brain. Hachinski and colleagues (Hachinski et al., 1974, 1975) dispelled this notion and introduced the concept of multi-infarct dementia (MID). However, since 1974, the term MID was used to describe or denote virtually all instances of vascular dementia. The term Binswanger's disease was associated with an obscure illness, or even marginalized as an epiphenomenon. Until the introduction of the diagnostic criteria from the Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC; Chui et al., 1992) and National Institute of Neurological Communicative Disorders and Stroke – Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN criteria, Roman et al., 1993), Hachinski's Ischemic Scale (HIS; Hachinski et al., 1975) has been the traditional means by which MID/vascular dementia has been diagnosed.

In recent years, the diagnosis of dementia has become increasingly complex. At the present time, differential diagnosis between the various dementing illnesses requires the consideration of entities such as Alzheimer's disease (AD), vascular dementia (VaD), Diffuse Lewy Body disease (DLB), frontal-temporal dementia (FTD), and cortical basilar degeneration (CBD). Moreover, as will be discussed in greater detail below, the situation is made more complex by the fact that, among some patients, there may be overlap with respect to the neuropathology underlying the clinical presentation of dementia.

RECENT NEUROPATHOLOGICAL CONCEPTS ASSOCIATED WITH VASCULAR DEMENTIA

The pathogenesis of vascular dementia (VaD) is complex in the sense that, unlike AD, there may not be a direct link or linear relationship between the type or location of cerebrovascular pathology and subsequent clinical presentation. Nonetheless, Olsson and colleagues (Olsson, Brun, & Englund, 1996) have suggested that it is useful to separate the events that underlie VaD into several broad categories, that is, processes originating from and involving extra-cranial versus intra-cranial vessels. Yet, in making this distinction, it must be acknowledged that there may be considerable overlap regarding these disease pathways. Perhaps, one utility or reason for making this distinction at all is that separate disease pathways may be associated with different clinical syndromes or presentations.

Extra-Cranial Disease Pathology

Three pathological mechanisms are commonly associated with extra-cranial vascular disease that may underlie VaD – emboli, thrombi, and atherosclerosis. Emobli can originate from either the heart or the lungs and reach the brain via the internal carotid arteries, often blocking branches of one of the three major cerebral arteries. Emboli formed as a result of cardiac dysfunction occur through atrial dysrhythmia and reduced ventricular function, both of which lead to increased pooling in the atria and ventricles, respectively (Olsson et al., 1996). Arterial thrombi formation is associated with endothelial cell damage of arteries (Capron, 1988). Endothelial pathology exposes blood to extracellular material to which platelet adhere and aggregate. Under such conditions, a thrombus can develop and ultimately travel to the brain. Finally, it is well understood that atherosclerosis is highly associated with VaD (Skoog, 1994). Atherosclerosis is an accumulation of lipids and extracellular materials that combine with calcifications and produce fibroblasts. Atherosclerosis often affects large vessels such as the internal carotid artery and the vessels around the Circle of Willis (DeGraba, Fischer, & Yatsu, 1992). Smaller vessels, such as the leptomenigeal arteries, can also be affected. Atherosclerotic disease is associated with arterial hypertension, narrowed blood vessels, and infarcts.

The pathology associated with extra-cranial vascular disease processes may underlie the occurrence of a stroke. As such, extra-cranial disease processes can be linked with clinical phenomena involving an abrupt onset, a step-wise decline of cognitive and/or neurologic functions and may be associated with vascular diagnostic entities such as MID.

Subcortical Intra-Cranial Disease Pathology

Cerebrovascular disease processes involving the intra-cranial vessels are often associated with

subcortical vascular pathology and are likely integral in the genesis of dementia syndromes such as Binswanger's disease and the presence of leukoaraiosis on MRI scans. Anatomically, there is a distinction between the vessels that supply the *cerebral white matter*, or white matter associated with the semi-centrum ovale, versus the vessels that supply the *deep, subcortical white matter* (Patoni & Garcia, 1997). The cerebral white matter is nourished by blood supply coming from long penetrating arteries. These penetrating arteries come from the surface of the brain arising from right angles at subarachnoid vessels and then course through the cortex perpendicular to the surface of the brain. The deep subcortical white matter located next to the lateral ventricles receives blood supply from the ventriculofugal vessels that support portions of the basal ganglia, internal capsule, and thalamus (Rowbotham & Little, 1965). de Reuck (1971) has suggested that this pattern of subcortical white matter vascularization may comprise a periventricular arterial border zone that may be very susceptible to injury due to alterations or decrease in cerebral blood supply. Patoni and Garcia (1997) have suggested that the deep subcortical white matter may be viewed as a ''distal irrigation field,'' an area easily compromised due to secondary effects of disease, in general, and ischemia in particular.

