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**FRONTAL LOBE DYSFUNCTION IN ALZHEIMER DISEASE:
ASSESSMENT AND PROGNOSTIC SIGNIFICANCE**

©Barbara Collins

**Thesis presented to the School of Graduate Studies of the University of Ottawa in
partial fulfillment of the requirements for the degree of Doctor of Philosophy.**



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**Frontal lobe Dysfunction in Alzheimer Disease:
Assessment and Prognostic Significance**

ABSTRACT

The purpose of the present study was twofold: 1) to investigate whether degree of frontal lobe dysfunction predicts dementia progression in early Alzheimer disease (AD) and age associated memory impairment (AAMI); and 2) to investigate the validity and potential utility of delayed alternation (DA) and delayed response (DR) paradigms, sensitive and specific markers of frontal lobe function in primates, as measures of frontal dysfunction in human patients with AD and AAMI. Subjects included 19 patients with early AD recruited from two local memory clinics and 18 community-residing volunteers meeting National Institute of Mental Health diagnostic criteria for AAMI. Mental status tests and a functional rating scale were administered at intake to the study and again one year later and scores on these scales were used to calculate an index of mental status change. Memory screening tests used in the diagnosis of AAMI were also readministered one year after intake to the study, thus permitting calculation of a memory change measure in the AAMI subgroup. At intake to the study, all subjects were also administered DA and DR tasks, clinical neuropsychological tests of frontal and parietal lobe functioning, and a SPECT (single photon emission computed tomography) brain scan. Contrary to prediction, frontal lobe functioning, whether assessed by means of clinical neuropsychological tests, regional cerebral blood flow, or experimental behavioural paradigms (DA and DR), did not predict mental status change in either the AD patients, the AAMI subjects, or the combined sample. However,

performance on frontal neuropsychological tests did predict the degree of positive practice effect on memory retesting in the AAMI subjects. Parietal lobe functioning, as measured by both regional cerebral blood flow and neuropsychological testing, was somewhat predictive of mental status change, with lower parietal perfusion associated with greater decline in mental status. Performance on the DA and DR tasks was not associated with frontal perfusion but did correlate with scores on frontal neuropsychological measures (more strongly than with scores on parietal neuropsychological measures). Some of the behavioural measures of executive functioning used in the current study, namely, the Colour-Form Sorting Test and the DA task, were found to be very specific markers of dementia (i.e., performance on these tasks was virtually never impaired in the nondemented subjects). These findings permit the following conclusions: 1) DA appears to be a valid measure of frontal lobe functioning in individuals with AAMI and early AD; 2) certain simple executive tasks, such as DA and the Colour-Form Sorting Test, may be worthwhile additions to dementia screening batteries which, for the most part, lack measures of executive functioning; 3) the ability of elderly adults to benefit from previous experience may depend on executive functioning and thus learning in this population may be enhanced by support of executive functioning; and 4) severity of parietal lobe dysfunction may predict dementia progression rate in early AD patients.

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LIST OF ABBREVIATIONS

Abbreviation	Term
5HT	serotonin
^{99m} Tc-ECD	technetium-99m-ethyl-cysteinate-dimer
^{99m} Tc-HMFAO	technetium-99m-hexamethyl-propyleneamine-oxime
AAMI	age-associated memory impairment
ACh	acetylcholine
AChE	acetylcholinesterase
AD	Alzheimer disease
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ApoE	Apolipoprotein E
APP	amyloid beta-protein precursor
BDAE	Boston Diagnostic Aphasia Examination
BVRT	Benton Visual Retention Test
CFST	Colour-Form Sorting Test
ChAT	choline acetyltransferase
CHEB	Elisabeth-Bruyère Health Centre
COWA	Controlled Oral Word Association Test
CSF	cerebrospinal fluid
CT	computed tomography
DA	delayed alternation
DFT	dementia of the frontal lobe type
DR	delayed response
DRS	Dementia Rating Scale
EEG	electroencephalogram
FLD	frontal lobe dementia of non-Alzheimer type
GABA	gamma-aminobutyric acid
JOLO	Judgment of Line Orientation Test
MANCOVA	multiple analysis of covariance
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NE	noradrenaline
NIMH	National Institute of Mental Health
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer and Related Disorders Association
OGH	Ottawa General Hospital
PET	positron emission tomography
PLB	Parietal Lobe Battery
rCBF	regional cerebral blood flow
ROI	region of interest

SMQ
SPECT
WAIS-R
WMS-R
WCST

Subjective Memory Questionnaire
single photon emission computed tomography
Wechsler Adult Intelligence Scale-Revised
Wechsler Memory Scale-Revised
Wisconsin Card Sorting Test

INTRODUCTION

Alzheimer disease (AD) is a degenerative brain disorder which relentlessly erodes intellect, memory, and personality until its victim is but a caricature of his or her former self. It accounts for about two-thirds of the cases of dementia occurring in older patients (Katzman & Jackson, 1991) and is the fourth leading cause of death in the population over age 65 (Katzman, 1976). As a disease associated with late life, its prevalence is growing steadily with the current explosion in the elderly population and it is projected that, by the year 2021, more than half a million Canadians will be afflicted with this devastating illness (Canadian Study of Health and Aging Work Group, 1994). The current cost of caring for dementia patients in Canada is estimated at more than four billion dollars per year (Ostbye & Crosse, 1994). Thus, both with regard to the numbers of individuals affected and the financial and emotional cost of caring for them, AD is a major public health concern.

Great strides are being made in the search for a reliable biological marker for AD. The most recent advance has been the discovery of a dramatic increase in the frequency of the ϵ_4 allele of the Apolipoprotein E (ApoE) gene located on chromosome 19 among late-onset AD patients. In that ApoE is a protein associated with AD pathology, the gene coding for ApoE would be considered a candidate gene in this disease. However, this genotype does not explain all cases of late-onset disease and there are examples of individuals with two ϵ_4 alleles or with an ϵ_4 allele and a strong family history of AD who have lived well into the age of risk without developing the disease phenotype (St. George-Hyslop, 1994). Thus, neither the ApoE genotype nor any other biological marker can yet be used to diagnose the disease and, except in rare cases where cerebral

biopsy is performed, the *antemortem* diagnosis of AD remains a provisional one that is based largely on clinical features and on exclusion of other potential causes for the dementia syndrome (Mendis & Mohr, 1993). The terms "probable AD" (McKhann et al., 1984) and "dementia of the Alzheimer type" are used to designate a provisional diagnosis based on clinical features.

Although there is still no definitive treatment or cure for AD, the consequences of misdiagnosis may be grave. False positive diagnostic errors may result in a failure to treat reversible forms of dementia secondary to depression or to metabolic, nutritional, and infectious disorder which, in some cases, may result in permanent neurological damage (Roth, 1978). According to current estimates, 8 to 15 percent of cases of dementia can be ameliorated and 3 percent completely reversed with appropriate intervention (Caplan & Richardson, 1986; Mendis & Mohr, 1993). More importantly, the prognostic information on which caregivers base management plans depends critically on accurate diagnosis. Error in case definition threatens the validity of research related to AD and undermines the comparability of scientific findings obtained at different centres. Finally, with pharmacological treatments for AD on the horizon, the ability to identify appropriate candidates for such therapies will make accurate differential diagnosis of dementia of unprecedented importance.

It is not surprising, then, that intense research efforts have been dedicated to improving the accuracy of clinical diagnosis of AD. These efforts have included attempts to standardize diagnostic criteria. Criteria proposed by the American Psychiatric Association (1994) and by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Work Group on the diagnosis of AD (McKhann et al., 1984) have been widely adopted in North America (Appendix 1). The

application of these criteria has undoubtedly contributed to the impressive accuracy of clinical diagnosis, which is touted to be between 85 and 100 percent (Edwards, Larson, Hughes, & Kukull, 1991; Katzman & Jackson, 1991; Morris & Rubin, 1991). However, these figures are most certainly inflated estimates of the diagnostic accuracy achieved in clinical practice as they tend to be based on highly selected samples of patients presenting with a classical clinical picture of the disease. As many as one-quarter to one-half of Alzheimer patients do not have such typical presentations (Dastoor & Cole, 1985-6; Katzman & Jackson, 1991; Rosen & Mohs, 1982) and accuracy of diagnosis is sure to be considerably less when this group is considered. More conservative estimates of diagnostic accuracy range from 55 to 82% (Homer et al., 1988; Rocca, Amaducci, & Schoenberg, 1986). The rate of misdiagnosis on initial examination, when intervention and accurate prognostic information are most vital, may be particularly high (Garcia, Reding, & Blass, 1981). Moreover, these clinical diagnostic criteria may fail to distinguish AD from other degenerative cortical dementias which have only been recognized as distinct clinicopathological entities since the development of these criteria (Neary, 1990). Thus, attempts have been aimed at more refined characterization of the clinical syndrome associated with AD in the hopes of developing more specific inclusion criteria for differential diagnosis.

