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NEUROPSYCHOLOGICAL FUNCTION IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE

by

Natalie A. Phillips

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosphy

at

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The undersigned hereby certify that they have read and recommend to the Faculty of Graduate Studies for acceptance a thesis entitled "Neuropsychological Function in Patients with Peripheral Vascular Disease"

by Natalie A. Phillips

in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

Atherosclerosis causes ischemia in cerebral and peripheral arteries. Patients with atherosclerosis in lower-extremity arteries (PVD) are at high risk for cerebrovascular disease (CVD). PVD and CVD can co-exist within an individual, although only the former might be recognized clinically. Three studies tested the hypothesis that PVD patients without diagnosed stroke have neuropsychological deficits, presumably due to concomitant CVD. Study 1 compared 14 PVD patients with 14 matched controls on a comprehensive neuropsychological battery. PVDs performed worse ($p<.002$) on tests of attention and psychomotor speed (WAIS-R Digit Symbol) and executive function (Modified Card Sorting). Study 2 tested whether PVDs show a similar pattern of neuropsychological impairment as *symptomatic* CVD patients. It also tested the hypothesis that, of the medical factors PVD severity, transient ischemic attack, heart disease, hypertension, diabetes, hyperlipidemia, and smoking, the best predictor of impairment would be PVD severity. Memory, attention, language, visuoconstructional ability, executive function, and sensory/motor function were examined in 29 PVDs, 29 CVDs, and 30 matched controls. PVDs were impaired ($p<.002$) in executive function (Wisconsin Card Sorting perseverative errors*, conceptual responses*; WAIS-R Picture Arrangement), attention (Trail Making B*; WAIS-R Digit Symbol), visuospatial ability (WAIS-R Block Design*; Rey Figure*), and non-verbal memory (Rey Figure recall*). On indicated tests (*), PVDs performed *as poorly* as CVDs. PVD severity and ischemic heart disease were medical predictors of impairment (mean variance explained: 14% and 19%, respectively). Depression did not relate to cognitive performance. Study 3 examined whether neuropsychological performance predicted functional outcome in 19 PVDs at one year. Deficits in attention, memory, and visuospatial function related to greater dependence in everyday activities. Summary: PVD patients have deficits in attention, executive function, and visuospatial ability. The nature and magnitude was similar to that in patients with known cerebrovascular infarcts. Markers of generalized athero-sclerosis predicted neuropsychological impairment. Even in the absence of demonstrable infarcts, atherosclerosis may be a factor in vascular-related cognitive decline.

Abbreviations Used

ABI	ankial/ brachial index
ADL	activities of daily living
ANOVA	analysis of variance
COWAT	Controlled Oral Word Association Test
CNS	central nervous system
CVD	cerebrovascular disease
CVLT	California Verbal Learning Test
FAQ	Functional Activities Questionnaire
FSIQ	Full Scale IQ
GSI	Global Symptom Index
HRB	Halstead-Reitan Battery
MANOVA	multiple analyses of variance
MCST	Modified Card Sorting Task
MID	multi-infarct dementia
PIQ	Performance IQ
PVD	peripheral vascular disease
RT	reaction time
SCL-90-R	Symptom Check List - 90, Revised
s.d.	standard deviation
TIA	transient ischemic attack
VIQ	Verbal IQ
WAIS-R	Wechsler Adult Intelligence Scale, Revised
WAIS-R-NI	Wechsler Adult Intelligence Scale, Revised, as a Neuropsychological Instrument
WCST	Wisconsin Card Sorting Test
WMLs	white matter lesions
WMS	Wechsler Memory Scale
WMS-R	Wechsler Memory Scale, Revised

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Peripheral vascular disease (PVD) is a broad term which refers to a group of distinct diseases involving the arterial, venous, or lymphatic vessels outside the heart (Fairbairn, 1980). This dissertation investigated patients with chronic atherosclerotic occlusive disease of the lower-extremity arteries, which falls within the peripheral vascular disease classification. This introductory section is organized in the following manner. First, an introduction to the terms and concepts of arterial disease and, specifically, atherosclerosis, is presented. Two major manifestations of atherosclerosis, PVD and cerebrovascular disease (CVD) are reviewed. The risk factors, course, and clinical manifestations of PVD and CVD are reviewed and evidence for their co-existence is presented. The literature regarding cognitive impairment in patients with CVD is reviewed. A rationale for hypothesizing that cognitive deficits may exist in patients with PVD is then presented.

Atherosclerosis

The normal human vascular system is comprised, to varying degrees, of five component parts: the endothelium, basement membrane and ground substance material, elastic tissue or fibres, collagen, and smooth muscles (Lie, 1980). These components are integrated in various permutations to form three basic coats: the *tunica intima* (inner coat), the *tunica media* (intermediate coat), and the *tunica adventitia* (outer coat). The significance of the endothelium lies in the fact that it lines the entire arterial system and regulates the flow of blood components into

and out of the vessel lumen. Next to the external surface of the endothelial cells is the basement membrane which functions as a transport barrier and a supporting structure. There are two extracellular components of the arterial wall, namely the internal elastic lamella, or elastic fibres, and collagen, which functions to prevent the overdistention of the vessel. Finally, the smooth muscle comprises the actively contracting element of the vessel (Lie, 1980).

Arteries typically undergo *diffuse intimal thickening*. This normal aging process, beginning in early infancy, is characterised by an increase in the thickening of the intimal area, loss of elasticity, increase in calcium content, and increase in diameter. These changes are believed to take place throughout the major arterial system (Fuster, Kottke, & Juergens, 1980). Diffuse intimal thickening is considered to be a physiologic rather than a pathological process (Lie, 1994). This growth and remodelling is considered an essential element of the arterial system's response to hemodymanic stress (Lie, 1994). *Arteriosclerosis* is a generic term used to describe all varieties of structural changes that result in hardening and thickening of the arterial wall. *Atherosclerosis* is one form of arteriosclerosis. It is a pathological process characterized by the focal accumulation of lipids, carbohydrates, blood products, fibrous tissue, and calcium deposits (Fuster et al., 1980). Its major negative effect is narrowing of the arterial lumen through stenosis and thrombosis and, consequently, ischemia of the end organ or tissue (Lie, 1994; Chisolm et al., 1991).

The three basic types of atherosclerotic lesions have been identified as fatty streaks, fibrous plaques, and complicated lesions. The fibrous plaque, which

results from the proliferation of the smooth muscle cell in the arterial wall, is considered the primary and the most pathognomonic and clinically significant lesion of atherosclerosis (Lie, 1994; Ganda, 1980; Lie, 1980). This lesion protrudes into the vessel lumen and is characterized by a central core of lipid and cell debris, and is surrounded by smooth muscle cells, collagen, elastic fibres, and proteoglycans (Lie, 1994). The subsequently altered and thickened intima constricts the lumen and forms the bulk of the vessel wall. In contrast to fatty streaks, fibrous plaques are not uniformly distributed amongst the world's population (Lie, 1994). Fatty streaks consist of the focal accumulation of a few subendothelial smooth muscle cells which contain and are surrounded by lipid deposits (Lie, 1994). The age at which fatty streaks appear throughout the various branches of the arterial tree is not uniform; however, regardless of race, sex, or environment, these lesions are present in the aorta of virtually every child by the age of 10 years (Lie, 1994). Finally, the complicated lesion is a fibrous plaque involving various degenerative changes including calcification, plaque hemorrhage, ulceration or rupture of the intima, and mural thrombosis (Lie, 1994).

It is not merely the presence of atherosclerosis but the degree of arterial stenosis it produces that determines its functional or hemodynamic significance. Critical stenosis of an artery is the degree of luminal narrowing at which further small decrements in luminal area result in abrupt changes in pressure and flow rate distal to the stenosis (Lie, 1994).

Peripheral Vascular Disease

Chronic atherosclerotic occlusive disease of the extremities involves the aorta, its major branches to the limbs, and the arteries of the extremities. The majority of cases affect the lower extremities and are due to the atherosclerosis of the terminal portion of the abdominal aorta, the iliofemoral and popliteal arteries, and the arteries below the knees (Juergens & Bernatz, 1980). The clinical manifestation of atherosclerotic occlusive disease of the lower extremities is often referred to as atherosclerosis obliterans; however, the present study will employ the more general term peripheral vascular disease (PVD). The average incidence of PVD is probably underestimated, but data from the Framingham study estimated that approximately 26 per 10,000 men and 12 per 10,000 women are affected (Kannel, Skinner, & Schwartz, 1970). The incidence rises sharply with age (Juergens & Bernatz, 1980).

Clinical Manifestations and Course of PVD

Pain of several different types is a significant problem produced by PVD and is generally classified as persistent or intermittent. Extreme and persistent rest pain can result from ulceration and gangrene of ischemic tissue (Fairbairn, 1980). Such pain may result in the significant disruption of sleep and other normal activities.

Intermittent claudication is a frequent and often initial symptom of PVD and its presence is considered to be a hallmark of an inadequate supply of arterial blood to contracting muscles (Fairbairn, 1980). Claudication, literally, means

limping or lameness. Intermittent claudication is pain (often described as a cramp, tightness, aching, or tiredness), tension, and/ or weakness in the legs. It is elicited only by a continuous exercise such as walking and is relieved by rest (*Dorland's Medical Dictionary*, 1982; Fairbairn, 1980). The site of claudication is approximately equivalent to the level of arterial occlusion (Fairbairn, 1980). The significance of intermittent claudication as a symptom should not be underestimated. Medical opinion indicates that by the time intermittent claudication is experienced by a patient there is usually objective evidence of impaired circulation (Fairbairn, 1980) and already an increased likelihood of morbidity and mortality from coronary and cerebrovascular disease (Juergens & Bernatz, 1980). In other words, intermittent claudication signals the presence of clinically significant and probably generalized atherosclerosis.

Within 5 years approximately 24% of patients with intermittent claudication will experience the onset of rest pain, which heralds the progression of the disease to the point of critical ischemia (Krajewski & Olin, 1991). Rest pain is described as a dull aching sensation in the toes or foot. This symptom can cause significant distress as it may awaken a patient from sleep or may cause him/ her to hang the affected limb over the side of the bed or to walk about to obtain relief from the pain (Krajewski & Olin, 1991).

Another frequent complication of PVD is ischemic ulceration and gangrene, defined as necrosis of the tissue. The first toes are most commonly affected, although other toes and areas of the foot and leg also can be involved (Fairbairn, 1980). A patient's ability to walk is often severely limited by the time tissue

necrosis occurs (Krajewski & Olin, 1991). Gangrene is the principal cause for amputation in PVD (Berardi & Keonin, 1978).

The clinical course of PVD can be quite variable. Prognosis for the survival of the affected limb depends on the extent and rapidity with which arterial occlusion develops, the frequency of occlusion, and the state of the disease at the time at which appropriate treatment is initiated (Juergens & Bernatz, 1980). For example, in a group of middle-aged non-diabetic PVD patients reporting intermittent claudication as the only symptom of the disease, 3% required amputation of the affected limb within 5 years of the initial examination (Juergens & Bernatz, 1980). This figure, however, increased to 20% for patients in whom ischemic ulceration or gangrene was present at the time of the initial assessment (Juergens & Bernatz, 1980).

Amputation secondary to PVD is an important health care issue. It has been estimated that 0.5% of all operations performed annually in the United States are amputations resulting from ischemia in the lower extremity (Warren & Kihn, 1968). In the United States in 1985, more than 50,000 major amputations were reported in diabetic PVD patients alone (Levin, 1991). More than two thirds of amputations in persons over the age of 50 years are necessitated by PVD (Schwartz & Hoaglund, 1989). Levin (1991) estimated that the cost of each hospitalization due to amputation, not including surgical or rehabilitation fees, was approximately $25,000 US in 1985.

In addition, the presence of PVD places patients at a higher risk of dying of vascular-related causes than non-PVD individuals. Criqui et al. (1992) showed that

the relative risk of dying within a 10 year period amongst patients with PVD compared to those without was 3.1 times higher for deaths from all causes and 5.9 times greater for deaths from cardiovascular disease (defined as myocardial infarction, coronary-artery bypass surgery, stroke, or stroke-related surgery). Thus, PVD is a significant risk factor for death caused by myocardial infarction and stroke. Approximately 50% of deaths in PVD men are caused by myocardial infarction, 15% by stroke, and 10% by atherosclerosis in the abdomen (Krajewski & Olin, 1991).

Cerebrovascular Disease

Cerebrovascular disease (CVD) is a general term referring to any brain abnormality resulting from a pathologic process involving the blood vessels (Adams & Victor, 1993). The term *ischemia* is used to indicate a reduction in the cerebral (and other tissue) blood flow sufficient to interfere with cerebral function (Hachinski, 1984). Disruption of blood flow for more than 4 to 5 minutes produces irreversible tissue necrosis or *infarction* (Adams & Victor, 1993). The following are brief definitions of ischemic syndromes considered to represent the ends of the spectrum of reduced cerebral blood flow. A transient ischemic attack (TIA) is a transient focal neurological deficit resulting from ischemia of less than 24 hours in duration (Sundt, Meyer, & Anderson, 1994). A TIA may result from an embolism or a hemodynamic factor (i.e., high-grade stenosis or occlusion). TIAs in the carotid system usually produce transient symptoms including weakness or sensory dysfunction in the hand, face, or lower extremity (Sundt et al., 1994). As the name

implies, the deficits are considered to be transient in nature, existing only for the period of cerebrovascular insufficiency. However, as will be discussed later, neuropsychological studies of patients with TIAs show that lasting subtle cognitive deficits can be demonstrated beyond this 24 hour period.

In contrast to TIAs, the term "cerebral infarction" denotes the death of neuronal tissue and is considered to represent the end stage of continued ischemia (Sundt et al., 1994). The characteristic temporal mode of presentation of CVD has resulted in the term *stroke*, which is defined as a "sudden, non-convulsive, focal neurologic deficit" (Adams & Victor, 1993, p. 670). In other words, stroke is a somewhat generic term used to refer to a broad spectrum of neurologic deficits varying in severity which result from cerebral ischemia.

There are five categories of cerebral blood vessels: 1) the extracranial internal carotid and vertebral arteries; 2) the arteries of the circle of Willis and their branches; 3) perforating arteries; 4) the microcirculation (consisting of arterioles, capillaries, and venules); and 5) the large veins and dural sinus (Lie, 1994). The most frequent cause of stroke is extracranial vascular disease and atherosclerosis is by far the most common cause of extracranial occlusive disease (Lie, 1994). The incidence of atherothrombotic brain infarction is substantially higher than other causes of stroke (such as intracerebral haemorrhage, subarachnoid haemorrhage, or cerebral embolism resulting from cardiac sources). Non-atherosclerotic causes of cerebrovascular insufficiency have been estimated to account for no more than 10% of all deaths from stroke (Lie, 1994).

Risk Factors for Atherosclerotic Development

Regardless of the arterial system involved, the risk factors for the development for atherosclerosis are the same. These include cigarette smoking (particularly in the case of PVD; Fuster et al., 1980), hyperlipidemia, diabetes mellitus (Fuster et al., 1980), hypertension (particularly in the case of cerebral and coronary arteries; Lie, 1994), and, as indicated above, increasing age and male sex (Juergens & Bernatz, 1980). Brief explanations of the proposed mechanisms by which some of these factors predispose an individual towards the development of atherosclerosis are described below. It is important to remember that the commonly accepted major risk factors (i.e., hypertension and hypercholesterolemia) account for only a portion of the high incidence of atherosclerosis in the continental United States. Thus, atherosclerosis must be the result of additional unidentified pathogenic factors acting singly or in concert with other recognized risk factors (Lie, 1994).

Since it will later be hypothesized that symptomatic atherosclerosis in the peripheral arteries is associated with impaired cognitive function, the neurobehavioural effects of atherothrombotic risk factors will also be reviewed. In general, the findings of only those studies employing appropriate control subjects will be discussed. Many of these studies can be criticized on a statistical basis for their failure to account for an increase in Type I error, due to the analysis of multiple neuropsychological measures.

Hypertension

Pathophysiology. Hypertension is considered to exert an accelerating effect on atherogenesis. Generally, atherosclerotic lesions are considered to be quantitatively, rather than qualitatively different in persons with hypertension relative to those without (Toole, 1994). The basic mechanism believed to underlie the increased propensity to atherosclerosis is increased thickening of the intima and increased endothelial permeability. This implies there is likely a synergistic effect with circulating blood lipid. The greater the endothelial permeability (which is, in part, a function of hypertension), the more lipids can penetrate the intima of the vessel (Toole, 1994).

Neurobehavioural Effects. Although hypertension has been the most extensively studied risk factor for atherosclerosis and stroke in terms of its impact on cognitive function, the corpus of data is limited by many studies which failed to include appropriate matched controls or to take into account factors such as age, concomitant disease, background, and/ or medication status in the study subjects (Bornstein & Kelly, 1991). In general, studies have indicated evidence of subtle neuropsychological dysfunction in otherwise healthy subjects with hypertension (e.g., Francheschi, Tandredi, Smirne, Mercinelli, & Canal, 1982; Light, 1978; Mazzucchi et al., 1986; Miller, Shapiro, King, Ginchereau, & Hosutt, 1984; Schultz, Elias, Robbins, Streeten, & Blakeman, 1989; Waldstein, Ryan, Manuck, Parkinson, & Bromet, 1991; Wilkie & Eisendorf, 1971; Wilkie, Eisendorf, & Nowlin, 1976; but see Elias, Robbins, Schultz, Streeten, & Elias for alternate findings).

Table 1 summarizes the results of studies of the neuropsychological

correlates of hypertension. The studies are summarized in terms of subject groups, biomedical factors examined, neuropsychological domains studied, and findings (detailed by neuropsychological test or experimental task). In one of the earlier studies, Light (1978) examined serial choice reaction time (RT) in hypertensive and normotensive subjects and patients with vascular disease (stroke, TIA, and coronary heart disease). She found no difference in RT between controls and hypertensive subjects who had not been treated for hypertension prior to the study. For hypertensive subjects who had a history of hypertensive treatment, there was evidence of slightly delayed RT (approximately 12 seconds) relative to controls. In contrast to this mild slowing of RT, the stroke and TIA groups' RT was significantly slowed relative to the other experimental groups.

The most consistent neuropsychological finding in hypertensive subjects has been that of mild impairment on tests of psychomotor integrity and/or tests requiring rapid responding across a wide variety of tasks (Light, 1978; Mazzucchi et al., 1986; Miller et al., 1984; see Table 1). Several studies have noted mild memory impairment in subjects with hypertension (e.g., Franceschi et al., 1982; Mazzucchi et al., 1986; Waldstein, et al., 1991; Wilkie et al., 1976; see Table 1), although others have not (e.g., Miller et al., 1984; see Table 1). Visuospatial processes may also be affected by hypertension (e.g., Franceschi et al., 1982; Mazzucchi et al., 1986; see Table 1). Language-related functioning appears to be relatively undisrupted (see Table 1).

Treatment status (i.e., treated vs. untreated) appears to be an important mediating factor; however, the data are unclear as to the direction of the effect.

Studies have indicated that, relative to untreated patients, hypertensives receiving effective drug treatment may perform better (Mazzucchi et al., 1986) or show more improvement in cognitive function over follow-up (Miller et al., 1984; Sands & Meredith, 1992). However, results from other studies (e.g., Franceschi et al., 1982; Light, 1978) have suggested that treated hypertensive patients may actually perform more poorly than untreated patients. The basis of this discrepancy have not yet been resolved.

Research has begun to address the natural history of neuropsychological impairment in hypertension. In a longitudinal study involving three measurement points of performance on the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955) separated by 5- to 6- year intervals, Schultz et al. (1989) found significantly lower Verbal non-age-corrected scaled scores in otherwise healthy middle-aged hypertensive subjects than in normotensive subjects at Times 2 and 3, but not at Time 1. No differences were found between the blood pressure groups for the Performance scores. There was no statistically significant change in either Verbal or Performance scores for the healthy hypertensive subjects at the three measurement points. This indicated that neither decline nor improvement in intellectual function took place over an approximately 10 year period in treated healthy hypertensive subjects. Sands and Meredith (1992) found that increased blood pressure significantly predicted poorer WAIS Digit Span performance 11 years later. However, no effects were found for the other WAIS subtests examined (Digit Span Backwards, Block Design, Digit Symbol, Object Assembly). Clarification of the long-term effects of hypertension of cognitive function awaits

further study.

In summary, the neuropsychological impairment found in otherwise healthy hypertensive patients tends to be mild. Deficits are typically observed on tests considered very sensitive to brain dysfunction (e.g., the Trail Making Test from the Halstead-Reitan Battery) and measures of response speed. As such, there is still limited information on the fundamental information-processing deficits or the site(s) of the underlying neuropathology of hypertension (Bornstein & Kelly, 1991). Data from Elias et al. (1987; see Table 1) have indicated that level of education within hypertension groups is an important variable to consider. Their findings suggest that cognitive function might be preserved in hypertensive subjects with high levels of education and disrupted in subjects with relatively lower levels of education (but who were not necessarily poorly educated). In addition, results from studies by Franceschi et al. (1982) and Schultz et al. (1989) suggest that cognitive dysfunction may be greater in or limited to hypertensive subjects who exhibit evidence of end-organ changes which are, in part, a result of hypertension. This issue is one that will be important to explore in future research.

Hyperlipidemia

Pathophysiology. Lipoproteins are blood plasma complexes which transport cholesterol and triglycerides (Olin, Cressman, Hoogwerf, & Weinstein, 1991). Lipoproteins are mainly synthesized in intestinal and liver cells. Evidence indicates that the greater the level of circulating low-density lipoproteins, which carry two-thirds of total blood cholesterol (Olin et al., 1991), the greater the likelihood they

will enter the arterial wall (Toole, 1994). The synergistic effect this has with hypertension has already been noted. Low-density lipoproteins are believed to produce the primary endothelial injury that initiates and maintains atherosclerotic lesions (Ganda, 1980). However, the exact mechanism(s) by which low-density lipoproteins induce arterial cellular events are unclear (Chisolm et al., 1991). Interestingly, it has also been shown that high levels of high-density lipoprotein are inversely correlated with the risk of developing atherosclerosis (Juergens & Bernatz, 1980; Olin et al., 1991). This probably relates to the fact that high-density lipoproteins are considered to function in reverse cholesterol transport (i.e., the transport of cholesterol from peripheral tissue to the liver; Chisolm et al., 1991; Olin et al., 1991).

Neurobehavioural Effects. Brown and Kelly (1991) noted the paucity of studies examining the potential neurobehavioural effects of abnormality in blood lipids. A search of the literature in the last 5 years revealed no new neuropsychological studies in this area. One relevant study found suggested that abnormal blood lipids may have a negative influence on cognitive function. In a longitudinal study involving repeated administrations of the same neuropsychological tests, Reitan and Shipley (1963; cited in Bornstein & Kelly, 1991) studied neuropsychological function in 156 healthy men, divided according to age (younger or older than 40 years) and on the basis of whether serum cholesterol levels were reduced by less or more than 10%. In the older subgroup only, the authors found greater practice effects in men who reduced their cholesterol levels by 10% or more, relative to those who did not achieve such large reductions in cholesterol.

This suggests that the latter group failed to benefit from the second exposure to the tests.

Diabetes

Pathophysiology. Diabetics tend to develop atherosclerosis at an earlier age and with greater severity than non-diabetics (Ganda, 1980). Vascular disease of the large vessels accounts for approximately 75% of all deaths in persons with diabetes (Ganda, 1980). Although the exact mechanism(s) underlying this increased risk of vascular disease is unclear, it is considered that accelerated atherogenesis in diabetics may result from the interplay of three factors: 1) the associated presence of small-vessel disease, 2) hyperglycemia, and 3) hormonal aberrations resulting from altered metabolic states (Ganda, 1980).

Neurobehavioural Effects. There are several putative means through which diabetes mellitus could have a deleterious effect on brain function. The dysregulation of blood glucose could result in episodes of hypoglycaemia (i.e., excessive control of blood glucose) or episodes of ketoacidosis (i.e., inadequate control of blood glucose). A secondary influence could be through the association of diabetes with hypertension and cerebral atherosclerosis (Bornstein & Kelly, 1991; Brown et al., 1986).

Table 2 reviews studies of the neurobehavioural effects of diabetes. The studies are summarized in terms of subject groups, biomedical factors examined, neuropsychological domains studied, and findings (detailed by neuropsychological test or experimental task). In general, studies employed either Type I diabetics

(juvenile-onset, insulin-dependent; e.g., Bale, 1973; Francheschi et al., 1984; Holmes, 1986; Holmes, Koepke, & Thompson, 1986; Prescott, Richardson, & Gillespie, 1990; Ryan & Williams, 1993; Skenazy & Bigler, 1984; see Table 2) or Type II diabetics (adult-onset, non-insulin dependent; e.g., Perlmutter et al., 1984; Reaven, Thompson, Nahum, & Haskins, 1990; Robertson-Tchabo, Arenberg, Tobin, & Plotz, 1986; U'Ren, Riddle, Lezak, & Bennington-Davis, 1990; see Table 2). The study of Meuter, Thomas, Grüneklee, Gries, and Lohmann (1980) is one exception which examined both groups on the same neuropsychological battery. In general, mild cognitive deficits have been documented in both types of diabetes. Studies which have sought to determine disease-related correlates of impairment (e.g., disease duration, glycemic control) have yielded mixed results.

Skenazy and Bigler (1984; summarized in Table 2) compared Type I adult diabetics (who were further classified as to whether or not they had visual impairment) with normal controls and patient controls on a large neuropsychological battery (22 measures). The authors found evidence of significant impairment in somatosensory and motor function, but limited only to male diabetics. They concluded that this impairment was more likely the result of peripheral neuropathy rather than an indication of central nervous system (CNS) involvement. Performance on tasks tapping visuopraxis (tested in the non-visually impaired patients only) was also impaired in the diabetic subjects. The relationship between diabetic severity and performance on the various neuropsychological tasks was inconsistent. Patients with more severe diabetes performed worse than less severe diabetics on some tasks, while the opposite pattern was true for other tests.

Also, no significant correlations with severity were found on some tasks. Complex sensory-motor integration and verbal learning and memory were considered by the authors to be intact in the diabetic patients, leading them to conclude that Type I diabetics show relatively little evidence of cortical impairment.

However, other studies have indicated that subtle higher-order cognitive deficits do exist in Type I diabetics. Deficits in performance have been observed on tests of visuospatial constructional ability (Francheschi et al. 1984; see Table 2) and reaction time (Holmes, 1986; Holmes et al., 1986; Meuter et al., 1986; see Table 2). The results regarding memory function are inconclusive. Several studies (e.g., Bale, 1973; Francheschi et al., 1984; Meuter et al., 1986; see Table 2) have demonstrated deficits, while other have not (e.g., Prescott et al., 1990). One study (Ryan & Williams, 1993; see Table 2) was particularly well-designed, employing large subject samples, appropriate controls, and sensitive neuropsychological measures. It failed to observe any deficits in memory function in Type I adult diabetics, suggesting that memory impairment may not be a robust finding.

In terms of disease-related variables, the results of studies of Type I diabetic adults are varied. Some find that long-term metabolic control is inversely related to cognitive performance. For instance, Holmes (1986; see Table 2) found that, relative to matched controls, men with poor long-term metabolic glucose control (as measured by glycosylated haemoglobin) performed more poorly on tests of verbal knowledge (the WAIS Information and Vocabulary subtests) and on a test of attention (a simple reaction time task). Ryan and Williams (1993; see Table 2) showed that poor long-term glucose control correlated with poorer WAIS-R

Performance IQ scores. However, other studies have found that disease duration but not poor metabolic control is associated with deficits in cognitive performance. Prescott, Richardson, and Gillespie (1990; see Table 2) examined memory function for abstract and concrete words in relation to disease chronicity and metabolic control in Type I diabetics. They found that only disease duration correlated significantly with poor recall, but only for concrete words. Finally, Francheschi et al. (1984; see Table 2) observed no significant relationships between disease variables and neuropsychological function.

In contrast to these findings, studies of typically older patients with Type II diabetes have yielded more consistent results. As can be seen in Table 2, studies of Type II diabetics demonstrated impairment in reaction time (Meuter et al., 1980; see Table 2), attention (Meuter et al., 1980; Perlmutter et al., 1984; Reaven et al., 1990; U'Ren et al., 1990; see Table 2), and memory (Meuter et al., 1980; Perlmutter et al., 1984; Reaven et al., 1990; U'Ren et al., 1990; see Table 2). For instance, in a well-designed study, Perlmutter et al. (1984) examined verbal learning and memory, attention, and working memory in 144 Type II diabetics and 38 nondiabetic control patients. Diabetics performed significantly worse than controls on the serial learning and memory task and the working memory task (Backwards Digit Span) administered. No differences were found on the one test of attention. Moreover, these cognitive deficits were found to relate to the presence of peripheral neuropathy (which the authors suggested might parallel a CNS abnormality) and a measure of long-term glucose control (glycosylated haemoglobin). Reaven et al. (1990) and U'ren et al. (1990) have also

demonstrated deficits in memory function in Type II diabetics (see Table 2).

In general, there is evidence of some cognitive impairment in both Type I and Type II diabetic adults. Memory deficits have been reported in both samples, although somewhat more consistently in Type II diabetics. It remains to be determined which disease variables (e.g., duration, age of onset, metabolic control) account for the impact on neuropsychological functioning. Interestingly, Ryan and Williams (1993) speculated that the negative effects of diabetes might interact with differential effects of age on various brain regions. This could account for some cognitive deficits (e.g., memory impairment) being observed more consistently in older (Type II) diabetic populations, while other functions appear to remain intact.

Finally, Bornstein and Kelly (1991) noted that many of neuropsychological studies of diabetics (*viz.*, Type I) are based on samples of young adults. The results of these studies, therefore, may not necessarily be generalized to stroke patients who will tend to be considerably older. The results of studies of Type II diabetics or older Type I diabetics are possibly more germane to the older patient with vascular disease.

Cigarette Smoking

Pathophysiology. There is evidence that smoking is a significant atherogenic factor (Juergens & Bernatz, 1980). The primary mechanism by which smoking exerts its adverse cardiovascular effects is probably increased concentration of carboxyhemoglobin and consequent tissue hypoxia (Ganda, 1980). Carboxyhemoglobin has been shown to impair hepatic metabolism of

lipoprotein remnants, while carbon monoxide-induced hypoxia is considered to result in increased endothelial permeability and has been shown to result in the proliferation of cultured human arterial smooth cells (Ganda, 1980).

Neurobehavioural Effects. It is reasonable to suspect that smoking could interfere with brain functioning and, as a result, neuropsychological functioning. Carbon monoxide is one of the many byproducts of tobacco smoking. It has a higher affinity for haemoglobin than does oxygen and displaces it, thereby interfering with oxygen transport to the brain and other organs (Royal College of Physicians, 1977). However, as indicated by the studies reviewed in Table 3 (see also Brown et al., 1986), the results of studies investigating the effects of smoking on neuropsychological function have been inconsistent. Also, as noted in the Comment section of Table 3, the majority of studies have employed young subject samples. As a result, their findings cannot necessarily be applied to aging samples at risk for stroke (Brown et al., 1986).

Most studies have focused on the effects of cigarette smoking on learning and memory. In a small sample of habitual smokers, Andersson (1975; see Table 3) demonstrated lower levels of initial learning but better delayed recall if subjects smoked during the learning task than if they had not been smoking. Houston, Schneider, and Jarvik (1978) demonstrated poorer immediate and delayed recall on a verbal learning task in subjects smoking nicotine-laden versus sham cigarettes. Carter (1974) found no negative effects of smoking during an intentional learning task; however, results by Andersson and Hockey (1977) showed that smoking during a learning task negatively affected incidental but not

intentional memory.

Poor performance by smokers has also been shown on other tasks, such as symbol-digit substitution (e.g., Carter, 1974) and auditory vigilance (Tong, Leigh, Campbell, & Smith, 1977). However, in subjects who were habitual smokers, Tong et al. (1977) showed a beneficial effect of smoking in subjects who were allowed to smoke during an auditory vigilance task. These subjects improved their performance over time relative to smokers who had to abstain from smoking.

One study (Hill, 1989; see Table 3) has examined the effects of smoking on cognitive function in elderly nondemented adults screened for health and intellectual impairments. Seventy-six subjects were administered a battery of neuropsychological tests of memory, attention, perception, language, problem solving, and psychomotor speed. The only difference between subjects who smoked and subjects who were non- or ex-smokers were found on the tests of psychomotor speed (i.e., WAIS-R Digit Symbol [Wechsler, 1981] and Cross Off [Botwinick & Storandt, 1973, cited in Hill, 1989). Smokers performed more poorly than non-smokers on these tests. Given that his elderly smoking subjects were free of health complications, Hill pointed out that these subjects may represent a particularly hardy group of individuals resistant to the negative effects of smoking. Thus, it is possible that the potential negative effects of smoking on cognitive function in the elderly may not be evident until other signs of physical decline are manifested.

Consistent impairment in neuropsychological function has been observed in patients with chronic obstructive pulmonary disease, a disease secondary to

heavy smoking (Grant, Heaton, McSweeny, Adams, & Timms, 1982; Grant et al., 1987). However, these findings will not be discussed further since this condition was an exclusion criterion in the studies reported here.

Cerebrovascular Disease and Cognitive Function

The majority of stroke patients have significant stenosis or occlusion of the extracranial (internal carotid and vertebral) arteries (Lie, 1994). There is a wide range of sites of predilection for atherosclerosis in these arterial systems, namely the carotid bifurcations, the origins of the internal cerebral arteries, the middle cerebral arteries, the origin and along the course of the vertebral arteries (Lie, 1994), the anterior and pericallosal arteries, and the posterior cerebral artery (Toole, 1994; see Figure 1). There is also considerable variability in the territorial distribution of the major cerebral arteries (van der Zwan & Hillen, 1991). As a result, the exact pattern of focal neuropsychological deficits one might observe following stroke obviously will vary from patient to patient. Deficits will depend on which cerebral vessels are critically diseased and, as a consequence, which cortical area(s) undergo infarction. For example, infarction of the cortical area supplied by the middle cerebral artery (which is larger than that supplied by the anterior or posterior cerebral arteries) might result in impairment of language ability such as an aphasia, alexia, agraphia, etc., if following left-sided occlusion, and sensory impairment of the contralateral arm, face, or leg (Adams & Victor, 1993). As the anterior cerebral artery supplies the anterior three-quarters of the medial surface of the cerebral hemisphere, significant stenosis or occlusion of this vessel

might produce frontal lobe dysfunction, such as perseveration, or possibly memory impairment (Adams & Victor, 1993). Finally, alexia (with or without agraphia), anomia, or more rarely memory deficits may result from occlusion to the branches of the posterior cerebral artery (Adams & Victor, 1993).

It is surprising to realize that there are relatively few investigations concerning the cognitive or neuropsychological sequelae of stroke. As noted by Farr, Greene, and Fisher-White (1986), there are little or no systematic data on neuropsychologic deficits of patients with stroke as a clinical entity. Given that strokes tend to occur in one cerebral hemisphere, they usually result in lateralized focal or multifocal neuropsychological deficits. Such clinical manifestations have been utilised to provide information on the lateralization of neuropsychological function (Brown et al., 1986; Farr et al., 1986). Lateralized deficits may include language impairment following infarction of the left hemisphere (Heilman, 1974), visuoperceptual impairment following right hemisphere stroke (Farr et al., 1986), and motor impairment contralateral to the involved hemisphere (Brown et al., 1986). While this information has been of great theoretical importance in terms of furthering our understanding of the neuroanatomical substrates of certain cognitive functions (e.g., language), there is an acknowledged need for information about other non-lateralized cognitive functions (Hom, 1991; Farr et al., 1986). Hom and Reitan (1990) indicated this need succinctly by stating that generalized cognitive functions have been essentially "ignored in the previous literature" (p. 652).

Hom (1991) has argued that the emphasis of neuropsychological studies on the identification of specific cognitive deficits and their anatomical localization

has arisen from the traditions of clinical and behavioural neurology. He also pointed out a corresponding lack of knowledge about the general intellectual, cognitive, and behavioural deficits associated with stroke. A behavioural neurology model tends to centre on specific behavioural deficits correlated with pathology of the CNS and to employ dichotomous classifications (i.e., normal *vs.* abnormal) to describe behaviour (see Davison, 1974, for further discussion). The resulting impact on neuropsychology has been the selection of behaviours for study that appear to be specifically affected by focal brain lesions and the relative neglect of behaviours that are less obviously linked to specific brain areas (Heilman & Valenstein, 1985). In contrast, a clinical neuropsychology model focuses on the behavioural consequences of brain pathology and attempts to understand the type and extent of neuropsychological dysfunction associated with brain disease (Hom, 1991). Davison described clinical neuropsychology as a discipline using "*comprehensive* approaches to *applied* problems concerning the *psychological* effects of brain damage in *humans* (p. 3, Davison, 1974, italics in the original text). A further aim of clinical neuropsychology is to understand the effects on the adaptive functioning of the individual (Hom, 1991).