Research has shown that the pathogenesis of what is labeled as white matter disease, as seen on MRI scans, is associated with a variety of structural alterations or lesions (Munoz, 1991). For example, chronic hypertension has been consistently associated with the clinical presentation of MRI periventricular and deep white matter alterations (Skoog, 1998). Chronic hypertension appears to compromise the tension and contractile properties of the smooth muscle cells within the arterial wall. Over time, these smooth muscles break down, collagen may be deposited, and hyalinosis may occur. This type of disease process results in vessels that are unable to respond to changes in hemodynamics, and serves to narrow the vessel diameter. Eventually, vessels can become permeable, with plasma penetrating into the walls of vessels. In this sense, hypertension contributes to a compromise in the blood brain barrier (Jellinger, 2002; Olsson et al., 1996). Ultimately, significant microangiopathy, including fibrohyalinotic thickening of the vessel wall and fibrinoid necrosis (the thinning of the vessel walls) can occur. Additionally, cerebral amyloid angiopathy (CAA) can also contribute to the structural alterations of the arterioles supplying the subcortical white matter (Skoog, Kalaria, & Breteler, 1999; Wisniewski & Wegiel, 1994). Although most often associated with Alzheimer's disease (Vinter, 1987), the amyloid deposits associated with CAA can accumulate in the arterial media and result in structural lesions within arterioles (Yamaguchi et al., 1994).

From a clinical perspective, the pathological mechanisms described above are very likely associated with the insidious clinical course associated with dementia syndromes such as Binswanger's disease. Indeed, our clinical investigations, derived from studying ambulatory patients who were evaluated in an outpatient memory disorder clinic, have shown that MRI scans with significant white matter alterations are rarely associated with an abrupt onset or step-wise decline in cognitive or neurological functioning.

Neuropathological Correlates of MRI White Matter Alterations

Neuroimaging studies reveal white matter alterations in the brain scans of older adults who may or may not have symptoms of cognitive impairment. Such changes have been termed ''subcortical hyperintensities,'' ''white matter lesions'' and ''unidentified bright objects'' (Roman, 1996). In 1987, Hachinski et al. (1987) used the term leukoaraiosis (literally meaning 'rarefied white matter') as a descriptive term for these signal changes.

Pathological investigations into the underlying pathology of leukoaraiosis implicate factors associated with cerebral ischemia (Filley, 2001). Arteriosclerotic changes within areas of leukoaraiosis have been reported (e.g., Chimowitz, Estes, Furlan, & Awad, 1992). The lumen of small penetrating arterioles are narrowed due to the build up of hyaline material (Fazekas et al., 1993; Pantoni & Garcia, 1997). This form of vessel change has been reported by other investigators studying the vasculopathy of Binswanger's disease (Caplan, 1995; Lin et al., 2000).

Additionally, Munoz, Hastak, Harper, Lee, and Hachinski (1993) speculate that the mechanisms that underlie MRI white matter alterations begin with microaneurysms of small vessels that cause leakage of serum protein from vessels. This can cause edema and demyelination of the affected white matter. Serum proteins, which may be toxic, may be absorbed by glial cells causing gliosis and frank cavitation of the white matter.

The Overlap Between Vascular Dementia (VaD) and Alzheimer's Disease (AD)

Studies have shown that the incidence of '*pure*' AD is substantially lower than previously reported. Victoroff, Mach, Lyness, and Chui (1995) reported that 86 percent of their patients meeting criteria for AD were also found to have evidence of other possible dementing disorders, including cerebrovascular disease. Bowler, Munoz, and Hachinski (1998) studied a group of 122 patients with dementia. Of this group, 81% of patients were diagnosed clinically with AD. However, upon autopsy, only 44% of cases had pure AD without any other coexisting causes of dementia. Crystal et al. (2000) reported that out of 56 patients meeting diagnostic criteria for AD, 28 had pure AD while the remaining 28 also displayed a wide variety of cerebrovascular lesions.