The symptom profile of the "typical" Alzheimer patient is quite well established. Its hallmarks have been referred to as the "four As" of AD, namely, amnesia, aphasia, apraxia, and agnosia. However, this classic syndrome is observed in only about half of all patients afflicted with the disease, while the remaining half shows marked heterogeneity in clinical presentation and course (Dastoor & Cole, 1985-6; Rosen & Mohs, 1982). Whereas some investigators, most notably Reisberg and colleagues in the United States (Reisberg, 1986; Reisberg, Ferris,

Borenstein, Franssen, & Sinaiko, 1988; Reisberg et al., 1986, 1989; Reisberg, Ferris, de Leon, & Crook, 1982), O'Carroll and coworkers in Scotland (Gilleard, Spain, & O'Carroll, 1987; O'Carroll, Whittick, & Baikie, 1991), and the Geneva school (e.g., Richard & Constantanidis, 1970 as cited in Joannette, Ska, Poissant, and Béland, 1992), attribute the observed clinical heterogeneity to different stages in the course of a unitary clinical syndrome, others postulate the existence of subgroups of Alzheimer patients with unique symptom clusters (Martin, 1990). The distinction is an important one. Because AD has been granted nosological status on the grounds of symptoms and pathology rather than etiology and pathogenesis (Chui, 1987), identification and characterization of clinical subtypes may be of etiologic, pathogenetic, and, ultimately, therapeutic relevance. Thus, ignoring the existence of subgroups by averaging data across individual patients may be compromising our understanding and treatment of this disease (Joannette et al., 1992; Martin, 1990; Martin et al., 1986). Differences in symptomatology may, for example, reflect differential involvement of neurotransmitter systems. Indeed, postmortem assays of brain tissue have revealed considerable individual variability in the involvement of certain neurotransmitter systems (e.g. gamma-aminobutyric acid [GABA] and dopamine; Carlsson, 1987; Mohr, Mann, & Chase, 1990). Such neurochemical heterogeneity may explain the disappointing results that have been obtained to date in clinical trials involving transmitter replacement in AD patients (Mohr & Chase, 1991) and success with this therapeutic approach may require correction of multiple transmitter deficits identified according to clinical subtype. Furthermore, the existence of distinct subgroups may account for some of the wide variability in the duration of AD and, if so, classification of subgroups may allow more accurate prognosis. Reliable information regarding the future course of the disease is crucial to those attempting to manage AD patients and

particularly to family members who "...must prepare emotionally, physically, and financially to care for their relatives..." (Ortof & Crystal, 1989, p. 512). Even should a reliable biological marker for AD become available, it is likely that only clinical criteria will be able to distinguish specific disease subtypes.

As yet, the validity of subtypes is not well established, either clinically or pathologically, the primary issue being whether the various subtyping factors that have been proposed have any independent significance outside of their relationship to disease severity (Galasko, Corey-Bloom, & Thal, 1991; Jorm, 1985). Some of the approaches which have been taken to classifying subgroups of AD patients will be reviewed following a description of the clinical and pathological features which characterize "typical" AD.

CLASSICAL CLINICAL FEATURES OF AD

The classic clinical features of AD are well documented (Cummings & Benson, 1983, 1986; Lishman, 1987; Price et al., 1993; Sourander & Sjögren, 1970). With rare exceptions, AD strikes during the presenium or senium. Typically, the onset is insidious and the course relentlessly progressive. Memory function is disturbed in the very early stages of the disease and the deficit quite rapidly advances to severe amnesia. Language disturbance, progressing from empty, anomic speech to a more full-blown transcortical aphasia, is another cardinal feature of the dementia of AD as is the early impairment and progressive deterioration of visuospatial functions. Cognitive abnormalities, detectable on tests of calculation and abstract reasoning, are also early and consistent signs. The dominant personality change is indifference and unconcern. Motor

functions, including psychomotor speed, posture, gait, speech, and coordination, are typically quite well preserved until the final stages of the disease.

Duration of AD is highly variable, ranging from less than one to more than twenty years (Chui, 1987). Various studies have cited a five-year cumulative mortality rate between 30% and 95% for senile-onset AD (Berg et al., 1988; Terry & Davies, 1980). Presenile AD often has a much longer duration. Nevertheless, life expectancy in this group is less than 50% of normal (Sjögren, Sjögren, & Lindgren, 1952). The typical course of the disease can be divided into three stages (Sjögren, 1956). The first stage, usually lasting from one to four years, is characterized by the insidious onset and steady progression of memory disturbance followed by changes in mood (perplexity, agitation, restless hyperactivity, asponaneity, and apathy), work habits, and social relationships, with impaired judgement and spatial orientation. Examination during this stage reveals abnormalities of orientation, abstracting ability, judgement, constructional skills, calculation, naming, affect and memory. Recent memory is affected more than immediate and remote memory. Stage two, occurring at two to ten years post-onset, is characterized by a worsening of all abnormalities found at stage one, a more pervasive memory disorder, motor restlessness and irritability and the appearance of focal symptoms, including apraxia, aphasia, agnosia, and acalculia. Language impairment is characterized by fluent but empty speech. Certain motor disturbances of a hypertonic-akinetic character may develop as may other extrapyramidal disorders including disturbances of posture and gait. Stage three is characterized by apathy and, eventually, immobility, dysphagia, profound intellectual impairment, and double incontinence indicative of a decerebrate vegetative state. Cerebral seizures and a Kluver-Bucy-like syndrome (visual agnosia, hyperorality, hypermetamorphosis, loss or diminution of emotions,

hypersexuality, and bulimia) are commonly observed. There may be rapid bodily wasting despite preservation of appetite. By this stage, there are hard findings on the neurological examination such as gait disorder, severe rigidity, tremor, primitive reflexes, extensor plantar reflexes, and a mute bedridden state often characterized by tetraplegia in flexion. The most common cause of death is bronchopneumonia (Burns, Jacoby, Luthert, & Levy, 1990; Corsellis, 1969; Mountjoy, Roth, Evans, & Evans, 1983).

PATHOLOGY OF AD

Morphological Changes

Gross inspection of the brain affected by AD reveals generalized atrophy as evident in narrowed gyri, widened sulci, narrowing of the cortical ribbon, ventricular dilatation, and reduction in size of the subcortical grey matter of the striatum and thalamus (Corsellis, 1969; Lishman, 1978). Brain weight is reduced (Gottfries et al., 1983; Mountjoy et al., 1983; Terry, Peck, DeTeresa, Schechter, & Horoupian, 1981). Histological examination reveals loss of neurons (Mountjoy et al., 1983; Sourander & Sjögren, 1970) and astrocytosis, usually more severe in the outer layers of the cortex (Corsellis, 1969; Sourander & Sjögren, 1970). Cell loss is most marked among large neurons measuring greater than 90 square micrometers and, since these large neurons are the primary efferent cells of the cortex, their loss may well account for shrinkage and thinning of the white matter that is also prominent in AD (Mountjoy et al., 1983;

Terry et al., 1981). However, white matter lesions in AD may occur independently of the Wallerian degeneration ensuing from cortical cell loss (Blennow, Wallin, Uhlemann, & Gottfries, 1991). Overall neuronal loss may exceed 50% in more advanced cases, but conforms to a distinct regional pattern (Brun & Englund, 1981). Basal medial temporal limbic areas, including the amygdaloid nucleus, uncus, hippocampus, and entorhinal cortex, are particularly vulnerable, both with respect to severity and chronology of degenerative changes. With regard to neocortex, involvement of the posterior cingulate gyrus and superior parietal lobule is followed by that of the inferior and middle temporal gyrus and inferior parietal lobule, and thereafter by the frontal and occipital lobes and superior temporal gyrus. In the more affected areas, cell loss may reach 60 to 80% and cortical narrowing as much as 50% in more advanced stages of the disease. The sensorimotor, calcarine, and anterior cingulate areas of the cortex are spared until very late stages. The frontal gyri are affected rather late (though prior to the primary projection areas) but subsequently develop widespread degeneration. There is also significant cell loss (exceeding 75% in the sample of Whitehouse et al., 1982) in the basal forebrain nucleus of Meynert, a group of cholinergic neurons lying in the substantia innominata which constitutes the major source of cholinergic input to the cortex. A 20 to 80% loss of neurons in the locus coeruleus, a brainstem nucleus which serves as the major source of noradrenaline (NE) in the brain, has also been found in AD patients (Bondareff, Mountjoy, & Roth, 1982; Bondareff, Mountjoy, Roth, Rossor, Iversen, & Reynolds, 1987; Zubenko & Moossy, 1988; Zweig et al., 1988). There also appears to be an extensive loss of dendritic arborization with associated loss of dendritic spines, sites of synaptic contact between cells.