A model of hierarchical brain function has been proposed by Reitan and Wolfson (1985), the essential elements of which are the combined role of both general and specific cerebral functions of the brain. Six categories of brain function are proposed in the model: 1) sensory input functions; 2) attention, concentration, and memory; 3) verbal skills, 4) visuospatial abilities; 5) abstract reasoning and concept formation; and 6) output motor functions (Reitan &

Wolfson, 1985; see Figure 2). Categories 1 and 6, the sensory and motor functions, are considered to represent the basic input and output components of brain function. Categories 3 and 4, verbal and visuospatial functions, respectively, are considered to reflect more specialized cerebral functions which can be related to specific brain regions. Well known examples of these are the findings that lesions to the perisylvian zone of the left but not right hemisphere result in language impairment and that lesions of the right posterior hemisphere impair visuospatial functions (Goodglass & Kaplan, 1979). In contrast to these well-localized functions, the Reitan and Wolfson model proposes that attention and concentration, memory, abstract reasoning and concept formation (categories 2 and 5) represent general brain functions which are less well localized in the brain. Some might take execption to this classification. It is well known that focal brain lesions in the anterior mesial temporal lobe can result in memory deficits (e.g., Milner, 1972) and that attention and executive function abilities can be disrupted by lesions involving pre-frontal cortex (e.g., Stuss & Benson, 1984). Nevertheless, the Reitan and Wolfson model describe these functions as being relatively non-localized because they are also dependent on the overall integrity and equipotentiality of cortical tissue (Hom, 1990, Reitan & Wolfson, 1985).

As indicated above, clinical neuropsychology has traditionally assessed focal abilities such as those in categories 3 and 4 in patients with CVD. Relatively little is known about the effects of CVD on generalized cognitive abilities (categories 2 and 5, according to Reitan & Wolfson's [1985] classification). Hom (1991; Hom & Reitan, 1990) has highlighted the need for studies of CVD to examine the nature

and degree of impairment of higher cognitive functions which are likely to be dependent on the general functional integrity of the brain, in addition to studying deficits attributable to focal lesions.

To this end, Hom and Reitan (1990) examined general cognitive function in three groups of patients with CVD, which included patients reported to have lateralized occlusive disease of the anterior or middle cerebral arteries, internal carotid artery, or internal capsule, arteriovenous malformation, aneurysm, or intracranial hemorrhage. Also included were patients with generalized or bilateral CVD, such as hypertensive encephalopathy, bilateral carotid insufficiency, basilar artery occlusion, or generalized atherosclerosis. Hom and Reitan (1990) divided these patients into three groups: patients with left-hemisphere lesions (n=30), right-hemisphere lesions (n=30), and diffuse or generalized lesions (n=30). These groups were compared with a non-CVD group (n=20) comprised of psychiatric and normal controls. Neuropsychological function was examined on an extensive battery of tests selected from the Halstead-Reitan Neuropsychological Test Battery (HRB; Reitan & Wolfson, 1985) and the WAIS (Wechsler, 1955). WAIS Verbal IQ (VIQ) scores were significantly lower in the left and diffuse CVD groups relative to the control group. WAIS Performance IQ (PIQ) and Full Scale IQ (FSIQ) scores were significantly lower in all CVD groups compared to controls. Not unexpectedly, significant patterns of lateralized dysfunction were revealed. Contralateral motor functioning (assessed by finger tapping) was impaired by unilateral lesions. Patients with left CVD performed more poorly than the other groups on individual verbal subtests; however, it is interesting to note that no differences were found

between the three CVD groups on individual performance tests, indicating similar extent of impairment of perceptual-motor IQ. Hom and Reitan (1990) also examined generalized cognitive abilities considered to be relatively independent of neuroanatomical location (according to the Reitan & Wolfson [1985] model), such as attention and concentration, abstraction, and incidental memory. Multivariate analysis of variance (MANOVA) revealed that controls performed better than CVD patients on tests of attention and concentration; univariate analyses of variance (ANOVAs) indicated that these differences were most frequently found between controls and left CVD patients. Analyses revealed significant impairment in abstraction and complex reasoning ability and tests of incidental memory in all CVD groups relative to the control group. Thus, Hom and Reitan (1990) found that the consequences of CVD included both focal, specific deficits, presumably related to the side of tissue infarction, and generalized cognitive dysfunction, presumably resulting from the disruption of overall brain functional integrity.

Interestingly, the issue of generalized cognitive function in CVD has been explored more fully in patients who present with symptoms of cerebrovascular insufficiency (e.g., patients with TIAs) rather than completed stroke. A review of the literature indicates that TIA patients show deficits on tests of oral fluency (Baird et al., 1984; Delaney et al., 1980; Hemmingsen et al., 1982), attention (Baird et al., 1984; Baird, et al., 1985; Hemmingsen et al., 1985; Delaney et al., 1980), visual and verbal memory (Hemmingsen et al., 1985, 1982; Delaney et al., 1980), abstraction (Hemmingsen et al., 1982; Delaney et al., 1980), manual dexterity (Baird et al., 1984; Delaney et al., 1980) and speech sounds discrimination (Baird

et al., 1984). As noted below, in some instances cognitive deficits were related to the side of vascular insufficiency.

Delaney, Wallace, and Egelko (1980) examined neuropsychological functioning in patients with carotid artery distribution TIAs. They found that patients with TIAs showed deficits on measures of complex memory, perceptual-motor integration, abstract concept formation, and verbal fluency. A control group was not employed. The study's findings were based on a comparison to published norms. The authors presented the data in terms of whether or not the TIA group mean fell within the impaired range for a given test and whether or not "most" individual scores fell within that range. Delaney et al. (1980) noted that two types of impairment patterns were found in their sample. The first type was patients who demonstrated largely lateralized deficits which were consistent with the vascular distribution of the TIA (e.g., impairment in right-hand motor function or in verbal fluency in patients with left carotid disease). The second type was considered to be a neuropsychological profile considered to be congruent with bilateral or diffuse dysfunction (e.g., impairment in abstraction ability).

Baird et al. (1984) attempted to determine if the pattern of impairment of neuropsychological tests could be used to detect the sites of arterial stenoses and occlusions. They examined neuropsychological performance on an extended version of the Halstead-Reitan battery in three groups of TIA and stroke patients: those with symptomatic occlusive disease in the carotid arterial system (n=22), those with primary angiographic lesions in the vertebrobasilar system (n=11), and those experiencing ischemic symptoms but with normal angiograms (n=11). All

three groups were found to be at least mildly impaired on the neuropsychological battery; however, there were no differences between the groups on any of the 31 test scores obtained. Baird et al. (1984) suggested a number of possible explanations for the failure to observe different patterns of neuropsychological impairment between the cerebrovascular groups. These reasons included a possible incompatibility between structural (i.e., angiographic) and functional (i.e., neuropsychologic) measures of cerebrovascular integrity, modulating vascular factors such as the development of collateral circulation, or a possible lack of specificity or sensitivity of the neuropsychological tests employed. In addition, the lack of a normal control group and the failure to control for Type I error given the multitude of neuropsychological tests administered constitute methodological problems with this study. Nevertheless, the results are consistent with those of Delaney et al. (1980) and Hom and Reitan (1990) in demonstrating that patients with CVD, regardless of the site or side of the symptomatic disease, show generalized cognitive dysfunction.

Relationship Between Peripheral Vascular and Cerebrovascular Disease

Atherosclerosis is the most common cause of ischemia in the central nervous system (Lie, 1994; Siekert, Whisnant, & Sundt, 1980) and in the periphery (Juergens & Bernatz, 1980). Given that arterial disease in the central nervous system and in the periphery share the same pathophysiological mechanism, it is reasonable to suspect an association between these two disease syndromes. Cerebrovascular disease is viewed as a consequence of a long-term process and

the association between it and atherosclerosis elsewhere in the body indicates that it is part of a generalized vascular disease (Kannel & Wolf, 1983). In fact, the histopathological changes of atherosclerotic lesions found in the periphery are identical to those of the cerebral arteries (Juergens & Bernatz, 1980).

There are a number of studies which demonstrate that PVD and CVD co-exist and, therefore, reflect a generalized pattern of vascular disease within an individual. PVD is a risk factor for minor ischemic strokes and TIAs (Dennis, Bamford, Sandercock, & Warlow, 1989). Its prevalence is significantly higher in patients with TIAs than in those without TIAs (Ostfeld, Shekelle, & Klawans, 1973). PVD has been identified as the third most strongly associated adverse prognostic factor for stroke outcome in TIA patients (Hankey, Slattery, & Warlow, 1992). The only factors more strongly correlated with subsequent stroke outcome were increasing number of TIAs in the three months prior to study participation and increasing patient age. Tonelli et al. (1993) demonstrated that the mortality rate following stroke is significantly higher in patients with concomitant PVD than in those without. Little (1975) mentioned briefly that 43% of PVD amputees showed some evidence of CVD upon admission to hospital for amputation. Finally, in a study designed to determine the prevalence of asymptomatic carotid artery stenosis in peripheral arterial disease, Ellis, Franks, Cuming, Powell, and Greenhalgh (1992) found that 13.7% of PVD patients had a stenosis of over 50% in either of the common or internal carotid arteries.

To summarize thus far, CVD and PVD arise from the same mechanism, atherosclerosis. As reviewed early, identical risk factors underlie the development

of clinical symptoms of atherosclerosis in the peripheral, coronary, and cerebral arteries. There is widespread agreement in the medical literature that the factors which lead to atherosclerosis in the lower extremities are likely to produce similar lesions in other arteries and that atherosclerosis of the extremities is just one manifestation of similar pathology in the heart and brain (p. 271; Juergens & Bernatz, 1980). As emphasized by Tonelli et al. (1993), the presence of PVD should be considered a strong marker of generalized atherosclerosis.

Peripheral Vascular Disease and Cognitive Function

Given the association between PVD and CVD, it would be reasonable to suspect that patients with PVD might also suffer from impairment in cognitive function as a result of concomitant CVD. In other words, it is likely that at least some proportion of PVD patients have experienced subclinical or "silent" cerebral ischemic episodes that have gone unrecognized by the patient, family, and/or medical practitioner. Or, if subtle changes in cognitive function have been noted, they might merely be attributed to the vagaries of aging. If true, neuropsychological measures of cognitive function should be sensitive to this brain dysfunction.

Frontal Lobe Damage

Some authors have suggested that silent infarctions in the frontal lobes are not considered uncommon (Sundt et al., 1994; Wiebe-Velazquez & Hachinski, 1991). What might be the possible consequences of damage to this area? Most information regarding cognitive function and the frontal lobes has come from patients with circumscribed lesions (e.g., due to surgical removal) rather than

vascular insults. Hebb (1939) demonstrated that frontal lobe excisions for medically intractable epilepsy resulted in no appreciable change in IQ (in contrast to posterior lesions which usually can result in significant decreases in IQ). Nevertheless, cognitive deficits are evident following frontal lobe lesions. Stuss, Eskes, and Foster (1994) have provided a comprehensive review of the literature published over the last decade. In order to place in context the findings of two of the studies reported here, the role of the frontal lobes in cognitive function is briefly summarized below.

The frontal lobes appear not to be involved in the primary sensory functions of the visual or auditory modalities (Stuss et al., 1994). However, they are involved in eye movements, simple motor function (see Stuss et al., 1994), olfaction (e.g., Jones-Gotman & Zatorre, 1991), intentional motor acts (e.g., utilization behaviour, see Lhermitte, 1983) and motor sequencing (e.g., Jason, 1986). Performance on simple perceptual and constructional tasks is considered to be generally preserved following frontal lobe damage, certainly relative to the more frequent and severe disturbances which follow from right parietal lesions (Stuss et al., 1994). Exceptions to this are seen if the perceptual/ constructional tasks are complicated and require complex skills such as integration, flexibility, and/ or planning (e.g., difficulty in copying a complex figure due to planning deficits, Pillon, 1981).

Deficits in attention are frequently observed following damage to the frontal lobes, with evidence accumulating that the damage to the right frontal areas may be particularly crucial to attention processes. Evidence indicates that specific attention processes are disrupted, such as sustained attention, selective attention

and inhibition, and directed exploratory motor attention (Stuss et al., 1994) and that impairment cannot be explained by reductions in arousal or alertness. It is also known, however, that control of certain attention processes is not specific to the frontal lobes (e.g., the contribution of the right parietal region to directed visual attention).

Although frontal lobe damage may result in disruption of memory processes, the nature of the deficit is quite different from that observed following anterior medial temporal injury. In contrast to the latter, patients with frontal lobe damage generally are considered to perform normally on numerous tests of long-term memory (Stuss et al., 1994). Frontal-lobe damaged patients have difficulty on memory tasks which require self-directed planning or the organization of material to be learned (e.g., a self-order pointing task; Petrides & Milner, 1982). Further, the frontal lobes have been implicated in the selection, operation, and coordination of the proposed subsystems of short-term or working memory (see Stuss et al., 1994 for a review and discussion of the debate surrounding this issue).

There is very good evidence that the frontal regions are important on tasks requiring fluency or flexibility of thought. On tasks requiring the generation of responses, impairments have been demonstrated on verbal tasks (e.g., Milner, 1963; although see Vilkki & Holst, 1994, for contrary evidence), visual tasks (Jones-Gotman & Milner, 1977), and gestural tasks (Jason, 1985).

The frontal lobes are also considered to be important on tasks requiring the active testing of hypotheses (e.g., trying out several alternative response strategies to determine the correct one) or response shifting and flexibility (Stuss et al., 1994).

The Wisconsin Card Sorting Test (WCST) has been considered a sensitive and specific indicator of frontal-lobe pathology since Milner's (1963) seminal paper. While the frontal lobes are implicated in the ability to formulate concepts and hypotheses, to plan, and to shift responding strategies, a caution has been raised against a reliance on the WCST as a sole indicator of frontal lobe integrity (Stuss et al., 1994). There is qualified support in the literature for the finding that frontal patients make more perseverative errors on the WCST test than do normals (Mountain & Snow, 1993). However, the evidence that frontal patients perform significantly more poorly on the WCST than patients with non-frontal damage or that the test is sensitive to specific regions of frontal-lobe dysfunction (*viz.*, dorsolateral lesions) is not at all compelling (Mountain & Snow, 1993).

In summary, the frontal lobes contribute to selective and sustained attention, working memory processes, planning and organizational ability (which can in turn influence performance on memory or constructional tasks if those contain a significant requirement for strategy or organization), fluent response/ behaviour generation, monitoring of responses, concept formation and active and flexible hypothesis testing. However, one is reminded that performance on these tasks may not be solely dependent on the function of the frontal lobes and that tests purported to be sensitive to frontal lobe damage may also be also impaired by damage to other brain regions (Stuss et al., 1994).

Studies Involving Patients with PVD

Despite the fact that PVD patients are at higher than normal risk for stroke, there is little known about their neuropsychological function. Some studies have included PVD patients as control subjects when examining neuropsychological outcome following surgery, for example, following carotid endarterectomy (Hemmingsen et al., 1986; van den Burg et al., 1985; Kelly, Garron, & Javid, 1980) and coronary artery bypass surgery (Shaw et al., 1987), to control for the effects of practice on post-operative performance. Mate-Kole (1985) employed PVD patients as surgical controls for cerebral revascularization candidates; it was noted that almost 50% of the PVD patients had to be excluded from that study as they showed marked cognitive deficits.

Kelly et al. (1980) examined pre- and post-operative cognitive change in 35 carotid endarterectomy patients and 17 age- and education-matched PVD surgical controls. The carotid endarterectomy sample was restricted to include patients with a history of TIAs only; no patients with completed stroke were included. All of these TIA patients had angiography-confirmed carotid stenosis of 70% or greater or ulcerated carotid artery plaque. All PVD control patients were considered to be free of neurological signs or symptoms at the time they were recruited into the study. Seventeen scores from neuropsychological tests were chosen to assess a broad range of functions including: learning and memory, attention, expressive language (including oral fluency), praxis, right-left discrimination, social judgement, visual perception, and problem solving. Pre-operatively, no differences were found between the carotid endarterectomy group

(i.e., patients with symptomatic CVD) and the PVD controls. With the exception of two tests (one of visual perceptual analysis and one of right-left discrimination), the PVDs did not show post-operative improvement, while the carotid endarterectomy group showed improvement on four tests. The authors were surprised at the failure to find pre-operative differences between their two groups (i.e., a group with identified cerebrovascular insufficiency and a putative "normal" control group). This led Kelly et al. to speculate that the restriction of the carotid endarterectomy sample to include TIA patients only might have eliminated those with gross structural central nervous system damage or that their sample was particularly heterogeneous. However, they also questioned the appropriateness of employing PVD patients as a normal control group, due to the possibility of intracranial atherosclerotic disease in some portion of the sample.

A suggestion that cognitive function in PVD patients may not be normal can be gleaned from two clues in this study. First, the carotid endarterectomy group and the PVD group did not differ from one another pre-operatively. Rather than supposing this finding was the result of *lack of impairment* in the carotid endarterectomy patients, an alternate interpretation would be to hypothesize that it was the result of comparing two group of patients, both of which exhibited cognitive deficits. In the absence of a normal healthy elderly control group, this possibility cannot be excluded. Second, it is interesting that the PVD patients improved on only half the number of tests as the carotid endarterectomy patients. Whether or not improvement in the endarterectomy group was attributable to the beneficial effects of surgery or was due to practice effects, it is notable that the

PVD patients failed to improve with repeated testing.

Shaw and colleagues (1987) evaluated neuropsychological function in 312 patients prior to and following coronary-artery-bypass-graft surgery. They employed 50 patients with PVD undergoing peripheral-bypass grafting as a surgical controls and 20 non-surgical patients (presumably without vascular disease, although this was not stated) as normal controls. Pre- and post-operative testing took place approximately 2 days prior to and 7 days following surgery, respectively. Evidence of mild neuropsychological dysfunction was found in the PVD control group. Thirty-one percent showed deterioration (greater than 1 *S.D.*) of postoperative test scores relative to preoperative levels on at least one neuropsychological measure. These changes were observed on tests of attention (Trail Making Test [Reitan, 1958], Wechsler Memory Scale [WMS] Mental Control [Wechsler & Stone, 1945], WMS Digit Span Total) and tests of learning and memory (WMS Logical Memory, WMS Associate Learning).

Hemmingsen et al. (1986) also assessed potential improvement in intellectual functioning following carotid endarterectomy. This Danish study examined cognitive function pre-operatively and 3 months post-operatively in 31 TIA patients with atherosclerotic disease of the carotid arteries who underwent carotid endarterectomy and 11 control patients who received vascular surgery for PVD. The PVD controls were considered asymptomatic for cerebrovascular or other brain disease upon admission to the study. Ten tests were employed to assess the areas of verbal learning and memory (using a word pairs test and story recall), visuospatial learning and memory (using a visual gestalts test), and

attention (using the WAIS [Wechsler, 1958] Digit Span Forwards and Backwards, WAIS Digit Symbol, and Trail Making Parts A and B [Reitan, 1958]). The results showed that the mean pre-operative performance of both TIA and PVD patient groups was below age-corrected norms on all the neuropsychological tests given, with the exception of the WAIS Digit Span. The mean TIA scores improved post-operatively on 95% of neuropsychological tests (and occurred mainly on tests sensitive to the function of the hemisphere ipsilateral to the side of operation), whereas no significant improvement was observed in the PVD group scores. The unexpected finding of poor cognitive function in the PVD controls was supported by cerebral pathophysiological and structural measures. These revealed that 2 of the PVD patients (18%) showed evidence of hypodense lesions on computed tomography (CT scan) and corresponding changes in regional cerebral blood flow and 7 (64%) showed evidence of cerebral atrophy.

To summarize, evidence of at least mild neuropsychological dysfunction has been coincidentally noted in PVD patients (e.g., Shaw et al., 1987; Hemmingsen et al., 1986; Mate-Kole, 1985). However, these studies were not designed to assess this patient group *per se*, which limits the information which might be drawn from these studies. For example, Kelly et al. (1980) and Hemmingsen et al. (1986) examined differences between carotid endarterectomy patients and PVD controls, but did not include a normal control group against which the performance of the two patient groups could be evaluated. Also, the number of PVD patients employed as controls was relatively small in both studies. Finally, the fact that PVD patients were used as control subjects meant that their data were not the primary

focus of scrutiny. Thus, relatively little is known about the sample characteristics of the PVD patients and interesting trends in their data went unexplored (e.g., the incidental finding of structural brain abnormalities noted in Hemmingsen et al., 1986).

To our knowledge, the only studies which have specifically evaluated cognitive function in patients with PVD are those of Pinzur, Graham, and Osterman (1988) and Phillips, Mate-Kole, and Kirby (1993). Pinzur et al. (1988) examined a group of 60 amputee patients, in whom amputation was secondary to PVD in 93% of the cases. Their purpose was to determine whether psychological evaluation would be predictive of rehabilitation potential. However, they did not explain how psychological function might affect rehabilitation nor did they provide a rationale for why cognitive function might be compromised in amputees. The authors found that six (10%) patients had severe cognitive deficits, eight (13%) had covert psychiatric illness, and three (5%) had both severe cognitive deficits and psychiatric illness. Of the six patients with severe cognitive deficits, only two were able to learn to use their prosthetic limb, but even they were unable to reach pre-amputation levels of ambulation. Pinzur et al. described the deficits found as including impairment in short-term memory, attention and concentration, orientation, and judgment. Unfortunately, this study has a number of methodological difficulties. First, Pinzur et al. employed different tests of cognitive function depending on whether a patient was above or below the age of 60; thus, test administration was not consistent across subjects. Even within each age group, test administration was not consistent, as not all tests were given to all

subjects. For example, an intelligence test (the WAIS) was used inappropriately as a screening measure for "neurological deficits" which, if detected, were further explored using a version of the Wechsler Memory Scale. The study did not include a control group with which to evaluate the patients' performance nor was it specified the method by which cognitive impairment was determined; rather, it appeared that these were clinical judgments made on an individual basis. Finally, the results (means and standard deviations) of the cognitive tests were not presented and no statistical analyses were conducted, making it impossible to evaluate the reliability of these findings. These methodological shortcomings make it difficult to draw any conclusions from this study.

STUDY ONE[1]

PVD and CVD share the same pathophysiological mechanism and risk factors. As reviewed above, there is abundant evidence to indicate that patients with PVD are likely also to have concomitant CVD which could result in impaired cognitive functioning. The present study was conducted as a preliminary test of the hypothesis that patients with PVD exhibit impairment in neuropsychological function. In light of the criticisms of the Pinzur et al. (1986) report, this represents

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[1] This study appeared in previously published form as: Phillips, N.A., Mate-Kole, C.C., and Kirby, R.L. (1993). Neuropsychological Function in Peripheral Vascular Disease Amputee Patients. *Archives of Physical Medicine and Rehabilitation, 74,* pp. 1309-1314. Permission to reprint these data was obtained from copyright sources: The American Congress of Rehabilitation Medicine and The American Academy of Physical Medicine and Rehabilitation.

the first systematic study of this question. Its findings have been previously published elsewhere (Phillips et al., 1993).

Neuropsychological function in 14 patients with lower-extremity amputations secondary to PVD and 14 age- and education- matched controls was examined. PVD amputees were selected as the target population in this study because, by virtue of having had an amputation secondary to lower-extremity ischemia, this patient group is considered to represent the severe end of a continuum of vascular disease (Rutherford et al., 1986). Thus, if chronic atherosclerosis relates to impaired cognitive function, these patients would be more likely to exhibit cognitive deficits than patients with milder disease.

The study was designed to assess a broad range of neuropsychological functions, including learning and memory, language, visuoperceptual and constructional abilities, and problem solving and abstract reasoning abilities. The rationale for sampling a range of cognitive domains was two-fold. First, as reviewed earlier, CVD can result in a heterogeneous and diverse pattern of cognitive impairment. Since this represented the first study of its kind, it was important to assess a broad range of cognitive functions in order to be able to detect the subtle deficits that might exist in this patient group. A more narrow focus on memory function alone, for example, would potentially miss other impairment(s) which might exist in this population.

Second, an attempt was made to make the study clinically relevant in view of the rehabilitation needs of the elderly amputees with PVD. As already indicated, amputation is a common outcome of chronic PVD. Most amputees are referred

for prosthetic rehabilitation. Presumably, adequate cognitive status helps a patient benefit maximally from prosthetic rehabilitation, given that rehabilitation involves learning many new skills, including gait training and care and maintenance of the prosthesis. Learning and memory, language ability, visuoperceptual and constructional abilities, problem solving and organizational ability are likely to be cognitive skills necessary in a rehabilitation setting.

Methods

Subjects

This project received ethical approval from the Ethics Review Committee of the Nova Scotia Rehabilitation Centre. Informed consent was obtained from all subjects prior to the commencement of neuropsychological testing and following an oral and written description of the study.

PVD Patients

Patients were recruited from inpatient and outpatient services of the Nova Scotia Rehabilitation Centre and had been referred for prosthetic rehabilitation. Patients admitted to the Rehabilitation Centre are not pre-screened with respect to cognitive status. The inclusion criterion was lower-extremity amputation secondary to PVD. The exclusion criteria were a history of diagnosed psychiatric or neurological disorder (e.g., head injury, developmental learning disability, epilepsy, cerebrovascular accident) or a history of alcohol and/or drug abuse. Approximately 25% of all patients approached to participate in the study either

declined or were deemed inappropriate due to one or more of the exclusionary criteria.

Fourteen patients (4 females, 10 males; mean age = 67.4 years, *S.D.* = 14.8; Table 4) with lower-extremity amputations secondary to PVD participated in this study. All were right-handed. They had received, on average, 10.3 years (*S.D.* = 3.6) of education. Five patients had unilateral above-knee, 7 had unilateral below-knee, and 2 patients had bilateral amputations. Table 4 summarizes the presence of conditions considered to be risk factors for cerebrovascular disease in the patients and the control subjects. Two patients had four medical conditions considered risk factors for cerebrovascular disease, four patients had three risk factors, three patients had two risk factors, four patients had one risk factor only, and one patient had no risk factors for cerebrovascular disease. This patient sample appeared similar to the general PVD population in terms of age, sex, and etiologic risk factors (Juergens & Bernatz, 1980).

The Beck Depression Inventory (Beck & Speer, 1987) was administered to seven of the 14 patients. The time constraints imposed by the rigourous rehabilitation schedules of the patients did not allow all patients to be tested. The mean score was 8.9 (*S.D.* =6.3), indicating that these patients reported either no or minimal depressive symptoms.

Normal Controls

Seventeen elderly volunteers (9 females, 8 males) were recruited from social clubs and senior exercise classes in the community. All control subjects were right-handed except one left-handed male. The exclusion criterion was a history of neurological disorder, diabetes, PVD, vascular bypass surgery, alcohol and/or drug abuse, or a recent history of psychiatric disorder (two control subjects had experienced and received pharmacotherapy for brief depressive episodes over 20 years ago). One control subject (a 59-year-old male with 18 years of education) was deemed inappropriate for inclusion in the study due to significant differences of up to 7 points between scaled subtest scores on the WAIS-R (Wechsler, 1981). Such differences in scores are considered significant and probably not due to chance (Lezak, 1995). Two male controls (aged 67 years and 73 years) with 18 years of education were dropped from the sample in order to match controls with patients in terms of the number of years of education. Thus, data from 14 control subjects (mean age = 69.9 years, *S.D.* = 9.3; mean education = 11.9 years, *S.D.* = 2.3) were used. The differences in age and number of years of education between the patients and controls were not significant (p's = .59 and .16, respectively).

Neuropsychological Test Battery and Procedure

The neuropsychological battery was designed to evaluate a broad range of cognitive functions. Neuropsychological tests used to evaluate learning and memory were the Digit Span subtest of the WAIS-R (Wechsler, 1981), the Logical Memory, Visual Paired Associates, and Verbal Paired Associates subtests of the Wechsler Memory Scale - Revised (WMS-R; Wechsler, 1987), the Rey-Osterrieth Complex Figure Test (Lezak, 1995; Osterrieth, 1944), and the Recognition Memory Tests for Faces and Words (Warrington, 1984). Tests of language and verbal ability included the Vocabulary subtest of the WAIS-R (Wechsler, 1981), the Graded Naming Test (McKenna & Warrington, 1983), and the Controlled Oral Word Association Test (COWAT, orthographic and semantic categories; Lezak, 1995). The Picture Completion and Block Design subtests of the WAIS-R (Weschler, 1981), and the copy administration of the Rey-Osterrieth Complex Figure were used to assess visuoperceptual organization and constructional abilities. The Similarities subtest of the WAIS-R and the Modified Card Sorting Test (MCST; Nelson, 1976) were used to assess problem solving, abstract reasoning, and concept formation. The Picture Arrangement subtest of the WAIS-R provided an estimate of social judgement and sequential reasoning. The WAIS-R Digit Symbol subtest was used as a measure of psychomotor function.

Attempts were made to administer the entire test battery to each control and patient during a single session. However, because periodic breaks were provided to reduce patients' fatigue, testing took place over a two-day period for 50% of the patients. All tests were administered to each control subject during a

single testing session, with the exception of one male and one female control for whom, due to scheduling difficulties, testing took place over two days.

Results

Two sample *t*-tests, using the BMDP3D Statistical Software Package (Dixon, 1990), were conducted on the neuropsychological test scores. The results are presented in Table 5. Given the relatively large number of comparisons made, a Bonferroni correction was applied which held the Type I error per comparison at α=.002. Thus, the probability of Type I error across this study was α=.05.

The PVD amputees performed more poorly than Controls on the WAIS-R Digit Symbol subtest (PVD: $\bar{x}$=9.0 [*s.d.*=1.7], Controls: $\bar{x}$=12.2 [*s.d.*=2.9]; *t*=-3.61, *p*=.0007) and obtained fewer categories on the MCST than did the Controls (PVD: $\bar{x}$=3.9 [*s.d.*=1.6], Controls: $\bar{x}$=5.6 [*s.d.*=0.8]; *t*=-3.70, *p*=.0005). In addition, there were trends ($p < .01$) towards lower patient scores on a number of other neuropsychological tests including the WAIS-R Vocabulary, Arithmetic, Similarities, and Picture Arrangement subtests, oral fluency (COWAT, orthographic condition), and the copy administration of the Rey-Osterrieth Complex Figure (see Table 5).

Discussion

The amputee patients with PVD performed significantly more poorly than normal elderly control subjects on certain neuropsychological measures of psychomotor speed, problem solving and abstract reasoning. Moreover, there were trends toward differences between patients and controls on several other

measures of problem solving and abstract reasoning, visuospatial skills, concentration, vocabulary and oral fluency. These data indicate that neuropsychological deficits in PVD amputees exist and may be more common and extensive than suggested by previous studies (Pinzur et al., 1988; Hemmingsen et al., 1986; Shaw et al., 1987; Mate-Kole, 1985).

The PVD patients were impaired on the Digit Symbol subtest which is considered to be the most sensitive of the WAIS-R subtests to brain damage (Lezak, 1995). In fact, the Digit Symbol subtest is very frequently included in neuropsychological test batteries as a general measure of cortical integrity (Berg, 1990). In light of its sensitivity to brain dysfunction in general, poor performance on this test does not provide much information regarding lesion laterality or localization (Lezak, 1995).

The PVD patients also achieved fewer categories on the MCST than did the Controls, although the two groups did not differ in terms of the percentage of perseverative errors made. This suggests that the PVD patients were impaired in abstracting the correct sorting principle rather than having difficulty in shifting their mental set. An alternate explanation is that the fewer categories obtained by the patients was due to a failure to persist in correctly sorting cards until criterion was met, despite the positive feedback provided. Using a method similar to that reported by Tarter and Parsons (1971), the number of interrupted sequences of "runs" in which three consecutive correct card sorts were followed by an error was examined. There was no significant difference in average number of instances of failure to maintain set between patients ($\bar{x}$= 0.30) and controls ($\bar{x}$= 0.14; t=.91,

$p > .05$), indicating that the lower number of categories obtained by the PVD patients was due to their failure to grasp the correct strategy.

The difference in performance between the PVD patients and Controls on oral fluency and the copy administration of the Rey-Osterrieth Complex Figure fell short of meeting the conservative criterion for statistical significance ($p < .002$). However, the performance of the PVD patients on the copy administration of the Rey-Osterrieth Figure can be considered below average (Lezak, 1995; Osterrieth, 1944) and their mean copy score was well below that of normal elderly subjects reported elsewhere (Berry, Allen, & Schmitt, 1991). This below average performance may reflect a deficit in developing a systematic approach to copying the Figure. Evidence that strategy plays an important role in well-constructed copies has been provided by Pillon (1981). He showed that patients with frontal lobe lesions failed to copy the Figure correctly without assistance but when given a plan to guide their approach to the task showed marked improvement in their copies. At present, however, it should be emphasized that these findings in the present study did not reach the criterion for statistical significance and need to be replicated.

Performance of the PVD patients was also impaired relative to Controls on the oral fluency task, but only under the Orthographic category condition. It has been suggested that this condition can prove difficult to subjects who cannot generate strategies to help organize their thinking (Estes, 1974). It is possible that a common thread runs between the impairment the PVD patients exhibited on the copy administration of the Rey Figure, oral fluency, and number of categories

obtained on the MCST. One cognitive skill presumably tapped by these three measures is the ability to organize a systematic approach to the problem at hand. The fact that patients with frontal-lobe lesions show deficits on the Rey copy (Pillon, 1981), oral fluency (e.g., Miceli, Caltagrione, Gainotti, Masullo, & Silveri, 1981), and the MCST (Nelson, 1976) provides some support for this notion.

The results of this preliminary study indicate that persons with lower-extremity amputations secondary to PVD do show impairment in cognitive function (namely, strategic problem-solving, reasoning abilities and concentration) relative to a healthy elderly control group. The hypothesis was supported. However, the factor or factors that underlie these deficits are not clear. The assumption underlying this study is that the processes that lead to chronic vascular disease in the periphery are part of a generalized vascular disease which also contributes to cerebrovascular insufficiency.

An alternate explanation is that the emotional distress associated with major life events such as amputation would influence cognitive performance in PVDs by decreasing motivation and increasing depression. A self-report measure of depression obtained from a number of patients in this sample indicated that depression was probably not an influential factor in this study. Nevertheless, research directed at identifying the relationship between PVD *per se* and cognitive function must continue to control for psychological factors such as depression.

It is also possible that the cognitive deficits identified in PVD amputee patients may be limited to a subgroup of patients or may vary as a function of the etiology of the vascular insufficiency and/ or its risk factors. A large proportion of

the subjects in this patient sample were either Type I or Type II diabetics, heavy smokers, or both. A number of studies have identified smoking as a significant contributing factor to both the onset and development of PVD (Coffman, 1983; Greenhalgh et al., 1981; Thomas, 1981) and smoking could have deleterious effects on cognitive function in the elderly (e.g., Hill, 1989). Impaired cognitive function has been identified in non-PVD patients suffering from Type I (Francheschi et al., 1984; Prescott et al., 1990) and Type II diabetes mellitus (Perlmutter et al., 1984). The possible influence of these and other atherosclerotic risk factors will be addressed in Study Two.

In summary, Study One showed that PVD amputees performed more poorly on measures of psychomotor speed (WAIS-R Digit Symbol subtest; Wechsler, 1981) and problem solving/abstract reasoning (Modified Card Sorting Test; Nelson, 1976) than control subjects. In addition, there were nonsignificant trends towards differences on measures of oral fluency and visuoperceptual organisation/constructional praxis. Taken together, this pattern of results could be interpreted as suggesting frontal lobe dysfunction. This conclusion is clearly speculative given the relatively small sample size and the failure of some of the tests to meet the stringent level required for statistical significance. Thus, this result needs to be replicated. Nevertheless, it is interesting to note that silent infarctions in the frontal lobes are not considered uncommon (Sundt et al., 1994; Wiebe-Velazquez & Hachinski, 1991).

STUDY TWO

Rationale and Background

Although Study One demonstrated that PVD amputees show cognitive deficits relative to normal controls, it raised more questions than it answered. First, it is not known whether these finding are specific only to amputee patients with PVD or are representative of patients with peripheral atherosclerosis in general. Second, it could not be inferred that these deficits were the result of underlying CVD because the PVD patients were not compared to a group with known CVD. Third, it is not clear whether cognitive impairment is related to PVD *per se* or whether the deficits can be accounted for by the neurobehavioural effects of the various risk factors for atherosclerosis found in many PVD patients.

Risk Factors. The Framingham Study (Wolf, Kannel, & Dawber, 1978) identified various medical factors associated with an increased likelihood of stroke in an individual. These included increasing age, male sex, hypertension, elevated serum cholesterol, abnormal triglyceride levels, diabetes mellitus, tobacco smoking, and cardiovascular disease. As pointed out by Brown et al. (1986), many of these factors are associated with neuropsychological performance. Therefore, before one can understand the neuropsychological effects of CVD, one must first be aware of the correlations between the risk factors and neuropsychological function. This literature was reviewed earlier. There is sufficient evidence that these various risk factors for atherosclerosis, both peripheral and cerebral, can have deleterious effects on neuropsychological function. The presence of these factors must be taken into account before it can be argued that PVD is related to impaired

cognitive performance, over and above the effects that these factors may have.

In addition, two other issues were raised in Study 1, namely the effects of depression and frontal lobe pathology on cognitive functioning. These factors also will be examined in Study 2. The effects of frontal lobe damage was reviewed earlier in the Introduction. At this point, the effects of depression will be briefly reviewed.

Depression. While the results showed that the mean level of depression as measured by the BDI was not significantly higher in the PVD amputees than the controls in Study 1, it is clear from the literature that depression remains an important issue to be addressed in neuropsychological research. In a 1986 review of neuropsychological studies of depression, Caine distilled the following findings. Depressed patients show deficits in attention, particularly on tasks requiring effortful rather than automatic processing. Depressed patients also show impairment in learning and memory in terms of poorer initial acquisition of information and retrieval deficits, with relatively intact retention ability. Although these finding were initially observed in studies which employed young adult depressed populations (Caine, 1986), the results have now been extended to older depressed individuals.