Some of the most intriguing research in recent years suggests pathological overlap between vascular processes and AD pathology. Some researchers (e.g., Nagy et al., 1997; Snowdon et al., 1997; Snowdon & Markesbery, 1999) have reported that the brains of patients with cerebrovascular disease and pathological changes of AD have lower numbers of senile plaques and tangles. This is in contrast to the brains of patients where cerebrovascular pathology was not considered a significant contributor to dementia symptoms. Thus, vascular diseases might possibly alter the development and distribution of senile plaques and neurofibrillary tangles associated with AD. Other associations are reported, as well. For example, there are data suggesting an association between the APOE 4 allele and atherosclerosis among patients with both AD and cerebrovascular dementia (Hofman et al., 1997; Slooter et al., 1997, 1998). Also, capillary microangiopathy might be directly related to the production of neurofibrillary tangles and senile plaques in AD (Zarow, Barron, Chui, & Perlmutter, 1997). Additionally, several mutations in the amyloid precursor protein (APP) gene have been found to associate with the accumulation of β-amyloid peptide in neuritic plaques (pathological hallmark of AD) and extensive leukoaraiosis/leukoencephalopathy (Grabowski, Cho, Vonsattel, Rebeck, & Greenberg, 2001).

NEUROPSYCHOLOGY OF SUBCORTICAL VASCULAR DEMENTIA

Cortical and Subcortical Dementia

The terms 'cortical' and 'subcortical' are traditional means by which dementias have been classified. These terms are generally used as shorthand to denote two different cognitive and behavioral presentations. While *cortical* dementia is associated with a disruption in 'higher' functions such as memory, language, and semantic knowledge, *subcortical* dementia describes a pattern of cognitive impairment involving difficulty in mental manipulation, forgetfulness, and personality/emotional changes (Albert, Feldman, & Willis, 1974). Recently, Royall and Polk (1998) have suggested the use of the term *type 1 dementia* to describe neuropsychological and behavioral deficits traditionally associated with AD. In contrast, *type 2 dementia* would be used to describe dementias that are associated with alterations in frontal-subcortical pathways.

Over the last several years, increasing numbers of studies have demonstrated a relationship between subcortical periventricular and deep white matter alterations (WMA) and subcortical lacunar infarctions, and differential impairment on tests of executive control. Other research has shown some relative sparing on tests of memory and language (Almkvist, 1994; Barr, Benedict, Tune, & Brandt, 1992; Bernard, Wilson, Gilley, Bennett, & Fox, 1992; Corbett et al., 1994; Doody, Massman, Mawad, & Nance, 1998; Gupta et al., 1988; Junque et al., 1990; Kertesz & Clydesdale, 1994; Kertesz, Polk, & Carr, 1990; Lafosse et al., 1997; Libon et al., 1993, 2001;

Mendez, Cherrier, & Perryman, 1997; Padovani et al., 1995; Pujol, Junque, Vendrell, Capdevila, & Marti-Vilalta, 1991; Roman & Royall, 1999; Royall, Mahurin, & Cornell, 1995; Royall, Mahurin, Cornell, & Gray, 1993; Starkstein et al., 1996; Tierney et al., 2001; Vanderploeg, Yuspeh, & Schinka, 2001; Villardita, 1993; Ylikoski et al., 1993). However, while many researchers have shown that patients with subcortical vascular lesions exhibit differential impairment on executive control tasks, few researchers have attempted to interpret these findings within any larger context. We believe that deficits in establishing and maintaining a *mental set* may be a construct which is useful in understanding the executive control impairment associated with subcortical VaD.

Mental Set and Executive Control

Based on findings from our laboratory, we characterize the ability to establish and maintain a mental set as the ability of patients to appreciate and understand the nature of a task, and to respond within the context of that task until the task is completed. Our conceptualization of the construct of mental set is similar to ideas put forth by Dias et al. (1997) and Rogers et al. (2000). In three recent studies, we have sought to elucidate the parameters regarding the difficulty patients with subcortical VaD exhibit in establishing and maintaining mental set.