The pathological features of AD have been extensively reviewed by Kemper (1984). The histopathological hallmarks of the disease, initially described by Alzheimer at the turn of the century, are the neurofibrillary tangle and the neuritic or senile plaque. The frequency of plaques and tangles has since been shown to correlate with extent of cell loss (Mountjoy et al., 1983) and with severity of dementia in life (Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992; Blessed, Tomlinson, & Roth, 1968; Constantinidis, 1978), corroborating Alzheimer's conviction that these were important disease phenomena. Plaques occupy the neuropil, often adjacent to a capillary, and are composed of degenerating presynaptic neuronal terminals and reactive glia and macrophages with a central core of amyloid, an abnormal protein. Accumulation of amyloid is suspected of being a crucial pathogenetic factor in AD (Katzman & Jackson, 1991). This may be due to mutations within the gene coding for the beta amyloid precursor protein with subsequent overexpression and mismetabolism of this precursor protein (Gentleman & Roberts, 1992). However, in view of evidence of the dissociability of amyloid deposition and plaque formation (i.e., existence of dystrophic neurites in the absence of amyloid in AD and findings of amyloid deposition in the absence of neuritic changes in other neuropsychiatric conditions), it has been argued that amyloid itself is unlikely to be the primary neurotoxic substance in plaque formation (Arendt, Bigl, Tennstedt, & Arendt, 1985).

The neurofibrillary tangle is an intraneuronal structure comprised of parallel bundles of silver-staining fibres which course through the perikaryon and often extend out into one or more neurites. These fibres are distinctive in that they are composed of paired helical filaments with a periodic twist every 80 nanometres. The tangle often displaces the nucleus and distorts the cell body. The neurofibrillary tangle is associated with a number of abnormal proteins, the major one

being the tau protein (Katzman & Jackson, 1991). These abnormal proteins are found in AD patients but are usually not seen in the brains of the cognitively normal elderly, who may show the presence of diffuse plaques.

Although it is now recognized that the senile plaque and the neurofibrillary tangle occur in many different conditions, including normal aging, in no other disease are they found so constantly together and in such numbers (McMenemey, 1970). Kemper (as cited in Kemper, 1984) found the density of neurofibrillary tangles in CA1 and subiculum of the hippocampal formation of AD patients to be 27.4 and 9.8 times greater, respectively, than that observed in homologous areas in age-matched controls. It is thus the quantity of lesions and their topographic distribution that are specific for AD (Constantinidis, 1978). Specific pathological criteria based on these parameters have been established for the diagnosis of definite AD (Khachaturian, 1985).

Although the senile plaque and the neurofibrillary tangle commonly co-occur in AD, their density and distribution are dissociable (Kemper, 1984; Moossy, Zubenko, Martinez, & Rao, 1988). Both are widespread throughout the neocortex, with a general gradient of increasing density from primary sensory and motor cortices, which are relatively spared, to their respective primary and secondary association cortices, with the highest density in multimodal association and limbic cortices. These degenerative changes also progress from superficial towards deeper cortical layers (Brun & Englund, 1981). Both are present in great numbers in the amygdala and the hippocampus, especially the CA1 zone. However, whereas neurofibrillary tangles reach their highest concentration in the entorhinal cortex and areas of hippocampus, neocortical rather than medial temporal lobe areas (except for the amygdala) tend to be most vulnerable to senile plaques (Arriagada et al., 1992). Numerous tangles and relatively few plaques are found in the basal

forebrain nucleus of Meynert (Candy et al., 1983) and the large neurons of the pontine tegmentum. Neurofibrillary tangles are also present in brainstem monoaminergic nuclei and in the reticular formation. Both plaques and tangles are found in the hypothalamus. The medulla and cerebellum are typically spared.

Other microscopic findings in AD include granulovacuolar degeneration (presence of single or multiple intracytoplasmic vesicles with a central dark granule which may be lipofuscin) of the large pyramidal neurons in the hippocampus, Hirano bodies in the hippocampus (highly refractive, eosinophilic, spindle-shaped, fusiform, or spheroidal bodies appearing in the perikaryon or more often in its processes), and congophilic angiopathy (amyloid deposits in the walls of small intracortical blood vessels; Corsellis, 1969; Heston, Mastri, Anderson, & White, 1981; Kemper, 1984; Terry & Katzman, 1983).

Of the various pathological and structural changes which correlate with dementia severity, including the number of senile plaques and neurofibrillary tangles (Arriagada et al., 1992; Blessed et al., 1968; Constantinidis, 1978) and loss of neurons in hippocampus and in association neocortex, it is the extent of synapse loss which correlates most strongly (Katzman & Jackson, 1991).

Biochemical Changes

The primary neurochemical disorder in AD is a significant reduction in acetylcholine (ACh) and in the activity of its synthetic and degrading enzymes, choline acetyltransferase (ChAT) and acetylcholinesterase (AChE), respectively. Decreases in ChAT and AChE are widespread

throughout the brain and, in neocortical areas, may be as great as 80 to 95% (Davies, 1979; Selkoe & Kosik, 1984). Although presumed to be secondary to the documented loss of cholinergic cells in the basal nucleus of Meynert (Perry et al., 1978; Wilcock & Esiri, 1983), evidence that the reduction in ChAT is substantially greater than the loss of cholinergic perikarya raises the possibility that loss of cell bodies from the subcortical nucleus may be secondary to degeneration of cholinergic axons projecting to the cortex (Candy et al., 1983; Hardy, Mann, Wester, & Winblad, 1986). ACh synthesis is inversely related to both cognitive impairment (Francis et al., 1985; Perry et al., 1978) and mean plaque count (Perry et al., 1978) in AD patients. AChE staining has been observed in both senile plaques and neurofibrillary tangles in the hippocampus further implicating this neurochemical system in the pathogenesis of AD (Perry, Blessed, Perry, & Tomlinson, 1980). The density of senile plaques in various regions of neocortex is strongly related ($r = .93$) to the extent of neuronal loss in those segments of the ipsilateral basal forebrain nucleus of Meynert which provide cholinergic innervation to them, suggesting that loss of this cholinergic input may be an important feature in the pathogenesis of neuritic plaques (Arendt et al., 1985).

NE deficiency in cortical tissue resulting from loss of cells in the locus coeruleus has been found in some Alzheimer patients and may be associated with more severe dementia and earlier death (Selkoe & Kosik, 1984). Dopamine and serotonin (5HT) deficiencies have also been reported in some cases (Gottfries et al., 1983; Gottfries, Bartfai, Carlsson, Eckernäs, & Svennerholm, 1986), probably resulting from involvement of projection systems originating in the brainstem ventral tegmental area (Hardy et al., 1986) and dorsal raphe nucleus (Katzman & Jackson, 1991), respectively. Somatostatin and substance P, two neuropeptides and putative

neurotransmitters intrinsic to cortical neurons, are also significantly reduced in the brains of AD patients. Indeed, it has been suggested that degeneration of the intrinsic cortical somatostatin-containing neurons may be the essential feature in AD in so far as neurofibrillary tangles have been identified in these neurons and both neurofibrillary tangles and somatostatin-containing neurons are found in cortical layers which are the source of cortico-cortical association fibres (Jagust, Davies, Tiller-Borich, & Reed, 1990). Cortical neurons expressing corticotrophin releasing factor are also involved as are glutaminergic cells both in the neocortex and in the hippocampal formation. The functional significance of many of these changes is unknown. It also remains unclear to what degree some of these less extensive biochemical changes are a consequence of the more prominent abnormality in cholinergic neurons (Terry & Davies, 1980).