King, Cox, Lyness, and Caine (1995) studied 44 elderly ($\bar{x}$ age = 68 years) inpatients with major depression and age- and education-matched controls. Depressed patients performed more poorly than the control subjects on tests of attention (WMS-R Attention/ Concentration Index; Trail Making Part B), word generation (COWAT/ Oral Fluency), immediate and delayed verbal recall (WMS-R

Logical Memory), and visuospatial (Hooper Visual Organization Test) and constructional ability (WAIS-R Block Design; Rey-Osterrieth Complex Figure). The authors also found significant effects of depression on confrontation naming (Boston Naming Test), although this finding was isolated to the depressed patients who were receiving psychotropic medication. No between group differences were demonstrated on measures of verbal retention or visual learning and memory. King et al. also demonstrated a significant interaction between age and depression on the Trail Making Part B, Rey-Osterrieth Figure Copy, and the Hooper Visual Organization Test whereby the performance of the depressed patients declined more rapidly with age on these tasks, relative to the control subjects.

In a study of 73 older ($\bar{x}$ age = 61 years) unmedicated outpatients with major depression and appropriate age- and education-matched controls, Boone et al. (1995) demonstrated that the presence of depression was associated with mild deficits in visual memory (WMS-R Visual Reproduction; Warrington's Recognition Memory Test for Faces; the Rey-Osterrieth Complex Figure recall) and WAIS-R Performance IQ. In addition, the severity of depression was found to be associated with subtle deficits in information processing speed (Stroop test, Parts A and B) and executive function (Stroop test, Part C; COWAT/Oral Fluency; Wisconsin Card Sorting Test). Verbal skills, visuospatial constructional ability, and attentional processes were considered to be relatively intact.

Depression is commonly observed following stroke, with estimates of the frequency of post-stroke depression ranging from 25-49% (Starkstein, Bolla, & Robinson, 1991). An interesting relationship has been reported between lesion

location and the frequency and severity of major depression following stroke. Specifically, major depression is more frequent (Robinson & Szetela, 1981) and more severe (e.g., Lipsey, Robinson, Pearlson, Rao, & Price, 1983) in patients with left anterior ischemic lesions than patients without lesions in this area. Severity of depression has been shown to be significantly negatively correlated with distance from the frontal pole for left-sided lesions, but not right-sided lesions (Lipsey et al., 1983). This relationship has been found for cortical and subcortical (mainly basal ganglia) lesions (see Starkstein et al., 1991). In patients equated for both lesion size and location, depressed post-stroke patients had greater cognitive impairment (as indexed by the Mini-Mental State Examination) than post-stroke patients who were not depressed (Starkstein, Robinson, & Price, 1988). Finally, using a comprehensive neuropsychological battery to study left- and right-hemisphere stroke patients with and without major depression, Bolla-Wilson, Robinson, Starkstein, Boston, and Price (1989) demonstrated that cognitive deficits were greater in left-hemisphere damaged patients with depression than without. These differences were observed on tasks tapping orientation, language (naming, repetition), and frontal lobe executive/ motor functions. No differences were found between right-hemisphere stroke patients with and without depression. Moreover, mainly on the basis of evidence of impaired learning but intact retention on memory tasks, Bolla-Wilson et al. (1988) argued that the pattern of cognitive impairment in depressed left-hemisphere patients was similar to that observed in "functionally" depressed patients without brain damage. Taken together, these findings indicate that post-stroke depression (in patients excluded for aphasia) may

be a lateralized (left) and localized (anterior) phenomenon. The results also suggest that post-stroke depression may not be a generalized psychological response to stroke, but rather may be a neurological manifestation of damage to specific brain regions.

Despite the compelling findings reviewed above, it is very important to note that the vast majority of neuropsychological studies of depression have been conducted with samples who meet clinical criteria for depression. For elderly subjects who are not clinically depressed, Bieliauskas (1993) has argued that the effects of depression symptomatology on cognitive function have been overemphasized and that the effect of depressive-like symptoms (rather than depressive syndromes) is minimal.

Objectives and Hypotheses

In order to address the questions raised in Study One, Study Two examined neuropsychological function in patients with symptomatic PVD, patients with symptomatic CVD (i.e., stroke patients), and normal age- and education-matched control subjects. The primary objectives of Study Two were to 1) replicate and extend the finding that PVD is related to impaired cognitive functioning by including patients representing a range of peripheral atherosclerosis (i.e., non-amputee PVD patients who represent the "mild" end of the continuum and amputee PVD patients who represent the "severe" end of the continuum); 2) to compare profiles of neuropsychological function in patients with PVD and patients with CVD in order to determine if similar patterns of impairment exist; and 3) to recruit a larger

sample of PVD patients in order to examine which medical/ health factors are predictive of the cognitive deficits in PVDs. In addition, in light of the literature reviewed previously, it was considered important to examine the potential role of depression in PVD patients on cognitive function. A secondary objective was to examine the possibility that deficits of the nature observed in patients with frontal lobe damage might also be observed in PVD patients.

From the objectives outlined above, the following specific hypotheses were generated:

1) Patients with PVD, as a whole, exhibit impaired neuropsychological function, relative to a age- and education-matched controls. This hypothesis was tested using ANOVAs and by analysis of individual data (i.e., the number of PVD patient *z*-scores falling in the lower 5% of the distribution of scores of Control subjects).

2) It was hypothesized that patients with symptomatic PVD suffer from concurrent CVD and will therefore exhibit a pattern of neuropsychological impairment similar to that of observed in a group of patients with recognized CVD. Recalling the model of Reitan and Wolfson (1985), two specific hypotheses were formulated:

a) it was predicted that, relative to controls, the performance of both PVD and CVD patient groups would be impaired in generalized cognitive abilities such as executive function (abstraction and problem solving), and attention.

This would result regardless of the presumed tissue infarction and would be demonstrable in the two groups as a whole, and,

b) it was predicted that, similar to the CVD group, PVD patients would show focal deficits on neuropsychological tests considered sensitive to the laterality of cerebral lesions: tests of language (the Graded Naming Test, the COWAT/ Oral Fluency Tasks), visuospatial skills (WAIS-R Block Design, Rey-Osterrieth Complex Figure Copy), and sensorimotor tests (Two-Point Discrimination, Grooved Pegboard). The performance of the PVD group should be bimodal, suggesting more extensive cerebrovascular involvement of one hemisphere over the other. In other words, it was predicted that a subgroup of PVD patients would show impairment primarily on tests sensitive to left-hemisphere function (i.e., poorer scores on language tests and on tests tapping right-sided sensorimotor control) while a second subgroup would show impairment primarily on tests sensitive to right-hemisphere function (i.e., poorer scores on tests of visuospatial function and on tests tapping left-sided sensorimotor control).

3) It was hypothesised that, over and above the potential neurobehavioural effects of atherosclerotic risk factors, the severity of PVD will be the single best predictor of impaired cognitive performance in the PVD patients. Following this, it was hypothesized that variables reflecting manifestations of atherosclerotic disease and those more closely associated with CVD risk (TIAs and the presence or absence of ischemic heart disease, in that order)

would be significantly related to cognitive deficits, after the effects of PVD had been taken into account. Finally, it was hypothesized that the remaining atherosclerotic risk factors (hypertension, smoking, hyperlipidemia, and diabetes, in that order) would retain increasingly less predictive power after the effects of atherosclerotic disease had been taken into account.

These hypotheses were tested in a group of 29 PVD patients (13 amputees and 16 non-amputees), 29 patients with CVD (*viz.*, atherothrombotic brain infarctions; 15 with right- and 14 with left-hemisphere infarcts) and 30 age- and education-matched controls. Differences in performance between these groups were tested in 6 cognitive domains: 1) attention and concentration, 2) abstraction and reasoning abilities, 3) memory, 4) visuospatial skills, 5) language, and 6) lateralizing tests (see Table 6 for specific tests). Furthermore, self-report measures of affective and cognitive functioning were employed to assess the possibly confounding effect that depression and psychological distress may have on neuropsychological functioning.

The Methods and Results of Study Two are presented next, followed by the Discussion. The Introduction, Methods, Results and Discussion of Study Three are next presented. A general discussion and conclusion of the results of all three studies then follows.

METHODS

Subjects

Peripheral Vascular Disease (PVD) Patients

Non-Amputee PVD Patients. Sixteen patients (5 females, 11 males; age: $\bar{x}$ = 62.0 [*s.d.* = 10.5]; education: $\bar{x}$ = 11.4 [*s.d.* = 2.5]; see Table 7) with PVD were recruited from the Non-Invasive Vascular Diagnostic Laboratory at the Victoria General Hospital. All patients were right-handed except for one 52-year-old male who wrote with his left-hand. The inclusion criterion was the positive identification of lower extremity vascular insufficiency, determined by an ankial/ brachial pressure index < 0.8[2].

Exclusion criteria included: 1) evidence that the peripheral vascular insufficiency was secondary to trauma or was non-atherosclerotic in nature; 2) history of completed stroke; 3) history of neurological disorder that could influence cognitive status (e.g., head injury, epilepsy, dementia); 4) history or presence of a major psychiatric disorder; 5) history of alcohol or drug abuse (not including cigarette smoking[3]); or 6) presence or history of renal or pulmonary disease which might have deleterious effects on cognitive function (Hart & Kreutzer, 1988; Prigatano & Levin, 1988).

The demographic and medical variables recorded included: age, sex,

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[2] A normal ankle-brachial pressure ratio should be 1.0 or greater. In limbs with one primary arterial occlusion, the index ratio is usually between 0.5-0.8 (Hallett, Brewster, & Darling, 1982).

[3] Cigarette smoking was not an exclusionary criterion as it is one of the principle causes of PVD.

education, handedness, presence of predisposing factors to PVD (i.e., diabetes mellitus, smoking, hypertension, hyperlipidaemia), possible history of TIAs, history and current status of smoking, history of ischemic heart disease, severity of PVD, and current medications. In addition, information regarding the integrity of the internal carotid system was obtained when possible by periorbital directional Doppler sonography. The health variables diabetes, hypertension, and hyperlipidaemia were characterized according to the guidelines suggested by Rutherford et al. (1986; see Table 8). Smoking behaviour was quantified in terms of pack-years of smoking, where one pack-year is equivalent to having smoked one pack or 20 cigarettes per day for an entire year. For example, if a patient smoked 2 packs of cigarettes per day for 20 years, then the number of pack-years of smoking equalled 40. The number and percentage of PVD patients reporting these conditions are summarized in Table 9.

Severity of PVD was categorized according to the criteria suggested by Rutherford et al. (1986), described in Table 10. Ten patients exhibited ischemic symptoms which placed them in Category 1 in terms of severity; the remaining 6 patients were classified in Category 2.

Amputee PVD Patients. Thirteen patients (3 females, 10 males; age: $\bar{x}$ = 68.2 [*s.d.* = 11.7]; education: $\bar{x}$ = 10.6 [*s.d.* = 2.1]; see Table 7) with lower-extremity amputations secondary to PVD were recruited from the Nova Scotia Rehabilitation Centre and were subject to the same exclusionary criteria as the non-amputee PVD patients (see above). All patients were right-handed. Table 9 contains a summary of the medical variables of diabetes, hypertension,

hyperlipidaemia, TIAs, and ischemic heart disease for these patients. By definition, all amputees fell within Category 6 in terms of PVD severity (see Table 10).

Cerebrovascular Disease Patients (CVD)

A total of 29 patients with cerebrovascular disease were recruited and selected to match the PVD samples on the basis of age and education. Patients with atherothrombotic brain infarctions involving either the carotid or vertebral-basilar arterial systems were eligible for inclusion.

Nineteen patients (8 females, 11 males; age: $\bar{x}$ = 66.5 [*s.d.* = 11.1]; education: $\bar{x}$ = 12.1 [*s.d.* = 3.5]) were recruited from the Nova Scotia Rehabilitation Centre, in Halifax, Nova Scotia. On average, patients were tested within 5 months (*s.d.* = 10.3) following their stroke; no patient was tested if he/ she was less than one month post-stroke or was not medically stable. In all cases, a patient was either an out-patient of the Rehabilitation Centre or else neuropsychological testing took place during the month prior to the patient's discharge to home.

Ten patients (3 females, 7 males; age: $\bar{x}$ = 65.4 [*s.d.* = 6.5]; education: $\bar{x}$ = 11.1 [*s.d.* = 1.3]) were recruited from the Calgary General Hospital, in Calgary, Alberta. All patients were between one to two years post-stroke and all were out-patients at the time of testing. The Halifax and Calgary subsamples differed in terms of time since stroke, with the Halifax group being a relatively more acute sample of patients. However, the subsamples were equivalent in terms of age, education, sex distribution, and estimated premorbid IQ (determined using the

National Adult Reading Test; all p's > 0.05). The subsamples did not differ in terms of neuropsychological performance, with the exception of one test (WAIS-R Block Design, $F(1, 27)=5.22$, $p=.03$), where the subsample from Calgary performed better.

Given the overall similarity between the two subsamples, their data were pooled to comprise a total sample of 29 CVD patients (11 females, 18 males; age: $\bar{x}$ = 66.1 [*s.d.* = 9.7]; education: $\bar{x}$ = 11.7 [*s.d.* = 2.9]; see Table 7). There was a virtually equal number of patients with unilateral involvement of each cerebral hemisphere: 15 patients had right-sided infarcts (10 males, 5 females) and 14 had left-sided infarcts (8 males, 6 females). All patients were right-handed, with the exception of 3 patients who were left-handed[4].

The exclusion criteria included: 1) cerebrovascular disease presumably resulting from non-atherothrombotic brain infarction (i.e., aneurysm, intracranial haemorrhage, arteriovenous malformation); 2) history of neurological disorder that could influence cognitive status (e.g., head injury, epilepsy); 3) history or presence of a major psychiatric disorder; or 4) history of alcohol or drug abuse (not including cigarette smoking).

Study One suggested a preponderance of deficits of the amputee PVD patients on tests of executive function which are sensitive to the functioning of the frontal regions of the brain. In light of this, an attempt was made to categorize

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[4] In terms of the implication for language lateralization, two of these patients had left-sided infarcts and, at the time of testing, demonstrated residual language disturbances post-stroke. The third patient had a right-sided infarct and had no documented history of or demonstrated language disturbance post-stroke.

CVD patients on the basis of whether or not they showed evidence of involvement of the anterior regions of the brain so that their data might be compared with the amputee PVD patients. Although all CVD patients had radiologically confirmed infarcts (usually by computed tomography or CT scan), the exact location of the brain regions involved often were not detailed in their charts. For instance, available data from a patient's chart might include the information that CT scan had identified the presence of an infarct in "the territory of the middle cerebral artery"; however, such information was not useful in terms of lesion localization since the middle cerebral artery supplies large portions of both the frontal and parietal lobes. Localization data were available for a subgroup of 20 CVD patients who were then classified according to whether or not there was involvement of the anterior aspects of the brain. Eight patients (3 left hemisphere, 5 right hemisphere) had radiologically confirmed evidence of infarction in, but not limited to, the frontal lobes, 12 had infarcts not involving the frontal region (6 left hemisphere). Unequivocal data were not available for the remaining 9 patients.

Normal Controls

Thirty-four healthy elderly control subjects were recruited from local community senior services, by notices placed in groceries stores, or by word of mouth. All participated in the study on a volunteer, non-renumerated basis. These subjects were selected to match the PVD patient groups on the factors of age and education. In order to match subjects according to amount of education, 4 controls were omitted from the statistical analyses. Thus, neuropsychological data

from 30 control subjects (16 females, 14 males; age: $\bar{x}$ = 68.3 [*s.d.* = 6.2]; education: $\bar{x}$ = 12.1 [*s.d.* = 1.6]; see Table 7) were used for the analyses reported here.

The exclusion criteria included: 1) evidence of PVD (i.e., symptoms of intermittent claudication or a history of arterial grafting); 2) history or presence of neurological disorder that could influence cognitive status (e.g., CVD, head injury, epilepsy); 3) history or presence of a major psychiatric disorder; 4) history of alcohol or drug abuse (including a heavy [i.e., > 1 pack/ day] current or past habit of cigarette smoking[5]); 5) Type I or II diabetes; 6) uncontrolled hypertension; or 7) history or presence of renal or pulmonary disease which might have deleterious effects on cognitive function (Hart & Kreutzer, 1988; Prigatano & Levin, 1988).

The demographic variables of age, education, and sex for all four subject groups are summarized in Table 7. As stated, control subject samples (CVDs and Normal Controls) were selected to match the PVD total sample on the factors age and education; indeed, the groups did not differ on these two factors (age: $F[2,85]=1.06$, $p=0.35$; education: $F[2,85]=1.49$, $p=0.23$). The groups were also compared on predicted pre-morbid IQ using the NART. The predicted pre-morbid

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[5] Note that this criterion was discrepant with that for the two vascular patient groups. It was not possible to include normal controls who had a current or past habit of heavy smoking as this is a risk factor for the development of PVD. Inclusion of controls with a heavy habit of smoking would, in theory, necessitate the arterial assessment of these individuals to ensure that they were asymptomatic of arterial disease; however, it was not feasible to have normal controls evaluated in the Vascular Diagnostic lab. Thus, in an attempt to balance this situation, it was decided to exclude normal controls only if they reported a current or past habit of *heavy* smoking.

IQ of control group ($\bar{x}$=113 [*s.d.*=6.2]) differed significantly ($F(2,85)=8.35, p<.05$) from that of the PVD total sample ($\bar{x}$=108 [*s.d.*=9.3]) and the CVD sample ($\bar{x}$=105 [*s.d.*=5.9]. However, the mean difference in predicted IQ between the controls and PVDs was only 5 points. Given that the standard deviation IQ scores in the WAIS-R standardization sample is 15 points (Wechsler, 1981), this small difference between the controls and PVDs was not considered to represent a meaningful difference in predicted premorbid IQ.

As Table 7 shows, there was a higher proportion of males than females in the patient samples (i.e., amputee PVDs, non-amputee PVDs, and CVDs) which is consistent with previous studies showing a greater incidence of PVD and CVD in males than females (e.g., Juergens & Bernatz, 1980). There was an approximately equal number of males and females in the Normal Control sample. It was not possible to match the Normal Control sample with the patient samples on the basis of sex given the difficulty of recruiting into the study health elderly males who met the inclusion/ exclusion criteria.

Power Analysis. Prior to the initiation of the study, a power analysis was conducted to determine the approximate number of subjects necessary for each group. It was known *a priori* that a stringent α-level would be employed given the number of univariate comparisons that would be made. It was also decided that a standardized effect size equal to the standard deviation for a given test (i.e., standardized effect size = 1) would be a clinically meaningful difference to detect between PVD patients and controls. Thus, with Type I and Type II error set equal to .005 (one-tailed) and .20, respectively, and employing a standardized effect size

of 1.0, sample size analysis (Hulley & Cummings, 1988) indicated that approximately 30 subjects would be required per group. This requirement was essentially met for all subject groups (PVD, n=29; CVD, n=29; controls, n=30).

Procedure and Data Analyses

Ethical approval was received from Dalhousie University and all health care institutions from which patients were recruited (Nova Scotia Rehabilitation Centre, Victoria General Hospital, Foothills Hospital, and Calgary General Hospital). In general, potential subjects were provided with a brief description of the project and permission was obtained for a medical chart review and/or brief interview to determine further their eligibility for the study. Subsequent to this, appropriate subjects were invited to participate and, if willing, an appointment was established for the neuropsychological testing.

All subjects were administered a battery of neuropsychological tests designed to evaluate the cognitive domains of memory, attention, language functions, visuospatial and constructional abilities, problem-solving and abstract reasoning abilities, and lateralizing tests of tactile and motor ability (see Table 6). In addition, self-report measures of depression, psychological distress, and cognitive errors were administered. The test battery consisted of the following tests: the Wisconsin Card Sorting Test (WCST; Heaton, 1981), the Controlled Oral Word Association test (COWAT; Lezak, 1995), selected subtests from the WAIS-R (Wechsler, 1981), namely Picture Arrangement, Similarities, Block Design, Digit Symbol, and Forward and Backwards Digit Span; the Rey-Osterrieth Complex

Figure copy and delayed recall administrations (Rey, 1941; Osterrieth, 1944); the California Verbal Learning Test, (Delis, Kramer, Kaplan, & Ober, 1987); the WAIS-R as a Neuropsychological Instrument (WAIS-R NI) Forward and Backward Spatial Spans (Kaplan, Fein, Morris, & Delis, 1991); the Graded Naming Test (McKenna & Warrington, 1983); the Trail Making Test, Parts A and B (Reitan & Davidson, 1974); the Grooved Pegboard (Reitan & Davidson, 1974); Two-Point Discrimination (e.g., Corkin, Milner, & Rasmussen, 1970); the National Adult Reading Test (NART; Nelson, 1982); Beck Depression Inventory (Beck & Steer, 1987); the Symptom Check List-90-Revised (SCL-90-R; Derogatis, 1979); and the Cognitive Failures Questionnaire (Broadbent, Cooper, FitzGerald, & Parkes, 1982).

A brief description of each test and detail on scoring procedures and/or norms is provided in Appendix A. In instances where multiple and non-redundant scores could be meaningfully derived from one neuropsychological test (e.g., the four scores from the WCST), those tests scores are reported.

Before proceeding with the data analyses, it was necessary to determine whether the amputee and non-amputee PVD patients should be considered separately or as one group representing a continuum of PVD. Medically, chronic peripheral ischemia sufficient to cause limb amputation is considered to represent the severest grade along a continuum of PVD (Rutherford et al., 1986); thus, combining the two groups was theoretically warranted. In terms of subject characteristics, the two PVD groups reported here were equivalent in terms of age (t=1.512, p=0.142) and education (t=0.861, p=0.397). Given that these two variables are important determinants of neuropsychological performance (Lezak,

1995), demonstrating the equivalency of the two groups on these demographic variables removed a potential methodological barrier to combining the amputee and non-amputee PVD patient groups. Finally, multivariate analysis of variance (MANOVA) computed across the neuropsychological test scores indicated that the two groups did not differ in overall neuropsychological performance (Hotelling's T^2=107.6, $F(21,7)$=1.33, p=0.3682). Therefore, data from amputees and non-amputees were combined to form a single PVD group (n=29) for the analyses reported below, unless otherwise specified.

Results

Cluster Analysis

One major purpose of cluster analysis is to reduce the complexity of a data set by partitioning elements into a smaller number of relatively homogeneous categories (Diekhoff, 1992). In order to determine overall patterns across neuropsychological domains of similarity/ dissimilarity between patients with PVD (amputees and non-amputees), patients with CVD, and normal controls, a cluster analysis was performed using the following 18 neuropsychological test scores: WAIS-R Digit Span, WAIS-R Similarities, WAIS-R Picture Arrangement, WAIS-R Block Design, Rey-Osterrieth Figure Copy, Rey-Osterrieth Figure Recall, Spatial Span Forwards and Backwards, Trail Making Test Parts A and B, Graded Naming Test, COWAT/ Oral Fluency (orthographic), COWAT/ Oral Fluency (animal category), WCST Categories Obtained, WCST Perseverative Errors, WCST Conceptual Responses, WCST Failure to Maintain Set, CVLT Long Delay Free

Recall. The BMDP KM program (Dixon, 1990) was used to partition all 88 subjects into clusters using a divisive process. Cases were iteratively reallocated to clusters until each case belonged to the cluster whose centre or mean was closest in Euclidean distance to the case. Due to the fact that computation of the Euclidean distance is sensitive to units of measurement, all neuropsychological test scores were first standardized using the unit variance.

Solutions involving two, three, and four clusters of subjects were obtained. Given that the procedure of cluster analysis does not provide a statistical test of each solution *per se*, it can be difficult to know which is the true or best solution to select. It is recommended that a solution be selected on the basis of the interpretability of the cluster solution (i.e., it should make theoretical sense) and parsimony (Diekhoff, 1992). These guidelines indicated that the 2-cluster solution provided a reasonable description of the data. Univariate comparisons between the two clusters revealed that Cluster 2 (the "Impaired" Cluster) had significantly poorer scores on all the neuropsychological tests included in the analysis (all p's = .0009, based on 1, 86 *d.f.*), with the exception of WAIS-R Digit Span, Spatial Span Forwards, and the WCST Failure to Maintain Set. On these latter tests, subjects in the two clusters did not differ.

Figure 3 illustrates the composition of the 2-cluster solution obtained. With respect to Cluster 1 (the Non-Impaired group) all normal control subjects (100%) were assigned to this cluster; these subjects make up approximately one-half of the cluster. Eighty-one percent of non-amputee PVD patients, 54% of the amputee PVDs, and 38% of the CVDs were also assigned to this cluster, suggesting that

these patients were largely similar to the control subjects in terms of cognitive function. In contrast, 0% of normal controls, 19% of non-amputee PVD patients, 46% of the amputee PVDs, and 62% of the CVDs were assigned to Cluster 2. Thus, a substantial proportion of PVD patients and in particular those with amputations were assigned to the Impaired Cluster.

Analyses of Variance (ANOVAs)

The cluster analysis provided a crude summary of the overall pattern of neuropsychological function in the different study groups. In order to determine on which tests the groups differed, one-way ANOVAs (summarized in Table 11) were computed to determine differences in performance between all patients with PVD (n=29), patients with cerebrovascular disease (n=29), and normal, age-matched control subjects (n=30). Given the large number (25) of univariate comparisons made, a Bonferroni correction was employed to control for Type I error. Thus, *p*-values ≤ 0.002 were considered significant. Tukey A post-hoc analyses were employed to delineate further significant group differences. Although for some measures higher scores indicate worse performance (i.e., WCST perseverative errors, Trail Making Parts A and B, Grooved Pegboard, and Two-Point Discrimination), the directional signs in the Tukey A column in Table 11 refers to the quality of the performance such that the "<" sign always indicates poorer performance.

Given the gross sensory and/or motor deficits of the CVD patients, their performance on three neuropsychological tests were omitted from the analyses.

For example, it was not possible to meaningfully compare differences between the three groups on the WAIS-R Digit Symbol test, a timed test, when a number of the CVD patients would have performed the test with their non-preferred hand as a result of hemiplegia. Thus, performance on the WAIS-R Digit Symbol test, the Grooved Pegboard and Two-Point Discrimination was compared between the PVDs and Control subjects only.

The results of the univariate tests are summarized in Table 11. The PVDs performed significantly worse ($p<.002$) than the normal controls on eight neuropsychological measures: WCST perseverative errors ($p=.0002$), WCST conceptual responses ($p=.0003$), WAIS-R Picture Arrangement ($p=.0000$), delayed recall administration of the Rey-Osterrieth Complex Figure ($p=.0006$), Trail Making Part B ($p=.0002$), WAIS-R Digit Symbol ($p=.0001$), WAIS-R Block Design ($p=.0000$), and copy administration of the Rey-Osterrieth Complex Figure ($p=0000$). Moreover, with the exception of performance on the WAIS-R Picture Arrangement and Digit Symbol subtests, the PVD and CVD patient groups both performed significantly more poorly than Controls on the aforementioned tests, but their means did not differ from one another.

Homogeneity of variance is one basic assumption underlying the use of ANOVA. If this assumption is violated, the standard ANOVA does not provide a valid test of the equality of group means. The assumption of homogeneity of variance was tested using Levene's procedure. For five of the univariate comparisons (WAIS-R Block Design, Rey Figure Copy, Trail Making Parts A and B, and WCST perseverative errors) the assumption did not hold. Not surprisingly,

this was primarily due to greater variability in the scores of the CVD group. In these instances the Welch procedure, which does not assume homogeneity of group variance, was also examined as an alternate test of the null hypothesis. In all instances (and despite the loss of degrees of freedom involved), results identical to the uncorrected ANOVAs were obtained.

Confidence Intervals for Mean Differences between PVDs and Controls

In an attempt to move away from a sole reliance on null hypothesis significance testing (*N.B.*, Cohen, 1994), 95% confidence intervals were calculated for the significant mean differences between the PVD and Control subjects. These are as follows: WCST perseverative errors, $CI(\mu_1 - \mu_2)$ = 11.2 to 15.2; WCST conceptual responses, $CI(\mu_1 - \mu_2)$ = 10.8 to 15.6; WAIS-R Picture Arrangement, $CI(\mu_1 - \mu_2)$ = 1.0 to 2.8; delayed recall administration of the Rey-Osterrieth Complex Figure, $CI(\mu_1 - \mu_2)$ = 3.8 to 6.2; Trail Making Part B, $CI(\mu_1 - \mu_2)$ = 50.0 to 58.9; WAIS-R Digit Symbol, $CI(\mu_1 - \mu_2)$ = 1.8 to 3.4; WAIS-R Block Design, $CI(\mu_1 - \mu_2)$ = 2.0 to 3.6; and copy administration of the Rey-Osterrieth Complex Figure, $CI(\mu_1 - \mu_2)$ = 3.6 to 5.8. Inspection of the confidence intervals indicates that the probable true difference between controls and PVDs never encompassed the value 0.

Standardization of Neuropsychological Test Scores

All individual test scores for all three groups (Controls, PVDs, and CVDs) were converted to *z*-scores, with a mean of 0 and a *s.d.* of 1, based on the performance of the Control group. This conversion was performed for two reasons. First, standardizing all test scores allowed the depiction of the overall pattern of results on different neuropsychological measures which originally employed different units of measurement. For example, by using standardized scores performance on tests of visuospatial constructional ability, such as the WAIS-R Block Design (which has a maximum age-scaled score of 19) and the Rey-Osterrieth Figure copy (which has a maximum score of 36) could be directly compared. This is despite the fact that the tests were based originally on different units of measurement.

Figure 4 illustrates the mean *z*-scores for all three subject groups on each neuropsychological test. Scales involving error scores or timed measures were inverted to ensure consistency across tests such that higher *z*-scores reflected better performance. Tests marked by a single asterisk are those on which PVDs performed significantly worse than Controls according to the univariate analyses (see above). A double asterisk indicates tests on which PVDs and CVDs performed significantly worse than Controls but whose mean performance did not differ from each other, according to the univariate analyses. Apart from the general difference in the magnitude of negative *z*-scores between the PVD and CVD patients (i.e., the CVD patients tended to have somewhat lower scores), the overall similarity between the pattern of test scores of the two patient groups is

very apparent.

The second reason for data standardization was due to the fact that it was likely the case that the PVD patients exhibited a heterogeneous pattern of impairment. That is, it was possible that some patients showed impairment on a given test while the majority of the sample did not. Unfortunately, these impaired performances would be obscured by the presentation of the group means alone. In order to identify these individuals, impaired performance was conservatively defined as a score falling in the bottom 5% of the distribution of the Controls' standardized scores (i.e., $z \leq -1.645$). The number of amputee and non-amputee PVD patients showing impaired performance and the percentage these patients represent of the total PVD sample are summarized in the bottom portion of Figure 4. Overall, there were eight tests on which more than 20% of the total PVD sample had scores falling in the bottom 5% of the distribution of Controls' scores: WCST perseverative error, WCST conceptual responses, WAIS-R Similarities, WAIS-R Block Design, the copy administration of the Rey-Osterrieth Complex Figure, Trail Making Parts A and B, and Graded Naming Test. These results are largely consistent with the results from the univariate ANOVAs, yet they reveal important additional information. For instance, 14% of PVD scores on the COWAT Oral Fluency Tasks (Oral FAS and Oral Animal) and 24% of scores on the Graded Naming Test fell below the *z*-score cut-off, indicating that a number of PVD patients were impaired on these tests, although the mean scores in Table 11 did not reveal this fact.

Hierarchical Multiple Regression Analyses

Hierarchical regression analyses using the BMDP program 2R were computed to identify those medical or demographic variables which predicted the cognitive performance of all PVD patients (n=29). Only those eight neuropsychological tests on which PVDs differed from Controls were chosen for analysis. Seven factors were used as independent variables: Diabetes, smoking (Pack Years), Hypertension, hyperlipidaemia (Lipid), history or question of transient ischemic attacks (TIA), presence or history of Heart Disease, and severity of peripheral vascular disease (PVD).

In order to determine whether the severity of PVD alone could predict neuropsychological performance (as was the hypothesis), this IV was forced into the equation during Step 1. The remaining variables were entered in the following order: TIA, Heart Disease, Hypertension, Pack Years of smoking, Lipid, and Diabetes. Variable entry was determined on the basis of which was more strongly related to cerebrovascular disease. Those IVs considered to have stronger associations on the basis of previous research (Ostfeld et al., 1973) were entered before those considered to be more weakly associated. For example, a possible history of TIAs was likely to be more indicative of cerebrovascular disease than having diabetes (Ostfeld et al., 1973).

Tables 12 through 19 display the results of the hierarchical regression analyses including the correlations between the IVs and the dependent variable, the unstandardized regression coefficients (*B*) and intercept, the standardized regression coefficients (β), the squared semipartial correlations (sr^2), and *R* and

R^2 for WAIS-R Picture Arrangement, the delayed recall administration of the Rey-Osterrieth Figure, WCST Perseverative Errors, WCST Conceptual Responses, Trail Making Part B, WAIS-R Digit Symbol, WAIS-R Block Design, and the copy administration of the Rey-Osterrieth Complex Figure, respectively. For testing the significance of the regression components, F_i for each IV was based on the change in R^2 (i.e., sr^2), the multiple R^2 after all IVs had been entered, and the residual degrees of freedom from the ANOVA table for the final step (*d.f.* = 21; see Tabachnick & Fidell, 1983, pp. 111-112).

For WAIS-R Picture Arrangement (Table 12) and the delayed recall of the Rey-Osterrieth Complex Figure (Table 13), no IV was found to contribute significantly to the regression equation.

For WCST Perseverative Errors (Table 14), the severity of peripheral vascular disease (PVD) explained a significant proportion (15%) of the variance in performance (Step 1: $R^2 = .15$, $F(1, 27) = 4.83$, $p < .05$); patients with more severe PVD tended to make more perseverative errors. The variable Heart Disease was also a significant predictor, explaining an additional 14% of the variance (Step 3: $R^2 = .32$, $F_{inc}(1, 25) = 4.51$, $p < .05$). No other variable reliably added to the regression equation (all p's > .05).

The results were strikingly similar for WCST Conceptual Responses (Table 15). Severity of peripheral vascular disease (PVD) explained a significant proportion (15%) of the variance in performance (Step 1: $R^2 = .15$, $F(1, 27) = 5.82$, $p < .05$), as did Heart Disease (14% of the variance; Step 3: $R^2 = .34$, $F_{inc}(1, 25) = 5.50$, $p < .05$). Both were significant negative predictors of performance.

Again, no other variable reliably added to the regression equation (all p's > .05).

Heart Disease explained 29% of the variance in performance on the Trail Making Test, Part B, and was the only IV to contribute significantly to the regression equation (Step 3: $R^2 = .30$, $F_{inc}(1, 25) = 10.43$, $p < .05$; see Table 16). Patients with a history of ischemic heart disease took longer to complete this task than patients without such a history.

For performance on the WAIS-R Digit Symbol subtest (Table 17), severity of peripheral vascular disease (Step 1: $R^2 = .12$, $F(1, 27) = 7.00$, $p < .05$) and the presence or history of Heart Disease (Step 3: $R^2 = .37$, $F_{inc}(1, 25) = 13.40$ $p < .05$) were significant negative predictors of performance, explaining 12% and 22% of the variance, respectively. Surprisingly, Lipid was a significant positive predictor (Step 7: $R^2 = .65$, $F_{inc}(1, 21) = 12.81$ $p < .05$).

For the Block Design subtest of the WAIS-R (Table 18), Heart Disease was a significant negative predictor of performance and explained 17% of the variance (Step 3: $R^2 = .28$, $F_{inc}(1, 25) = 5.71$, $p < .05$). It was the only IV to contribute significantly to the regression equation.

For performance on the copy administration of the Rey-Osterrieth Complex Figure (Table 19), the presence or history of Heart Disease (Step 3: $R^2 = .32$, $F_{inc}(1, 25) = 8.00$; $p < .05$) was the only significant negative predictor of performance, explaining 22% of the variance.

Discriminant Function Analyses on Lateralizing Tests

If patients with PVD show a pattern of cognitive deficits similar to that of CVD patients, then there should be evidence of impairment similar to that seen in patients with lateralized cerebrovascular lesions. In general, one would expect to see impairment of language-related functions following a left-hemisphere cerebrovascular lesion and impairment of visual-spatial functions following right-hemisphere cerebrovascular lesions (Heilman, 1974). If subgroups of PVD patients indeed show these patterns, the difficulty lies in being able to identify them within the total PVD sample.

Discriminant function analysis (BMDP 7M program; Dixon, 1990) was employed in an attempt to do this. The scores of the left-hemisphere (n=14; 8 males, 6 females; $\bar{x}$ age = 66.6 years [*s.d.*=9.6]; $\bar{x}$ education = 12.4 [*s.d.*=2.7]) and right-hemisphere (n=15; 10 males, 5 females; $\bar{x}$ age = 65.7 years [*s.d.*=10.1]; $\bar{x}$ education = 11.1 [*s.d.*=3.0]) CVD patients on tests generally considered to have lateralizing significance were used as variables. These two subgroups did not differ in terms of age (t=0.23, p=0.82), education (t=1.28, p=0.21), or sex (χ^2=0.28, p>0.05). Tests considered sensitive to left-hemisphere dysfunction were the Graded Naming Test, COWAT/ Oral Fluency Orthographic and Animal categories, and the Long Delay Free Recall of trial of the CVLT. Tests considered sensitive to right-hemisphere dysfunction were the WAIS-R Block Design and the copy and delayed recall administrations of the Rey-Osterrieth Complex Figure.