For example, Lamar et al. (1997) studied deficits in establishing and maintaining mental set by looking at the perseverative behavior produced by patients with AD and subcortical VaD with the Graphical Sequence Test (Goldberg, 1986). It was found that the severity or the overall volume of errors was much greater among the subcortical VaD patients as compared to AD patients. Also, the types of perseverative errors made by patients with subcortical VaD were quite distinctive. For example, patients with subcortical VaD frequently persisted in producing responses even when there was no command to do so. Lamar and colleagues used the term *hyperkinetic/interminable* perseverations to describe this behavior. For example, after asking a patient to "draw a circle, draw a circle, draw a circle, etc." such behavior persists even when there is no request on the part of the examiner to produce any response. By contrast, the perseverative errors made by patients with AD were different. For example, when asked to *write* the sentence "three squares and two circles," AD patients might *draw* three squares and two circles; or when asked to draw a target figure such as a circle, AD patients often produced a different figure such as a square or a triangle (i.e., termed *semantic/element perseverations*).

The mechanisms that underlie difficulties in establishing and maintaining mental set were different for each group. Among patients with subcortical VaD, their difficulty tended to be ubiquitous, and was correlated with poor performance on tests of motor functions. Therefore, impaired regulation of motor behavior appeared to be the mechanism that was responsible for their difficulty. By contrast, among patients with AD, their perseverative errors were correlated with tests of naming and output on the 'animal' word generation task. Thus, problems in language and the response selection of lexical/semantic information may underlie their difficulty.

In a companion study, Giovannetti et al. (2001) studied problems exhibited by dementia patients in establishing mental set as assessed by the WAIS–R Similarities subtest, a test of verbal concept formation. In this study, zero-point responses were recoded on the basis of whether the response retained some capacity to convey a superordinate relationship (i.e., how the word pair is alike). An *in-set error* was coded when a response was vague, but retained some superordinate relationship (i.e., *dog-lion – they're alive*). An *out-of-set* error was coded when no superordinate relationship was conveyed (i.e., *dog-lion – one barks and the other growls*). Similar to Lamar et al. (1997) study of perseveration, Giovannetti et al. (2001) found that deficits in concept formation among subcortical VaD patients were more severe in that they tended to make more out-of-set errors. Additionally, these errors were associated with other neuropsychological measures consistent with gross deficits in establishing and maintaining mental set. On the other hand, AD patients tended to make more in-set errors and, similar to Lamar et al. (1997) study regarding perseveration, these errors continued to be associated with

neuropsychological measures related to language and response selection.

In a third study, Lamar et al. (2002) investigated the capacity of dementia patients to establish and maintain a complex mental set using the Boston Revision of the Wechsler Memory Scale Mental Control subtest. This test consists of tasks such as asking patients to identify letters that rhyme with the word 'key', and to identify printed letters that contain a curved line. Previous research has shown that patients with subcortical VaD and dementia associated with PD (matched for age, education, and MMSE test performance) obtain lower overall accuracy indices on these tasks as compared to patients with AD (Libon et al., 1997). Lamar and colleagues sought to investigate a patient's ability to maintain mental set on these tasks by summing the errors and correct responses made in the first, middle, and latter third on each task. Among patients with AD, performance dropped from the first to the middle third of these tasks; however, there was no further decline when the middle third test performance was compared to the latter third test performance. By contrast, among patients with subcortical VaD, errors accumulated and performance declined throughout all three portions of the task suggesting differential impairment in maintaining the necessary mental set for these tasks. In a second experiment, the number of responses generated across the four 15s quadrants on tests of letter fluency ('FAS') was examined. Interestingly, when controlled for output by converting the number of responses produced in each 15s quadrant as a percent of the total number of words generated; patients with VaD generated a larger percent of words than the AD and normal control participants during the first 15s. After the first 15s, however, the output of VaD patients dropped precipitously below that of the AD patients. In contrast, the percent of responses generated by the AD patients within each 15s quadrant was no different as compared to normal control participants.

In sum, when these three studies are viewed as a whole it appears that executive control deficits associated with subcortical VaD tended to be rather pandemic, while the executive control deficits associated with AD are restricted and context-specific (i.e., related to lexical/semantic operations). These findings are consistent with the theoretical constructs put forth by Luria (1980), as well as the factor structure described by Lamar et al. (this issue). This factor structure suggests that executive function deficits in dementia may be hierarchically arranged in the sense that some deficits are related to higher-level disorders of cognition, while other deficits are related to more rudimentary motor/cognitive functions.