Biological Markers of AD Pathology

The search for a reliable biological marker for AD has involved attempts to identify genetic abnormalities, abnormal levels of neurotransmitters or their metabolites, and abnormal proteins associated with the pathological features of AD in serum or cerebrospinal fluid (CSF). To date, the degree of overlap between AD patients and control subjects in the concentrations of neurotransmitters and their metabolites in blood and CSF has shown them to have limited potential in this regard (Gottfries et al., 1983).

Abnormal proteins may hold greater promise as biological markers of AD. Amyloid, found at the core of neuritic plaques and in the blood vessels in Alzheimer patients, is composed of various proteins, the principal one being the amyloid beta-protein which is believed to be

derived from the much larger amyloid beta-protein precursor (APP). Prior and colleagues (1991) observed significant decreases in the major isoforms of amyloid beta A4 precursor protein in the cerebrospinal fluid of Alzheimer patients. However, the range of APP values among Alzheimer patients was found to be wide and to overlap considerably with that observed in patients with multi-infarct dementia and in normal control subjects.

Molecular genetic studies have provided the most exciting recent advances in the search for a biological marker of AD. Recently published findings attest to a threefold increase in the frequency of the ϵ_4 allele of the ApoE gene in patients with sporadic AD (Poirier et al., 1993). ApoE is a protein involved in the repair, growth, and maintenance of myelin and neuronal membranes during development and in response to injury. Moreover, it is associated with Alzheimer neurofibrillary tangles and with the beta-amyloid protein found in senile plaques. The gene for ApoE is on chromosome 19 in the same genomic region found to be associated with late-onset familial AD. However, as with the biochemical and protein markers tested to date, this genetic marker is not completely reliable in differentiating between cases and noncases: Several investigators have reported individuals homozygous for ApoE ϵ_4 who have survived well into the age range of risk without developing any neurological abnormality (St. George-Hyslop, 1994). Furthermore, the risk associated with this genetic marker remains to be tested in a prospective fashion (St. George-Hyslop, 1994). Thus, ApoE genotypes cannot yet be used in the diagnosis or prognosis of AD.

CLINICAL SUBGROUPS OF AD

Subtypes of AD have been variously classified according to demographic, genetic, neuropathological, neurological, psychiatric, and neuropsychological parameters. These classifications are by no means exclusive and subgroups are often distinguished according to combinations of these variables.

Age at Onset

AD can develop in persons in the fourth and fifth decades of life but its prevalence increases with age according to an exponential model (Henderson, 1990). The tradition of classifying AD according to age at symptom onset dates back to Alois Alzheimer's original case description. Alzheimer (as cited in McMenemey, 1970) described a patient who manifested the clinical features of parenchymatous senile dementia but who was only 51 years of age at symptom onset. Alzheimer proposed that the disease affecting this patient was a theretofore unrecognized clinicopathological entity, characterized by distinctive neuropathological changes in the brain and by the onset of dementia in the presenium. This distinction according to age at onset was reinforced by Emil Kraepelin who, in the 1910 edition of his influential textbook, Clinical Psychiatry, distinguished this newly-characterized disease from senile dementia and proposed the eponym *Alzheimer disease* (Amaducci, Rocca, & Schoenberg, 1985). In contrast to AD, senile dementia was not associated with a specific pathological process and was characterized clinically as progressing from amnesia for recent events to more general deterioration in intellect and

personality without definable focal symptoms such as aphasia, apraxia, and agnosia (Lishman, 1978; Roth, 1978). However, over the ensuing years, it has become apparent that, in the majority of cases of senile dementia, the histopathological changes are qualitatively indistinguishable from those considered diagnostic of AD (Blessed et al., 1968; Katzman, 1976; Sourander & Sjogren, 1970). Accordingly, the practice of distinguishing between AD and senile dementia as distinct nosological entities has been abandoned (Brun & Englund, 1981; Constantinidis, 1978; Corsellis, 1969; Katzman, 1976; Rocca et al., 1986; Sulkava, 1982; Terry, 1978).

Nevertheless, differentiation between presenile and senile variants of AD is still widely recognized, largely on the grounds of genetic evidence (Raskind, Carta, & Bravi, 1995; Whitehouse, 1995). For example, a greater risk of dementia in first-degree relatives has been reported in early-onset AD (Heston et al., 1981; Sulkava, 1982). Though some senile cases do appear to be familial, the fact that these cases are usually confined to one generation suggests recessive transmission (Constantinidis, 1978) in contrast to the pattern of dominant transmission suggested by the pedigrees of cases of presenile AD.

The nature of the association between AD and Down's syndrome (trisomy-21) further suggests a genetic differentiation between presenile and senile AD. Virtually all patients with Down's syndrome who survive into their fourth decade are found to have significant numbers of plaques and tangles in cerebral cortex and hippocampus as well as a decrease in ChAT activity (Terry & Katzman, 1983). Conversely, there is a greater incidence of Down's syndrome among relatives of AD patients than in the general population (Heston et al., 1981; Heyman et al., 1983). However, this augmented prevalence of Down's syndrome, as well as of lymphoma and other immune system disorders, is greater in, if not exclusive to, relatives of probands with onset of AD

in the presenium (Heston et al., 1981). Consistent with this, a genetic defect on the long arm of chromosome 21 has been associated with some familial cases of presenile AD (Goate et al., 1990; St. George-Hyslop et al., 1987) but not with late-onset familial AD (Roses et al., 1990). A second gene, the ApoE gene on chromosome 19, has been implicated in both familial and sporadic late-onset disease (Mullan, 1991). Such genetic heterogeneity serves as strong evidence that presenile- and senile-onset AD are distinct disorders with differing etiologies. It should be noted, however, that some investigators have failed to replicate any association between age-at-onset and family history of dementia (Heyman et al., 1983), even in large series of patients (Henderson et al., 1992).

Early- and late-onset AD have also been differentiated in terms of clinical signs and symptoms. Reminiscent of earlier clinical distinctions between senile dementia and AD, several investigators maintain that focal parietal symptoms such as aphasia, agnosia, and apraxia are more frequent and more severe in early- than in late-onset AD (Bayles, Tomoeda, & Trosset, 1991; Chui, Teng, Henderson, & Moy, 1985; Faber-Langendoen et al., 1988; Filley, Kelly, & Heaton, 1986; Jacoby & Levy, 1980; McDonald, 1969; Seltzer & Sherwin, 1983) whereas late-onset AD is more characterized by generalized cognitive decline and confusion (Blennow et al., 1991; Constantinidis, 1978). These clinical observations are supported by results of functional imaging studies which show that metabolic impairment is more generalized in senile AD patients while that in patients with presenile onset is focused on frontal and temporoparietal cortex (Mielke, Herholz, Grond, Kessler, & Heiss, 1991). The more diffuse clinical and metabolic patterns associated with senile onset may be attributable to the greater frequency and severity of white matter lesions in cases of late-onset AD (Blennow et al., 1991; Leys, Scheltens, & Steinling, 1991b).

There is also some evidence to suggest that early- and late-onset AD may be associated with different risk factors. Whereas underactivity in earlier life stages and a history of nervous breakdown are more strongly associated with earlier-onset disease, factors such as previous malnutrition bear a stronger relationship with later-onset dementia (Henderson et al., 1992).