The means, *s.d.*s, and the results of univariate tests comparing the left-

versus right-hemisphere CVD patients' scores on these tests are presented in Table 20. As can be seen from the *F*-values presented, the differences between the two subgroups on these lateralizing tests did not reach traditional levels of significance (all *p*'s > .05). However, for all neuropsychological tests concerned, the differences between the two subgroups were in the expected direction. In other words, there was a trend for the right-hemisphere CVD group to perform more poorly than left-hemisphere patients on the visuospatial tasks (WAIS-R Block Design, right-hemisphere $\bar{x}$=7.4 *vs.* left-hemisphere $\bar{x}$=9.5; Rey-Osterrieth Figure Copy, right-hemisphere $\bar{x}$=22.4 *vs.* left-hemisphere $\bar{x}$=25.2; Rey-Osterrieth Figure Delayed Recall, right-hemisphere $\bar{x}$=9.5 *vs.* left-hemisphere $\bar{x}$=12.2), while the opposite pattern was observed on the language-related tasks (Graded Naming Test, right-hemisphere $\bar{x}$=15.4 *vs.* left-hemisphere $\bar{x}$=13.3; COWAT/ Oral Fluency FAS, right-hemisphere $\bar{x}$=34.7 *vs.* left-hemisphere $\bar{x}$=26.6; COWAT/ Oral Fluency Semantic, right-hemisphere $\bar{x}$=13.6 *vs.* left-hemisphere $\bar{x}$=12.6; CVLT Long Delayed Free Recall, right-hemisphere $\bar{x}$=7.6 *vs.* left-hemisphere $\bar{x}$=6.4). Thus, it was decided to persist in the discriminant function analysis by allowing a variable to enter the analysis if the *F*-to-enter was ≥ 1.00.

A discriminant function was computed on the basis of four variables, WAIS-R Block Design, COWAT/ Oral Fluency Orthographic task, COWAT/ Oral Fluency Semantic task, and the Graded Naming Test. The resultant *U*-statistic or Wilks' Λ was 0.736 and the associated approximate $F(4,27) = 2.149$, which fell short of reaching the critical *F*-value of 2.78. Nevertheless, the discriminant function was successful in correctly classifying 79% of the left-hemisphere CVDs

and 67% of the right-hemisphere CVDs (mean classification rate = 72%). Given this good rate of discrimination, the resultant discriminant function was then used to classify the PVD patients (n=29) as showing either a "left-hemisphere" or "right-hemisphere" pattern of performance on the four neuropsychological tests included in the analysis.

Ten PVD patients (7 amputees, 3 non-amputees; 8 males, 2 females) were classified as showing a predominantly "left-hemisphere" pattern of performance; 19 PVD patients (6 amputees, 13 non-amputees; 13 males, 6 females) were classified as showing a predominantly "right-hemisphere" pattern of performance. Univariate comparisons were conducted between the PVD patients classified in this manner on the tests used to compute the obtained discriminant function and on two demographic variables, age and education. The results are summarized in Table 21. The PVD patients classified as showing a "left-hemisphere" pattern performed significantly more poorly than the PVDs assigned to the "right-hemisphere" category on two language tests, the Graded Naming Test ("left-hemisphere" $\bar{x}=14.1$ *vs.* "right-hemisphere" $\bar{x}=19.9$, $F[1,27]=10.34$, $p=.003$) and the COWAT/Oral Fluency Orthographic Test ("left-hemisphere" $\bar{x}=34.7$ *vs.* "right-hemisphere" $\bar{x}=49.7$, $F[1,27]=7.35$, $p=.012$). No other significant differences were found on the other neuropsychological tests, suggesting that these two subgroups differed mainly in terms of their language function. Importantly, the two groups did not differ in terms of age, education (p's > .05, Table 21) or sex ($\chi^2=0.441$, $d.f.=1$, $p>.05$), indicating that the differences in language-related test scores were not an artefact of these factors.

Comparison of Amputee PVD Patients (n=13), and Frontal CVD (n=8), and Non-Frontal (n=12) CVD Patients

It was suggested from the results of Study One that one way of conceptualizing the deficits observed in the PVD amputees was as an impairment in executive function or organizational ability. As this type of cognitive function is considered to be mediated by the frontal lobes, the following analysis was conducted to directly compare the PVD amputees from Study Two with the CVD patients with and without infarctions involving the frontal lobe.

The PVD amputees ($\bar{x}$ age = 68.2 years [*s.d.* = 11.7]; $\bar{x}$ education = 10.6 years [*s.d.* = 2.1]), frontal CVDs ($\bar{x}$ age = 64.9 years [*s.d.* = 9.3]; $\bar{x}$ education = 10.9 years [*s.d.* = 2.5]), and non-frontal CVDs ($\bar{x}$ age = 64.8 years [*s.d.* = 15.8]; $\bar{x}$ education = 12.8 years [*s.d.* = 3.7]) were equivalent in terms of age ($F[2,30]=0.28$, $p=0.759$) and education ($F[2,30]=2.06$, $p=0.145$). Their performance on tests considered to be sensitive to frontal lobe functioning were examined using ANOVAs (WCST perseverative errors and number of categories obtained, WAIS-R Similarities, WAIS-R Picture Arrangement, COWAT/ Oral Fluency Orthographic and Semantic tasks, and the copy administration of the Rey-Osterrieth Complex Figure). The Bonferroni correction was employed to minimize Type I error. Only comparisons involving $p<.0071$ were considered significant.

The group means, *s.d.*'s, and the results of the ANOVAs are presented in Table 22. From this Table it can be seen that, with the exception of COWAT/ Oral Fluency Semantic Category, none of the comparisons reach even conventional levels of significance (all p's $> .05$). Although it might be argued that the failure to find differences on these tasks might be the result of reduced statistical power

due to small sample sizes, examination of the group means reveals that the differences between the means are in the expected direction (i.e., poorer performance for the Frontal CVDs) on only four measures (WCST perseverative errors, WCST number of categories, WAIS-R Similarities, and the copy administration of the Rey-Osterrieth Complex Figure).

Self-Report Affective and Cognitive Measures

Self-report measures of affective (BDI and SCL-90-R) and cognitive function (Cognitive Failures Questionnaire) were obtained from the majority of subjects (27/ 30 Controls, 9/ 13 amputee PVDs, all non-amputee PVDs, and 16/ 29 CVDs). In the majority of cases involving Controls and amputee PVDs, data were missing as a result of their time constraints. This was especially true for the patients recruited from the Nova Scotia Rehabilitation Centre whose physiotherapy schedules were very rigorous. Of the 16 sets of self-report measures obtained from the CVDs, 14 were from patients with right-hemisphere infarcts and 2 were from patients with left-hemisphere infarcts. Some of these data were missing due to time constraints, but the majority of instances of missing data were the result of the impaired reading ability of the CVD patients with left-hemisphere infarcts. Despite a lengthy period of introduction, four patients with left-hemisphere lesions made errors completing the measures (e.g., endorsing two options on a single test item or failing to answer a significant number of items), indicating that they had difficulty comprehending or completing the task. These protocols were omitted from the analyses. For other patients, attempts were made to administer the

questionnaires orally by the examiner. However, in all instances, this proved to be too time consuming for a patient to endure and in some instances the patient's comprehension level was too impaired to appreciate the subtleties of the questions being asked.

A second issue pertains to the potential problem of employing the BDI as a measure of depression in medically ill populations (e.g., Rodin, Craven, & Littlefield, 1991). As noted by Rodin et al. (1991), the BDI contains nine somatic performance items (items 13-21) which medically ill patients might endorse due to symptom overlap rather than as a result of true depressive symptomatology. Examination of the individual items on the BDI suggest that this is very likely an issue in elderly patients with lower-extremity amputations (e.g., Item 13, "I can work about as well as before") although, to this writer's knowledge, no specific studies have investigated this. Indeed, unsolicited comments from several amputee patients indicated that this confound might be at play. For example, for Item 19 assessing weight loss, one patient endorsed the highest scorable option for this item and wrote in the margin "had amputation." It was decided to compute an alternate BDI score based on a reduced number of items (16) in order to reduce the potential effects of symptom overlap. The five items omitted from the BDI were: Item 14 (Feelings about Appearance), Item 15 (Work Inhibition), Item 16 (Sleep Disturbance), Item 19 (Loss of Weight), and Item 20 (Worry about Physical Problems; see Appendix B for exact wording of these items). In the absence of any studies investigating the factor structure of the BDI in an elderly amputee population, these items were chosen on the basis of their face validity. Scores for

all subject groups were recalculated, omitting these five items. As can be seen from the means presented in Table 23, use of the BDI-Alternate score resulted in a mean negative change from the original BDI score of approximately 2.2 points for all groups. The exception was that of the amputee PVD group whose score changed, on average, 4.7 points suggesting that the correction served its purpose.

The group means, *s.d.*'s, and results of univariate tests of group differences for the BDI, the BDI Alternate score, the Global Symptom Index (GSI) and the nine subtests of the SCL-90-R, and the Cognitive Failures Questionnaire are presented in Table 23 for Controls, amputee PVDs, non-amputee PVDs, and CVDs. The results are presented separately for the amputee PVDs and non-amputee PVDs because it could be argued that there is a potentially greater likelihood of depression in the amputee PVDs. Mean group scores did not differ (all p's $> .05$) on the Cognitive Failures Questionnaire, the SCL-90-R GSI, or 6 of the 9 SCL-90-R subscales (i.e., Obsessive-Compulsive, Interpersonal Sensitivity, Hostility, Phobic Anxiety, Paranoid Ideation, Psychoticism). These results indicate no difference between the four groups in global measures of psychological distress (the SCL-90-R) or frequency of minor cognitive failures (the Cognitive Failures Questionnaire).

Significant group differences were found for the BDI ($F[3,64]=4.85, p<0.05$), the BDI-Alternate score ($F[(3,64]=3.31$, $p<0.05$), and the Depression ($F[3,61]=4.16$, $p<0.05$), Somatization ($F[3,61]=4.53$, $p<0.05$), and Anxiety ($F[3,61]=4.76, p<0.05$) subscales of the SCL-90-R (see Table 23). Tukey A post-hoc tests conducted on the mean score from the BDI revealed higher scores

($p<0.05$) for the amputee PVDs ($\bar{x}=12.7$; falling in the mild depression range; Beck & Speer, 1987) relative to the Controls ($\bar{x}=5.3$) and non-amputee PVDs ($\bar{x}=6.8$). For the BDI-Alternate score, post-hoc tests revealed higher mean scores for the amputee PVDs ($\bar{x}=8.0$) relative to the Controls ($\bar{x}=3.5$). For the SCL-90-R Depression subscale, post-hoc tests showed that the amputee PVDs had significantly higher *T* scores ($p<0.05$) than the three other groups and that CVD patients had higher mean *T* scores than Control subjects (see Table 23). Post-hoc tests conducted on the SCL-90-R Somatization subscale demonstrated that all three patient groups had significantly higher *T* scores ($p<0.05$) than did the Controls (see Table 23). For the SCL-90-R Anxiety subtest, the effect was due to lower than average scores in the normal control group. Post-hoc tests revealed that Control subjects had significantly *lower* mean *T* scores ($p<0.05$) than the three patient groups and that the non-amputee PVDs had lower mean *T* scores than did the amputee PVD patients (see Table 23). The Controls' mean *T* score of 44.8 represented approximately the 30th percentile of normative values while the mean *T* scores of the patient groups fell in approximately the 50th percentile.

Correlation analyses were conducted to determine whether the higher levels of self-reported depression, somatization, and anxiety were negatively associated with neuropsychological performance. No significant relationship between an overall index of cognitive function (i.e., the mean of the standardized neuropsychological measures [*z*-scores] for each individual amputee and non-amputee PVD patient) and BDI scores ($R=-0.062$ on $d.f.=23$, $t=-0.299$, $p>.05$), BDI-Alternate scores ($R=-0.035$ on $d.f.=22$, $t=-0.170$, $p>.05$), or the Depression

(R=-0.144 on $d.f.$=22, t=-0.684, p>.05), Somatization (R=-0.080 on $d.f.$=23, t=-0.379, p>.05), or Anxiety (R=-0.187 on $d.f.$=22, t=-0.891, p>.05) subscales of the SCL-90-R. These results indicate that relatively higher levels of depression, anxiety, or somatization in the PVD patients did not relate to poorer performance on the neuropsychological tests.

Given that depression is not likely to have an equivalent effect on all cognitive functions, it is possible that examining its relationship to global cognitive impairment (i.e., mean z-score) might have obscured any significant results. It was decided to examine the effects of depression on the raw scores of the eight neuropsychological tests on which the PVD patients were impaired. In light of the criticisms of the use of the BDI in medical populations and in order to minimize Type I error, the BDI-Alt score was selected as the single measure of depression. No significant correlations ($d.f.$=23; all p's > .05) were found between the BDI-Alt scores of the PVD patients and performance on any of the neuropsychological tests (WAIS-R Picture Arrangement: R=0.055, t=0.264; WAIS-R Block Design: R=-0.060, t=-0.286; WAIS-R Digit Symbol: R=-0.173, t=-0.845; Rey Figure Copy: R=-0.213, t=-1.044; Rey Figure Delayed Recall: R=-0.121, t=-0.586; Trail Making Test Part B: R=0.153, t=0.741; WCST perseverative errors: R=-0.075, t=-0.362; WCST conceptual responses: R=-0.144, p=-0.700)..

Discussion

Cognitive Impairment in PVD Patients

The results of Study Two indicated that, relative to age- and education-matched controls, patients with PVD show evidence of neuropsychological impairment that varies largely as a function of the severity of their peripheral atherosclerosis and the presence or absence of ischemic heart disease. Thus, the previous finding of impaired cognitive function in PVD amputees demonstrated in Study One was replicated in a new sample of patients and was extended to include non-amputee PVD patients as well. The first hypothesis was supported.

The univariate ANOVAs revealed that, as a group, PVD patients exhibited cognitive deficits in the areas of attention and psychomotor speed (Trail Making Test Part B, WAIS-R Digit Symbol), executive function (WCST perseverative errors and conceptual responses, WAIS-R Picture Arrangement), visuospatial ability (WAIS-R Block Design, Rey-Osterrieth Complex Figure Copy), and visual memory (Rey-Osterrieth Figure Delayed Recall). No overall impairment for the PVD group was found for tests of language ability, verbal memory, or lateralizing tests of sensory-motor functioning (although see below for important exceptions to this statement when individual patient data are examined). These data are even more compelling when considered in terms of their potential clinical significance. For a number of measures of executive function (WCST perseverative errors), attention (Trail Making Parts A and B), and visuospatial ability (WAIS-R Block Design and the Rey-Osterrieth Figure Copy), between approximately 30-50% of the total PVD sample had scores falling in the bottom 5% of the distribution of normal scores,

suggesting that impaired performance on these tests was the rule and not the exception.

The overall similarity in the results of Studies One and Two is important, in light of differences in tests employed in the two studies. The neuropsychological battery in Study Two involved a combination of tests both identical to and different from those administered in Study One for all cognitive domains examined with the exception of language function (in which the same tests were employed in both studies) and lateralizing tests of sensory-motor function (which was only examined in Study Two). Both studies found evidence of impairment in psychomotor speed (WAIS-R Digit Symbol, a test particularly sensitive to brain dysfunction; Lezak, 1995) and executive function (on two different tests of abstract reasoning/ problem solving). In general, neither study found that verbal ability or memory function were significantly impaired in PVD patients as a group (although see below for exceptions to this rule). Both studies employed appropriate age- and education-matched control subjects and both studies accounted for the possible effects of depression on cognitive function.

The consistent pattern of results found between the two studies is important because it indicates that the findings are robust, replicable, and not a function of peculiarities in test selection. For example, inspection of group means revealed no evidence of impairment in verbal memory function in either study, despite the fact that different tests of this function were employed. Impaired performance in executive function, as measured by performance on a card sorting task, was observed in both studies using two versions of the WCST, the original version

(Study Two) and a modification (the MCST, Study One), indicating that this is indeed a reliable finding. Although originally touted as a test comparable to the original WCST in terms of its sensitivity to frontal pathology while lessening the distress of the examinee (Nelson, 1976), the differential sensitivity of the MCST to frontal impairment has recently been questioned (van den Broek, Bradshaw, & Szabadi, 1993). In light of the fact that one of the criticisms of the MCST is that it might not provide a sufficient opportunity for subjects to develop a strong response set (Lezak, 1995), it is interesting to note that the percentage of perseverative errors was found to differ between PVD patients relative to controls in Study Two (which used the WCST), but not in Study One (which used the MCST). This suggests that perseverative responding was elicited only in Study Two because subjects had the opportunity to develop a strong response set given the longer exposure to the stimuli of the WCST.

It is not clear how replicable the finding of memory impairment is in these patients. Verbal and visual memory deficits were not found in Study One. Impairment on a test of visual memory, the delayed recall of the Rey-Osterrieth Figure, was demonstrated in Study Two. However, interpretation of this result is complicated by the fact that the group showed poor performance on the copy administration of this task and on the other visuospatial constructional task (WAIS-R Block Design). This makes it difficult to distinguish between poor recall of the Figure or merely impaired reproduction of its details. Performance on a test of visual memory not requiring a drawing response from the subjects would have helped to clarify this issue; unfortunately, such a test was not included in the study.

With respect to verbal memory, some individual PVD patients showed deficits relative to the normal controls in this domain, as evidenced by the *z*-score transformations. However, this statement cannot be considered true of the group as a whole in light of the group mean score. It appears that memory deficits may not be a common finding in PVD patients.

Predictors of Cognitive Impairment

Depression. One main objective of Study Two was to determine which factors predict cognitive impairment in PVD patients. First, the influence of a potentially confounding variable, increased depression or psychological distress particularly amongst the PVD amputees, will be considered. Study Two showed that most measures of depression and global psychological distress (as measured by the BDI and the SCL-90-R, respectively) did not differ between the groups. The exception was that of amputee PVDs' self-report on the BDI relative to that of the normal control subjects. A similar finding was obtained for a modified BDI score which was computed to correct for the possible over-influence of the endorsement of somatic symptoms in the amputee sample and a roughly parallel finding was obtained for the Depression subscale of the SCL-90-R. The mean BDI score of the PVD amputees fell in the mild depression range, indicating a level of depressive symptomatology far below that which is reported in studies of the neurobehavioural effects of clinical depression (e.g., Boone et al., 1995; King et al., 1995; Richards & Ruff, 1989; for a review, see Caine, 1986). Moreover, in the present study, none of the depression measures correlated with overall neuropsychological

performance on tests on which the PVD patients were impaired. Similarly, the modified BDI score, selected as the best measure of depression in this study, did not correlate with any of the "impaired" individual neuropsychological tests. This indicates that level of depression did not influence cognitive performance on the neuropsychological tests.

The fact that significant levels of depression were not an issue in the patient sample recruited here is consistent with previous studies, although the available literature is meagre. A great deal of what is known about the psychological response to amputation has been gleaned from studies of young veterans who have suffered traumatic amputation. Therefore, it is not wise to assume that the response of older individuals, who generally have amputations for different medical reasons (largely, PVD), will be the same. In a cross-sectional study, Frank et al. (1984) examined responses on the BDI and the Symptom Check List-90 (SCL-90; Derogatis, 1977) in 66 amputees ranging in age from 18 to 88 years (median=65 years). Two age groups were formed by a median split of age. The majority of older amputees underwent amputation because of PVD, while the majority of amputations in the younger group were because of trauma. These groups were further subdivided on the basis of whether the subject was interviewed less than or greater than 18 months since amputation. In general, lower levels of psychopathology were found in the older amputee group than in the younger group. Moreover, there were significant interactions between the factors age and time since amputation on BDI and SCL-90 scores. In general, scores were lower in older amputees tested 18 months after their amputation and higher in younger

amputees 18 months after amputation, relative to the scores of their respective age group who were tested soon after amputation. Frank et al. (1984) suggested various factors to explain these findings, including age-related developmental changes in body-image (and their requisite alteration following amputation) and the fact that amputation for PVD is usually proceeded by a long period of medical problems, pain, and previous (failed) vascular reconstructive surgeries. In another study using the Geriatric Depression Scale, Schubert, Burns, Para, and Sioson (1992) found low levels of depression amongst amputee and stroke patients upon admission to a rehabilitation hospital and found that even these levels decreased from the beginning to the end of the 1-2 month rehabilitation hospital admission. This is relevant to the present amputee sample reported here, since the large majority of patients were tested at least one month following their amputation.

Risk Factors. When one considers the results of regression analyses conducted on the neuropsychological tests on which the PVD sample showed impairment, a very consistent pattern emerged. The severity of PVD and a history of ischemic heart disease were the two most reliable predictors of cognitive deficits. PVD severity was a significant negative predictor of performance on measures of executive function (WCST perseverative errors and conceptual responses) and on a test of attention (Trail Making Test Part B), accounting for approximately 14% of the variance in performance on these measures. The hypothesis that the extent of PVD, a *peripheral* manifestation of atherosclerosis, would be a significant marker of neurocognitive deficits was supported and underscores the generalized pathological nature of the atherosclerotic process

(Frederic, 1982). Thus, the clinical effects of atherosclerosis in the major arterial systems appear to manifest themselves in a roughly parallel manner. The clinical implication of this finding is that patients with the most severe PVD, especially those with amputations, are at greatest risk for suffering cognitive decline. This finding was foreshadowed by the cluster analysis performed which showed that almost half of the PVD amputees were assigned to the Impaired Cluster, which contained the majority of CVD patients. However, the amputee PVDs do not account entirely for the neuropsychological impairment demonstrated in the group as a whole. Inspection of the standardized neuropsychological test scores indicated that the neuropsychological deficits were observed in the non-amputee PVD patients as well.

A history of ischemic heart disease was more frequently a significant predictor of cognitive impairment in the PVD patients than was PVD severity. It was a significant negative predictor of performance on measures of executive function (WCST perseverative errors and conceptual responses), attention (Trail Making Test Part B and WAIS-R Digit Symbol), and visuospatial ability (WAIS-R Block Design and Rey-Osterrieth Figure Copy). In fact, it accounted for 20-30% of the variance on Trail Making, Digit Symbol, and the Rey-Osterrieth Figure Copy. There are at least three possible explanations for this phenomenon. First, the fact that ischemic heart disease is very strongly associated with atherosclerosis in the cerebral and peripheral arteries is well recognized (Criqui et al., 1992; Krajewski & Olin, 1991; Toole, 1994; Juergens & Bernatz, 1980). Thus, in the present study, the presence of ischemic heart disease in some patients was yet another marker

of the generalized and severe nature of their atherosclerotic disease. Second, in addition to the common co-occurrence of coronary artery disease and cerebrovascular disease, ischemic heart disease can also perform a causative role in stroke, generally in the form of embolization from a thrombus (Adams & Victor, 1993; Frederic, 1982). In fact, after carotid occlusive disease, embolism from the heart is the second most common cause of thromboembolic stroke in the territory of the middle cerebral artery (Lhermitte, Gautier, & Derouesne, 1970). The third possibility relates to the fact that the most important protective mechanism the brain has against cerebral infarction is the development of collateral circulation (Jack & Houser, 1994). In the presence of sufficient collateral circulation, infarction may not occur despite the occlusion of an artery. However, hypotension from reduced cardiac output can render these anastomotic channels ineffective (Adams & Victor, 1994) thereby functionally removing this protective collateral supply. Possibly, the presence of heart disease in PVD patients played such a role.

In general, none of the other medical/ health variables examined (TIAs, hypertension, blood lipid abnormalities, smoking, and diabetes) were related to impaired cognitive performance. The two exceptions to this was a non-significant ($p<.05$) trend towards a negative effect of the number of smoking pack-years on the copy administration of the Rey-Osterrieth Figure and a significant positive relationship between blood lipid abnormality and performance on the WAIS-R Digit Symbol subtest. The former finding is not entirely unexpected given a previous report in the literature which demonstrated negative effects of smoking in the elderly on measures of cognitive function (on two speeded psychomotor tasks; Hill,

1989). Although there is evidence of negative neurobehavioural effects of the various risk factors for the development of atherosclerosis (see Introduction; for other reviews, see Bornstein & Kelly, 1991; Brown et al., 1986), they were not significant predictors of cognitive function in this study when the effects of the clinical manifestations of atherosclerosis (i.e., PVD severity and ischemic heart disease) were considered. It has been previously suggested that the correlations between risk factors and neuropsychological function may ultimately be mediated through their association in the development of cerebral atherosclerosis (e.g., Light, 1978) and their expression in "end organ change" (Schultz et al., 1989). This suggests that the negative effect of the risk factors may be the result of their role in the development of atherosclerosis (i.e., an indirect effect), rather than due to the presence of those pathologies *per se* (i.e., a direct effect). This possibility is depicted in Figure 6 which shows that athrosclerotic risk factors may have a direct but weak effect (dotted line) on cognitive function through hyperglycemia (diabetes), anoxia (smoking), etc. However, these risk factors may have a stronger indirect effect through their role in the pathogenesis of atherosclerosis. According to this argument, more serious cognitive impairment may not be evident in patients with risk factors until atherosclerosis is manifested clinically. The results of this study raise the interesting possibility that the presence of atherosclerotic symptoms such as PVD and ischemic heart disease should be examined more closely in future studies of the neurobehavioural effects of medical conditions such as diabetes and hypertension.

One important criticism of the evaluation of risk factors in this study is that,

with the exception of smoking, risk factors were rather crudely quantified as either present or absent or by employing a somewhat arbitrary ordinal ranking system of severity, following the accepted standards in the PVD literature (Rutherford et al., 1986). Studies designed to evaluate the effects of risk factors have often used more fine-grained methods to quantify the risk factor (e.g., by using continuous measures of glycemic control or hypertension; see Bornstein & Kelly, 1991). Although there is evidence that learning and memory deficits are more commonly observed in Type II than Type I diabetics, the method of coding diabetes in this study placed greater weight on Type I rather than Type II diabetes (i.e., 0=not diabetic; 1=adult-onset, diet controlled [Type II]; 2=adult-onset, insulin controlled; 3=juvenile onset [Type I]; see Table 8). This method of coding would have obscured the ability to detect any effect of diabetes given the linear model employed in the regression analyses. It is possible that the failure of this study to observe any effects of the atherosclerotic risk factors on cognitive function could have been the result of artificially dichotomizing/ categorizing these variables rather than looking at their full range of levels.

Cognitive Function in PVD and CVD Patients

It was hypothesized that patients with symptomatic PVD suffer from concurrent CVD and would therefore exhibit a *pattern* of neuropsychological impairment similar to that observed in a group of patients with recognized symptomatic CVD. In support of this, it is to be recalled that the group performance of the PVD patients did not differ from that of the CVD patients, a

group with verified cerebrovascular lesions, on the Trail Making Test Part B, WCST perseverative errors, WCST conceptual responses, WAIS-R Block Design, and the Rey-Osterrieth Complex Figure Copy and Delayed Recall administrations. In fact, comparison of the two patient groups revealed that there were essentially no differences between mean scores on the Rey-Osterrieth Figure copy, Rey-Osterrieth Figure delayed recall, and the WCST perseverative errors. For the other comparisons (WCST conceptual responses, Trail Making Test Part B, and WAIS-R Block Design) one is not able to rule out the possibility that Type II error resulted in the failure to detect differences between the two patient groups. It is impossible to prove *statistically* that PVD patients show cognitive impairment similar to that of CVD patients, since that would involve arguing that one has proven the null hypothesis. However, it is not essential to demonstrate that there are no statistical differences between the mean performance of the two patient groups. In fact, one could argue that differences in magnitude of mean performance between the two groups are to be expected since the CVD patients have been identified as having had a clinically significant cerebrovascular event resulting in lasting neurobehavioural deficits, while the PVD patients were considered neurologically asymptomatic. Differences between the PVD and CVD patients in the magnitude of impairment notwithstanding, Figure 3 illustrates an important finding about the pattern of neuropsychological performance. The similarity between the two groups is striking in terms of which tests are sensitive to cognitive dysfunction and the pattern of the impairment.

Perhaps the pattern of neuropsychological deficits depicted in Figure 4 of

the PVD and CVD groups is *too* striking. Is it possible that some varying feature of the tests explains the pattern of performance? For example, perhaps it was the case that PVD patients only performed poorly on tests that were difficult or required a speeded response (i.e., time tests). For the reasons presented below, it is argued that the answer to the question is no, although in reality this cannot be known for certain. It is not the case that PVD patients performed poorly only on timed tests. For example, these patients were impaired relative to the controls on two tests tapping visuospatial function, one test in which response speed contributes to the score (WAIS-R Block Design) and one test in which it does not (Rey-Osterrieth Figure Copy). Further, the PVD patients were impaired on measures from the WCST, which is not a timed task.

The suggestion that variation in test difficulty might account for group differences is a more difficult issue to address. To this author's knowledge, the question of test difficulty generally has not been explored in the literature (one exception is the fact that Part B of the Trail Making Test is considered to be more difficult than Part A; Gaudino, Geisler, & Squires, 1995; Lezak, 1995). On the WCST, PVD patients differed significantly from controls in terms of the percentage of conceptual level responses (WCST Concept), but not the number of categories obtained (WCST Cat.). Both scores are taken as measures reflecting the subject's insight into or knowledge of the correct sorting strategy, with one measure partialing out the effects of failures to maintain set (WCST Concept). It is hard to argue that the two measures reflect discrepancies in level of difficulty since they are both derived from the same test. In term of attention performance, PVD

patients were impaired on the WAIS-R Digit Symbol subtest but not on the WAIS-R Digit Span. Again, to this author's knowledge, there is no information regarding whether or not these tests could be considered equated in terms of task difficulty. However, subjectively it would seem that the latter is a more difficult task than the former. The Digit Symbol requires a subject to transcribe, as quickly as possible, abstract symbols according to their paired numerical cues, which are always visible to the person. In contrast, the Digit Span Backward test requires a subject to register in immediate memory a series of digits read aloud, maintain them in memory long enough to mentally manipulate their order, and then to repeat them aloud in the reverse order. Of course, this is speculative and, in the absence of clinical tests matched for level of difficulty, the question remains unsettled.

An alternate interpretation of the question of task difficulty is also possible. If PVD patients did perform more poorly only on the difficult tasks, this could be interpreted as reflecting the sensitivity of those tasks to cerebral dysfunction. Certainly, if a task is too easy, many subjects, including non-impaired, healthy individuals and those with all but the most severe cognitive impairment, could perform adequately on it. Thus, it could be the case that a task is more sensitive to cerebral dysfunction *because* it is difficult and taxes a subject's cognitive resources to the point where the functioning of the cognitive system breaks down.

Returning to the other findings, two other hypotheses were generated by the model of Reitan and Wolfson (1985) and were examined in the comparison of the PVD and CVD patient groups in Study Two. First, it was predicted that, similar to the CVD group, PVD patients would be impaired in generalized cognitive abilities

such as executive function and attention. Second, it was predicted that, similar to the CVD group, PVD patients would show focal deficits on neuropsychological tests considered sensitive to the laterality of cerebral lesions. Evidence supporting the first hypothesis was found: the PVD patients were impaired in their performance on the WCST and the WAIS-R Picture Arrangement, tests reflecting executive functioning, problem solving ability, and abstract reasoning, and on the WAIS-R Digit Symbol subtest and Trail Making Test Part B, tests tapping complex attention. It is interesting to note that no impairments were found in the PVD group for arguably more basic attention tests, the span tests which examine short-term storage capacity (the WAIS-R Digit Span Forward and WAIS-R-NI Visual Span Forward) and working memory (the WAIS-R Digit Span Backward and WAIS-R-NI Visual Span Backward), suggesting that the attentional deficits observed in this group are subtle and are only elicited by tasks with complex cognitive demands. However, deficits on these tests might also result from the fact that they are considered highly sensitive to the presence of brain dysfunction, regardless of the locality of the lesion (Lezak, 1995).

The second hypothesis, that the PVD patients would show focal deficits, similar to the CVDs, on tests considered sensitive to the laterality of cerebral lesions (i.e., tests of language, visuospatial ability, and sensorimotor function), received partial support. There was evidence of visuospatial impairment (i.e., right-hemisphere involvement) in the PVD group as a whole, evidence of language dysfunction (i.e., left-hemisphere involvement) in a subsample of patients, and no evidence of lateralized sensorimotor dysfunction. For tests of sensorimotor

control, absolute differences between the two hands were examined in order to detect the presence of large discrepancies between the two hands, regardless of the direction of the difference. Relative to the normal controls, there was no evidence of lateralized sensorimotor impairment on the Two-Point Discrimination and Grooved Pegboard tests in the PVD patients.

As a group, the PVD patients were impaired on both tests of visuospatial ability administered, the WAIS-R Block Design and the Rey-Osterrieth Complex Figure, tests which are *generally* considered sensitive to right-hemisphere dysfunction (Lezak, 1995; Goodglass & Kaplan, 1979).

Testing the focal deficit hypothesis presented a challenge since cerebrovascular insults typically involve one cerebral hemisphere (Adams & Victor, 1993) and result in characteristic focal deficits (Heilman, 1974; Goodglass & Kaplan, 1979). In PVD subjects putatively experiencing stroke, the involved hemisphere presumably would be approximately equally distributed within the sample. In other words, roughly 50% of the sample might show evidence of left-hemisphere involvement while approximately the other 50% would show right-hemisphere deficits. However, it was impossible to know *a priori* which patients would fall into these subgroups. Any evidence of focal impairment would likely be obscured when considering the data from the group as a whole.

An attempt was made to identify subgroups of PVD patients who showed a pattern of focal deficits by classifying them according to a discriminant function computed on the basis of differences in language and visuospatial performance between the CVD patients with left- and right-hemisphere lesions. This resulted in

the formation of two subgroups of PVD patients, equivalent in sex, age, and education, that differed significantly in their performance on the Graded Naming Test and the Oral Fluency (Orthographic category) test. With respect to left-hemisphere function, no deficits in language function were noted in the PVD sample as a whole. However, examination of the standardized individual test scores indicated that a significant portion of PVD patients (between 14-24%) had scores on the Graded Naming and COWAT/ Oral Fluency tests in the bottom 5% of the distribution of normal control scores. This finding, coupled with the results from the discriminant function analyses, indicated that a subgroup of patients showed evidence of impaired language function. Thus, it appears that impairment in language function was present in a subsample of the PVD patients.

There is an important caveat regarding the interpretation of the analyses of lateralized neuropsychological performance. The discriminant function analysis was conducted despite the fact that the differences between the left- and right-hemisphere CVD patients did not reach traditional levels of statistical significance, although the differences between the two subgroups were in the expected direction (i.e., lower verbal scores in the left-hemisphere CVDs and lower non-verbal scores in the right-hemisphere CVDs). This failure cannot be attributable to differences between the two subgroups in terms of distribution of age, education, or sex because the subgroups were equivalent on these factors. It is possible that some other variable which was not controlled accounts for the weakness in these laterality findings. Broadly speaking, the cerebral cortex is organized along two planes, one lateral (left, right) and the other longitudinal (anterior, posterior; Lezak,

1995; Kolb & Whishaw, 1990). While this study classified CVD patients according to the laterality of their stroke, it did not attempt to classify CVD patients according to the *location* of their lesions within the longitudinal plane. Therefore, even though the differences between left- and right-hemisphere CVD patients were in the expected direction, the failure to account for lesion location (or some other variable(s) such as lesion size) could have resulted in the failure to obtain statistically significant differences between the two subgroups.

Executive Function/Frontal Lobe Deficits in PVD Patients

In addition to the central study questions addressed above, an ancillary analysis was conducted to determine if, as suggested by the results of Study One, amputee PVD patients showed evidence of neuropsychological impairment characteristic of frontal lobe impairment. To this end, the performance of amputee PVDs on tests tapping executive function was compared with two subgroups of CVD patients whose infarcts did or did not encroach upon the anterior cortical brain region. The hypothesis was not supported. No differences were found between patients with infarcts involving the frontal lobes and amputee PVDs, and patients with lesions not involving this cortical region.

There are several possible explanations for this finding. First, the numbers of patients involved in the comparisons were small, which could have resulted in reduced statistical power. However, this does not likely account for the findings since, for several comparisons, the mean differences between the groups were not in the predicted direction (i.e., the frontal CVD patients did not perform more poorly

than non-frontal CVD patients).

Weaknesses in the tests employed in these analyses could account for the findings. It is becoming increasingly recognized that the sensitivity and specificity of clinical neuropsychological tests to frontal lobe pathology fall short of ideal. With respect to verbal fluency, frontal lesions tend to negatively influence oral fluency scores (Lezak, 1995; Stuss et al., 1994). However, Vilkki and Holst (1994) failed to find statistically significant differences in performance between left- and right-hemisphere damage patients with either anterior or posterior lesions. (This failure to detect significant differences may have been attributable to very large *s.d.*s recorded for the left-anterior and left-posterior patients, although the authors themselves did not discuss this possibility). Fluency tests are sensitive to more generalized brain pathology, as well as frontal lobe damage. This is evidenced by the fact that poor fluency performance is observed in a wide variety of dementing illnesses (e.g., in patients with Alzheimer's disease, [e.g., Chertkow et al., 1994], and in some patients with Parkinson's disease; Lezak, 1995). This indicates that pathology elsewhere in the brain can affect performance on these tasks. As discussed previously, until recently, the WCST has enjoyed relatively unscrutinized favour and has been employed under the assumption that it is a sensitive and specific test of frontal lobe dysfunction. While there is evidence that frontal patients tend to make more perseverative errors on this test than controls (Lezak, 1995; Mountain & Snow, 1993), there is little evidence that the test successfully discriminates between patients with frontal lesions and those with damage elsewhere in the brain (Mountain & Snow, 1993). Moreover, the WCST is also

sensitive to the effects of diffuse brain damage (e.g., Robinson, Heaton, Lehman, & Stilson, 1980; Lezak, 1995).