Another means by which to put the data derived from these three experiments into some greater context revolves around speculation that subcortical white matter alterations may be a surrogate with respect to the role of the basal ganglia in maintaining or shifting mental set. For example, several researchers have speculated that the inhibitory actions of the basal ganglia serves as a *selective gating mechanism* that updates and directs operations that are fed back to the frontal lobes through the thalamus (Beiser & Houk, 1998; Frank, Loughry, & O'Reilly, 2001). When the basal ganglia are damaged or become disinbitited, the frontal lobes cannot effectively maintain or shift mental set to meet the needs that may be required when task demands are changed or become complex. A derailment with respect to this type of gating mechanism might explain the pattern of response reported by Lamar et al. (2002) regarding the accumulation of errors as VaD patients attempt to complete complex mental control tasks or the diminished output of VaD and PD patients on tests of letter fluency. Clearly, this is an area requiring further research.

Memory and Learning

If patients with subcortical VaD are differentially impaired on executive control tasks, past research also tends to show some relative preservation on tests of episodic or declarative memory (Bernard et al., 1992; Lafosse et al., 1997; Libon, Malamut, Swenson, & Cloud, 1996, 1998; Tierney et al., 2001). On the 9-word California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987; Libon, Mattson, & Glosser et al., 1996), AD patients display poor retention, rapid forgetting, little to no benefit from cued recall or recognition test conditions, and the production of many intrusion errors. In contrast,

patients with subcortical VaD produced the opposite profile such that they obtained significantly higher scores on all measures of delayed free and cued recall memory, and showed significant improvement on the recognition discriminability index. These analyses are similar to prior research showing that AD patients are more impaired relative to patients with Parkinson's Disease (PD) and Huntington's disease (HD; Delis et al., 1991; Kramer et al., 1988; Massman, Delis, Butters, Levin, & Salmon, 1990).

In more recent research we have sought to disambiguate some of the mechanisms that underlie the production of errors AD and subcortical VaD patients produce on CVLT free recall test trials. For example, Davis, Price, Kaplan, and Libon (2002) used the term *initial intrusion* to describe the first time an intrusion error is produced. A *trans-trial perseveration* was coded when intrusions reoccurred in the later free recall learning trials. Finally, *within-trial perseverations* were scored when patients repeated a response that was produced earlier in any single free recall learning trial. Davis et al. (2002) speculated that deficits in response selection/semantic knowledge might be the mechanism that underlies the production of initial and transtrial errors; while poor self-monitoring might be responsible for the production of within-trial perseverations. Some support for these predictions were obtained in that *Initial* intrusion errors were correlated with poor scores on the 'animal' word list generation Association Index (AI; Carew, Lamar, Cloud, Grossman, & Libon, 1997), a measure of the lexical-semantic organization. The 'animal' Association Index is a special scoring technique that measures the number of attributes that are shared between successive responses on the animal fluency task (see Appendix 1).

Davis et al. (2002) also examined the distribution of false positive responses produced by AD and subcortical VaD patients on the CLVT-9 word delayed recognition task. Within-group analyses indicated that, as a percentage of the number of foils endorsed, patients with subcortical VaD tended to endorse more interference (list B) foils than semantic or unrelated foils. By contrast, patients with AD endorsed more semantic and unrelated foils. Also, there was a significant correlation between the production of interference (list B) foils and the production of perseverations as measured with the Graphical Sequence Test (Goldberg, 1986; Lamar et al., 1997).

When these data are assessed as a whole, we believe that deficits in semantic knowledge and executive control associated with AD and subcortical VaD patients, respectively, are responsible for the pattern of intrusions, perseverations, and false positive responses on the CVLT-9 free recall (list A) learning and recognition test trials. Indeed, as Luria (1980) postulated, perseverations and other errors occur in domains of cognition in which patients are experiencing their deficits. Thus, the errors produced on the CVLT-9 by patients with AD appear to be related to their lexical/semantic knowledge deficits, while the errors produced by patients with subcortical VaD may be associated with deficits in executive function.

Language and Semantic Knowledge

Among patients with subcortical VaD, deficits in language have not been studied as extensively as problems associate with executive control or memory problems. While a variety of language-related tasks have been administered, the procedures most commonly reported revolve around performance on tests of naming and letter and/or category word fluency. Two general findings emerge from this literature. First, output from tests of letter fluency produced by patients with subcortical VaD is reduced as compared to AD patients (Carew et al., 1997; Lafosse et al., 1997). This finding is often interpreted within the context of greater executive control deficits associated with subcortical VaD. Second, patients with subcortical VaD sometimes produce better scores on tests of naming (Cannata, Alberoni, Franceschi, & Mariani, 2002; Kontiola, Laaksonen, Sulkava, & Erkinjuntti, 1990).