Certainly many studies, in documenting a more malignant course (faster progression of dementia, higher rates of institutionalization, and/or decreased survival duration) in patients younger at onset of dementia symptoms, have supported a quantitative, if not qualitative, distinction between senile and presenile variants of AD (Barclay, Zemcov, Blass, & McDowell, 1985; Capitani, Della Sala, & Spinnler, 1990; Christie & Wood, 1988; Constantinidis, 1978; Dastoor & Cole, 1985-6; Go, Todorov, Elston, & Constantinidis, 1978; Heston et al., 1981; Heyman et al., 1987; Huff, Growdon, Corkin, & Rosen, 1987; Jacobs et al., 1994; Lucca, Comelli, Tettamanti, Tiraboschi, & Spagnoli, 1993; McDonald, 1969; Rasmusson, Barr, & Brandt, 1994; Seltzer & Sherwin, 1983). These clinical findings have been validated by quantitative pathological differences, including a greater reduction in brain weight (Mountjoy et al., 1983; Sourander & Sjögren, 1970; Terry & Davies, 1980), greater neuronal loss in various areas (Mountjoy et al., 1983; Kemper, 1984) including the nucleus basalis (Wilcock & Esiri, 1983) and brainstem aminergic nuclei (Zweig et al., 1988), greater loss of dendrites and dendritic spines (Kemper, 1984), and a higher average density and wider cortical distribution of neurofibrillary tangles and/or senile plaques (Bondareff, 1983; Bondareff et al., 1987; Constantinidis, 1978; Kemper, 1984; Mountjoy et al., 1983; Sjögren, 1956; Yates et al., 1983; Zubenko et al., 1989) in early-onset AD, as defined by age at onset or age at death. Consistent

findings have been obtained in living patients using structural and functional imaging techniques. Using computerized tomographic (CT) scanning, Jacoby and Levy (1980) found a much lower frequency of ventricular enlargement in late-onset AD patients compared to early-onset patients with equivalent duration of illness. At least one study has shown that regional cerebral blood flow (rCBF) in the temporoparietal area as measured by single photon emission computed tomography (SPECT) is more reduced in early- than in late-onset AD patients (Weinstein et al., 1991).

There is also evidence to suggest that early-onset AD may be associated with more severe neurochemical disturbances (Bondareff, 1983; Francis et al., 1985; Gottfries et al., 1983; Rossor, Iversen, Reynolds, Mountjoy, & Roth, 1984; Winblad, Adolfsson, Carlsson, & Gottfries, 1982). Several studies attest to a significant inverse relationship between the neuronal loss in the basal forebrain nucleus of Meynert and age at onset, whether the latter is treated as a dichotomous (presenile/senile; Candy et al., 1983) or a continuous (Tagliavini & Pilleri, 1983) variable. Consistently, younger age at onset and death in AD patients has been associated with a more profound and widespread decline in ChAT and AChE (Bird, Stranahan, Sumi, & Raskind, 1983; Bondareff et al., 1987; Bowen et al., 1979; Davies, 1979; Yates et al., 1983). More neurotransmitter systems may also be implicated in early-onset AD. Younger age at death, which is taken to imply earlier disease onset, has been associated with a more significant loss of noradrenergic neurons in the brainstem locus coeruleus (Bondareff et al., 1982 but see Bondareff et al., 1987) and smaller concentrations of NE in cerebral cortex, cingulate gyrus, hippocampus, hypothalamus, and mammillary bodies (Bondareff et al., 1987; Rossor et al., 1984; Yates et al., 1983). More pervasive reductions in somatostatin and GABA have also been documented in AD patients younger at age of death (Rossor et al., 1984).

Some investigators (e.g., Sulkava, 1982; Terry, 1978; Terry & Davies, 1980) have argued that most of these clinical and pathological features purported to differentiate between cases of presenile- and senile-onset AD can be explained by longer disease duration in early-onset cases. They point out that patients younger at onset are less susceptible to age-associated medical complications, such as intercurrent infections and arteriosclerotic disorders, and thus live longer. The prolonged morbidity in turn permits the development of a more severe terminal dementia and accounts for the greater concentration and distribution of brain lesions. However, the relationship between disease severity and age-at-onset appears to hold even after controlling for duration of illness (Bird et al., 1983; Zubenko et al., 1989) or severity of dementia prior to death (Rossor et al., 1984).

The validity of the senile/presenile dichotomy has been more seriously challenged by the frequent failure to find differences in dementia severity, rate of dementia progression, risk of nursing home placement, or life expectancy associated with age-at-onset, particularly when the latter is treated as a continuous variable (Boller et al., 1991; Burns, Jacoby, & Levy, 1991; Chui et al., 1985; Drachman, O'Donnell, Lew, & Swearer, 1990; Haupt, Kurz, Pollman, Romero, & Lauter, 1991; Huff, Belle, Shim, Ganguli, & Boller, 1990; Katzman et al., 1988; Mayeux, Stern, & Spanton, 1985a; Ortoft & Crystal, 1989; Teng, Chui, Schneider, & Metzger, 1987; Thal & Grundman, 1986). In fact, Huff et al. (1987) actually cite evidence suggesting a more rapid progression of dementia in senile-onset patients. Others (Francis et al., 1985) have failed to find differences in ChAT, NE, and 5HT in temporal cortex according to age at death (older or younger than 80) and even suggest, on the basis of findings of selective increases in an NE metabolite in the younger group, that late-onset cases may be less able to compensate for loss of noradrenergic

terminals by increasing rate of turnover. While results of clinical studies have occasionally suggested a bimodal distribution of age-at-onset of dementia (Huff et al., 1987; Mayeux et al., 1985a), epidemiological work indicates that the age-specific incidence curves for AD show a smooth exponential increase after age 40 (Rocca et al., 1986). Finally, while several investigators (e.g., Botwinick, Storandt, & Berg, 1986; Burns et al., 1991; Mayeux et al., 1985a) have confirmed the existence of a more benign variant of Alzheimer-type dementia, they have found this to be unrelated to age at onset or any other demographic variable.

These discrepant findings with respect to the relevance of age at onset as a subgrouping dimension undoubtedly derive in part from the difficulty inherent in dating the onset of an insidiously progressive disease. Most patients do not present to health care professionals until there has been significant disease progression. Age-at-onset must therefore be estimated from the more-or-less reliable history provided by patients and family members. Some investigators have preferred to use age at death as an index of age at onset. Although more objective, such inferences can be distorted by the wide variability in disease duration. Finally, whereas some studies have adopted the traditional criterion of 65 in defining early and late onset, all manner of age distinctions can be found in this literature.

Currently, age at onset is more generally regarded as having a modulatory role on disease expression (through interacting with the pathogenesis of the disease) or as a secondary expression of disease severity (i.e., more severe cases become symptomatic earlier) than as an etiological factor (Chui, 1987).

Gender

There is a greater incidence and prevalence of AD among women than men (Corsellis, 1969; Fitch, Becker, & Heller, 1988; Rocca et al., 1986). Although Constantinidis (1978) holds that this is true only of late-onset disease, a preponderance of women has also been observed among populations of presenile cases (Sjögren, 1956). At the same time, male AD patients have decreased survival duration compared to females (Barclay et al., 1985; Berg et al., 1988; Burns et al., 1991; Go et al., 1978; Heston et al., 1981; Knopman, Kitto, Deinard, & Heiring, 1988; Naguib & Levy, 1982), even after taking into account higher expected mortality in aged males than aged females (Barclay et al., 1985). This suggests that gender may be a relevant subgrouping factor with important pathogenetic implications which may be related to the influence of sex hormones (Roberts, 1986). There does not, however, appear to be a difference between men and women in terms of the severity, age at onset, or rate of progression of dementia (Boller et al., 1991; Burns et al., 1991; Drachman et al., 1990; Galasko et al., 1991; Huff et al., 1987) (though see Lucca et al., 1993 for findings to the contrary).

Motor Signs

A more malignant form of AD has been associated with extrapyramidal motor signs such as bradykinesia and rigidity (Girling & Berrios, 1990; Huff & Growdon, 1986; Mayeux, Stern, Spanton, & Cote, 1984; Mayeux et al., 1985a; Miller, Tinklenberg, Brooks, & Yesavage, 1991b; Morris, Drazner, Fulling, Grant, & Goldring, 1989; Stern, Hesdorffer, Sano, & Mayeux, 1990;

Stern et al., 1996; Stern, Mayeux, Chen, & Sano, 1989) (though see Burns et al., 1991; Huff et al., 1990 for negative findings). This relationship has been attributed to more widespread degeneration of neurotransmitter systems (Chui et al., 1985; Mayeux et al., 1985a; Stern, Mayeux, Sano, Hauser, & Bush, 1987) and, in particular, to impaired dopaminergic and noradrenergic neurotransmission (Girling & Berrios, 1990; Mayeux et al., 1985a).