Another strong possibility for the failure to observe differences between the frontal and non-frontal stroke subgroups was due to the fact that the subgroups of CVD patients studied did not represent particularly "pure" cases of frontal vs. non-frontal pathology. CVD patients classified in the frontal group included those whose lesions involved, but were not limited to, the frontal lobes. This was the due to the fact that infarction of the lateral aspects of the frontal lobes results from occlusion of the middle cerebral artery, which also supplies parietal and superior temporal areas (Victor & Adams, 1993). In this way, various brain regions may be involved following occlusion of this artery.

The human frontal lobes consist of all the tissue anterior to the central sulcus (Kolb & Whishaw, 1990). These large brain regions include primary motor cortex, premotor cortex, supplementary motor cortex, Broca's area, basomedial cortex, and prefrontal cortex, which receives projections from the dorsomedial nucleus of the thalamus. The human frontal lobes are richly interconnected with other brain regions. There exists a hierarchical system of connections arising in the prefrontal motor cortex projecting to premotor cortex, and to the motor cortex. There are also reciprocal corticocortical connections between areas of the frontal lobe and the posterior temporal auditory and visual association regions, and the anterior temporal cortex and medial temporal region. These two sets of reciprocal corticocortical connections appear to be extensions of the spatial and recognition systems identified in the monkey's sensory system. There are thalamocortical

projections from the anterior nuclei, the dorsomedial nucleus, and the pulvinar, and reciprocal connections with the amygdala. There is a major, unidirectional connection from the frontal lobe to the caudate. Finally, the frontal lobe projects to subcortical areas including the superior colliculus and the hypothalamus, and receives projections from brainstem structures. Probably the most important of these connections are those with the basal ganglia (with caudate lesions associated with cognitive impairment), the medial temporal structures, and those in the spatial and recognition systems of the parietal and temporal cortex (Kolb & Whishaw, 1990).

According to Cummings (1993), the anatomic specificity of so-called frontal lobe deficits has been challenged in light of similar neurobehavioural changes observed following lesions to areas outside the cortical frontal areas (e.g., caudate, thalamus, basal ganglia). Wolfe et al. (1994) described the emergence of frontal neurobehavioural symptoms after a series of posterior cortical lesions in a patient with an initial subcortical insult. Following a synthesis of available literature, Cummings (1993) argued that executive function deficits, classically considered to arise from dorsolateral prefrontal cortical lesions, can arise from lesions involving any level of a given frontal-subcortical circuit. According to this schema then, a model of behavioural disorders based solely on cortical lesions, as was the case in this study, would have reduced explanatory power.

STUDY THREE

Neuropsychological studies have been chastised for failing to relate the anatomical and/or physiological effects of neurological disease to subjects' capacity for self-care and independent living (e.g., Hom, 1991; Brown et al., 1986). Heaton and Pendleton (1981) argued that, in contrast to a preoccupation with diagnostic issues, everyday functioning has been an ignored topic of neuropsychological research. Brown et al. (1986) noted that despite the need to study the performance of neuropsychological patients in their ecological environments, many neuropsychological studies do not do so. In an attempt to avoid this shortcoming, a follow-up study was conducted with the PVD patients to determine whether neuropsychological performance (as assessed in Study Two) predicted their everyday level of functioning after one year.

Jongbloed (1986) reviewed 33 studies of prognostic indicators of function following stroke. In addition to the factors of prior stroke, older age, and urinary and bowel incontinence, several studies identified the presence of visuospatial deficits as an adverse prognostic indicator. For instance, Lehmann et al. (1975) found that the sum of WAIS subtest scores tapping perceptual functions (i.e., Block Design, Digit Symbol, Picture Completion) correlated with gains in functional status, namely self-care, ambulation, and mobility. Similarly, Lorenze and Cancro (1962) found that the sum of WAIS Block Design and Object Assembly subtests (both of which tap visuoperceptual skills) related to independent dressing and grooming.

The generalizability of this finding has been demonstrated more recently in a large sample (n=108) of psychogeriatric in-patients hospitalized for various

reasons ranging from psychiatric disturbances (e.g., depression) to dementia. Richardson, Nadler, and Malloy (1995) assessed language, visuospatial, executive, and memory function in relation to performance on tasks measuring both basic (i.e., hygiene) and instrumental (e.g., money management) activities of daily living (ADLs). Using canonical correlation, they found a strong overall relationship between neuropsychological and ADL performance. However, performance on the Hooper Visual Organization Test, which reflects visuospatial ability, was shown to be the best predictor of functional dependence across each ADL domain. Memory function (assessed by the immediate recall trials of the WMS-R Logical Memory and Visual Reproductions subtests) was the second best neuropsychological predictor of independence in ADL. Verbal function (assessed by the Boston Naming Test) and a measure sensitive to frontal lobe functioning (the COWAT/ Oral Fluency Orthographic condition) did not predict ADLs.

The Functional Assessment Questionnaire (FAQ; Pfeffer, Kuroaski, Harrah, Chance, & Filos, 1982; see Appendix E) was selected as the outcome measure in the current study for several reasons. First, it purports to measure an individual's level of adaptive functioning (the authors employ the term "social functioning") and was specifically designed to tap the range of activities in which an elderly or retired person is typically engaged, rather than more low-level activities which are appropriate for individuals in a institutional setting (Pfeffer et al., 1982). Second, it was designed to be independent of socioeconomic status, level of education, and intelligence (Pfeffer et al., 1982; Hershey, Jaffe, Greenough, & Yang, 1987). Third, it has been shown to distinguish between normal elderly persons and those

with mild senile dementia (Pfeffer et al., 1982) and those with vascular dementia (Hershey et al., 1987). Fourth, the FAQ is completed by a lay person who is familiar with the study participant and can be administered by mail (which was the procedure followed here).

The FAQ was designed to assess independence in 10 high level instrumental daily activities, such as shopping, managing fiscal affairs (i.e., balancing a cheque book), following current events, and remembering appointments (see Appendix E for complete examples). It is completed by a close lay informant, such as a spouse or relative, who rates the designated subject on each activity at one of four levels, ranging from: dependent = 3, requires assistance = 2, has difficulty but does by self = 1, and normal = 0. Two additional options are included in the event that an individual had never performed the task in question: "Never did [the activity], but could do it now" which is scored as normal (i.e., equal to 0), and "Never did [the activity] and would have difficulty now" which is scored as 1. The total score is the sum of individual item scores, where higher scores reflect greater dependency. The FAQ has been shown to correlate with measures of cognitive function in normal elderly and those with mild to moderate dementia living in the community (Pfeffer, Kurosaki, Chance, Filos, & Bates, 1984; Pfeffer et al., 1982). Using a cut-off scoring of 5 points, the FAQ has been shown to distinguish between normal elderly individuals and mildly demented community-dwelling older adults, with a specificity of 0.81 and a sensitivity of 0.85 (Pfeffer et al., 1982).

The present study examined whether neuropsychological performance

(measured in Study Two) related to everyday functioning one year later in PVD patients. The standardized neuropsychological data were grouped into five domains, namely Frontal/ Executive Function, Attention, Memory, Verbal Function, and Visuospatial Function (see Method section for further details). Previous research has indicated that visuospatial and perceptual functions may be important prognostic indicators of outcome in stroke patients (Lehmann et al., 1975; Lorenze & Cancro, 1962; Richardson et al., 1995). In light of these findings, it was specifically hypothesized that poorer visuospatial function would be associated with poorer everyday functioning (i.e., greater dependence) at one-year follow-up. In other words, it was hypothesized that mean visuospatial standardized scores would be significantly negatively correlated with scores on the FAQ. It was also predicted, based on the findings of Richardson et al. (1995) that memory function would be significantly negatively related to FAQ scores. Similarly, it was predicted that attention performance would be significantly inversely related to FAQ scores. Despite the negative findings of Richardson et al. (1995), the present study predicted that frontal lobe functions would be significantly related to everyday functioning. This prediction was made for two reasons: one, because of the potential important contribution of organizational and planning skills (i.e., frontal lobe or executive functions) to everyday activities, and two, because this study sampled executive functions more broadly than did Richardson et al., who relied on only one measure. It was further predicted, based on previous findings (Richardson et al., 1995), that verbal ability would not significantly relate to functional outcome.

Method

Subjects and Procedure

Approximately one year following their participation in the neuropsychological study (Study Two), all PVD patients (amputees and non-amputees, n=29) were sent by mail a covering letter explaining that they were invited to participate in a follow-up study. The letter indicated that they were under no obligation to do so and that not doing so would have no negative implications for their health care. A copy of the FAQ, contained in a separate sealed envelope, was sent with the covering letter along with a pre-stamped envelope for return of the completed questionnaire. Subjects were informed that they could discard the questionnaire without reading it, if they so decided. The letter also contained explicit instructions indicating that, if the subject chose to participate, the questionnaire was to be filled out by an individual who was very familiar with him/her. An additional mailing, essentially identical to the first, was sent to those individuals who had not responded within the first three weeks.

One non-amputee PVD subject was unable to be located at the address recorded for him. A response was received from the spouse of second non-amputee PVD patient who had participated in the neuropsychological testing 16 months previously, indicating that the patient had very recently died as a result of cancer (which was not diagnosed at the time of Study Two). Completed FAQs were received from 10 amputee PVDs and 9 non-amputee PVDs, yielding a total return rate of 66%. Six females and 13 males had FAQs completed on their behalf; these patients had a mean age of 66.3 years (*s.d.*=11.3) and mean education of

10.8 years (*s.d.*=2.1). Eight subjects (2 females, 6 males; $\bar{x}$ age = 61.5 years [*s.d.*=12.4]; $\bar{x}$ education = 11.1 years [*s.d.*=3.0]) failed to respond to either mailing. Responders and non-responders did not differ in terms of age (t=0.971, p=.034) or education (t=-0.278, p=0.782). The FAQ was completed by the study patients' spouses in all but two instances; in those cases it was completed by the study patient's daughter or daughter-in-law.

Results

The mean FAQ score of the patients rated by their lay informant was 3.4 (*s.d.*=5.2, range 0-20 points), where a total maximum score is 30 points. Five patients were given ratings greater than or equal to the recommended cut-off score of 5 points (Pfeffer et al., 1982).

An analysis was conducted to determine whether bias was present in the return rate of the questionnaires. The possibility that only those patients who were least impaired in their cognitive function participated in the follow-up study was tested. A MANOVA computed across all raw neuropsychological test scores indicated that patients who responded (n=19) versus those who did not respond (n=8) did not differ in overall neuropsychological performance (Hotelling's T^2=1760.59, $F(26,2)$=5.02, p=0.3682). Although the sample sizes involved in this comparison were very small and could well have resulted in diminished statistical power, inspection of means of the two groups revealed them to be highly similar in all instances.

The relationships between neuropsychological function and functional

outcome was tested by examining the relationship between FAQ scores and five neuropsychological domains. The Frontal/ Executive Function composite score was the mean *z*-score of 7 tests considered sensitive to frontal lobe function: WCST perseverative errors, WCST number of categories, WCST conceptual responses, COWAT/ Oral Fluency Orthographic, COWAT/ Oral Fluency Semantic, WAIS-R Similarities, and WAIS-R Picture Arrangement. The Attention composite score was comprised of the mean *z*-scores of 5 measures: the WAIS-R Digit Span, WAIS-R Digit Symbol, WAIS-R-NI Visual Span, Trail Making Part A, and Trail Making Part B. The Memory composite score was made up of the mean *z*-score of 2 tests: the Rey-Osterrieth Figure Delayed Recall and the CVLT Long Delay Free Recall trial. The Verbal domain was a composite score consisting of the mean *z*-score of 3 measures: the Graded Naming Test, COWAT/ Oral Fluency Orthographic, and COWAT/ Oral Fluency Semantic. The Visuospatial domain composite score was the mean *z*-score of 2 tasks: WAIS-R Block Design and the Rey-Osterrieth Figure Copy administration. Figure 5 illustrates the relationship between FAQ ratings and these five neuropsychological domains. In order to minimize Type I error, correlations whose *t*-value met or exceeded the critical value at $\alpha=0.01$ were considered significant. Initial analyses ($d.f.=17$) indicated that FAQ scores were significantly negatively related to the standardized scores of 4 of the 5 neuropsychological domains (Attention: $R=-0.798$, $t=-5.45$, $p<.01$; Memory: $R=-0.602$, $t=-3.11$, $p<.01$; Verbal: $R=-0.602$, $t=-3.11$, $p<.01$; Visuospatial: $R=-0.610$, $t=-3.18$, $p<.01$). The exception was that of the Frontal domain ($R=-0.441$, $t=-2.02$, $p>.01$).

However, inspection of Figure 5 suggests that the presence of the subject with an FAQ score of 20 might have represented an outlier exerting undue influence on the correlations. Due to this possibility, analyses were again conducted, omitting that subject's data. The results remained largely unchanged. Significant relationships ($d.f.=16$) were still obtained between FAQ scores and the domains of Attention ($R=-0.620$, $t=-3.17$, $p<.01$), Memory ($R=-0.620$, $t=-3.17$, $p<.01$), and Visuospatial ($R=-0.584$, $t=-2.88$, $p<.01$) function. However, the correlation between the FAQ and the Verbal domain was no longer significant after the correction ($R=-0.330$, $t=-1.40$, $p>.01$).

The influence of affect and psychological distress were also examined in relation to functional outcome at one-year follow-up. Ideally, these factors should have been considered together with the neuropsychological predictors. However, as indicated earlier, affective data were not available on all PVD patients and not all PVD patients participated in this follow-up study. This combination of factors resulted in a reduced number of cases available for analysis and precluded the use of regression analyses to clarify the predictive role of cognitive and affective variables. Instead the Pearson product-moment correlation coefficient (R) was calculated for each variable. Chosen for analyses were those affective measures on which PVD patients differed from Controls in Study Two, namely the BDI and the Somatization and Anxiety subscales from the SCL-90-R. The BDI-Alternate score and the SCL-90-R Depression subscale were not examined as they would have provided information redundant with the BDI. Neither the Somatization ($R=0.30$, $d.f.=14$, $t=1.18$, $p>0.05$) nor the Anxiety ($R=0.31$, $d.f.=14$, $t=1.21$,

$p>0.05$) subscales significantly related to scores on the FAQ. However, level of depression, as measured by the BDI during Study Two, was significantly related to scores on the FAQ at one-year follow-up ($R=0.48$, $d.f.=15$ $t=2.11$, $p<0.05$).

Discussion

Study Three examined the potential clinical significance of the cognitive deficits demonstrated in the PVD patients. It was found that visuospatial, memory, and attentional processes predicted everyday adaptive functioning as rated by the subjects' relative one year following neuropsychological testing. Performance on tests sensitive to frontal lobe functions and tapping verbal ability were not significantly related to everyday adaptive functioning.

Specifically, lower performance of the PVD patients on the composite visuospatial score (i.e., standardized scores from the WAIS-R Block Design and the Rey-Osterrieth Complex Figure copy) was related to greater dependence in complex everyday functioning one year later. These findings are consistent with those studies cited earlier (Lehmann et al., 1975; Lorenze & Cancro, 1962; Richardson et al., 1995) which indicated that impaired visuospatial abilities were prognostic indicators of poor function in stroke patients. Richardson et al. (1995) questioned whether visuospatial skills are specifically related to everyday living skills or, alternately, whether the single test of visuospatial function used in their study (the Hooper Visual Organization Test) merely represented a sensitive index of overall cognitive status. However, previous findings (Lehmann et al., 1975; Lorenze & Cancro, 1962) and the finding in the present study that functional

outcome related to performance on two different tests of visuospatial function indicates that this is a reliable finding, specific to visuospatial ability.

The finding that memory performance also predicted functional outcome one year later is consistent with previous research (Richardson et al., 1995). The current study also observed a significant relationship between attentional processes and functional outcome. Unfortunately, it was not possible to determine the relative importance of these various cognitive functions in predicting everyday functioning given the relatively small sample size available.

It is not clear why this study failed to demonstrate a relationship between frontal lobe/ executive functions and everyday functional outcome. It was not likely due to bias in the sample of patients who participated in the follow-up study; no differences were found between respondents versus non-respondents in terms of demographic variables or overall cognitive function. The FAQ was carefully selected to assess everyday functions that would likely be affected by cognitive deficits (e.g., managing money), rather than more basic activities (e.g., toiletting) that might not be. This study assumed that having the assessment made by a close lay observer (a relative) rather than a health care worker would be valuable since the lay observer has the opportunity to see the study participant in more and varied circumstances, situations to which a third party is not exposed (e.g., Prigatano & Altman, 1990). This assumption may not have held, however, and it is possible that the relatives denied or underestimated any neurobehavioural handicaps in their loved ones. It could also be the case that the PVD patient with frontal lobe deficits manage to function reasonably well in an environment which

is very familiar to them and sufficiently structured to compensate for any potential neurobehavioural limitations. It could be that the negative functional effects of frontal lobe impairment might only be evident in a more challenging or stressful environment, such as a rehabilitation setting. This remains to be determined. It has been argued that neuropsychological tests demonstrate relatively weak validity in relation to ecological criteria such as measures of everyday functioning and quality of life (Guilmette & Giuliano, 1991; Heinrichs, 1990). In terms of tapping the impact of frontal lobe dysfunction, this study may be no exception.

Nevertheless, the results of this study indicate the importance of looking at specific measures of cognitive function (e.g., visuospatial ability, memory, attention) in order to establish a relationship between cognitive functions and everyday functional ability. Further, the consistency in findings between this study and others for visuospatial functions (Lehmann et al., 1975; Lorenze & Cancro, 1962; Richardson et al., 1995) and memory (Richardson et al., 1995) indicate that these are reliable and generalizable relationships.

Finally, the preliminary finding of a significant relationship between depression and functional outcome one year later indicates that factors in addition to cognitive function may contribute to long-term functional outcome. It will be important to address these issues together in future research. Subsequent research should address the issue of whether or not cognitive impairments in PVD amputees impede their progress while in a rehabilitation setting. For example, patients with severe deficits might require longer hospitalization, more intensive training, or more contact with follow-up clinic in order to maintain their prosthetic

competence. Such research should include expert third-party observers (e.g., physiotherapists, physiatrists) and also lay observers to provide information on functioning in the home. The present results indicate that specific cognitive deficits (e.g., visuospatial deficits) are strong predictors of everyday functions. By identifying specifically which factors pose an impediment to rehabilitation, steps can be taken to address and/ or circumvent the deficits during rehabilitation training (see below for further suggestions).

General Discussion

Prior to undertaking a general discussion, the hypotheses and results of the three studies will be restated to consolidate and to remind the reader of the findings.

Study One was conducted as a preliminary study to test the hypothesis that patients with severe PVD (i.e., PVD amputees) exhibit impaired cognitive performance relative to age- and education-matched controls. This hypothesis was supported by the findings that PVD patients differed significantly from controls on tests of psychomotor functioning, and problem solving and abstract reasoning.

Using a larger and broader sample of PVD patients, Study Two examined the following:

a) The hypothesis that PVD patients suffer from concomitant CVD and show a pattern of impairment similar to patients with symptomatic CVD (i.e., both generalized and lateralized deficits) was tested. It was predicted that the PVD patients as a group would exhibit generalized cognitive deficits in

executive function and attention processes. ANOVAs supported this hypothesis. PVD and CVD patients differed from controls but not from each other on tests of executive function (WCST perseverative errors, WCST conceptual responses) and attention (Trail Making Test Part B). It was also predicted that PVD patients would be differentiated into subgroups showing evidence of right- and left-hemisphere dysfunction. This hypothesis was partially supported by the results of a discriminant function analysis, which implicated poorer language-related function (i.e., left-hemisphere) in a subgroup of PVD patients (although see above for limitations to this finding). In addition, PVD patients as a whole performed as poorly as CVD patients on tests sensitive to right-hemisphere dysfunction (WAIS-R Block Design, Rey-Osterrieth Figure Copy).

b) With respect to the predictors of cognitive function, Study Two hypothesized that the severity of PVD would be the best predictor of cognitive impairment, followed by other markers of symptomatic atherosclerosis (TIAs and ischemic heart disease). This hypothesis was largely supported. Hierarchical regression analyses demonstrated that PVD severity and ischemic heart disease were the only two negative predictors of cognitive performance. Heart disease was a significant negative predictor of performance on two measure of executive function (WCST perseverative errors, WCST conceptual responses), two measures of attention (WAIS-R Digit Symbol, Trail Making Test Part B), and two measures of visuospatial ability (WAIS-R Block Design, Rey-Osterrieth Figure Copy). PVD severity

was a significant negative predictor of performance on two measure of executive function (WCST perseverative errors, WCST conceptual responses), and on one measure of attention (WAIS-R Digit Symbol). Generally speaking, atherosclerotic risk factors (hypertension, cigarette smoking, hyperlipidemia, diabetes) were not related to impaired cognitive function.

c) Studies One and Two demonstrated the replicability and consistency in PVD of cognitive impairment in attention and executive function. Study Two demonstrated that possibly confounding factors such as depression could not account for the findings.

Study Three hypothesized that, within the PVD patients, performance on tests of memory, attention, executive function, and visuospatial ability would predict everyday functional performance at one-year follow-up. The results showed that memory, visuospatial ability, and attention were significantly related to ratings of long-term functional performance, but that verbal and executive functions were not. It was also found that depression was significantly related to poorer functional outcome one year later.

Implications of Cognitive Impairment in PVD

There are a number of implications following from the demonstration that PVD patients show neuropsychological deficits relative to age- and education-matched controls. Two implications were suggested in the Discussion section of Study Two. First, it was suggested that neuropsychological deficits in PVD amputees might present an impediment to prosthetic rehabilitation, resulting in prolonged or unsuccessful rehabilitation. This remains to be determined and would be an important area to address in future research. Prosthetic rehabilitation is likely to be a multi-determined process, depending on perceptual and organizational/ executive function skills, and learning and memory processes. Currently, it is not known if success in rehabilitation calls upon some skills more heavily than others. The results of Study Three indicated that specific neuropsychological deficits, namely visuospatial, attention, and memory deficits, were related to poorer functional outcome at home. Future research should examine the predictive power of specific neuropsychological deficits in relation to the rehabilitation process. It is also possible that physical rehabilitation, which involves the learning and/ or reprogramming of certain motor routines, is dependent upon certain cognitive processes typically not examined in neuropsychological assessments. For example, preserved ability on procedural or motor skill learning tasks, such as a smooth-pursuit rotor task, could relate to preserved ability to gain from rehabilitation in patients, even in the presence of other neuropsychological deficits.

Secondly, it is possible that neuropsychological assessment of PVD patients

receiving rehabilitation services would lead to the early identification of patients in greatest need due to their neuropsychological deficits. As suggested earlier, this would facilitate our ability to provide more specialized rehabilitation services to these patients (e.g., more intensive training, more simplified and concrete instructions).

A third implication is that patients with PVD, especially those with evidence of generalized atherosclerosis (e.g., ischemic heart disease) and/or severe atherosclerosis (e.g., those with amputations or who have had multiple reconstructive surgeries) who are already showing evidence of neuropsychological compromise are at high risk for potentially more devastating strokes in the future. Many of the atherosclerotic risk factors (hypertension, diabetes, blood lipids, smoking) are amenable to treatment and patients should be educated about these. While it is likely that PVD patients have already received medical advice to control these factors (especially to quit smoking) in order to arrest or slow the progressive of atherosclerotic disease in their legs (Krajewski & Olin, 1991; Playfer, 1983), it is possible that raising the spectre of potential stroke would provide further impetus for these patients to modify harmful lifestyle habits (e.g., smoking, failure to adhere to diet or medication regimes, etc.).

Fourth, the demonstration of cognitive deficits in PVD patients has implications for the results of studies evaluating neuropsychological outcome following vascular surgery, such as coronary artery bypass surgery (Shaw et al., 1987) and especially carotid endarterectomy (e.g., Hemmingsen et al., 1986; van den Burg et al., 1985; Kelly, Garron, & Javid, 1980). These studies employed PVD

patients as "normal" surgical control patients. A recent review of the efficacy of cerebral revascularization indicated both positive and negative results (Baird, 1991). Baird (1991) argued that the literature does not strongly support the hypothesis that surgical revascularization procedures produce significant behavioural gains.

PVD patients undergoing surgery have been used in some studies involving repeated psychometric measures to control for test-retest or practice effects with the assumption that these patients have normal cognitive function. The present study has demonstrated that this assumption is not correct, which calls into question some of the conclusions drawn from cerebral revascularization studies which have used PVD controls. Studies which have observed post-operative improvement in cognitive function in carotid endarterectomy patients have attributed gains to the beneficial effects of surgery if post-operative improvement was not similarly observed in the control group (e.g., Hemmingsen et al., 1986). Conversely, failure to observe differences between carotid endarterectomy and PVD control groups preoperatively led one group of researchers to speculate that cognitive deficits did not exist in the target study group (e.g., Kelly et al., 1980). The results of the present series of studies would indicate that the carotid endarterectomy group in Kelly et al. (1980) was being compared with a control group that in fact had cognitive deficits. In general, the present data indicate that it is possible that the inclusion of PVD patients as control patients in previous studies of cerebral revascularization outcome may have contributed to the variability in the findings of studies in this area.

Clinical Assessment of PVD Patients

How might the results of these studies assist in the clinical neuropsychological assessment of patients with PVD? Although *some* of the deficits of PVD patients exhibited were relatively mild compared to the impairment of the symptomatic CVD patients, Study Three demonstrated that the cognitive performance of PVD patients was significantly related to their functional performance one year later. This suggests that, although arguably mild, the cognitive deficits in the PVD subjects had a significant real-life impact for these patients. Of course, a stronger interpretation of these findings is not warranted, given that the nature of a correlational study does not allow us to infer causality.

The tests that successfully differentiated between the PVD patients and normal controls were tests tapping attention processes and psychomotor function (WAIS-R Digit Symbol and Trail Making Part B), tests of visuospatial function (WAIS-R Block Design and the Rey-Osterrieth Copy), and tests of executive function/ problem solving (the WCST). As such, these tests, or related measures, would be important measures to include in a clinical assessment of a PVD patient with suspected cognitive decline. In particular, tests of attention and visuospatial function would be important to include if a goal of the assessment is to predict everyday adaptive functioning. Although only one test of memory (delayed recall of the Rey-Osterrieth Figure) distinguished between PVD patients and controls in Study Two, Study Three indicated that memory function is an important prognostic variable to consider. Perhaps it is the case that intact memory function predicts *independence* in long-term everyday functioning in PVD patients, while deficits in

other cognitive domains predict poor everyday functioning. Study Three was not able to sort out these possibilities; however, this would be an important issue to explore in future research.

Previous research (reviewed in the Introduction; see also Bornstein & Kelly, 1991; Brown et al., 1986) has raised our level of awareness of the possibility that atherosclerotic risk factors (hypertension, smoking, diabetes, hyperlipidemia) may have subtle negative effects on cognitive functioning. The results of the studies reported here may provide an alternate explanation. It was shown that symptomatic manifestations of clinical atherosclerotic disease (PVD severity and ischemic heart disease) were better predictors of cognitive impairment than were the risk factor themselves. The risk factors did not predict cognitive impairment after the effects of symptomatic atherosclerosis had been removed. The results suggest that hypertensive or diabetic patients who are showing signs of vascular disease are more likely to suffer cognitive impairment (or show greater impairment) than those who do not show vascular signs. Study Two also indicates that, for the individual who shows evidence of multiple levels of vascular compromise (i.e., PVD patients with ischemic heart disease), the risk of cognitive impairment is even greater.

What Accounts for Neuropsychological Impairments in PVD Patients?

What is actually wrong with the PVD patients to produce neuropsychological impairment? Are they in the early stages of multi-infarct dementia (MID)? Are there other vascular syndromes that could explain their deficits? It was not

possible to obtain structural information on the brains and cerebral arteries of these patients in order to be able to answer these questions. Obtaining this information and relating it to neuropsychological function and rehabilitation and functional outcome represents the next logical avenue of research in this area. In the meantime, one must search the literature for possible explanations for the neuropsychological deficits observed in these subjects.

Subcortical Impairments?

As discussed earlier, Hemmingsen et al. (1986) incidentally observed physiological and structural evidence of brain abnormalities in PVD control patients. More compelling evidence has also been found. Bots et al. (1993) conducted a population-based study of MRI scans of brains of community-dwelling elderly people in order to determine the relationship between cerebral white matter lesions (WMLs) and atherosclerosis in the cerebral, coronary, and peripheral arteries. Peripheral atherosclerosis was assessed using the ratio between the systolic blood pressure in the ankle to systolic blood pressure in the arm (i.e., the ABI); lower ratios reflect greater abnormality in the arterial blood supply to the leg. The presence or absence of WMLs was assessed in 111 subjects; raters were blind to any clinical information about the subjects. The sample was divided into those subjects with and without WMLs. The ABI was significantly reduced in subjects with WMLs, after adjusting for sex and age. In fact, a decrease of 0.1 in the ABI ratio was associated with a 20% increase in WML probability. The odds ratio of subjects with PVD having WMLs (after adjustment of sex and age) was 2.4. No change was observed in the magnitude of association between PVD and WMLs

after additional adjustment of risk factors for cardiovascular disease (i.e., hypertension, hyperlipidemia, and smoking). Moreover, the severity of WMLs was positively related to severity of PVD.

What is the significance of this finding? Hachinski, Potter, and Merskey (1987) introduced the term "leukoaraiosis" to describe WMLs observed in CT scans (as areas of lucency) and MRI scans (as areas of hyperintensity on T_2-weighted images). The term leukoaraiosis is not etiology-specific. Microscopic studies have suggested that leukoaraiosis may represent areas of infarction, gliosis, or demyelination (Mirsen et al., 1991). Inzitari et al. (1987) demonstrated a strong positive correlation between leukoaraiosis and history of stroke and, to a lesser extent, hypertension. These authors argued that this is evidence that leukoaraiosis is vascular in origin, although they acknowledge that its precise etiology remains unknown. In addition, however, the data of Bots et al. (1993) showing positive associations between WMLs and atherosclerosis is further evidence that leukoaraiosis may be vascular in origin.

A relationship has been observed between cognitive decline and WMLs detected by CT, but not by MRI (Mirsen et al., 1991), perhaps owing to the fact that CT scans are only sensitive enough to detect WMLs that are severe or large (Boone et al., 1992). Nevertheless, Mirsen et al. (1991) suggest that, even if it does not result in deficits itself, leukoaraosis or WMLs may represent a marker or risk factor for cognitive decline.

Studies of the relationship between WMLs and cognitive function have yielded variable results. Boone et al. (1992) noted that these discrepancies may

result from differences between studies in the neuropsychological tests used (ranging from screening tools to comprehensive batteries), the cognitive domains sampled, and the sensitivity of the imaging technique employed (i.e., CT scan versus MRI). Negative results have been found. For example, Hunt et al. (1989) detected moderate to severe WMLs in 31% of their sample of 46 healthy, elderly subjects. The severity of WML increased and neuropsychological test performance decreased with age. However, there was no statistically significant relationship between WML severity and cognitive function, leading the authors to question the clinical significance of white matter hyperintensities in the elderly.

However, a number of positive results have been reported. Van Swieten et al. (1991) compared cognitive function in hypertensive patients with confluent WMLs detected on MRI, hypertensive patients with either normal white matter or only small, focal lesions, and normal elderly controls with either normal white matter or only small, focal lesions. Subject groups were matched for age, education, and sex. Relative to the other two groups, the hypertensive patients with WMLs performed significantly more poorly on tests of attention (Trail Making, Parts A and B) and executive function (the Stroop test) and on a test of global mental status that has a significant attentional component to it (the Mini Mental State Examination). No group differences were found on tests of memory, with the exception of a test of delayed recall of visual designs on which the patient group with WML performed worse than the other two groups.

Boone et al. (1992) studied the clinical significance of WMLs in 100 healthy elderly adults by examining the cognitive domains of intelligence, memory,

attention, executive function, language, and visuospatial skills. Forty-six percent of the subjects had no WMLs, approximately one quarter had minimal WMLs and another quarter had moderate WMLs. Six subjects were found to have large (> 10 cm^2) WMLs. The subjects in this latter group were found to perform significantly more poorly on tests of attention and information processing (WAIS-R Digit Span and Digit Symbol subtests) and executive function (WCST perseverative errors and number of categories, the Stroop, and Auditory Consonant Trigrams) relative to the groups with no or small WMLs. No group differences were observed on tests tapping the other cognitive domains examined. The authors speculated that the presence of mild impairments in attention and executive function could herald the early stages of a subcortical dementia/ frontal systems deficit.

Junqué et al. (1990) examined the clinical relevance of WMLs detected by MRI in 41 patients with cerebrovascular risk factors (i.e., diabetes mellitus or hypertension) and symptoms (i.e., TIAs, reversible ischemic neurological deficits, or classic lacunar syndromes) with no demonstrable cortical lesions. Patients were administered tests of IQ, verbal and visual memory, attention, executive functions, and language function. The authors used a composite scoring method for quantifying WMLs, which was the mean of ratings based on the percentage of white matter that appeared hyperintense on T_2-weighted images (where a score of 0 indicated no changes and a score of 4 indicated 75% or greater hyperintense area) on scans of 10 brain areas. After partialing out the effects of age, tests of speed and attention (Trail Making Test, Part B, Mental Control from the WMS, all

measures from the Stroop tests, in addition to other tests) correlated significantly with the WML score. Significant correlations were not found between the WML score and tests of the other cognitive domains noted above, after controlling for the effects of age. Junqué et al. (1990) interpreted their findings as indication of impairment in the speed of complex mental processing. The relationship between WMLs and cognitive slowing, neurological soft signs, and behavioural disturbances led these authors to speculate that WMLs may reflect subcortical/ frontal systems impairment.

The concept of subcortical dementia was introduced in the 1970's (Ross & Cummings, 1994). Parkinson's disease (Marsden, 1994) and Huntington's disease (Kolb & Whishaw, 1990; Lezak, 1995) are the most common degenerative disorders involving subcortical structures. Patients suffering from these diseases and the less common pathology of progressive supranuclear palsy can present with impairment in cognitive functioning. Similarities between the cognitive deficits in these disorders led to the concept of subcortical dementia (Ross & Cummings, 1994), which stands in contrast to the so-called cortical dementias such as Alzheimer's disease or Pick's disease (Lezak, 1995). The distinction between cortical and subcortical dementia was proposed primarily for three reasons[6]

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[6] The notion of subcortical vs. cortical dementia has been criticized, however (Lezak, 1995; Ross & Cummings, 1994). The arguments against the maintenance of the concept has been: 1) overlap between the two dementia categories in cognitive and affective alterations; 2) the absence of dementia in at least 50% of Parkinson's disease patients, and 3) the lack of a clearly distinctive pattern of deficits in those patients who are demented. Even more importantly, however, is the evidence that, given the incredible interconnectedness of brain areas, damage to cortical and subcortical brain areas is not necessarily expressed in distinct behavioural or cognitive deficits.

(Lezak, 1995; Ross & Cummings, 1994). First, there are apparent similarities between the cognitive deficits observed in patients with subcortical pathology, namely mental slowing, impairment in attention, visuospatial abnormalities, impaired executive function, and a memory disorder characterised by retrieval rather than encoding deficits. Second, there is an apparent absence of the classical symptoms of cortical damage, such as aphasia, agnosia, and apraxia. Third, it has been argued that the preponderance of mood disturbances such as apathy and depression is similar in subcortical disorders (Lezak, 1995). These features have also been noted in other neurological disorders involving subcortical pathology, for example, multiple sclerosis, lacunar infarctions, and white matter lesions (Ross & Cummings, 1994).

Can this explain the neuropsychological impairment demonstrated in PVD patients? First, as with the subjects of Junqué et al. (1990) and Boone et al. (1992), it is not clear that the PVD subjects in the present study exhibited deficits sufficient to warrant a diagnosis of dementia. Diagnostic criteria for dementia according to the DSM-IV (American Psychiatric Association, 1994) include: 1) memory impairment; 2) at least one other cognitive impairment, including aphasia, apraxia, agnosia, difficulty with abstraction, visuospatial impairment, impaired judgement, or personality change; and 3) associated functional impairment. The pattern of impairment in the PVD patients meets the second criterion, and for some patients may satisfy the third criterion. There is not yet strong evidence that the first criterion has been met; this remains to be determined. Nevertheless, the similarities between the impairments observed in the PVD sample and the

characteristic impairments seen in subcortical dementia, namely mental slowing, attentional impairment, visuospatial abnormalities, and impaired executive function, are interesting. There was evidence that some PVD patients had memory impairment; whether these could be characterised as retrieval rather than encoding deficits is not known and awaits further study.

The PVD patients did not, as a group, meet criteria for dementia. It is possible that they suffer from early or prodromal brain changes that may, for some, lead to dementia. This question is speculative and could only be addressed through longitudinal study. It would also be important to replicate the relationship shown by Bots et al. (1993) between WMLs and atherosclerosis and to relate this directly to neuropsychological function in PVD patients.

Do PVD Patients Suffer From Vascular Dementia?

Vascular dementia is a syndrome caused by a number of different vascular mechanisms (i.e., atherosclerotic, cardiogenic, and lacunar stroke; ischemic WMLs, hemodynamic mechanisms) and brain mechanisms (e.g., total volume of brain tissue destroyed, location of infarcts, functional disconnection). It is not a disease entity *per se* (Erkinjuntti, Hachinski, & Sulkava, 1994). Some conceptualize it as a dementia syndrome emerging from multiple ischemic lesions of the brain (Hachinski, Lassen, & Marshall, 1974). This definition is founded on the concept of ischemic brain infarcts, which include large and small cortical and subcortical infarcts, lacunar infarcts, and dispersed "microinfarcts" in white matter (Erkinjuntti et al., 1994). However, other "noninfarct" factors are hypothesized to play a role

in vascular dementia. These factors include "incomplete infarcts" and functional inactivity of nerve cells resulting from ischemia, hypoperfusion, vessel-wall changes, and possible dysfunction of the oligodendrocytes (Erkinjuntti et al., 1994).