The observation that patients with subcortical VaD make fewer intrusion errors and demonstrate less forgetting than patients with AD on tests of memory suggest that, in general, lexical/semantic knowledge may be less disrupted in subcortical VaD as compared to AD. Only a few studies have examined this issue. For example, Lukatela, Malloy, Jenkins, and Cohen (1998) found that

patients with VaD made fewer errors on the Boston Naming Test (BNT) as compared to patients with AD. Also, there were distinct differences regarding BNT errors. Patients with AD tended to make superordinate errors (*acorn* – nut), that is, errors that tend to place the response within a broader semantic class as the stimulus. Patients with subcortical VaD made more coordinate errors, (*acorn* – peanut), that is, errors that tend to place the response within the same semantic class as the stimulus. Lukatela et al. (1998) interpreted their findings as evidence for relative preservation of semantic knowledge in VaD as compared to AD.

Laine, Vuorinen, and Rinne (1997) also administered the BNT to patients with AD and VaD. Unlike the data reported by Lukatela et al. (1998), there was no between-group difference on the BNT. Laine and colleagues administered a multiple choice task measuring word meaning. On this task, patients were asked to choose specific semantic features related to BNT target items. Patients with AD tended to make more errors regarding semantic, as opposed to the superordinate features of target items as compared to patients with VaD. In this sense, these findings are similar to those reported by Lukatela et al. (1998).

Additionally, Carew et al. (1997) designed a paradigm to measure semantic organization on the 'animal' word list generation task. On this task, patients were asked to generate as many different animal names as they could in one minute. All responses were coded into the following six attribute categories: size (big, small), geographic location (foreign, North American), diet (herbivore, carnivore, omnivore), zoological class (insect, mammal, bird, etc), habitat (farm, Africa/jungle, widespread, etc), and biological order/related groupings (feline, canine, bovine, etc). An Association Index (AI; Appendix 1) was calculated by totaling the number of shared attributes and then dividing by the number of total responses. The AI is believed to provide a measure of the semantic organization between successive responses independent of the number of words produced. Carew et al. (1997) found that the total number of responses made by patients with AD and subcortical VaD did not differ. With respect to the AI, normal control participants and subcortical VaD patients did not differ; however, both groups obtained higher scores on this measure as compared to patients with AD. Carew et al. (1997) interpreted their data as consistent with the idea that semantic knowledge is relatively intact in subcortical VaD as compared to AD.

NEUROIMAGING AND VASCULAR DEMENTIA

A major methodological issue concerning the significance of MRI periventricular and deep white matter alterations revolves around the means by which white matter alterations are measured. Many studies have measured MRI white matter alterations using 3–6 point visual rating ordinal scales. From a statistical perspective, the restricted range of measurement inherent in such scales means that truly robust analyses examining the relationship(s) between white matter alterations and neuropsychological functioning are difficult to compute. Considering the sophistication of current imaging technology, the reliance on these visual rating scales is surprising. Moreover, in a review of 13 scales that rate and measure MRI/CT white matter and periventricular alterations, Mantyla et al. (1997) reported that there appears to be significant disagreement regarding the operational criteria of white matter alterations.

Only a handful of studies have derived semiquantitative scales to measure MRI white matter alterations that have sufficient statistical properties to permit more sophisticated statistical operations. For example, Junque et al. (1990) devised a Leukoaraiosis scale (LA) designed to measure the total amount of white matter alterations observed on MRI scans. This scale divides each hemisphere into five areas: the frontal centrum semiovale, the parietal centrum semiovale, the white matter around the frontal horns, the white matter around the body of the lateral ventricles, and the white matter around the atrium and occipital horns. This scale rates the extent of white matter alterations in each area from 0 to 4. A score of 0 equal no white matter alteration. Scores between 1 and 4 equals $<25\%$, 25–50%, 50–75%, and $>75\%$) white

matter alterations, respectively. The effective range of this scale is between 0 and 40 when white matter alterations from each hemisphere are summed. Junque et al. reported that as Leukoaraiosis increases, performance on tests of information processing speed and executive function declines. Libon et al. (1998) found a dissociation such that as patients obtained a higher LA scores, (i.e., MRI scans positive for greater white matter involvement), performance on the procedural, pursuit motor learning task declined. By contrast better performance on the CVLT-9 recognition discriminability index was associated with greater parahippocampal volume.