The fact that extrapyramidal signs afflict all AD patients who survive to an advanced stage of the disease (Sulkava, 1982) rather than constituting a distinguishing feature of select patients raises the issue as to whether such features mark subgroups or only stages of disease. In a longitudinal study using life table analyses, Drachman et al. (1990) found that extrapyramidal features had no prognostic significance after controlling for disease severity. On the other hand, evidence suggesting atypical pathological changes in those AD patients with early extrapyramidal signs lends some support to the subgroup model. Independent groups of researchers have identified a group of patients characterized clinically by mild extrapyramidal features early in the disease course and a more rapidly progressive dementia, and neuropathologically by Lewy bodies in neocortex and brainstem in addition to the senile plaques and neurofibrillary tangles typically seen in AD (Förstl, Burns, Luthert, Cairns, & Levy, 1993; Hansen, Masliah, Terry, & Mirra, 1989; Hansen et al., 1990; Perry et al., 1990). Lewy bodies in diencephalic and brainstem nuclei constitute one of the primary pathological features of Parkinson's disease. In a recent autopsy series, between 20% and 30% of patients with a clinical and pathological diagnosis of AD were found to have Lewy bodies in the cerebral cortex (Katzman & Jackson, 1991). Interpretation of these findings has varied, with some investigators (e.g., Hansen et al., 1989, 1990) regarding this entity as a variant of AD and others, emphasizing the clinical and pathological differences between

patients with and without the presence of Lewy bodies, calling for recognition of "diffuse Lewy body disease" or "dementia of the Lewy body type" as a nosologic entity distinct from AD (Dickson et al., 1991; Gibb, Luthert, Janota, & Lantos, 1989; Kosaka, Yoshimura, Ikeda, & Budka, 1984; Perry, Irving, Blessed, Perry, & Fairbairn, 1989; Perry et al., 1990).

Still others propose that the presence of extrapyramidal signs in AD reflects coexistent Parkinson's disease. However, a number of findings suggests that the pathogenesis of these motor signs may differ in the two diseases: 1) tremor is rarely observed in AD patients but is virtually always present in Parkinson's disease (Mayeux et al., 1984, 1985a; Sulkava, 1982); 2) pathologic changes in the substantia nigra (the primary locus of pathology in Parkinson's disease) may not occur early in AD when rigidity may be apparent; 3) positron emission tomography (PET) scanning of AD patients with rigidity fails to reveal a decrease in dopamine uptake into the putamen which is reduced by 60% in Parkinson's patients (Tyrrell et al., 1990); and 4) the rigidity associated with AD has been found to be completely unresponsive to oral levodopa treatment (Duret, Goldman, Messina, & Hildebrand, 1989). This does not, however, rule out the possibility that a subgroup of patients afflicted with both AD and Parkinson's disease may be represented in research studies of AD and contribute to the poor prognosis associated with extrapyramidal signs.

Other motor signs have also been suggested as markers of distinct AD subgroups.

Greater disease severity and a younger age at onset have been associated with the presence of myoclonus in AD patients (Bird et al., 1983; Chui et al., 1985; Mayeux et al., 1984, 1985a; Stern et al., 1989), although not unequivocally so (Burns et al., 1991a; Huff & Growdon, 1986). ChAT activity is particularly depressed in Alzheimer patients with myoclonus (Bird et al., 1983), suggesting that more severe cholinergic dysfunction may account for the more profound dementia

observed in these patients (Chui et al., 1985). Findings of strong familial aggregation of dementia with extrapyramidal motor signs (Heston, Lowther, and Leventhal, 1966; Morris, Cole, Banker, & Wright, 1984) and myoclonus (Jacob, 1970) have led to speculation that these signs may represent genetically and etiologically distinct syndromes, despite the overlap of histological features with those of AD. However, Chui and colleagues (1985) found no relationship between extrapyramidal signs or myoclonus and family history of degenerative dementia in a general sample of clinically-diagnosed Alzheimer patients.

It has also been proposed that the presence of primitive reflexes, such as palmomental, glabellar, snout, sucking, and grasp reflexes, which are assumed to reflect release of brainstem structures from cortical, and in particular, frontal cortical inhibition, may be a marker of a subtype of AD and that this variant may be associated with a more severe course (Bakchine, Lacomblez, Palisson, Laurent, & Derouesne, 1989; Franssen, Reisberg, Kluger, Sinaiko, & Boja, 1991). The presence of these reflexes has been shown to correlate with severity of cognitive impairment (Bakchine et al., 1989; Crichton & McDonald, 1991) and with the presence of extrapyramidal signs which, as just reviewed, may characterize a subgroup of AD patients with a more malignant course. Crichton and McDonald (1991) found the frequency of primitive reflexes to be bimodally distributed by age and interpreted this as supporting the existence of distinct subtypes of AD. However, in so far as release reflexes are also associated with normal aging (Drachman & Long, 1984; Jacobs & Gossman, 1980), such a bimodal distribution may represent the overlap of disease-related and normal developmental changes.

As mentioned previously, primary sensory and motor cortices are relatively spared in typical AD and focal motor findings early in the disease course usually militate against the

diagnosis of AD. However, there has been a recent report of a case of pathologically-confirmed AD presenting with a slowly progressive left hemiparesis in conjunction with a progressive dementia (Jagust et al., 1990). Autopsy revealed focal accentuation of Alzheimer neuropathology in the somatosensory cortex of the right hemisphere (which gives rise to up to 40% of fibres in the pyramidal tract).

Familial versus Sporadic AD

AD patients have also been subtyped according to whether or not they have a positive family history of the disease. In some families, there appears to be an autosomal dominant mode of inheritance of AD in view of a lifetime risk approaching 50% to relatives of AD probands (Boerrigter et al., 1991; Fitch et al., 1988; Heston et al., 1981). However, the far-from-perfect concordance of AD in monozygotic twins (with estimates ranging from 40% to 50%), even after long periods of follow-up, constitutes strong evidence that not all cases of AD can be explained solely on a genetic basis (Kumar et al., 1991; Whalley, 1991). Approximately 40% of AD probands have affected relatives (Chui et al., 1985; Fitch et al., 1988; Folstein & Breitner, 1982; Heston et al., 1981; Mayeux et al., 1985a).

There appears to be considerable etiological heterogeneity even among familial cases of AD (St. George-Hyslop, 1994). Mutations in exon 16 or exon 17 of the beta APP gene on chromosome 21 has been shown to be largely confined to cases of presenile onset but accounts for less than three percent of all familial cases of AD. A genetic defect on chromosome 14, which has not yet been more precisely localized, appears to be a much more common cause of early-

onset autosomal dominant familial AD, associated with approximately 70% of such cases. The ϵ_4 allele of the ApoE gene on chromosome 19 is much more frequent in cases of late-onset AD than in either early-onset patients or normal control subjects. However, this increased frequency characterizes sporadic as well as familial cases of AD. No genetic defect has been found to correspond perfectly with disease expression, underscoring the importance of genetic interactions and interactions among genetic predisposition and environmental factors.

The risk associated with various environmental factors appears to differ for familial and sporadic types of AD. For example, a history of head injury and previous starvation/malnutrition are more highly associated with sporadic than with familial cases, while the opposite is true with regard to use of minor tranquilizers (Edwards et al., 1991; Henderson et al., 1992).

Some of the clinical and demographic features purported to differentiate the familial from the sporadic variant of AD have already been discussed. For example, there is evidence to suggest that Alzheimer patients with a positive family history of degenerative dementia may be younger at symptom onset (Thal & Grundman, 1986). Although Chui and colleagues (1985) did not observe a significant difference in mean age at onset for familial and nonfamilial cases of AD, the distribution of age-at-onset for familial cases was negatively skewed while sporadic cases were more normally distributed on this variable. Others, however, have found no relationship between familial aggregation and age-at-onset (e.g., Edwards et al., 1991; Fitch et al., 1988). Breitner and Folstein (1984; Folstein & Breitner, 1982) contend that the relationship between familial aggregation and age-at-onset is a spurious one. They argue that a more typical age of onset of familial AD is after the eighth decade but that prevalence data in this cohort are distorted due to the fact that the majority of predisposed individuals die of competing causes before

dementia symptoms become manifest. Conversely, estimates of the prevalence of familial AD in younger cohorts are inflated due to the large numbers of relatives surviving to the age of risk. They predict that the current trend towards increased survival into late old age will be accompanied by a dramatic increase in the appearance of familial dementia in older age groups and that familial aggregation will prove the rule rather than the exception.