As indicated above, the concept of vascular dementia was largely predicated on the notion of multiple ischemic lesions of the brain. Emery and colleagues (Emery, Gillie, & Ramdev, 1994; Emery & Oxman, 1994) recently have argued that the term vascular dementia has been taken wrongly to be synonymous with multi-infarct dementia (MID). They emphasize that other causes of vascular dementia exist. They argue that while multiple infarcts can be considered a proximal cause of dementia, the arteriosclerotic process (which subsumes atherosclerosis) is a major vascular variable in the distal cause of vascular dementia. They point out that it is essentially true that infarcts do not come out of the blue (despite what the unfortunate terms *stroke* or cerebrovascular *accident* might imply) and that there are a series of pathologic processes which precede actual tissue infarction. These authors suggest the term *preinfarct state* to account for cognitive changes in patients with arteriosclerotic diseases in whom cerebral infarcts may or may not be demonstrated.

Emery et al. (1994) conducted a study designed to examine neuropsychological function in two groups of patients with vascular disorders, those with radiologically identified focal cerebral dysfunction (including either grey or white matter infarcts, TIAs, or reversible ischemic neurologic deficits; n=14) and those without evidence of cerebral infarction or stroke (n=17). Both groups consisted of patients with various vascular conditions, including atherosclerosis,

ischemic heart disease, hypertension/ hypotension, etc. Forty-five percent of the total vascular sample (n=31) had PVD, although this condition was not the primary focus of their study. These two vascular groups were compared with 20 age- and education-matched control subjects in terms of their performance on 23 tests of general mental status, language, and memory function. The authors found that the total vascular sample differed from the normal controls on the majority of mental status, language, and memory tests administered. More interestingly, however, when the two vascular subgroups were compared, no differences in neuropsychological test scores were found between the cerebral infarct and non-infarct vascular subgroups. In fact, a trend towards poorer neuropsychological function in the non-infarct group was observed. Emery et al. (1994) argued that general vascular disease variables (e.g., arteriosclerosis [including atherosclerosis], hypertension/ hypotension, ischemic heart disease) which cut across both subgroups could account for the cognitive impairments, especially in the absence of demonstrated cerebral infarction in the non-infarct group.

Support for the concept of a preinfarct state has been found in the animal literature. Sekhon, Morgan, Spence, and Weber (1994) used a model to assess the effects of chronic noninfarctional hypoperfusion on brain tissue. Their procedure involved an arteriovenous fistula that reduced global cerebral blood flow in rats by approximately 25% to 50% without an acute ischemic insult. The results demonstrated that long-term potentiation (a continued enhancement of synaptic efficiency following short, repetitive stimulation of afferent pathways which is considered to play a role in the coding of memory at a synaptic level) in rat

hippocampi was impaired after 6 months of chronic noninfarctional cerebral hypoperfusion. Sekhon et al. speculated that this might represent a category of chronic cerebral ischemia, one in which chronic hypoperfusion might lead to impaired neuronal function but without resulting in cerebral infarction.

See Figure 6 for a model of proposed distal and proximal causes of vascular-related cognitive impairment. This model is based in part on the arguments of Emery and colleagues. However, it also makes provision for the role of atherosclerotic risk factors (i.e., hypertension, diabetes, hyperlipidemia, smoking). In this model, tissue infarction is the most proximal direct cause of cognitive impairment. However, non-infarct factors, which include ischemia-related functional inactivity of neurons, can also have a direct deleterious effect on cognitive function. These factors may exert their power either prior to (the "pre-infarct state") or in the absence of actual tissue infarction. Lastly, atherosclerotic risk factors may themselves have a direct, albeit weak effect (dotted line) on cognitive function or a stronger, indirect effect through their role in atherogenesis.

As indicated above, the PVD patients studied here would not, as a group, meet criteria for the diagnosis of dementia, although some individual patients may have met these criteria. Nevertheless, it appears that more and more researchers in the area of cerebrovascular disease are moving away from the absolutism of infarcts being the only cause of vascular-related cognitive decline. In the absence of any definitive structural data on the brain integrity of PVD patients, the pre-infarct concept can be proposed to account for their neuropsychological deficits. It is possible that the deficits observed in PVD patients represent a vascular dementia

in statu nascendi. Only longitudinal study would answer this question.

Directions for Future Research

This series of studies raised a number of questions which should be addressed in future research. First, it is not yet known whether cognitive impairments in PVD amputees actually impede their progress in rehabilitation. It is possible that patients with severe cognitive deficits might require longer hospitalization or more intensive, specialized training. It is also possible that such a patient might require more follow-up contact with rehabilitation specialists in order to maintain prosthetic competence in the home environment. An analysis of which cognitive domains relate to rehabilitation competence is also warranted. The results of Study Three and previous research (e.g., Richardson et al., 1995) indicate that specific cognitive deficits (e.g., visuospatial, attention, and memory deficits) are strong predictors of everyday functions. It may also be the case that physical rehabilitation, which involves the learning or reprogramming of certain motor routines, is dependent upon certain cognitive processes usually not examined in neuropsychological assessments. For instance, preserved ability on procedural or motor skill learning tasks, such as a smooth-pursuit rotor task, could relate to success in rehabilitation, even in the presence of other neuropsychological deficits.

By identifying specifically which factors pose an impediment to rehabilitation, steps can be take to address and/ or circumvent the deficits during rehabilitation training. For example, it might be possible to develop a simple written manual or

visual chart for the care and maintenance of a prosthesis for a patient to take home with him/ her in order to circumvent poor memory ability. Or, by screening for cognitive function, patients with greater needs can be more thoroughly assessed and provided with additional support (e.g., scheduling more frequent follow-up clinic appointments; the training of and support by family members to assist in some aspects of rehabilitation at home). Also, as suggested by Study Three, research examining rehabilitation outcome and everyday functional outcome should also evaluate the potential role that depression may play.

Previous research has indicated that that atherosclerotic risk factors (hypertension, smoking, diabetes, hyperlipidemia) may have subtle negative effects on cognitive functioning. The present research may provide an alternate explanation. It was shown that symptomatic manifestations of clinical atherosclerotic disease (PVD severity and heart disease) were better predictors of cognitive impairment than were the risk factor *per se*. These results raise the interesting possibility that the presence of atherosclerotic symptoms such as PVD and ischemic heart disease, rather than being exclusionary factors, should be examined more closely in future studies of the neurobehavioural effects of medical conditions such as diabetes and hypertension. It is possible that the greatest impairments are found in patients with these risk factors who show clinical evidence of atherosclerosis.

The results also indicate that future studies of the neuropsychological morbidity of cerebral or coronary revascularization procedures should not employ PVD patients as normal, surgical controls.

Finally, the question remains as to whether PVD patients are suffering from early or prodromal brain changes that may, for some, lead to dementia. Subsequent research should attempt to determine the exact nature of the structural brain changes underlying cognitive decline (e.g., WMLs, cortical infarcts). The validity of the concept of a pre-infarct state should also be addressed through animal models of non-infarctional cerebral ischemia and by studying the natural history of cognitive function in patients with atherosclerosis.

Summary

In a series of studies, neuropsychological deficits were demonstrated in patients with PVD when compared with healthy age- and education-matched controls. Neuropsychological deficits were observed in the areas of attention and executive function in Studies One and Two, indicating that these are robust and replicable findings. These generalized cognitive impairments were of a magnitude similar to that demonstrated by patients with symptomatic cerebrovascular disease (Study Two). In terms of lateralized findings, Study Two demonstrated impairment in visuospatial ability in PVD patients as a group. Evidence of language and memory deficits were demonstrated on a individual basis in some patients. Thus, the nature and, in some instances, the magnitude of neuropsychological deficits were similar to those observed in age- and education-matched control patients with known cerebrovascular infarcts. The possible confounding role of depression was controlled in these studies. The results showed no or minimal evidence of depression in the PVD patients and in no instance was depressive symptomatology

related to cognitive performance.

The severity of PVD and the presence of ischemic heart disease, both indicators of generalized atherosclerosis, were significant negative predictors of variance in neuropsychological performance. These two factors each accounted for approximately 14% and 19%, respectively, of the variance in performance on certain neuropsychological tests. Atherosclerotic risk factors (hypertension, smoking, hyperlipidemia, diabetes) were not significantly related to cognitive performance. This finding indicates that cognitive impairment is strongly related to the presence of vascular disease in the body. It also suggests that the mild neuropsychological deficits found in previous studies of atherosclerotic risk factors might be related to their role in pathogenesis of atherosclerosis, rather than related to the negative effects of the risk factors *per se*.

In the absence of information demonstrating cerebrovascular lesions in these subjects, it was suggested that the presence of cognitive impairment in these patients with chronic atherosclerosis might represent a preinfarct state. These individuals may be in a prodromal stage of vascular dementia. However, this will be confirmed only by longitudinal study. It was also noted that the pattern of neuropsychological deficits demonstrated was not inconsistent with that observed in patient groups with subcortical pathologies. A potential mechanism for this, leukoaraiosis, was suggested. Again, further research must be conducted to solidify the relationship between leukoaraiosis and vascular risk factors and between leukoaraiosis and cognitive decline.

A third study showed that attention, memory, and visuospatial function, were

negatively related to ratings of greater dependence in complex everyday functions one year later after neuropsychological assessment. Longitudinal studies should also be conducted to elucidate the relative importance of neuropsychological deficits on the rehabilitation outcome and everyday functional outcome of vascular patients. Such research should consider specific neuropsychological domains, such as visuospatial function and procedural learning, and should include the assessment of affective factors as well.

Appendix A

Neuropsychological Test Description

Controlled Oral Word Association Test (COWAT). (Lezak, 1995). This test of spoken oral fluency involves a subject saying as many words as possible that begin with a designated letter (F, A, and S) or belong to a specified category ("animals") within 60 seconds. In the absence of aphasia, this test can be sensitive to lesions of either frontal lobe, although left frontal lesions tend to result in lower scores than do right sided lesions (Lezak, 1995). In this study, the orthographic category raw scores were adjusted according to sex, age, and education according to the conversion of Benton and Hamsher (1976; cited in Lezak, 1995) and the adjusted score was used in data analyses.

Wisconsin Card Sorting Test (WCST). (Heaton, 1981). This is a problem-solving test in which subjects must ascertain different strategies in card sorting and alternate amongst them on the basis of feedback from the examiner. It has been shown to be sensitive to the effects of frontal lobe lesions (e.g., Milner, 1963), although cautions have been raised about its localizing ability (Lezak, 1995; Mountain & Snow, 1993). Scores obtained and analysed were a) the number of categories completed (0 to 6), b) percentage of perseverative errors (in general, defined as an incorrect response which would have been correct in the preceeding category, divided by the total number of trials in the test), c) percent of conceptual level responses (defined as 3 or more correct responses divided by the total number of trials in the test), and d) failure to maintain set (defined as the number

of times five correct responses in a row are made but do not lead to completed category. More detailed scoring criteria are presented in Heaton (1981). The percentage of perseverative errors is considered to be the score which best discriminates between patients with frontal lesions and control subjects (Lezak, 1995).

Selected Subtests from the Wechsler Adult Intelligence Scale - Revised (WAIS-R). The following four tests were administered and scored according to the criteria set out by Wechsler (1981). Age-scaled scores were employed for statistical analyses, where the mean is 10 points and the *s.d.* is 3 points. Age-scaled scores were obtained from the WAIS-R manual (Wechsler, 1981) for subjects aged up to and including 74 years. For subjects aged 75 years and older, age scaled scores were obtained from Ryan, Paolo, and Brungardt (1990).

WAIS-R Picture Arrangement. (Wechsler, 1981). This is a test of reasoning ability in which a subject is presented with sets of cards in a scrambled order. He/ she must rearrange the cards to make a more logical story. Evidence indicates that, in general, patients with right-hemisphere lesions do more poorly on this test than do left-hemisphere damaged patients. However, the test is also considered to be particularly sensitive to right frontal lobe damage (McFie & Thompson, 1972).

WAIS-R Similarities. (Wechsler, 1981). This is a test of verbal abstract reasoning and concept formation in which a subject must explain what concept is common

between pairs of words.

WAIS-R Block Design. (Wechsler, 1981). This is a timed test of visuospatial organization and construction in which a subject must use blocks to replicate line-drawn patterns of increasing difficulty. Decreased scores tend to be observed in the presence of any kind of brain injury and are most pronounced with lesions involving parietal areas, particular on the right side (Lezak, 1995).

WAIS-R Digit Symbol. (Wechsler, 1981). This is a timed test requiring a subject to substitute symbols for digits. It calls upon visual attention and concentration. It is the most sensitive of the WAIS-R subtests to the presence of brain damage and tends to be affected regardless of the locality of the lesion (Lezak, 1995).

WAIS-R Digit Span, Forward and Backsward Spans. (Wechsler, 1981). In general, this test measures short-term storage capacity or attention span by having a subject immediately repeat, in a forward or backward order, a series of digits which he/ she had been read. Scoring the WAIS-R Digit Span according to the WAIS-R manual combines these two relatively different tests (i.e., forward and backward administrations) which measure different mental activities. Digit Span Forward taps the efficiency of attention or the passive span of apprehension, while Digit Span Backward requires working memory in that one must briefly store information in memory and manipulate it (Lezak, 1995). Combining performance on these two subtests into one scores obscures this important information. In the present study,

Digit Span performance is presented as the two raw scores (i.e., the maximum number of digits a subject correctly repeated under each condition).

Rey-Osterrieth Complex Figure, Copy Administration. (Rey, 1941; Osterrieth, 1944). In this test, the subject is required to copy a complex visual figure. Although a piecemeal approach in copying may be observed in patients with either left- or right-hemisphere lesions, copies by patients with right-sided lesions tend to be more distorted and less accurate than those made by patients with left-sided damage (Binder, 1982; cited in Lezak, 1995). Patients with frontal lesions tend to have a disorganized approach to the task (Pillon, 1981). Scoring criteria used in this study were those developed by L. Taylor, cited in Spreen and Strauss (1991); maximum number of points is 36.

Rey-Osterrieth Complex Figure Delayed Recall. (Rey, 1942; Osterrieth, 1944). This involves the unexpected requirement that the subject recall the Rey-Osterrieth Complex Figure by drawing it 30 minutes after having copied it. Patients with right-sided lesions tend to perform more poorly than those with left-sided damage (Lezak, 1995; Spreen & Strauss, 1991). Scoring criteria used were those developed by L. Taylor, cited in Spreen and Strauss (1991); maximum number of points is 36.

California Verbal Learning Test (CVLT). (Delis, Kramer, Kaplan, & Ober, 1987). This test of verbal memory involves learning a list of 16 "shopping list" items

belonging to one of four semantic categories presented over 5 trials. Measures include the number of items recalled on short-delay and long-delay (20 minutes) immediate and cued recall trials, plus a recognition trial and indices of semantic and serial clustering. Hermann, Wyler, Richey, and Rea (1987) have shown performance on this test to be impaired in patients with left temporal lobe seizures than in those with right-sided foci or normal controls.

In the present study, the four recall measures examined in the CVLT (short delay with free recall, short delay with cued recall, long delay with free recall, long delay with cued recall) were very highly correlated with each other (*R*'s ranged from 0.879 to 0.938). Thus, only one measure, the number of items recalled following a long delay with free recall (LDFR), was selected for most analyses. However, all four recall scores were used in the univariate comparisons in order to be able to detect any possible differences between the Controls and patients groups in their use of strategy or capacity for concept formation.

WAIS-R NI Spatial Span, Forward and Backward Span. (Kaplan, Fein, Morris, & Delis, 1991). This test is the visual analog of the Digit Span test and, as such, evaluates attention and immediate memory span and working memory in the visual domain. The subject must immediately recall, in forward and reversed orders according to condition, the correct sequence of blocks tapped. Visual Span performance is presented in the form of the two raw scores (i.e., the maximum number of blocks a subject correctly tapped, forward and backward order).

Graded Naming Test. (McKenna & Warrington, 1983). This is a confrontation naming task involving 30 black-and-white drawings which are arranged in order of increasing difficulty. It has been shown to be sensitive to left-hemisphere dysfunction (McKenna & Warrington (1983). Maximum score is 30 points.

Trail Making Test, Parts A and B. (Reitan & Davidson, 1974). These are tests of complex visual scanning, involving attention and motor speed. The dependent measure is the time taken to complete each part (in seconds). This test is sensitive to brain dysfunction, in general (Lezak, 1995). Part A involves simple visuomotor tracking; Part B is more difficult and requires that the subject attend to and alternate between two sequences. In the present study there were instances in which a subject failed to complete Part B due to an inability to maintain attention and tracking. In other words, the data were not actually missing randomly; instead, the failure probably reflected an impairment on the task *per se*. In such instances, the age-stratified norms provided by Spreen and Strauss (1991; page 328) were employed. The mean of normal control subjects performing at the 10th percentile (selected according to the patient's age) was substituted for that patient's score.

Groved Pegboard. (Reitan & Davidson, 1974). This test assesses manual dexterity and complex coordination. A subject must unimanually place 25 individual ridged pegs in slotted holes, using first the dominant hand, followed by the non-dominant hand. The dependent variable analysed here was the absolute

difference between the two hands in time to completion (in seconds).

Two-Point Discrimination. (e.g., Corkin, Milner, & Rasmussen, 1970). This assesses somatosensory function and is sensitive to post-central gyrus dysfunction. One point or two simultaneously applied points are placed on the palm of the hand. Over trials, the two points become increasingly close together. The threshold for the palm of each hand is the point at which the subject can no longer discriminate between the application of one versus two points. The dependent variable analysed here was the absolute threshold difference between the two hands (in cm).

National Adult Reading Test (NART). (Nelson, 1982). This reading test of irregularly pronounced words provides an estimate of pre-morbid intellectual ability. The dependent measure analysed in this study is the predicted WAIS Full Scale IQ, derived from the number of errors made on the test.

Beck Depression Inventory. (Beck & Steer, 1987; Appendix B). This is a widely accepted 21-item self-report assessment of depression during the week leading up to the assessment (e.g., Sadness, Sense of Failure, Insomnia, etc). The highest possible score is 63. Higher scores indicate greater depressive symptomatology. The large number of items tapping somatic symptoms (7 items) can prove problematic in persons with genuine physical complaints. This issue is addressed further in the Results and Discussion section.

Symptom Check List-90-Revised (SCL-90-R). (Derogatis, 1979; Appendix C). This is a simple self-report instrument designed to provide information on a subject's current psychological status, including the Global Severity Index, indicating the overall severity of general psychological distress, and nine primary psychological dimensions (i.e., Somatization, Depression, Anxiety, Obsessive Compulsive, Interpersonal Sensitivity, Hostility, Phobic Anxiety, Paranoid Ideation, Psychoticism). All raw scores can be converted to *T*-scores; the latter are reported here.

Cognitive Failures Questionnaire. (Broadbent, Cooper, FitzGerald, & Parkes, 1982; Appendix D). This is a 25-item self-report measure of failures in perception, memory, and motor function and appears to reflect a general liability to cognitive failure, rather than being sensitive to state changes. It is relatively independent of measures of intelligence, education level, and stress.

APPENDIX B- BDI (pages 149-150)

SCL-90-R

Appendix C

Name: _____ Technician: _____ Ident. No. _____

Location: _____ Visit No.: _____ Mode: S-R _____ Nar___

Age: _____ Sex: M _____ F _____ Date: _____ Remarks: _____

INSTRUCTIONS

Below is a list of problems and complaints that people sometimes have. Read each one carefully, and select one of the numbered descriptors that best describes HOW MUCH DISCOMFORT THAT PROBLEM HAS CAUSED YOU DURING THE PAST _____ INCLUDING TODAY. Place that number in the open block to the right of the problem. Do not skip any items, and print your number clearly. If you change your mind, erase your first number completely. Read the example below before beginning, and if you have any questions please ask the technician.

EXAMPLE

HOW MUCH WERE YOU DISTRESSED BY:

Ex. Body Aches..... Ex. [3]

Answer

Descriptors
0 Not at all
1 A little bit
2 Moderately
3 Quite a bit
4 Extremely

HOW MUCH WERE YOU DISTRESSED BY:

Descriptors
0 Not at all
1 A little bit
2 Moderately
3 Quite a bit
4 Extremely

1. Headaches.....
2. Nervousness or shakiness inside .....
3. Repeated unpleasant thoughts that won't leave your mind..
4. 'ntness or dizziness.....
5. Loss of sexual interest or pleasure .....
6. Feeling critical of others .....
7. The idea that someone else can control your thoughts ....
8. Feeling others are to blame for most of your troubles.....
9. Trouble remembering things .....
10. Worried about sloppiness or carelessness .....
11. Feeling easily annoyed or irritated .....
12. Pains in heart or chest .....
13. Feeling afraid in open spaces or on the streets .....
14. Feeling low in energy or slowed down .....
15. Thoughts of ending your life.....
16. Hearing voices that other people do not hear .....
17. Trembling.....
18. Feeling that most people cannot be trusted .....
19. Poor appetite .....
20. Crying easily .....
21. Feeling shy or uneasy with the opposite sex.....
22. Feelings of being trapped or caught.....
23. ddenly scared for no reason .....
24. Temper outbursts that you could not control.....
25. Feeling afraid to go out of your house alone.....
26. Blaming yourself for things .....
27. Pains in lower back .....
28. Feeling blocked in getting things done .....
29. Feeling lonely .....
30. Feeling blue .....
31. Worrying too much about things .....
32. Feeling no interest in things.....
33. Feeling fearful .....
34. Your feelings being easily hurt.....
35. Other people being aware of your private thoughts .....
36. Feeling others do not understand you or are unsympathetic .....
37. Feeling that people are unfriendly or dislike you.....
38. Having to do things very slowly to insure correctness ...
39. Heart pounding or racing.....
40. Nausea or upset stomach.....
41. Feeling inferior to others .....
42. Soreness of your muscles.....
43. Feeling that you are watched or talked about by others..
44. Trouble falling asleep .....
45. Having to check and doublecheck what you do .....
46. Difficulty making decisions .....
47. Feeling afraid to travel on buses, subways, or trains.....
48. Trouble getting your breath .....
49. Hot or cold spells .....
50. Having to avoid certain things, places, or activities because they frighten you .....
51. Your mind going blank .....
52. Numbness or tingling in parts of your body. .....

Appendix C (con't)

SCL-90-R

HOW MUCH WERE YOU DISTRESSED BY:	Descriptors: 0 Not at all, 1 A little bit, 2 Moderately, 3 Quite a bit, 4 Extremely	HOW MUCH WERE YOU DISTRESSED BY:	Descriptors: 0 Not at all, 1 A little bit, 2 Moderately, 3 Quite a bit, 4 Extremely
53. A lump in your throat	☐	71. Feeling everything is an effort	
54. Feeling hopeless about the future	☐	72. Spells of terror or panic	
55. Trouble concentrating	☐	73. Feeling uncomfortable about eating or drinking in public	
56. Feeling weak in parts of your body	☐	74. Getting into frequent arguments	
57. Feeling tense or keyed up	☐	75. Feeling nervous when you are left alone	
58. Heavy feelings in your arms or legs	☐	76. Others not giving you proper credit for your achievements	
59. Thoughts of death or dying	☐	77. Feeling lonely even when you are with people	
60. Overeating	☐	78. Feeling so restless you couldn't sit still	
61. Feeling uneasy when people are watching or talking about you	☐	79. Feelings of worthlessness	
62. Having thoughts that are not your own	☐	80. The feeling that something bad is going to happen to you	
63. Having urges to beat, injure, or harm someone	☐	81. Shouting or throwing things	
64. Awakening in the early morning	☐	82. Feeling afraid you will faint in public	
65. Having to repeat the same actions such as touching, counting, washing	☐	83. Feeling that people will take advantage of you if you let them	
66. Sleep that is restless or disturbed	☐	84. Having thoughts about sex that bother you a lot	
67. Having urges to break or smash things	☐	85. The idea that you should be punished for your sins	
68. Having ideas or beliefs that others do not share	☐	86. Thoughts and images of a frightening nature	
69. Feeling very self-conscious with others	☐	87. The idea that something serious is wrong with your body	
70. Feeling uneasy in crowds, such as shopping or at a movie	☐	88. Never feeling close to another person	
		89. Feelings of guilt	
		90. The idea that something is wrong with your mind	

Appendix D

Cognitive Failures Questionnaire

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to you in the last six months. Please circle the appropriate number.

		Very Often	Quite Often	Occasionally	Very Rarely	Never
1.	Do you read something and find you haven't been thinking about it and must read it again?	4	3	2	1	0
2.	Do you find you forget why you went from one part of the house to the other?	4	3	2	1	0
3.	Do you fail to notice signposts on the road?	4	3	2	1	0
4.	Do you confuse right and left when giving directions?	4	3	2	1	0
5.	Do you bump into people?	4	3	2	1	0
6.	Do you find you forget whether you've turned off a light or a fire or locked a door?	4	3	2	1	0
7.	Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
8.	Do you say something and realize afterwards that it might be taken as insulting?	4	3	2	1	0
9.	Do you fail to hear other people speaking to you when you are doing something else?	4	3	2	1	0
10.	Do you lose your temper and regret it?	4	3	2	1	0
11.	Do you leave important letters unanswered for days?	4	3	2	1	0
12.	Do you find you forget which way to turn on a road you know well but rarely use?	4	3	2	1	0
13.	Do you fail to see what you want in a supermarket (although it's there)?	4	3	2	1	0

		Very Often	Quite Often	Occasionally	Very Rarely	Never
14.	Do you find yourself suddenly wondering whether you've used a word correctly?	4	3	2	1	0
15.	Do you have trouble making up your mind?	4	3	2	1	0
16.	Do you find you forget appointments?	4	3	2	1	0
17.	Do you forget where you put something like a newspaper or a book?	4	3	2	1	0
18.	Do you find you accidentally throw away the thing you want and keep what you meant to throw away - as in the example of throwing away the matchbox and putting the used match in your pocket?	4	3	2	1	0
19.	Do you daydream when you ought to be listening to something?	4	3	2	1	0
20.	Do you find you forget people's names?	4	3	2	1	0
21.	Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	4	3	2	1	0
22.	Do you find you can't quite remember something although it's "on the tip of your tongue"?	4	3	2	1	0
23.	Do you find you forget what you came to the shops to buy?	4	3	2	1	0
24.	Do you drop things?	4	3	2	1	0
25.	Do you find you can't think of anything to say?	4	3	2	1	0

Appendix E

Functional Activities Questionnaire

The following pages list 10 common activities. For each activity, please read all the choices, then choose the *one* statement which best describes the *current* ability of the *participant* (the person who gave you this questionnaire). Your answers should apply to *that person's* abilities, *not your own*. Please be sure to read each option carefully, as they differ from question to question. Please check off a choice for *each* of the 10 activities; do not skip any.

Please indicate your relationship with the participant (e.g., spouse, son/ daughter, etc.):

_____

---

1. Writing checks, paying bills, balancing checkbooks, keeping financial records:

____ A. Someone other than the participant has recently taken over this activity completely or almost completely.
____ B. The participant requires frequent advice or assistance from others (for example, relatives, friends, business associates, banker), which was *not previously necessary*.
____ C. The participant does the activity without advice or assistance, but finds the task more difficult than used to be or does it less well.
____ D. The participant does the activity without any difficulty or advice.
____ E. The participant never did it and would find it quite difficult to start now.
____ F. The participant didn't do the activity regularly but could do it normally now with a little practice if they had to.

2. Making out insurance or government forms, handling business affairs or papers, assembling tax records:

____ A. Someone other than the participant has recently taken over this activity completely or almost completely.
____ B. The participant requires more frequent advice or more assistance from others than in the past.
____ C. The participant does without any more advice or assistance than he/ she used to, but finds the activity more difficult or does it less well than in the past.
____ D. The participant does the activity without any difficulty or advice.
____ E. The participant never did the activity and would find it quite difficult to start now, even with practice.
____ F. The participant didn't do it routinely, but could do it normally now if they had to.

3. Shopping alone for clothes, household necessities and groceries:

____ A. Someone has recently taken over this activity completely or almost completely.
____ B. The participant requires frequent advice or assistance from others.
____ C. The participant does the activity without advice or assistance, but finds it more difficult than he/ she used to or does it less well.
____ D. The participant does the activity without any difficulty or advice.
____ E. The participant never did this activity and would find it difficult to start now.
____ F. The participant didn't do this activity routinely but could do it normally now if they had to.

4. Playing a game of skill such as bridge, other card games or chess, or working on a hobby such as painting, photography, woodwork, stamp collecting, etc.:

____ A. The participant hardly ever does this now or has great difficulty doing it.
____ B. The participant requires advice, or others have to make allowances.
____ C. The participant does the activity without advice or assistance, but finds it more difficult or is less skillful than he/ she used to be.
____ D. The participant does the activity without difficulty or advice.
____ E. The participant never did this and would find it difficult to start now.
____ F. The participant didn't do this regularly, but could do it normally now if they had to.

5. Heating the water, making a cup of coffee or tea, and turning off the stove:

____ A. Someone other than the participant has recently taken over this activity completely, or almost completely.
____ B. The participant requires advice or has frequent problems (for example, burns pots, forgets to turn off stove).
____ C. The participant does this activity without advice or assistance, but has occasional problems.
____ D. The participant does this activity without difficulty or advice.
____ E. The participant never did this activity and would find it difficult to start now.
____ F. The participant didn't usually do this activity, but could do it normally now, if they had to.

6. Preparing a balanced meal (e.g., meat, chicken or fish, vegetables, dessert):

____ A. Someone other than the participant has recently taken over this activity completely or almost completely.
____ B. The participant requires frequent advice or has problems with the task (for example, he/ she forgets to make a given dish).
____ C. The participant does this activity without much advice or assistance, but finds it more difficult (for example, he/ she has switched to frozen dinners most of the time because of difficulty).
____ D. The participant does this without any difficulty or advice.
____ E. The participant never did this and would find it difficult to do so now even after a little practice.
____ F. The participant didn't do this regularly, but could do this normally now if they had to.

7. Keeping track of current events, either in the neighbourhood or nationally:

____ A. The participant pays no attention to and/ or doesn't remember current events.
____ B. The participant has some idea about *major* events (for example, he/ she comments on national elections, major events in the news, or major sporting events).
____ C. The participant pays somewhat less attention to or has somewhat less knowledge of current events than before.
____ D. The participant is as aware of events now as he/ she ever was.
____ E. The participant never paid much attention to current events, and would find it quite difficult to start now.
____ F. The participant never paid much attention to current events, but could do as well as anyone else now if they tried.

8. **Paying attention to, understanding, and discussing the plot or theme of a television program, book or magazine article:**

____ A. The participant doesn't remember or seems confused by what they have watched or read.
____ B. The participant is aware of the general idea, characters, or nature while they are watching or reading, but may not recall this later; may not grasp the theme or have an opinion about what they saw.
____ C. The participant pays less attention to or has a poorer memory for such things than before; he/ she is less likely to catch the humour or subtle points, or points which are made quickly.
____ D. The participant grasps plots or themes as quickly as ever.
____ E. The participant never paid much attention to or commented on T.V. or never read much before and would probably find it very difficult to start now.
____ F. The participant never read or watched T.V. much, but reads or watches as much as ever and gets as much out of it as ever.

9. **Remembering appointments, plans, household tasks, car repairs, family occasions (such as birthdays or anniversaries), holidays, medications:**

____ A. Someone other than the participant has recently taken this over.
____ B. The participant has to be reminded some of the time (more than in the past or more than most people).
____ C. The participant manages without being reminded but has to rely heavily on notes, calendars, schemes.
____ D. The participant remembers appointments, plans, occasions, etc. as well as he/ she ever did.
____ E. The participant never had to keep track of appointments, medications or family occasions, and would find it very difficult to start now.
____ F. The participant didn't have to keep track of these things in the past, but could do as well as anyone else should they try.

10. **Travelling out of the neighbourhood; driving, walking, arranging to take or change buses, trains, or planes:**

____ A. Someone other than the participant has taken this over completely or almost completely.
____ B. The participant can get around in his/ her own neighbourhood but gets lost if outside of the neighbourhood.
____ C. The participant has more problems getting around than he/ she used to (for example, occasionally gets lost, has trouble finding the car, has less confidence, etc.) but is usually OK with this activity.
____ D. The participant gets around as well as ever.
____ E. The participant rarely did much driving or, if he/ she had to get around alone, he/ she would find it quite difficult to learn bus routes or make similar arrangements now.
____ F. The participant didn't have to get around alone much in past, but could do as well as ever when he/ she has to.

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Table 1
Studies of Neurobehavioural Effects of Hypertension

Author	Study Sample	Factor(s) Studied	Function Studied	Findings (*Sig./N.S.*)	Comments/ Issues
Elias et al. (1987)	hypertensive Ss, high education (n=23; x̄ age = 44 yrs; x̄ education = 17 yrs) hypertensive Ss, lower education (n=31; x̄ age = 42 yrs; x̄ education = 13 yrs) normotensive Ss, high education (n=27; x̄ age = 41 yrs; x̄ education = 17 yrs) normotensive Ss, lower education (n=27; x̄ age = 45 yrs; x̄ education = 13 yrs)	hypertension status; level of education	general cognitive functioning (including the Average Impairment Index from the HRB, based on Digit Symbol, Categories, TPT Time, TPT Memory, TPT Localization, Trail Making Part B	no differences between highly educated hypertensive and normotensive Ss, but lower educated hypertensive Ss sig. worse than normotensive Ss on the Average Impairment Index, Categories Test, TPT Memory, TPT Localization lower-education hypertensives worse than higher-education hypertensives on Trail Making Part B	Ss excluded for evidence of CVD, cardiovascular disease, diabetes, etc.

Note: BP = blood pressure; CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; N.S. = not significant; RT = reaction time; Ss = subjects; sig. = significant; TIA = transient ischemic attack; TPT = Tactual Performance Test; WB = Wechsler Bellevue Scale; WMS = Wechsler Memory Scale. Unless otherwise noted, *N.S.* findings are omitted from the Table.

Table 1 (con't)

Franceschi et al. (1982)	newly diagnosed untreated hypertensives (HUT, n=17; $\bar{x}$ age = 35 yrs) treated hypertensives (HT, n=22; $\bar{x}$ age = 43 yrs) normotensive controls (n=15) matched for age and education	hypertension status; treatment status	Intellectual Function Learning and Memory Executive Function/ Reasoning Visuospatial Function Psychomotor Function	*Sig.*: Raven's Progressive Matrices: both HT and HUT worse than controls *Sig.*: WMS Memory Quotient, WMS Logical Memory Immediate: HT and HUT worse than controls; Benton Visual Retention Test: HT worse than controls *N.S.*: WMS Associates, WMS Logical Memory Delayed, WMS Visual Reproduction *Sig.*: Wisconsin Card Sorting Test, WB Picture Arrangement: HT worse than controls *N.S.*: WB Similarities *Sig.*: WB Block Design: HT & HUT worse than controls *N.S.*: WB Digit Symbol	patients excluded for diabetes and other medical conditions; vascular conditions not noted

Note: BP = blood pressure; CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; N.S. = not significant; RT = reaction time; Ss = subjects; sig. = significant; TIA = transient ischemic attack; TPT = Tactual Performance Test; WB = Wechsler Bellevue Scale; WMS = Wechsler Memory Scale. Unless otherwise noted, *N.S.* findings are omitted from the Table.

Table 1 (con't)

Light (1978)	Normal controls (n=52; age range 18-77 yrs) Untreated hypertensives (n=47; age range 18-77 yrs) Treated hypertensives (n=130; age range 18-77 yrs) Coronary heart disease (CHD, n=13; age range 37-77 yrs) TIA (n=10; age range 37-77 yrs) Stroke (n=19; age range 37-77 yrs)	vascular status; treatment status	Reaction time (RT; 2-, 3-, and 8-choice RT conditions)	Between groups: controls' RT faster than treated hypertensive, TIA, and stroke groups on all tasks; TIA and stroke groups slower than 3 cardiovascular groups; trend towards greater slowing in treated vs. untreated hypertensives	treated hypertensives required to discontinue medication 3-21 days prior to study and medicated during test to normalize BP

Note: BP = blood pressure; CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; N.S. = not significant; RT = reaction time; Ss = subjects; sig. = significant; TIA = transient ischemic attack; TPT = Tactual Performance Test; WB = Wechsler Bellevue Scale; WMS = Wechsler Memory Scale. Unless otherwise noted, *N.S.* findings are omitted from the Table.

Table 1 (con't)

Mazzucchi et al. (1986)	untreated, recently diagnosed, hypertensives (H1, n=20; $\bar{x}$ age=34 yrs) diet-treated, previously diagnosed (3-5 yrs) hypertensives (H2; n=20; $\bar{x}$ age = 35 yrs) drug-or-diet-treated, previously diagnosed (6-10 yrs) hypertensives (H3; n=20; $\bar{x}$ age = 39 yrs) normotensive controls (n=60), matched for age, education, and SES		Intellectual Function Learning and Memory Attention Visuospatial Psychomotor Language	*N.S.*: WAIS Information, WAIS Picture Completion *Sig.*: Figure Memory (Immediate and Delayed Recall), WMS Logical Memory (Immediate & Delayed Recall), Iconic Memory (neologisms); *N.S.*: List Learning, Maze Learning and Recall *Sig.*: WAIS Digit Span, WAIS Digit Symbol *Sig.*: WAIS Block Design, Gestalt *Sig.*: Finger Tapping (left hand) *N.S.*: Verbal Fluency	Type I error high; small subgroup of H3 patients on drug therapy performed better than patients on diet treatment; conclusion: no cognitive decline with disease duration, but the 3 groups not compared; exclusion: diabetes, general medical conditions

Note: BP = blood pressure; CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; N.S. = not significant; RT = reaction time; Ss = subjects; sig. = significant; TIA = transient ischemic attack; TPT = Tactual Performance Test; WB = Wechsler Bellevue Scale; WMS = Wechsler Memory Scale. Unless otherwise noted, *N.S.* findings are omitted from the Table.