Ylikoski et al. (1993) report similar results. These researchers constructed two separate scales that measure white matter changes involving the deep white matter versus alterations found in the centrum semiovale. As with the Junque LA scale, a semiquantitative rating (i.e., from 0 to 3) is assigned to each area. When all ratings are summed, each scale ranges from 0 to 24, or a total score of 48. Ylikoski et al. (1993) found significant correlations between both scales and neuropsychological measures of visuoconstruction, information processing speed, and executive control. Schelten et al. (1992, 1993) also described a similar semiquantitative MRI rating scale that includes separate subscales that measure periventricular, deep white matter, basal ganglia, and infratentorial white matter alterations. Recently, the European Task Force on Age-Related White Matter Changes has developed a new semi-quantitative rating scale to measure white matter alterations (Wahlund et al., 2001). Similar to the scales developed by Junque, Ylikoski, and Scheltens this scale has an effective range of measurement between 0 and 30. This scale has the added advantage of being applicable to both MRI and CT scans.

Jenkins et al. (1998), Moser et al. (2001), and Davis-Garrett et al. (this issue) have described a technique in which the hyperintense regions indicative of white matter alterations are measured with a semiautomated computerized thresholding technique. With this technique, a threshold based on an intensity histogram is generated for the hyperintense pixels representing white matter alterations and then applied to measure consecutive slices. The pixel volume is then calculated for each slice, summed to generate a total volume, and then expressed as a percentage of total brain volume (not including ventricles and other cerebrospinal fluid spaces). Similar to studies utilizing the traditional visual rating scales, Moser et al. (2001) and Davis-Garrett et al. (this issue) report a significant negative correlation between percentage of white matter alteration and decline in psychomotor slowing, and reduced performance on tests of attention and executive control.

Aside from which measurement scale to use, another aspect to consider when measuring white matter alterations is the type of image sequence. The conventional approach is to use moderately to heavily T2-weighted images. This provides discrimination between the gray and white matter because of the long repetition time. This weighting, however, also causes the cerebral spinal fluid (CSF) to appear bright. This CSF brightness, however, can mask or obscure the appearance of white matter changes that occur in the periventricular regions or in the high convexities. Some researchers have shorter repetition time to ensure that the CSF is darker than the hyperintense markers that possibly signal white matter abnormalities (Jackson, Ginsberg, Schomer, & Leeds, 1997). Recent research suggests, however, that WMAs are better viewed with fluid-attenuated inversion recovery (FLAIR) images than conventional T2-weighted images (Furukawa et al., 2001; Tomura et al., 2002). FLAIR images suppress the signal from the ventricular CSF while preserving the T2-weighting of the brain parenchyma (De Coene et al., 1992). Thus, white matter abnormalities should be more visible and easier to measure with FLAIR, than with conventional T2-weighted, technique.

SUMMARY

It has now been approximately 15 years since the introduction of MRI technology has rekindled interest in vascular dementia in general, and subcortical white matter lesions in particular. Rather than providing answers, we believe that past research has served to clarify the questions that need to be addressed. On the basis of the

association between differential impairment on tests of executive control as compared to other domains of cognitive functioning often observed with patients with periventricular and deep white matter alterations, we believe that this kind of vascular dementia can and should be regarded as a subtype of subcortical dementia.

We have suggested that impairment in establishing and maintaining mental set is the construct that best describes the executive control deficits associated with subcortical VaD. In this regard we have attempted to investigate the mechanisms that underlie the executive control deficits seen in patients with subcortical VaD. We speculate that two mechanisms appear to be responsible for the executive control deficits seen in subcortical VaD. First, the executive control deficits seen in subcortical VaD tends to be ubiquitous or *pervasive*. As noted above, patients with subcortical VaD produce low accuracy scores on tests of mental control, and diminished output on tests of letter fluency. Among patients with VaD, perseveration and poor mental planning typified their performance when they are asked to copy geometric figures (Freeman et al., 2000; Libon, Malamut, & Swenson et al., 1996). Executive control impairment is also associated with their retrieval deficits on verbal serial list learning tests, and in attaining mental set on tests of verbal concept formation.