Familial AD has been associated with more prominent extrapyramidal motor signs and myoclonus which, as discussed above, may reflect differential involvement of neurotransmitter systems (Heston et al., 1966; Jacob, 1970; Morris et al., 1984). Again, however, this relationship has not been consistently replicated (Edwards et al., 1991).

Familial AD has also been associated with more rapid disease progression (Burns et al., 1991a), although the negative findings with regard to the prognostic significance of family history are perhaps more impressive (Chui et al., 1985; Drachman et al., 1990; Edwards et al., 1991; Fitch et al., 1988; Ortoft & Crystal, 1989; Thal & Grundman, 1986). Lower ChAT activity has been observed in the brains of familial AD patients but the difference between familial and sporadic groups was statistically insignificant and sample sizes were small (Bird et al., 1983). Capacity for DNA repair, which may have effects on the expression of genes important for neuronal function and survival, is decreased in AD patients with a strong family history of dementia (two or more affected first-degree relatives) but not in sporadic cases (Boerrigter et al., 1991).

In view of their inability to differentiate familial and sporadic cases on the basis of clinical findings or risk factors despite longitudinal study, Edwards and colleagues (1991) proposed a genetic-environmental model of AD which holds that some genetic predisposition, environmental

factor, or both may precipitate the onset of AD and that it is only the etiology, not the clinical expression of the disease, which differentiates the genetic and environmental subtypes.

Discrepant findings with regard to clinical, pathological, and epidemiological differentiation between familial and sporadic AD may derive in part from differences among studies in the criteria adopted for identification of secondary cases. In many studies, anecdotal evidence of one affected family member in the pedigree was sufficient to characterize a case as familial. However, in view of the high prevalence of dementia in the elderly, such cases could well be sporadic, particularly in that members of the same family are more likely than non-related individuals to share exposure to environmental risk factors. In some studies, the criterion for a secondary case was simply dementia, whereas in others a more stringent criterion of AD was adopted.

Psychiatric Manifestations

Significant psychopathology occurs in 30 to 40 percent of patients with AD (Jeste, 1994; Wragg & Jeste, 1989). Although it has been suggested that psychotic and affective symptoms in AD may constitute secondary psychological reactions to cognitive impairment, the consistency in phenomenology observed across studies tends to support the argument that affective and psychotic symptoms are primary manifestations of AD pathophysiology (Wragg & Jeste, 1989). The DSM III-R (American Psychiatric Association, 1987) recognizes AD with delusions and AD with depression as distinct subtypes of primary degenerative dementia.

Psychotic symptoms such as hallucinations and delusions early in the disease may bode a more malignant course. The presence of such features has been found to correlate with poorer performance on neuropsychological tests of receptive language (Lopez et al., 1991), more severe electroencephalographic (EEG) disturbance (Lopez et al., 1991), more rapid intellectual and functional decline (Drevets & Rubin, 1989; Jeste, Wragg, Salmon, Harris, & Thal, 1992; Lopez et al., 1991; Mayeux, Stern, & Sano, 1985b; Rosen & Zubenko, 1991; Rubin, 1990; Stern et al., 1987, 1990), though only rarely with shortened survival duration (Naguib & Levy, 1982). The presence of psychosis in life has also been associated with significant increases in the density of senile plaques and neurofibrillary tangles, particularly in the prosubiculum and the middle frontal cortex, alterations in the relative distribution of these morphologic lesions, and higher concentrations of NE and lower concentrations of 5HT in cortical and subcortical regions (Zubenko et al., 1991). AD patients with and without psychosis have not been found to differ with respect to sex ratio, age at onset or death, or brain weight (Drevets & Rubin, 1989; Stern et al., 1990; Zubenko et al., 1991).

In that 1) the probability of psychotic symptoms is a function of stage of disease (Chen, Stern, Sano, & Mayeux, 1991; Morris & Rubin, 1991; Rosen & Zubenko, 1991) and 2) some of the foregoing studies failed to match psychotic and non-psychotic patients for overall severity of dementia, it is possible that the relationship between psychotic symptoms and malignancy of disease can be explained by a stage model. Indeed, two recent studies failed to replicate findings of an association between psychotic symptoms and disease course after controlling for severity of dementia (Drachman et al., 1990; Huff et al., 1990). However, contradictory findings may also reflect differences in the nature of the psychotic symptoms under study. Burns, Jacoby, & Levy

(1990a, 1990b) observed more rapid cognitive decline in AD patients with hallucinations but found no such relationship between rate of decline and disorders of thought content (delusions or persecutory ideation) or misidentifications (e.g. belief that others are in the house, misidentification of mirror image) in the same sample. Thus, the negative findings of Huff and colleagues (1990) with respect to the relationship between disease course and psychosis may be due to the fact that the most prevalent psychotic symptom in their sample was paranoid ideation.

Other psychiatric manifestations early in the disease, including behavioural disturbances such as aggression, wandering, incontinence, and elements of the Kluver-Bucy syndrome (Burns, Jacoby, & Levy, 1990d) and personality changes such as passivity, agitation, and self-centredness (Rubin, 1990; Rubin, Morris, & Berg, 1987) do not appear predictive of more rapid disease progression.

The case is somewhat more complex with regard to depression. Although AD patients with depressive symptoms tend to be less cognitively impaired than those without (Pearson, Teri, Reifler, & Raskind, 1989), depression and mania do not have predictive value with respect to the course of cognitive deterioration in AD (Burns, Jacoby, & Levy, 1990c; Lopez, Boller, Becker, Miller, & Reynolds, 1990; Mayeux et al., 1985b). Nevertheless, findings that a past history of depression is associated with less rapid cognitive decline (Burns et al., 1990c), that the emergence of major depression may be associated with an increased mortality rate (Zubenko & Moossy, 1988), and that depression in AD patients homogeneous with respect to overall dementia severity correlates with degenerative changes in brainstem aminergic nuclei including the locus coeruleus (Zubenko & Moossy, 1988; Zweig et al., 1988), the substantia nigra (Zubenko & Moossy, 1988)

and the raphe nuclei (Zweig et al., 1988), have led to the proposal of a biological subtype of AD marked by depressive features (Drevets & Rubin, 1989; Zubenko & Moossy, 1988).

Emotional incontinence in AD patients has been found to bode a more malignant course (Huff et al., 1990). However, emotional incontinence is considered a hallmark of vascular pathology and thus a mixed etiology of AD and vascular dementia may explain the prognostic significance of this sign.

Neuropsychological Profile and Distribution of Pathology

Subtypes of AD have also been delineated according to differences in the profile of impaired and preserved neuropsychological functions. Although the pattern of cognitive deficits is known to vary as a function of stage of disease, neuropsychological heterogeneity has been demonstrated even after controlling for disease duration and overall severity of dementia (e.g. Capitani et al., 1990; Faber-Langendoen et al., 1988; Neary et al., 1986). It has been argued that apparent neuropsychological heterogeneity may actually reflect individual differences in premorbid cognitive abilities or differential difficulty (and hence sensitivity to dementia) of the neuropsychological tests used to tap different cognitive domains (Bayles, 1991; Becker, Huff, Nebes, Holland, & Boller, 1988; Rosen & Mohs, 1982). Joannette et al. (1992) have suggested that inter-individual variability in cognitive functioning is particularly relevant in the case of an age-associated condition such as AD given that such variability increases with age and that the functional organization of a given individual's brain changes with age and so, the behavioural effects of brain disease will be age-dependent. While there is undoubtedly some merit to these

points, such alternative interpretations seem inadequate in view of evidence from functional imaging studies of compatible heterogeneity in the pattern of cerebral blood flow and metabolism (as measured by PET and SPECT) among AD patients.