Table 1 (con't)

Miller et al. (1984)	untreated hypertensives (HU; n=13; $\bar{x}$ age = 36; 7 females) treated hypertensives (HT; n=21; $\bar{x}$ age = 33; 11 females) normotensives (N; n=24); matched for age and education to their respective sex subsample Ss tested initially (Time 1) and 15 months later (Time 2)	hypertension status; treatment status	Sensory-Perception	Time 1: *Sig.*: Visual Recognition time: HT and HU worse than controls *N.S.*: Two-Flash Threshold, Perception of Spaced Stimuli, Critical Flicker Fusion Time 2: *Sig.*: Two-Flash Threshold: improvement in HT *N.S.*: Visual Recognition Time, Perception of Spaced Stimuli, Critical Flicker Fusion	Sex subsamples not matched for education or race (higher proportion of black females than black males; males more highly educated than females); exclusion criteria not indicated
			Memory	Time 1: *N.S.*: Memory for Designs Time 2: *N.S.*: Memory for Designs	
			Visuospatial Function	Time 1: *N.S.*: WAIS Block Design Time 2: *N.S.*: WAIS Block Design	

Note: BP = blood pressure; CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; N.S. = not significant; RT = reaction time; Ss = subjects; sig. = significant; TIA = transient ischemic attack; TPT = Tactual Performance Test; WB = Wechsler Bellevue Scale; WMS = Wechsler Memory Scale. Unless otherwise noted, *N.S.* findings are omitted from the Table.

Table 1 (con't)

			Time Estimation	Time 1: *Sig.*: hypertensive women worse than controls and hypertensive men Time 2: *Sig.*: improvement greater in HT women relative to all other groups	
			Psychomotor function	Time 1: *Sig.*: WAIS Digit Symbol, Finger Tapping: hypertensives worse than controls *N.S.*: Reaction Time, Grip Strength Time 2: *Sig.*: WAIS Digit Symbol, Finger Tapping: improvement greater in HT relative to other groups; Grip Strength: decline greater in HU relative to other groups *N.S.*: Reaction Time	

Note: BP = blood pressure; CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; N.S. = not significant; RT = reaction time; Ss = subjects; sig. = significant; TIA = transient ischemic attack; TPT = Tactual Performance Test; WB = Wechsler Bellevue Scale; WMS = Wechsler Memory Scale. Unless otherwise noted, *N.S.* findings are omitted from the Table.

Table 1 (con't)

Sands & Meredith (1992)	103 adults ($\bar{x}$ age = 55 at Time 2); Ss with diabetes, CVD, or other vascular diseases excluded; assessed twice, approximately 11 yrs apart	diastolic blood pressure (Time 1 and Time 2)	attention; performance on timed tasks considered to have a psychomotor component	WAIS-R Digit Span Forward: Time 1 BP (-), Time 2 BP (+), and medication status (+) correlate with Time 2 performance WAIS-R Digit Span Backward, Block Design, Digit Symbol, Object Assembly: no BP variables correlated with Time 2 performance	Ss well-educated, high IQs, therefore, results may not be generalizable
Schultz et al. (1989)	treated hypertensive adults without medical/vascular complications (HU, n=20; $\bar{x}$ age = 45 yrs at Time 1) treated hypertensive adults with medical/vascular complications (HC, n=5) normotensive controls (n=22; $\bar{x}$ age = 46 yrs at Time 1), matched for education subjects followed over two 5- to 6-year intervals	hypertension status	intellectual function	WAIS Verbal Scale: HU sig. different from normotensives at Times 2 and 3; in normotensives, sig. improvement in scores from Time 1 to Time 2, no change from Time 2 to 3; for HU only, no change over time; for HU & HC combined, sig. decline from Time 1 to Time 3 WAIS Performance Scale: no between (HU vs. control) or within group (HU only) differences; sig. decline in HC relative to HU	small subsample of complicated hypertensives (HC)

Note: BP = blood pressure; CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; N.S. = not significant; RT = reaction time; Ss = subjects; sig. = significant; TIA = transient ischemic attack; TPT = Tactual Performance Test; WB = Wechsler Bellevue Scale; WMS = Wechsler Memory Scale. Unless otherwise noted, *N.S.* findings are omitted from the Table.

Table 1 (con't)

Waldstein et al. (1991)	males with untreated, previously unidentified elevated blood pressure (EBP, n=20; $\bar{x}$ age = 43 yrs) normotensive male controls (n=20) matched for age, education, anxiety, lead exposure	hypertension status	Memory	*Sig.*: poorer performance of Ss with EBP on Symbol Digit Learning Test (Immediate Recall) and WMS Visual Reproductions (Immediate and Delayed Recall) *N.S.*: Symbol Digit Learning Test Delayed Recall	Ss recruited from lead-exposure study and unaware of hypertension status; Ss had only mild BP elevations

Note: BP = blood pressure; CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; N.S. = not significant; RT = reaction time; Ss = subjects; sig. = significant; TIA = transient ischemic attack; TPT = Tactual Performance Test; WB = Wechsler Bellevue Scale; WMS = Wechsler Memory Scale. Unless otherwise noted, *N.S.* findings are omitted from the Table.

Table 1 (con't)

Wilkie & Eisdorfer (1971)	adults aged 60-69 yrs at initial assessment: normal (n=31), borderline (n=10), or high blood pressure (n=10) adults aged 70-79 yrs at initial assessment: normal (n=28), or borderline-elevated (n=8) blood pressure all subjects free of CVD	hypertension status	Intellectual function (WAIS) assessed twice over a ten-year period	60-69 yr olds: *Sig.*: greater decline in PIQ in hypertensives relative to normotensives and borderlines; elevated BP correlated with decline in Verbal, Performance, and Full Scale weighted scores, and decline in Digit Span, Digit Symbol, Block Design, Object Assembly *N.S.*: no group differences in change in Verbal scale 70-79 yrs olds: *Sig.*: elevated BP sig. correlated with decline in verbal weighted scores *N.S.*: no group differences in change in WB scales	

Note: BP = blood pressure; CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; N.S. = not significant; RT = reaction time; Ss = subjects; sig. = significant; TIA = transient ischemic attack; TPT = Tactual Performance Test; WB = Wechsler Bellevue Scale; WMS = Wechsler Memory Scale. Unless otherwise noted, *N.S.* findings are omitted from the Table.

Table 1 (con't)

Wilkie et al. (1976)	Borderline hypertensives (n=10; $\bar{x}$ age = 68 at Time 1) Hypertensives (n=9; $\bar{x}$ age = 68 at Time 1) Normotensives (n=23) matched for age and SES Ss assessed initially (Time 1) and 6.5 yrs later (Time 2)	hypertension status	Memory (Wechsler Memory Scale)	Time 1: *N.S.*: Logical Memory (Immediate, Delayed), Associate Learning, Visual Reproduction Time 2: *Sig.*: Visual Reproduction: hypertensive Ss worse than borderline and control Ss *N.S.*: Logical Memory (Immediate, Delayed), Associate Learning	Some hypertensive patients showed signs of vascular-related end-organ change

Note: BP = blood pressure; CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; N.S. = not significant; RT = reaction time; Ss = subjects; sig. = significant; TIA = transient ischemic attack; TPT = Tactual Performance Test; WB = Wechsler Bellevue Scale; WMS = Wechsler Memory Scale. Unless otherwise noted, *N.S.* findings are omitted from the Table.

Table 2

Studies of Neurobehavioural Effects of Diabetes Mellitus

Author	Study Sample	Factor(s) Studied	Function Studied	Findings (*Sig./N.S.*)	Comments/ Issues
Bale (1973)	Type I diabetics (n= 100, $\bar{x}$ age = 48 yrs) controls (n=100) matched for age, sex, and social class	hypoglycemic history, disease duration, CVD	Verbal Learning and Memory	Walton Black Learning Task: greater proportion of patients with hypoglycemic episodes classified as impaired than patients without such history; no relationship with disease duration or CVD	
			Intelligence	evidence of deterioration (based on VIQ-PIQ discrepancy) found in 1 patient	

Note: CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; PIQ = performance IQ; sig. = significant; SES = socioeconomic status; N.S. = not significant; RT = reaction time; Ss = subjects; Trails A = Trail Making Test Part A; Trails B = Trail Making Test Part B; VIQ = verbal IQ; WAIS = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale, Revised; WMS = Wechsler Memory Scale. Unless otherwise noted, non-significant findings are omitted from the Table.

Table 2 (con't)

Author	Study Sample	Factor(s) Studied	Function Studied	Findings (*Sig./N.S.*)	Comments/ Issues
Francheschi et al. (1984)	Type I diabetics (n=37; $\bar{x}$ age = 26 yrs); hospitalized to achieve better metabolic control age-, education-, and SES-matched controls (n=26)	metabolic control (glycosylated hemoglobin, Schilintkrull Index); disease duration	Intellectual Function	*N.S.*: Raven's Progressive Matrices	young Ss
			Attention/ Concentration	*N.S.*: WAIS Digit Symbol, Konzentration Verlouls Test	
			Memory	*Sig.*: WMS Memory Quotient: diabetics worse than controls; *N.S.*: WMS: Logical Memory, Associative Learning, Visual Reproduction	
			Visuospatial Function	*Sig.*: WAIS Block Design: diabetics worse than controls; *N.S.*": Upside-Down Figures Test", Overlapping Figures Test	
			Problem Solving/ Reasoning	*Sig.*: WAIS Similarities	

Note: CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; PIQ = performance IQ; sig. = significant; SES = socioeconomic status; N.S. = not significant; RT = reaction time; Ss = subjects; Trails A = Trail Making Test Part A; Trails B = Trail Making Test Part B; VIQ = verbal IQ; WAIS = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale, Revised; WMS = Wechsler Memory Scale. Unless otherwise noted, non-significant findings are omitted from the Table.

Table 2 (con't)

Author	Study Sample	Factor(s) Studied	Function Studied	Findings (*Sig./N.S.*)	Comments/ Issues
Holmes (1986)	Type I diabetic males with good metabolic control (n=19; $\bar{x}$ age = 23) Type I diabetic males with poor metabolic control (n=8; $\bar{x}$ age = 21) groups matched for age, education, and SES	metabolic control (discrete: good vs. poor); age of onset; disease duration; glucose level during testing	Intellectual Function/ Academic Achievement	*Sig.*: WAIS Verbal IQ, and WAIS Information and Vocabulary subtests lower in poor control diabetics; lower scores in patients with early onset and poor control relative to other groups *N.S.*: WAIS Performance IQ, WRAT Math, Iowa Silent Reading Test Reading Comprehension	results not generalizable beyond males; young Ss
			Reaction Time (RT)	*Sig.*: slower simple RT in poor control diabetics *N.S.*: Go/NoGo RT, choice RT	
			Letter Recognition	no group differences	
			Finger Tapping	no group differences	

Note: CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; PIQ = performance IQ; sig. = significant; SES = socioeconomic status; N.S. = not significant; RT = reaction time; Ss = subjects; Trails A = Trail Making Test Part A; Trails B = Trail Making Test Part B; VIQ = verbal IQ; WAIS = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale, Revised; WMS = Wechsler Memory Scale. Unless otherwise noted, non-significant findings are omitted from the Table.

Table 2 (con't)

Author	Study Sample	Factor(s) Studied	Function Studied	Findings (*Sig./N.S.*)	Comments/ Issues
Meuter et al. (1980)	Type I diabetics (n=112; $\bar{x}$ age = 38) Type II diabetics (n=35; $\bar{x}$ age = 57) controls matched to each patient group according to age and education (n=112, n=35)	diabetes type	Speed of Reaction	both diabetic groups significantly worse than matched controls	
			Memory-Concentration	both diabetic groups significantly worse than matched controls; large group difference between Type II diabetics and controls	
			Visual Perception	no group differences	
			"quality of performance"	no group differences	

Note: CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; PIQ = performance IQ; sig. = significant; SES = socioeconomic status; N.S. = not significant; RT = reaction time; Ss = subjects; Trails A = Trail Making Test Part A; Trails B = Trail Making Test Part B; VIQ = verbal IQ; WAIS = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale, Revised; WMS = Wechsler Memory Scale. Unless otherwise noted, non-significant findings are omitted from the Table.

Table 2 (con't)

Author	Study Sample	Factor(s) Studied	Function Studied	Findings (*Sig./N.S.*)	Comments/ Issues
Perlmuter et al. (1984)	Type II diabetics (n=100; $\bar{x}$ age = 64 yrs); out-patients age- and education-matched normal controls (n=38)	disease duration; long-term (glycosylated hemoglobin) and short-term (fasting blood glucose) glucose control; peripheral neuropathy; autonomic neuropathy	Serial verbal learning task	Between groups: overall poorer recall in diabetics vs. controls (# of words recalled; # of trials to criterion) Within groups: measures of peripheral neuropathy and poor long-term glucose control associated with poorer memory performance	
			Attention/ immediate memory	Between groups: Forward Digit Span: no group differences Backward Digit Span: diabetics worse than controls Within groups: not examined	
			Simple reaction time	no group differences	

Note: CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; PIQ = performance IQ; sig. = significant; SES = socioeconomic status; N.S. = not significant; RT = reaction time; Ss = subjects; Trails A = Trail Making Test Part A; Trails B = Trail Making Test Part B; VIQ = verbal IQ; WAIS = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale, Revised; WMS = Wechsler Memory Scale. Unless otherwise noted, non-significant findings are omitted from the Table.

Table 2 (con't)

Author	Study Sample	Factor(s) Studied	Function Studied	Findings (*Sig./N.S.*)	Comments/ Issues
Prescott et al. (1990)	Type I diabetic adults (n=20; $\bar{x}$ age = 40); poor metabolic control Type I diabetic adults (n=20; $\bar{x}$ age = 40); good metabolic control groups matched on age, sex, social class, disease duration	metabolic control (discrete: good vs. poor; continuous: glycosylated hemoglobin); age of onset; disease duration; # of daily insulin injections; mean short-term blood sugar level	Memory: Free Recall of 5 lists of 10 concrete words and 5 lists of 10 abstract words	Between groups: no differences Within groups: sig. relationship between disease duration and recall of concrete words	no normal controls

Note: CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; PIQ = performance IQ; sig. = significant; SES = socioeconomic status; N.S. = not significant; RT = reaction time; Ss = subjects; Trails A = Trail Making Test Part A; Trails B = Trail Making Test Part B; VIQ = verbal IQ; WAIS = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale, Revised; WMS = Wechsler Memory Scale. Unless otherwise noted, non-significant findings are omitted from the Table.

Table 2 (con't)

Author	Study Sample	Factor(s) Studied	Function Studied	Findings (*Sig./N.S.*)	Comments/ Issues
Reaven et al. (1990)	Type II diabetics (n=29; $\bar{x}$ age = 70); rated by self to be in "reasonably good health" normal controls (n=30) matched for age and education	long-term glycemic control (glycosylated hemoglobin; HbA_{1c}); short-term glycemic control (fasting blood glucose, FBG); cardiovascular status;	Attention	*Sig.*: Trails A: diabetics worse than controls; sig. correlated with HbA_{1c}; Trails B: diabetics worse than controls; *N.S.*: WAIS-R Digit Span	no effect of presence of cardio-vascular disease on cognitive function
			Visuospatial Constructional	*N.S.*: WAIS-R Block Design	
			Memory	*Sig.*: California Verbal Learning Test (Recall, Trials 1-5): diabetics worse than controls; sig. correlated with HbA_{1c} and FBG	
			Executive Function/ Reasoning	*Sig.*: Wisconsin Card Sorting Test: diabetics worse than controls; sig. correlated with HbA_{1c} and FBG	
			Psychomotor Function	*Sig.*: WAIS-R Digit Symbol *N.S.*: Finger Tapping	
			Verbal Ability	*N.S.*: WAIS-R Vocabulary	

Note: CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; PIQ = performance IQ; sig. = significant; SES = socioeconomic status; N.S. = not significant; RT = reaction time; Ss = subjects; Trails A = Trail Making Test Part A; Trails B = Trail Making Test Part B; VIQ = verbal IQ; WAIS = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale, Revised; WMS = Wechsler Memory Scale. Unless otherwise noted, non-significant findings are omitted from the Table.

Table 2 (con't)

Author	Study Sample	Factor(s) Studied	Function Studied	Findings (*Sig./N.S.*)	Comments/ Issues
Robertson-Tchabo et al. (1986)	Type II diabetic males (n=52; $\bar{x}$ age = 62 yrs); 6 year follow-up data available on a subset of patients (n=31) age- and education-matched male case controls (n=52)	health status (decline relative to first assessment), analysis limited to the subset of available subjects	Verbal ability (WAIS Vocabulary)	No group differences	
			Visual memory (Benton Visual Retention Test)	No group differences at Time 1 Longitudinal change: no difference in rate of change (increase in errors) between patients and controls; exception: greater decline in a subset of patients who did not maintain previous good health	

Note: CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; PIQ = performance IQ; sig. = significant; SES = socioeconomic status; N.S. = not significant; RT = reaction time; Ss = subjects; Trails A = Trail Making Test Part A; Trails B = Trail Making Test Part B; VIQ = verbal IQ; WAIS = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale, Revised; WMS = Wechsler Memory Scale. Unless otherwise noted, non-significant findings are omitted from the Table.

Table 2 (con't)

Author	Study Sample	Factor(s) Studied	Function Studied	Findings (*Sig./N.S.*)	Comments/ Issues
Ryan & Williams (1993)	Type I adult diabetics (n=82; $\bar{x}$ age = 33 yrs) 82 age-, education-, and sex-matched controls	disease duration; metabolic control (glycosylated hemoglobin); retinopathy; peripheral neuropathy, history of severe hypoglycemia	Intelligence (WAIS-R)	Between Group: diabetics worse than controls on PIQ; Within Group: neuropathy and metabolic control scores inversely predict PIQ scores	young Ss
			Psychomotor Efficiency	Between Group: diabetics worse than controls on Boston Embedded Figures, Digit Vigilance, Grooved Pegboard (no differences on Trail Making Test); Within Group: no biomedical variables predicted psychomotor summary *z*-score	
			Learning and Memory	Between Group: no group differences on any measure (Verbal Paired Associate Learning, Symbol Digit Paired Associates, Four-Word Short-Term Memory Test, WMS Logical Memory, Rey Complex Figure)	

Note: CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; PIQ = performance IQ; sig. = significant; SES = socioeconomic status; N.S. = not significant; RT = reaction time; Ss = subjects; Trails A = Trail Making Test Part A; Trails B = Trail Making Test Part B; VIQ = verbal IQ; WAIS = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale, Revised; WMS = Wechsler Memory Scale. Unless otherwise noted, non-significant findings are omitted from the Table.

Table 2 (con't)

Author	Study Sample	Factor(s) Studied	Function Studied	Findings (*Sig./N.S.*)	Comments/ Issues
Skenazy & Bigler (1984)	39 Type I diabetics ($\bar{x}$ age = 30 yrs; 20 with visual impairment [D-VI], 19 without [D-nVI] 44 non-diabetic non-neurologic patient controls (PC; $\bar{x}$ age = 32 yrs) 24 healthy controls (NC; $\bar{x}$ age = 23 yrs)	index of disease severity based on: disease duration, hospitalizations (#), diabetic comas (#), hypoglycemic episodes (#), complications (#)	HRB; WAIS-R; WMS (22 neuropsych. variables in total)	<u>sig. group difference</u> D-nVI group worse than PC and NC on Performance IQ and Trails B; D-nVI worse than NC on the Category Test, Trails A; both diabetic groups impaired in grip strength from NC but not PC <u>sig. correlations in expected direction</u>: disease severity with Finger Oscillation, Trails A & B, Grip Strength, Visual Field Errors; disease duration with Trails A & B; insulin reactions with Performance IQ, Finger Oscillation, Trails A & B; diabetic coma with Finger Oscillation, Trails B, Grip Strength (dominant hand), Visual Field Errors	somatosensory deficits limited to male diabetics; relationship between disease severity and neuropsychological impairment inconsistent (several incidences of better performance in diabetics with more severe disease); high likelihood of Type I statistical error (approx. 66 statistical

Note: CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; PIQ = performance IQ; sig. = significant; SES = socioeconomic status; N.S. = not significant; RT = reaction time; Ss = subjects; Trails A = Trail Making Test Part A; Trails B = Trail Making Test Part B; VIQ = verbal IQ; WAIS = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale, Revised; WMS = Wechsler Memory Scale. Unless otherwise noted, non-significant findings are omitted from the Table.

Table 2 (con't)

Author	Study Sample	Factor(s) Studied	Function Studied	Findings (*Sig./N.S.*)	Comments/ Issues
U'Ren et al. (1990)	Type II diabetics (DM; n=19; $\bar{x}$ age = 70) Ss with previously unrecognized hyperglycemia (UH; n=9; $\bar{x}$ age = 70) normal controls (NC; n=19) matched for age and education all Ss screened for CVD, neurological and psychiatric disease		Attention	*Sig.*: Digit Span Forward; Serial Subtraction (Easy and Hard); Perceptual Speed Changing Target: DM worse than controls *N.S.*: Digit Span Backward; Symbol Digit Modalities Test	
			Verbal Learning and Memory	*Sig.*: Babcock Paragraph (Immediate and Delayed Recall); 4-Word Memory Test Spontaneous Recall: DM worse than controls	
			Language	*Sig.*: Vocabulary Recognition *N.S.*: COWAT/Oral Fluency	

Note: CVD = cerebrovascular disease; HRB = Halstead-Reitan Battery; PIQ = performance IQ; sig. = significant; SES = socioeconomic status; N.S. = not significant; RT = reaction time; Ss = subjects; Trails A = Trail Making Test Part A; Trails B = Trail Making Test Part B; VIQ = verbal IQ; WAIS = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale, Revised; WMS = Wechsler Memory Scale. Unless otherwise noted, non-significant findings are omitted from the Table.

Table 3

Studies of Neurobehavioural Effects of Smoking

Author	Study Sample	Function Studied	Findings (*Sig./N.S.*)	Comments/Issues
Andersson (1975)	male habitual smokers (n= 10; x̄ age = 22 yrs); all tested in both smoking and non-smoking sessions	Verbal learning of 25 nonsense syllables; delayed recall (45 min.)	poorer initial learning (immediate recall) but better delayed recall during smoking vs. non-smoking sessions	young subjects; small sample size
Andersson & Hockey (1977)	female habitual smokers (x̄ age = 26 yrs); divided into smoking (n=25) or non-smoking (n=25) experimental groups	Intentional and incidental memory on verbal learning task	better performance of non-smoking vs. smoking group on incidental memory task (word location) no group differences in intentional memory (overall # of words recalled)	young subjects
Carter (1974)	college students (x̄ age = 20 yrs; habitual smoking status unknown); divided into smoking (n=10) or non-smoking groups (n=10)	Letter-digit substitution, 20 trials administered twice 7 days apart Serial verbal learning	no group differences for Trials 1-10 during either administration; poorer performance of smoking group on Trials 11-20 for first administration only no group differences	young subjects; small sample size

Note: COWAT = Controlled Oral Word Association Test; sig. = significant; N.S. = not significant; Ss = subjects; WAIS-R = Wechsler Adult Intelligence Scale, Revised; WMS = Wechsler Memory Scale. Unless otherwise noted, non-significant findings are omitted from the Table.

Table 3 (con't)

Author	Study Sample	Function Studied	Findings (*Sig./N.S.*)	Comments/Issues
Hill (1989)	non-smokers (n=53, $\bar{x}$ age = 71 yrs) ex-smokers (n=12, $\bar{x}$ age = 70 yrs) smokers (n=11, $\bar{x}$ age = 74 yrs; not smoking during assessment) Ss tested initially and at 15 month follow-up	"problem solving" psychomotor speed memory attention visuospatial perception language	*N.S.*: WAIS-R Block Design, Trail Making Part A; both assessments *Sig.*: WAIS-R Digit Symbol, Cross Off; poorer performance of smokers vs. non-smokers at both assessments *N.S.*: WMS Logical Memory, WMS Associative Learning; both assessments *N.S.*: WAIS-R Digit Span, WMS Mental Control; both assessments *N.S.*: Bender Gestalt; both assessments *N.S.*: COWAT/Oral Fluency; both assessments	elderly subjects; matched for age, education, verbal IQ, blood pressure; screened for medical problems; small sample sizes in smoker and ex-smoker groups
Houston et al. (1978)	habitual smokers ($\bar{x}$ age = 24 yrs); divided into a nicotine (n=11) and non-nicotine (n=12) smoking groups; only 8 subjects from each group returned for 1-week follow-up	verbal learning and memory of 75-item list amenable to (spontaneous) semantic clustering of items; delayed recall tested 2 days later	significantly poorer immediate and delayed recall in nicotine group vs. non-nicotine group no group differences in semantic clustering	young subjects; small sample sizes, especially during delayed recall trial

Note: COWAT = Controlled Oral Word Association Test; sig. = significant; N.S. = not significant; Ss = subjects; WAIS-R = Wechsler Adult Intelligence Scale, Revised; WMS = Wechsler Memory Scale. Unless otherwise noted, non-significant findings are omitted from the Table.

Table 4

Study One
Summary of Demographic Factors (Means and [*S.D.*]s) and Number of Subjects (% of Sample) with Cerebrovascular Risk Factors

		PVD Amputees	Controls
Age		67.4 (14.8)	69.9 (9.3)
Education		10.3 (3.6)	11.9 (2.3)
Sex		4F, 10M	9F, 5M
Risk Factor			
Diabetes - Type I		5 (35.7%)	0
Diabetes - Type II		5 (35.7%)	0
Hypertension		6 (42.9%)	2 (14.3%)
Smoking:	Current	4 (28.3%)	2 (14.3%)
	Previous history	4 (28.3%)	3 (21.4%)
Hyperlipidaemia		2 (14.3%)	0
Obesity		1 (7.1%)	0

Table 5

Study One: Summary of *T*-tests of Neuropsychological Scores

Neuropsychological Test	Mean (Standard Deviation)		t^1	p
	PVD	Controls		
WAIS-R[2] Digit Span	9.4 (2.6)	11.6 (2.7)	-2.22	.0176
WAIS-R[2] Vocabulary	9.9 (2.6)	12.6 (2.4)	-2.64	.0069
WAIS-R[2] Arithmetic	8.9 (2.7)	11.7 (2.7)	-2.79	.0049
WAIS-R[2] Similarities	8.9 (2.7)	11.8 (3.1)	-2.69	.0062
WAIS-R[2] Picture Completion	10.8 (1.8)	11.6 (3.2)	-0.86	.1981
WAIS-R[2] Picture Arrangement	8.9 (2.6)	11.7 (2.8)	-2.70	.0060
WAIS-R[2] Block Design	8.6 (2.2)	11.1 (3.4)	-2.29	.0152
WAIS-R[2] Digit Symbol	9.0 (1.7)	12.2 (2.9)	-3.61	.0007
WMS-R[3] Logical Memory; Immediate	16.0 (6.5)	21.6 (7.1)	-2.16	.0200
WMS-R[3] Logical Memory; Delayed	11.8 (7.1)	17.9 (7.5)	-2.19	.0189
WMS-R[3] Visual Paired Associates; Immediate	8.8 (3.9)	11.2 (3.7)	-1.71	.0500
WMS-R[3] Visual Paired Associates; Delayed	4.1 (1.5)	5.0 (1.1)	-1.83	.0395
WMS-R[3] Verbal Paired Associates; Immediate - Total Score	15.3 (4.4)	18.9 (3.9)	-2.31	.0147
WMS-R[3] Verbal Paired Associates; Delayed - Total Score	6.2 (1.5)	7.1 (1.0)	-1.76	.0453
Recognition Memory for Words	45.3 (3.2)	47.1 (2.6)	-1.69	.0511
Recognition Memory for Faces	38.3 (3.9)	40.4 (5.1)	-1.25	.1107
Rey Complex Figure Copy	27.5 (6.3)	33.1 (3.9)	-2.79	.0049
Rey Complex Figure Delayed Recall	12.3 (6.0)	14.8 (8.4)	-0.91	.1859
Graded Naming Test	15.8 (4.7)	19.0 (5.1)	-1.72	.0483
Oral Fluency (Orthographic)	9.7 (3.8)	13.7 (4.4)	-2.57	.0082
Oral Fluency (Animal)	14.9 (4.2)	16.4 (3.6)	-1.01	.1642
Modified Card Sorting Task - # of Categories	3.9 (1.6)	5.6 (0.8)	-3.70	.0005

Table 5 (con't)

Modified Card Sorting Task - % Perseverative Errors	25.1 (15.3)	27.3 (16.2)	-0.36	.3599

[1] df=26; [2] WAIS-R: Wechsler Adult Intelligence Scale, Revised; [3] WMS-R: Wechsler Memory Scale, Revised.

Table 6

Study Two
Neuropsychological Tests Administered

Executive Function
- Wisconsin Card Sorting Test (Heaton, 1981)
- WAIS-R[1] Similarities (Wechsler, 1981)
- WAIS-R[1] Picture Arrangement (Wechsler, 1981)
- Rey-Osterrieth Complex Figure Copy (Lezak, 1983; Pillon, 1981)

Memory
- California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987)
- Rey-Osterrieth Complex Figure Delayed Reproduction (Lezak, 1983; Osterrieth, 1944)

Language Function
- COWAT[2]/Oral Fluency - FAS/Orthographic (Lezak, 1995)
- COWAT[2]/Oral Fluency - Category Naming (Animals; Lezak, 1995)
- Graded Naming Test (McKenna & Warrington, 1983)

Attention
- Trail Making Test, Parts A and B (Reitan & Davison, 1974)
- WAIS-R[1] Digit Symbol (Wechsler, 1981)
- WAIS-R[1] Digit Span (Wechsler, 1981)
- WAIS-R NI[3] Visual Span (Kaplan, Fein, Morris, & Delis, 1991)

Visuospatial, Constructional Ability
- WAIS-R[1] Block Design (Wechsler, 1981)
- Rey-Osterrieth Complex Figure Copy (Lezak, 1983; Osterrieth, 1944)
- WAIS-R[1] Digit Symbol (Wechsler, 1981)

Lateralizing Tests of Tactile and Motor Ability
- Grooved Pegboard (Reitan & Davison, 1974)
- 2-Point Discrimination

Affective and Cognitive Self-Report Measures
- Beck Depression Inventory (Beck & Steer, 1987)
- SCL-90-R; Symptom Check List-90, Revised (Derogatis, 1979)
- Cognitive Failures Questionniare (Broadbent, Cooper, FitzGerald, & Parkes, 1982)

Estimate of General Intellectual Ability
- National Adult Reading Test (Nelson, 1982)

[1] WAIS-R; Wechsler Adult Intelligence Scale, Revised.
[2] COWAT; Controlled Oral Word Association Test.
[3] WAIS-R NI; Wechsler Adult Intelligence Scale, Revised, as a Neuropsychological Instrument.

Table 7

Study Two
Summary of Means (and *S.D.*s) of Demographic Factors for PVD, CVD, and Normal Controls

	Non-Amputee PVDs (n=16)	Amputee PVDs (n=13)	Total PVDs (n=29)	CVDs (n=29)	Normal Controls (n=30)
Age	62.0 (10.5)	68.2 (11.7)	64.8 (11.3)	66.1 (9.7)	68.3 (6.2)
Education	11.4 (2.5)	10.6 (2.1)	11.0 (2.4)	11.7 (2.9)	12.1 (1.6)
Sex	5F, 11M	3F, 10M	8F, 21M	11F, 18M	16F, 14M

Table 8

Study Two
Coding[1] of Medical Variables for PVD Patients

Condition	Code	Description
Diabetes	0	none
	1	adult-onset, diet controlled
	2	adult-onset, insulin controlled
	3	juvenile onset
Hypertension	0	none
	1	controlled with 1 drug
	2	controlled with 2 drugs
	3	requires 2 or more drugs, or uncontrolled
Hyperlipidaemia	0	normal
	1	mild elevation, controlled by diet
	2	requires strict diet control
	3	requires diet and drug control

[1] Taken from Rutherford, et al. (1986).

Table 9

Study Two
Number (and Percentage) of Patients with Vascular Disease Risk Factor

Condition	Description	PVDs (n=16)		Amputees (n=13)	
Diabetes	none	10	(62.5)	2	(15.4)
	adult-onset, diet controlled	3	(18.8)	5	(38.5)
	adult-onset, insulin controlled	2	(12.5)	6	(46.2)
	juvenile onset	1	(6.3)	0	(0.0)
Hypertension	none	7	(43.8)	7	(53.8)
	controlled with 1 drug	5	(31.3)	4	(30.8)
	controlled with 2 drugs	0	(0.0)	2	(15.4)
	requires 2 or more drugs, or uncontrolled	4	(25.0)	0	(0.0)
Hyperlipidaemia	normal	10	(62.5)	10	(76.9)
	mild elevation, controlled by diet	3	(18.8)	1	(7.7)
	requires strict diet control	1	(6.3)	1	(7.7)
	requires diet and drug control	2	(12.5)	1	(7.7)
TIAs		9	(56.3)	3	(23.1)
Heart Disease		9	(56.3)	6	(46.2)

Table 10

Study Two
Clinical Categories [1] of Chronic Limb Ischemia or PVD

Category	Clinical Description
0	Asymptomatic - no hemodynamically significant occlusive disease
1	Mild Claudication
2	Moderate Claudication
3	Severe Claudication
4	Ischemic rest pain
5	Minor tissue loss - nonhealing ulcer, focal gangrene with diffuse pedal ischemia
6	Major tissue loss - extending above transmetatarsal level, functional foot no longer salvageable

[1] Taken from Rutherford, et al. (1986).

Table 11

Study Two
Summary of Means, *S.D.s*, Univariate *Fs*, and Tukey A Tests
for PVDs (n=29), CVDs (n=29), and Controls (n=30)

Neuropsychology Test	Mean (*S.D.*)			F^1	*p*	Tukey A
	PVD	CVD	CTRL			
Abstraction/Problem Solving						
WCST categories (#)	3.5 (2.0)	2.7 (1.9)	4.1 (1.7)	4.33	.0162	
WCST perseverative errors (%)	29.4 (19.5)	33.8 (18.6)	16.2 (9.0)	9.29	.0002	PVD & CVD < CTRL
WCST conceptual responses (%)	46.2 (23.9)	36.8 (19.1)	59.4 (18.7)	8.91	.0003	PVD & CVD < CTRL
WCST failure to maintain set	0.9 (1.3)	1.1 (1.0)	1.8 (1.4)	4.63	.0124	
WAIS-R Similarities	10.5 (2.9)	9.7 (3.1)	12.2 (2.3)	6.23	.0030	CVD < PVD & CTRL
WAIS-R Picture Arrangement	10.6 (2.7)	8.5 (3.2)	12.5 (2.9)	13.98	.0000	CVD < PVD < CTRL
Memory						
CVLT Short Delay Free Recall	8.5 (3.3)	6.6 (4.0)	10.6 (3.1)	10.10	.0001	CVD < PVD & CTRL
CVLT Short Delay Cued Recall	10.1 (3.2)	8.0 (3.3)	11.9 (2.4)	12.72	.0000	CVD < PVD & CTRL
CVLT Long Delay Free Recall	9.4 (3.2)	7.0 (4.0)	11.1 (2.8)	11.08	.0001	CVD < PVD & CTRL
CVLT Long Delay Cued Recall	10.0 (3.3)	7.9 (3.9)	11.9 (2.7)	10.53	.0001	CVD < PVD & CTRL
Rey-Osterrieth Figure Delay Recall	10.9 (5.1)	10.8 (5.7)	15.9 (5.7)	8.18	.0006	CVD & PVD < CTRL

[1] For 3-way comparisons, *d.f.* = 2, 85. For 2-way comparisons, *d.f.* = 1, 57.

Table 11 (con't)

Neuropsychology Test	Mean (*S.D.*)			F^1	*p*	Tukey A
	PVD	CVD	CTRL			
Attention						
WAIS-R Digit Span Forward	6.4 (1.1)	5.7 (1.1)	6.7 (1.5)	4.84	.0097	
WAIS-R Digit Span Backward	4.7 (1.2)	4.1 (1.1)	5.1 (1.3)	4.66	.0120	
Spatial Span Forward	5.4 (0.8)	4.9 (1.0)	5.5 (0.8)	4.25	.0173	
Spatial Span Backward	5.0 (1.1)	4.2 (1.1)	5.1 (0.9)	5.79	.0044	
Trails A (in sec)	52.0 (24.2)	75.7 (33.1)	40.0 (10.4)	16.39	.0000	CVD < CTRL & PVD
Trails B (in sec)	149.9 (102.4)	191.0 (102.7)	95.3 (32.0)	9.55	.0002	PVD & CVD < CTRL
WAIS-R Digit Symbol	10.0 (2.4)		12.6 (2.5)	17.19	.0001	PVD < CTRL
Language						
Graded Naming Test	17.9 (5.4)	14.4 (4.6)	20.3 (3.5)	12.71	.0000	CVD < PVD & CTRL
Oral Fluency (Orthographic)	44.5 (15.6)	30.9 (14.7)	51.1 (11.7)	15.83	.0000	CVD < PVD & CTRL
Oral Fluency (Semantic)	17.3 (4.9)	13.1 (6.0)	20.2 (6.0)	11.58	.0000	CVD < PVD & CTRL
Visuospatial/Constructional Abilities						
WAIS-R Block Design	9.5 (2.4)	8.4 (3.8)	12.3 (2.2)	14.50	.0000	CVD & PVD < CTRL
Rey-Osterrieth Figure Copy	25.1 (5.4)	23.8 (5.1)	29.8 (2.8)	14.03	.0000	CVD & PVD < CTRL

[1] For 3-way comparisons, *d.f.* = 2, 85. For 2-way comparisons, *d.f.* = 1, 57.