The executive control deficits in AD are different. Not only is this domain of cognitive functioning not as impaired as compared to patients with subcortical VaD, but the mechanisms that underlie executive control problems in AD appear to be restricted to the response selection of lexical/semantic information. The pervasiveness, or the means by which executive control deficits intrude into virtually all other aspects of cognition among patients with subcortical VaD is consistent with theoretical ideas suggested by Luria (1980). In this sense the executive control deficits in subcortical VaD are context nonspecific, whereas the executive control deficits in AD are, by contrast, rather context specific.

The second mechanism that underlies the executive control deficits associated with subcortical VaD revolves around how well patients with subcortical VaD *regulate* their behavior. As noted by Lamar et al. (2002), when patients with subcortical VaD attempt to work through various tasks, such as tasks of mental control, they tend to accumulate more and more errors. On tests of letter fluency, patients with subcortical VaD tend to produce their output during the initial portion of the test. Again, these behaviors are different as compared to AD patients. The disruption of frontal lobe-basal ganglia-thalamic pathways may be the aetiology of both take out the pervasiveness and poor regulation of executive control deficits in subcortical VaD (Alexander, DeLong, & Strick, 1986; Sultzer et al., 1995). We also speculate that subcortical white matter alterations may alter the capacity of the basal ganglia and thalamus to selectively gate information that is ultimately fed back to the frontal lobes.

All of these ideas require additional research. In this regard, investigating the significance of subcortical periventricular and deep white alterations not only has important clinical implications, but may also serve as a platform from which to investigate larger issues regarding brain-behavior relationships.

A necessary tool to facilitate this research is the development of more sophisticated ways to measure and quantify MRI white matter alterations. The use of 3 to 5 point ordinal rating scales is insufficient for both clinical as well as research needs. We have shown that semi-quantitative rating scales (e.g., Junque et al., 1990; Schelton et al., 1992; Ylikoski et al., 1993) can provide the necessary statistical utility for more meaningful analysis. Similar to the work presented by Davis-Garrett et al. (this issue), intensive research needs to be carried out to develop fully quantitative systems that can measure both total, as well as regional, subcortical white matter alterations.

More work needs to be carried out to investigate the interrelationships regarding the neuropathology that underlie both AD and VaD. There are now a handful of studies that seem to suggest that the presence of cerebrovascular disease has some influence on the expression of Alzheimer's neuropathology. It has also been observed that AD and subcortical VaD share many of the same risk factors (de la Torre, 2002; Skoog, 1998). Among the questions that need to be addressed is whether the two disease processes run in parallel, or whether cerebrovascular alterations

or the disease processes that give rise to cerebrovascular alterations might also be an aetiological factor with respect to AD pathology.

Recently Erkinjunntti et al. (2000) have proposed a new paradigm to identify patients who might be suitable for a diagnosis of subcortical vascular dementia. Also, Cosentino et al. (this issue) have suggested that paradigms that both diagnose and *describe* the dementias may be useful. We support these efforts.

Does white matter *matter*? Does vascular dementia exist? The relationship between AD and subcortical VaD appears to be more complex than previously believed. We suspect that for many patients the disambiguation of 'plaque and tangle' disease from cerebrovascular disease may require a more sophisticated level of analysis than is now applied in clinical practice.

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APPENDIX 1

Calculating the 'Animal' Association Index

Responses	Size		Location		Diet			Zoological class						Habitat						Biological order										Sum of attributes
	big	small	foreign	local	herbivore	carnivore	omnivore	mammal	bird	fish	insect	reptile	amphibian	farm	African/jungle	prairie	water	forest	widespread	artiodactyla	bovine	canine	equine	feline	fowl	pachyderm	porcine	primate	ursine	
response 1: horse	x			x	x			x						x									x							6
response 2: mule	x		x	x	x			x						x									x							6
response 3: lion	x					x		x							x									x						2
response 4: cougar	x			x		x		x											x					x						4
response 5: wolf		x		x		x		x										x				x								3
response 6: jackal		x		x		x		x										x				x								6
response 7: camel	x		x		x			x						x						x										1

Note. Total sum of attributes = 22. Association Index = 3.67. All possible attributes are not listed within each category in this table.