Table 11 (con't)

Neuropsychology Test	Mean (*S.D.*)			F^1	*p*	Tukey A
	PVD	CVD	CTRL			
Lateralizing Tests						
Grooved Pegboard (absolute difference)	27.4 (42.8)		12.6 (12.1)	3.40	.0703	
Two-Point Discrimination (absolute difference)	0.17 (0.23)		0.20 (0.20)	0.30	.5853	

[1] For 3-way comparisons, *d.f.* = 2, 85. For 2-way comparisons, *d.f.* = 1, 57.

Table 12

Study Two
Hierarchical Regression of Health Variables on
WAIS-R Picture Arrangement

Step	IV	*R* with DV Picture Arrangement	*B*	β	sr^2 (Incremental)
1	PVD	-0.11	-0.10	-.09	0.01
2	TIA	0.31	1.69	0.32	0.08
3	Heart Disease	-0.14	-1.21	-0.23	0.05
4	Hypertension	0.19	0.32	0.13	0.01
5	Pack Year	0.11	0.00	0.03	0.03
6	Lipid	-0.14	-0.56	-0.22	0.03
7	Diabetes	0.18	0.50	0.17	0.02
		Intercept =	10.34		
				R^2 =	.23
				Adjusted R^2 =	.00
				R =	.48

Table 13

Study Two
Hierarchical Regression of Health Variables on Rey-Osterrieth Figure Delayed Recall Administration

Step	IV	*R* with DV Rey Recall	*B*	β	sr^2 (Incremental)
1	PVD	-0.28	-0.17	-0.08	0.08
2	TIA	0.04	1.89	0.19	0.00
3	Heart Disease	-0.16	-1.83	-0.18	0.04
4	Hypertension	0.00	-0.28	-0.06	0.00
5	Pack Year	0.11	0.04	0.21	0.01
6	Lipid	-0.03	0.46	0.09	0.13
7	Diabetes	-0.43	-2.50	-0.45	0.00
		Intercept =	12.64		
				R^2 =	0.27
				Adjusted R^2 =	0.03
				R =	0.52

Table 14

Study Two
Hierarchical Regression of Health Variables on WCST Perseverative Errors

Step	IV	*R* with DV Perseverative Errors	*B*	β	sr^2 (Incremental)
1	PVD	0.38	3.26	0.40	0.15 *
2	TIA	-0.31	-7.02	-0.18	0.04
3	Heart Disease	0.26	16.02	0.42	0.14 *
4	Hypertension	-0.26	-3.23	-0.18	0.02
5	Pack Year	0.02	-0.01	-0.01	0.00
6	Lipid	-0.05	-0.62	-0.03	0.02
7	Diabetes	0.00	-3.37	-0.16	0.00
		Intercept =	19.41		
				R^2 =	0.36
				AdjustedR^2 =	0.15
				R =	0.60

* $p < .05$.

Table 15

Study Two
Hierarchical Regression of Health Variables on WCST Conceptual Responses

Step	IV	*R* with DV Conceptual Responses	*B*	β	sr^2 (Incremental)
1	PVD	-0.39	-3.14	-0.31	0.15 *
2	TIA	0.32	8.14	0.17	0.05
3	Heart Disease	-0.26	-20.54	-0.44	0.14 *
4	Hypertension	0.43	8.08	0.36	0.10
5	Pack Year	-0.09	0.03	0.03	0.00
6	Lipid	0.13	2.87	0.12	0.00
7	Diabetes	-0.09	1.08	0.04	0.00
		Intercept =	53.65		
				R^2 =	0.45
				Adjusted R^2 =	0.27
				R =	0.67

* $p < .05$.

Table 16

Study Two
Hierarchical Regression of Health Variables on Trail Making Part B

Step	IV	*R* with DV Trail Making B	*B*	β	sr^2 (incremental)
1	PVD	0.10	2.96	0.07	0.01
2	TIA	0.03	-5.83	-0.03	0.00
3	Heart Disease	0.52	118.70	0.59	0.29 *
4	Hypertension	0.02	0.03	0.00	0.00
5	Pack Year	0.20	-0.20	-0.06	0.02
6	Lipid	-0.20	-36.11	-0.36	0.07
7	Diabetes	0.27	21.71	0.20	0.03
		Intercept =	89.07		
				R^2 =	0.42
				AdjustedR^2 =	0.23
				R =	0.65

* $p < .05$.

Table 17

Study Two
Hierarchical Regression of Health Variables on WAIS-R Digit Symbol

Step	IV	*R* with DV Digit Symbol	*B*	β	sr^2 (Incremental)
1	PVD	-0.34	-0.29	-0.28	0.12 *
2	TIA	0.28	0.33	0.07	0.03
3	Heart Disease	-0.37	-2.84	-0.60	0.22 *
4	Hypertension	0.27	0.51	0.22	0.03
5	Pack Year	-0.22	0.01	0.15	0.03
6	Lipid	0.46	1.43	0.61	0.22 *
7	Diabetes	-0.13	-0.02	-0.01	0.00
		Intercept =	10.57		
				R^2 =	0.65
				Adjusted R^2 =	0.53
				R =	0.80 *

* $p < .05$.

Table 18

Study Two
Hierarchical Regression of Health Variables on WAIS-R Block Design

Step	IV	*R* with DV Block Design	*B*	β	sr^2 (Incremental)
1	PVD	-0.31	-0.18	-0.18	0.10
2	TIA	0.21	0.89	0.19	0.01
3	Heart Disease	-0.33	-2.15	-0.46	0.17 *
4	Hypertension	0.33	0.68	0.31	0.07
5	Pack Year	0.10	0.02	0.22	0.02
6	Lipid	-0.03	0.20	0.09	0.01
7	Diabetes	-0.19	-0.31	-0.12	0.00
		Intercept =	9.76		
				R^2 =	0.39
				Adjusted R^2 =	0.18
				R =	0.62

* $p < .05$.

Table 19

Study Two
Hierarchical Regression of Health Variables on Rey-Osterrieth Figure Copy Administration

Step	IV	*R* with DV Rey Copy	*B*	β	sr^2 (Incremental)
1	PVD	-0.29	-0.84	-0.37	0.08
2	TIA	-0.06	-0.67	-0.06	0.03
3	Heart Disease	-0.44	-4.82	-0.46	0.22 *
4	Hypertension	-0.04	-0.44	-0.09	0.00
5	Pack Year	-0.35	-0.05	-0.27	0.12 **
6	Lipid	0.16	0.69	0.13	0.01
7	Diabetes	-0.32	-0.56	-0.10	0.01
			Intercept =	33.14	
				R^2 =	0.46
				Adjusted R^2 =	0.28
				R =	0.68

* $p < .05$.
** trend: $p < .01$.

Table 20

Study Two
Summary of Means, *S.D.*s and Univariate *F*s for
Left-Hemisphere (n=14) and Right-Hemisphere (n=15) CVD Patients

Variable	Mean (*S.D.*)		*F*(1,27)[1]
	Left	Right	
Age	66.6 (9.6)	65.7 (10.1)	
Education	12.4 (2.7)	11.1 (3.0)	
Graded Naming Test	13.3 (4.9)	15.4 (4.1)	1.58
COWAT[2] Oral Fluency (FAS/Orthographic)	26.6 (13.4)	34.9 (15.1)	2.43
COWAT[2] Oral Fluency (Animal/Semantic)	12.6 (5.9)	13.6 (6.2)	0.18
CVLT[3] Long Delay Free Recall	6.4 (4.3)	7.6 (3.8)	0.69
WAIS-R[4] Block Design	9.5 (3.6)	7.4 (3.9)	2.11
Rey-Osterrieth Figure Copy	25.2 (3.7)	22.4 (6.1)	2.17
Rey-Osterrieth Figure Delay Recall	12.2 (6.1)	9.5 (5.3)	1.60

1 Critical $F = 4.22$.
2 COWAT, Controlled Oral Word Association Test.
3 CVLT, the California Verbal Learning Test.
4 WAIS-R, the Wechsler Adult Intelligence Scale, Revised.

Table 21

Study Two
Summary of Means, *S.D.*s and Univariate *F*s for PVDs Classified as Showing a "Left-Hemisphere" (n=10) and "Right-Hemisphere" (n=19) Neuropsychological Pattern on the Basis of Discriminant Function Analyses

Variable	Mean (*S.D.*)		*F*(1,27)	*p*
	"Left"	"Right"		
Age	64.7 (10.7)	64.8 (11.9)	0.00	0.975
Education	10.0 (2.6)	11.6 (2.1)	3.18	0.086
Graded Naming Test	14.1 (5.7)	19.9 (4.0)	10.34	0.003
COWAT[1] Oral Fluency (FAS/Orthographic)	34.7 (7.8)	49.7 (16.4)	7.35	0.012
COWAT[1] Oral Fluency (Animal/Semantic)	17.1 (5.5)	17.4 (4.7)	0.03	0.871
CVLT[1] Long Delay Free Recall	8.6 (2.9)	9.8 (3.3)	0.94	0.342
WAIS-R[2] Block Design	9.3 (2.4)	9.6 (2.4)	0.13	0.724
Rey-Osterrieth Figure Copy	24.8 (4.7)	25.3 (5.8)	0.08	0.784
Rey-Osterrieth Figure Delay Recall	9.6 (3.7)	11.7 (5.6)	1.07	0.309

1 COWAT, Controlled Oral Word Association Test.
2 CVLT, the California Verbal Learning Test.
3 WAIS-R, the Wechsler Adult Intelligence Scale, Revised.

Table 22

Study Two
Summary of means, *s.d.*, and ANOVAs of Tests Sensitive to Frontal Lobe Function
In Amputee PVDs (n=13), Frontal CVDs (n=8), and Non-Frontal CVDs (n=20)

Neuropsychology Test	Mean (*S.D.*)			F^1	*p*
	Amputee PVDs	Frontal CVDs	Non-Frontal CVDs		
WCST[2] # of categories	2.5 (0.4)	2.1 (0.7)	2.5 (0.4)	0.21	.8111
WCST[2] perseverative errors	38.2 (4.8)	42.1 (9.2)	37.5 (5.7)	0.13	.8764
WAIS-R[3] Similarities	9.6 (0.9)	9.3 (0.8)	9.5 (0.6)	0.05	.9490
WAIS-R[3] Picture Arrangement	10.1 (0.6)	8.1 (1.5)	7.6 (0.4)	3.08	.0608
COWAT[4]/Oral Fluency (FAS/Orthographic)	31.2 (1.2)	26.1 (1.1)	22.5 (1.4)	1.45	.2495
COWAT[4]/Oral Fluency (Animal/Semantic)	16.8 (1.0)	13.9 (2.0)	10.8 (1.9)	3.80	.0339
Rey-Osterrieth Figure Copy	23.2 (1.4)	21.5 (2.4)	23.8 (1.0)	0.53	.5961

1 *d.f.* = 2, 30.
2 WCST, the Wisconsin Card Soring Task.
3 WAIS-R, the Wechsler Adult Intelligence Scale, Revised.
4 COWAT, Controlled Oral Word Fluency Test

Table 23

Study Two
Summary of Means, *s.d.*, and ANOVAs of Affective and Cognitive Measures

Measure	Mean (*S.D.*)				*F*(3,64)
	Amputee PVD (n=9)	Non-Amputee PVD (n=16)	CVD (n=16)	CTRL (n=30)	
BDI[2]	12.7 (7.2)	6.8 (4.2)	7.8 (6.1)	5.3 (4.0)	4.85
BDI - Alternate[3]	8.0 (5.5)	4.6 (3.5)	5.1 (4.3)	3.5 (2.8)	3.31
CFQ[4]	32.3 (14.3)	38.5 (14.3)	35.8 (12.0)	36.0 (10.5)	0.46
SCL-90-R[5]:					
Global Symptom Index (GSI)	58.0 (9.8)	53.7 (8.6)	55.3 (5.4)	50.8 (8.2)	2.03
Somatization	59.1 (11.3)	56.4 (9.6)	59.0 (7.2)	48.8 (10.9)	4.53
Depression	62.0 (10.2)	53.7 (8.5)	56.9 (5.8)	50.0 (10.9)	4.16
Obsessive-Compulsive	60.6 (14.7)	55.1 (10.6)	56.2 (9.6)	53.5 (8.4)	0.87
Interpersonal Sensitivity	54.8 (11.5)	50.6 (10.2)	50.8 (7.0)	47.7 (7.4)	1.68
Anxiety	55.4 (11.1)	49.0 (8.9)	52.5 (7.9)	44.8 (7.5)	4.76
Hostility	52.1 (10.2)	48.5 (9.0)	51.4 (6.6)	45.3 (7.5)	2.56
Phobic Anxiety	52.1 (11.9)	52.1 (8.0)	47.9 (5.2)	49.0 (6.6)	1.04
Paranoid Ideation	53.1 (11.4)	48.2 (7.1)	44.9 (10.6)	49.1 (7.8)	1.50
Psychoticism	60.3 (3.3)	52.4 (8.5)	54.6 (7.6)	49.6 (7.3)	2.14

Table 23 (con't)

1 *df* = 3, 64.
2 Beck Depression Inventory.
3 Beck Depression Inventory, items 14, 15, 16, 19, and 20 omitted.
4 Cognitive Failures Questionnaire.
5 Symptom Check List 90 - Revised.

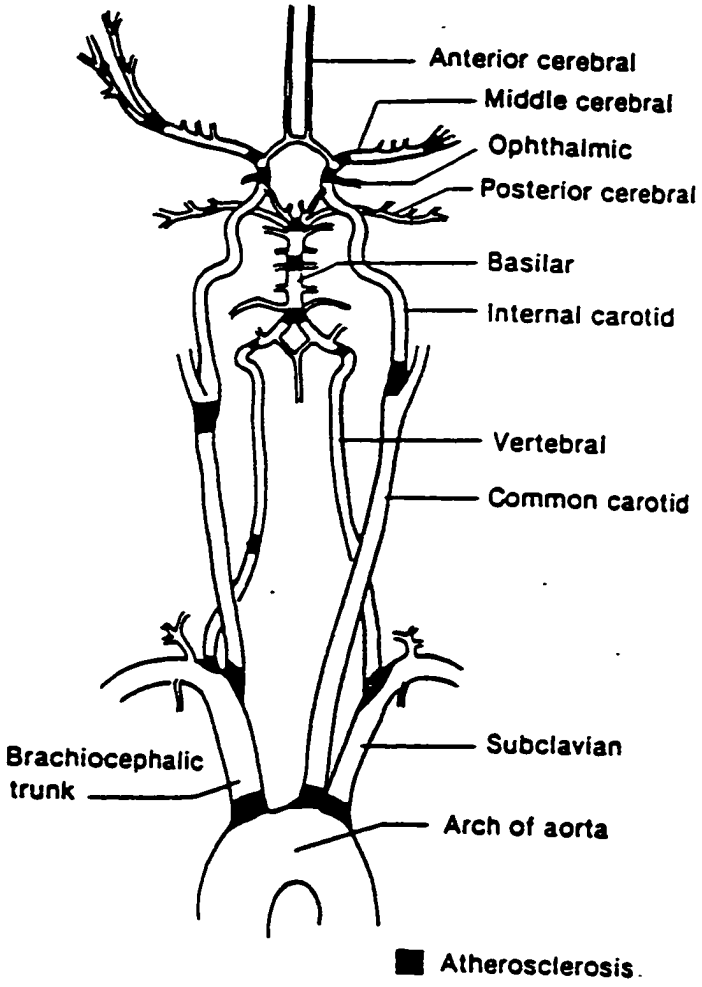


Figure 1. Sites of predilection for atherosclerotic plaques in aortocranial arteries (adapted from Şundt et al., 1994).

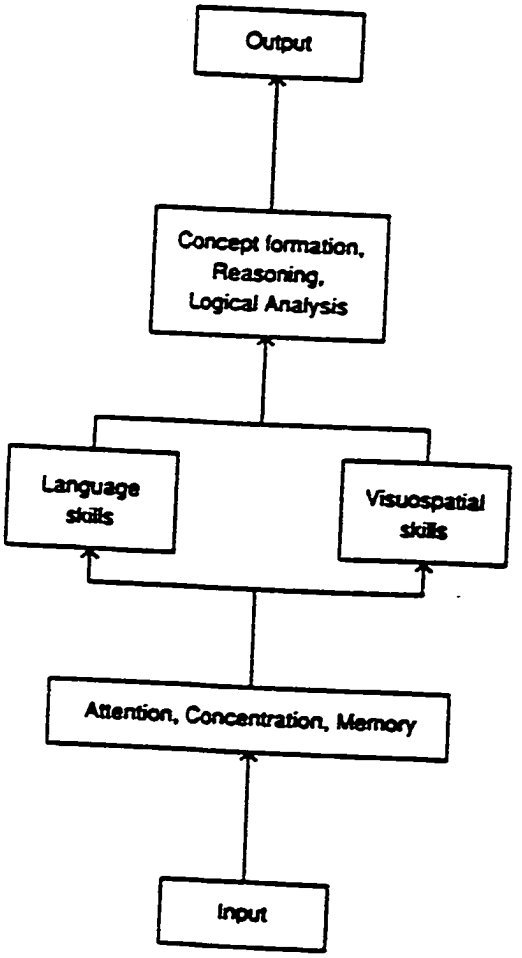


Figure 2: Reitan-Wolfson conceptual model of brain-behaviour relations (from Reitan & Wolfson, 1985).

Figure 3. The percentage of Cluster 1 (Non-Impaired) and Cluster 2 (Impaired) constituted by Normal Control (n=30), Non-Amputee PVD (n=16), Amputee PVD (n=13), and CVD (n=29) subjects.

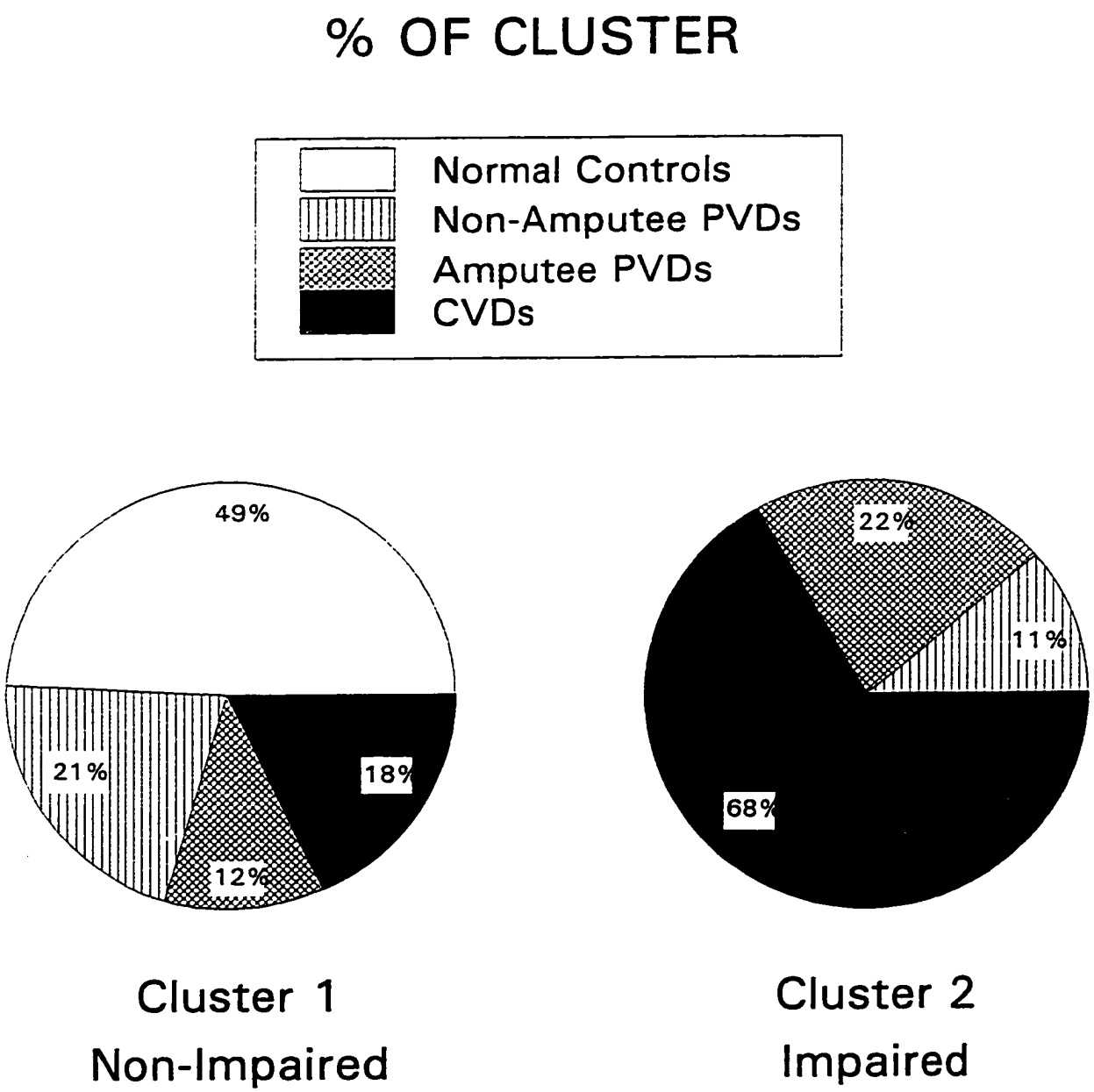
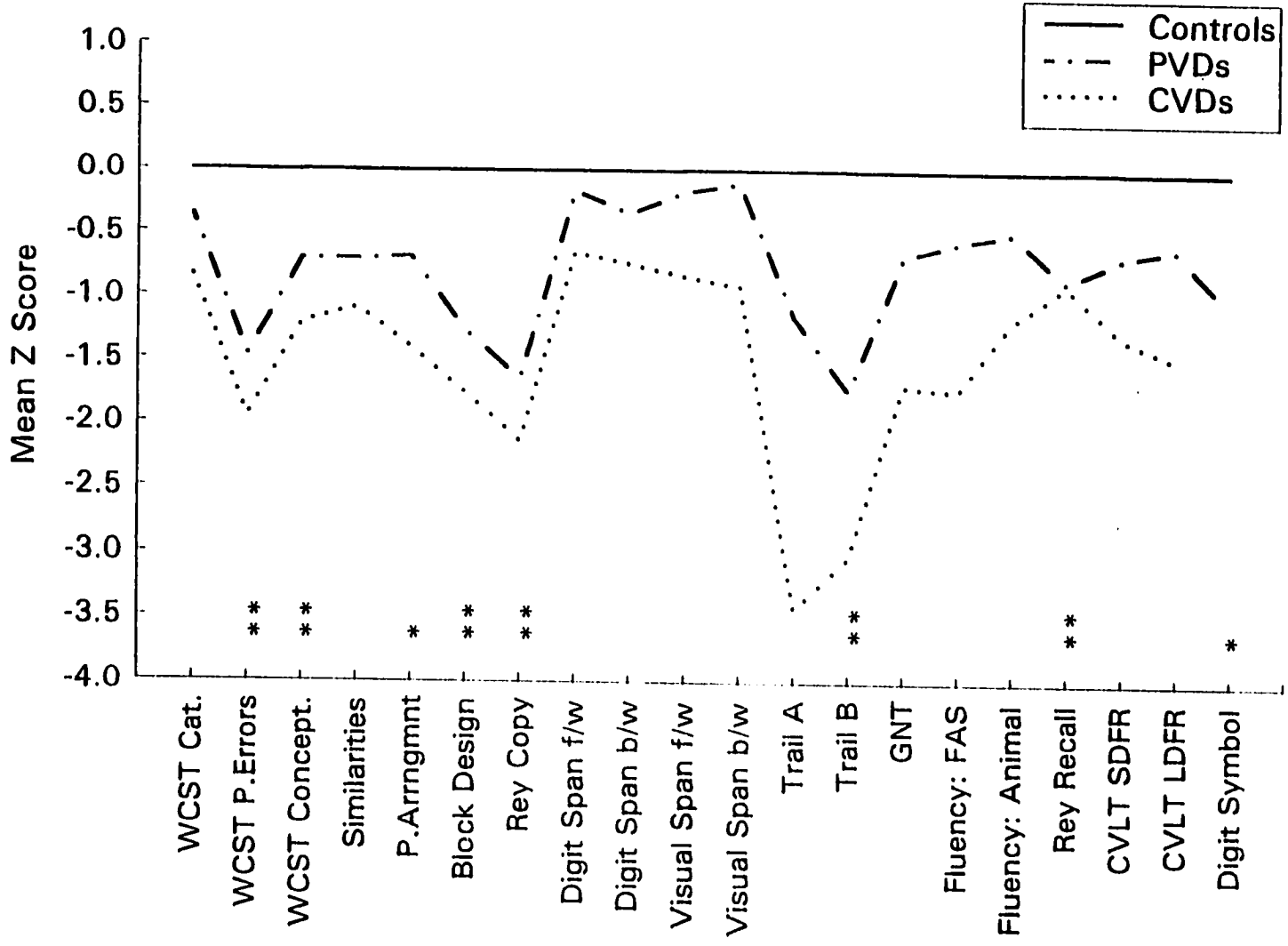

% OF CLUSTER
Normal Controls
Non-Amputee PVDs
Amputee PVDs
CVDs
49%
21%
12%
18%
22%
11%
68%
Cluster 1
Non-Impaired
Cluster 2
Impaired

Figure 4. Mean *z*-scores for Normal Controls (——), PVD (-·-·-·-), and CVD (····) subjects for each neuropsychological test. Tests on which PVD subjects differed from Controls are indicated by *. Tests on which PVD and CVD subjects differed from Controls, but not from each other are indicated by **. The number of Amputee and Non-amputee PVDs (and total % of PVD sample) falling in the bottom 5% of the distribution of Normal Control scores (i.e., $z \leq -1.645$) is indicated beneath each test.

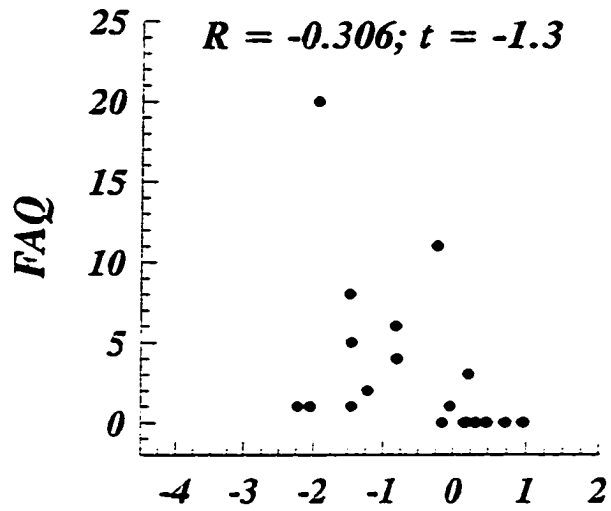
Note: b/w = backwards; Cat. = number of categories; Concept. = Conceptual Responses; CVLT = California Verbal Learning Test; f/w = forwards; GNT = Graded Naming Test; LDFR = long delay, free recall; P.Arrngmnt = WAIS-R Picture Arrangement; P.Errors = Perseverative Errors; Rey = Rey-Osterrieth Complex Figure; SDFR = short delay, free recall; Trail = Trail Making Test; WCST = Wisconsin Card Sorting Test.

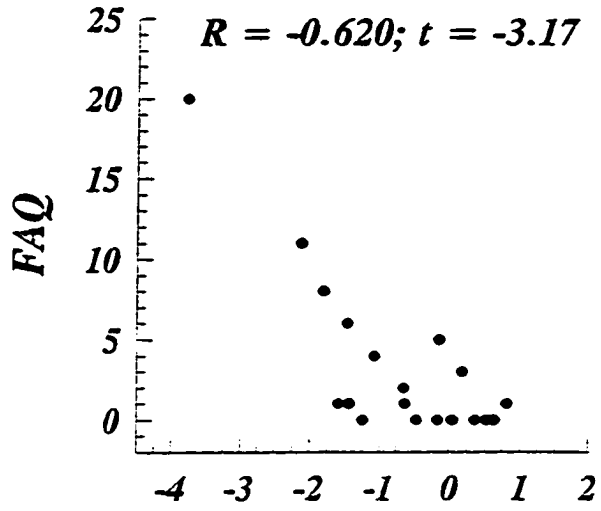


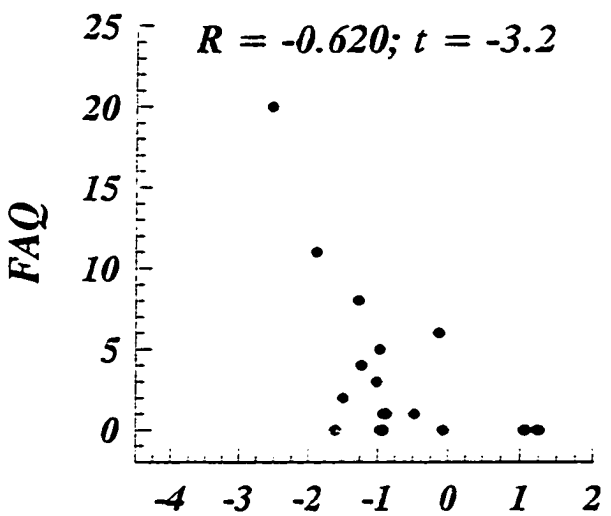
# of PVDs below z <-1.645

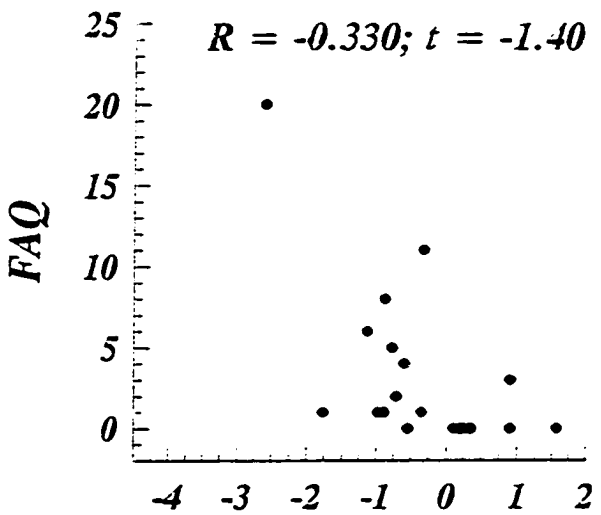
Non-amputees:	2	4	3	3	3	5	4	0	0	1	1	3	4	3	1	3	3	1	2	2
Amputees:	1	8	4	3	1	6	10	1	0	2	1	6	5	4	3	1	2	2	2	3
% total:	10	41	24	21	14	38	48	3	0	10	7	31	31	24	14	14	17	10	14	17

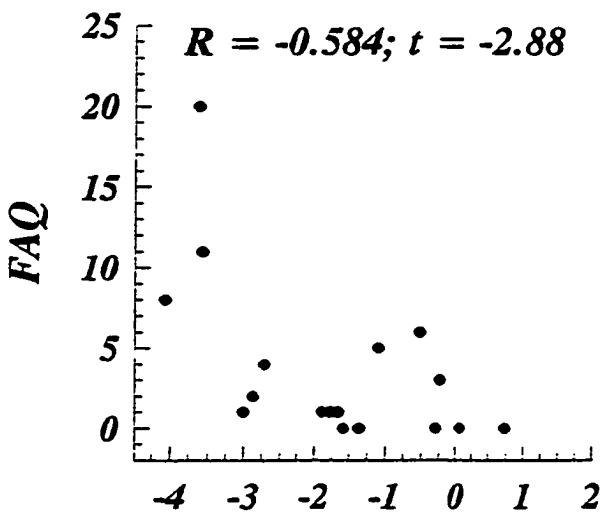
Figure 5. Scatter plots of the relationship between one-year functional outcome (FAQ) of PVD patients and composite neuropsychological function (mean *z*-score) in five neuropsychological domains: Frontal/ Executive Function, Attention, Memory, Verbal, and Visuospatial. After correction for an outlier, FAQ scores were significantly negatively correlated ($d.f. = 16$, $p < .01$) with performance in the Attention, Memory, and Visuospatial domains.


R = -0.306; t = -1.3
FAQ
25
20
15
10
5
0
-4 -3 -2 -1 0 1 2
Mean Z-Score: Frontal


R = -0.620; t = -3.17
FAQ
25
20
15
10
5
0
-4 -3 -2 -1 0 1 2
Mean Z-Score: Attention


R = -0.620; t = -3.2
FAQ
25
20
15
10
5
0
-4 -3 -2 -1 0 1 2
Mean Z-Score: Memory


R = -0.330; t = -1.40
FAQ
25
20
15
10
5
0
-4 -3 -2 -1 0 1 2
Mean Z-Score: Verbal


R = -0.584; t = -2.88
FAQ
25
20
15
10
5
0
-4 -3 -2 -1 0 1 2

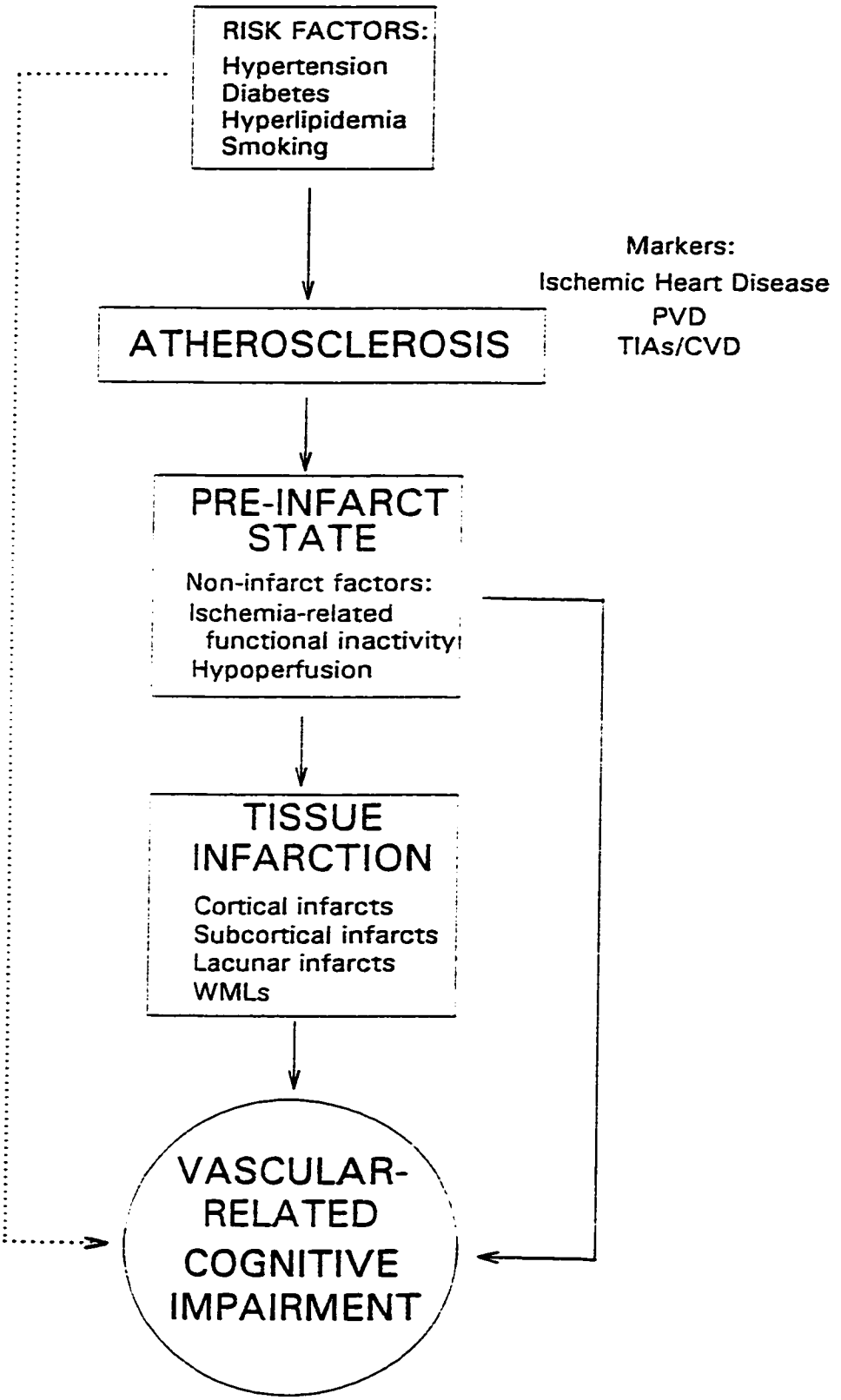


Figure 6. Model of distal and proximal causal effects on vascular-related cognitive impairment. CVD = cerebrovascular disease; PVD = peripheral vascular disease; TIAs = transient ischemic attacks; WMLs = white matter lesions.