Functional Imaging in AD

Functional imaging techniques have proved invaluable in the *in vivo* study of cerebral dysfunction in AD and in differentiating AD from other dementing illnesses (Risberg, 1987; Terry & Katzman, 1983). This approach has greatly advanced our knowledge of AD over that allowed by postmortem study, which is generally restricted to the advanced stages of the disease and thus may obscure critical initial changes (Foster et al., 1984). Determination of whether decreases in cerebral blood flow and metabolism are a cause or an effect of cell loss is a continuing problem associated with these techniques. However, findings that cerebral glucose metabolism as revealed by functional imaging techniques corresponds better with the distribution of neuronal loss and astrocytosis found in autopsy material (e.g., Ingvar, Brun, Hagberg, & Gustafson, 1978; McGeer et al., 1986) than with the regional atrophic changes seen during life on CT and magnetic resonance imaging (MRI; Fazekas et al., 1989) suggests that metabolic dysfunction in neurons may predict cell death. Such a conclusion is consistent with findings that tangle-bearing neurons seem to undergo a progressive reduction in metabolic capability in relation to the accumulating mass of neurofibrillary tangle (Hardy et al., 1986). Moreover, disturbances in the pattern of metabolism in neocortical association areas can be documented even before deficits in nonmemory cognitive functions become manifest (Haxby et al., 1986) and predict the neuropsychological

profile to emerge in later stages of dementia (Haxby et al., 1990). Thus, metabolic dysfunction may be the first indication of a degenerative cortical process in AD, whereas structural changes like cortical atrophy, while still associated with hypometabolism, become evident on CT or MRI only later in the course of the disease process (Fazekas et al., 1989). Findings that PET is more sensitive to AD than either CT or MRI accord well with such an interpretation (Fazekas et al., 1989). Regional cortical hypometabolism may also reflect dysfunction of projection systems to the cerebral cortex and, thus, not correspond exactly to the distribution of cortical atrophy. The absence of any increase in oxygen extraction in relation to the reduced blood flow in AD indicates that the diminished flow is due to a decrease in metabolic demand rather than to chronic brain ischemia (Frackowiak et al., 1981).

Studies of rCBF in AD patients using multi-detector techniques and, more recently, PET and SPECT, have demonstrated global reductions in cortical glucose metabolism, cerebral blood flow, and oxygen utilization proportional to severity of cognitive impairment as well as a characteristic regional pattern of resting blood flow characterized by prominent bilateral temporoparietal hypometabolism consistent with the classic symptomatological triad of agnosia, aphasia, and apraxia, and by relative sparing (at least in the early stages of the disease) of primary sensory and motor cortices, cerebellum, and subcortical areas such as the basal ganglia and thalamus (Benson, 1982; Benson et al., 1983; Chase et al., 1984; Chase, Foster, & Mansi, 1983; Chawluck et al., 1990; Cutler et al., 1984; Duara et al., 1986; Fazekas et al., 1989; Foster et al., 1984; Frackowiak et al., 1981; Friedland, Budinger, Koss, & Ober, 1985; Gustafson, Brun, & Risberg, 1990; Haxby, Duara, Grady, Cutler, & Rapoport, 1985; Haxby et al., 1986; Holman, Johnson, Gerada, Carvalho, & Satlin, 1992; Ingvar et al., 1978; Ingvar & Lassen, 1979; Kuhl,

Metter, & Riege, 1985; Kumar, Schapiro, Haxby, Grady, & Friedland, 1990; Mielke et al., 1991; Neary et al., 1987; Nybäck, Nyman, Blomqvist, Sjögren, & Stone-Elander, 1991). There is some disagreement as to the extent of hypometabolism in the frontal lobes, with some investigators including this among the areas of maximal depression (e.g. Benson, 1982; Benson et al., 1983; Ingvar et al., 1978). This discrepancy appears related to differences in the stage of dementia of the subjects under study and, in the typical case, significant frontal hypometabolism appears to occur in more advanced stages of dementia only after temporoparietal metabolic changes are well established (Duara et al., 1986; Foster et al., 1983; Frackowiak et al., 1981; Kumar et al., 1990).

Interhemispheric Variability in Neuropsychological and Neurophysiological Profile

There have now been numerous reports of subgroups of patients meeting current diagnostic criteria for probable AD with lateralizing neuropsychological profiles characterized by disproportionate impairment on tests of language or visuospatial skills (Becker et al., 1988; Capitani et al., 1990; Shuttleworth, 1984). In some cases, a compatible discrepancy between verbal and nonverbal memory has also been noted (Tröster, Butters, Salmon, Jacobs, & Delis, 1991). Such lateralized neuropsychological profiles have been shown to persist over several years of clinical follow-up (Brouwers et al. as cited in Martin et al., 1986; Grady, Haxby, Schlageter, Berg, & Rapoport, 1986; Price et al., 1993). Hemispheric asymmetry in the distribution of cortical atrophy (Pogacar & Williams, 1984; Tariska, 1970), in the density of senile plaques in cortex (Arendt et al., 1985), and in the extent of neuronal loss in the nucleus basalis of Meynert (Arendt et al., 1985) has been observed in some cases at autopsy. These cases stand in contrast

to the typical AD brain in which histopathological changes and cholinergic abnormalities are quite symmetrically distributed in the two hemispheres (Moossy et al., 1988; Zubenko et al., 1988, 1989) and suggest that lateralized neuropsychological profiles may reflect distinct subgroups rather than merely different stages of a relatively uniform disease process.

CT, MRI, and EEG often reveal localized abnormalities compatible with the neuropsychological profile (Crystal, Horoupian, Katzman, & Jotkowitz, 1982; Mesulam, 1982), but PET and SPECT are more sensitive to these functional asymmetries (Celsis, Agniel, Puel, Rascol, & Marc-Vergnes, 1987; Chawluck et al., 1986). Though decreased blood flow and metabolism are generally bilateral in AD, there is greater asymmetry among AD patients than among normal control subjects both with respect to overall hemispheric metabolism (Chawluck et al., 1990; Gemmell et al., 1989; Kuhl et al., 1985; Nybäck et al., 1991; Waldemar et al., 1994) and to metabolic rates in homologous regions of the two hemispheres (Duara et al., 1986; Friedland et al., 1985; Haxby et al., 1985, 1986, 1990; Perani et al., 1988). This metabolic asymmetry has been found in most cases to correspond closely to the neuropsychological profile such that preponderant language disturbance is associated with greater hypometabolism in the left hemisphere whereas disproportionate disturbance of visuospatial processing is associated with greater right hemisphere, and particularly right posterior, hypometabolism (Celsis et al., 1987, 1990; Chase et al., 1984; Foster et al., 1983, 1984; Friedland et al., 1985; Grady et al., 1986; Haxby et al., 1985, 1986; Kumar et al., 1990; Martin et al., 1986; Nybäck et al., 1991; Poeck & Luzzatti, 1988). These relationships appear to hold regardless of whether or not the patient sample has been preselected for the presence of lateralizing cognitive deficits. Metabolic asymmetry has been demonstrated across a wide range of dementia severities and longitudinal

study has shown that, as with cognitive profiles, direction of metabolic asymmetry is reliably maintained for up to two years in mildly and moderately demented AD patients (Celsis et al., 1990; Grady et al., 1986; Haxby et al., 1990) with the degree of asymmetry becoming, if anything, somewhat more pronounced over time (Haxby et al., 1990). These correlations between asymmetries in cerebral metabolism and neuropsychological profile persist over much of the course of the disease, although a trend toward diminishing metabolic asymmetry is observed in the late stages of AD (Haxby et al., 1990).

The reasons for this neuropsychological and metabolic asymmetry are not known but there is speculation that it may reflect right-left differences in affected neurotransmitters such as ACh and 5HT (Friedland et al., 1985). Such asymmetries have been demonstrated in normal animals and in humans (e.g., Arato, Frecska, Tekes, & MacCrimmon, 1991).

In the absence of histologically-confirmed diagnosis, the inferences drawn from such studies are tentative in so far as some of the patients presenting with lateralized dysfunction may represent diseases other than AD. Focal neuropsychological presentations have frequently been found at autopsy to be manifestations of Pick's disease (Caplan & Richardson, 1986; Cole, Wright, & Banker, 1979; Holland, McBurney, Moossy, & Reinmuth, 1985). Indeed, the original case described by Pick (as cited in Poeck & Luzzatti, 1988) had a prominent language disorder in association with severe atrophy of the left temporal cortex. Pick went on to describe other cases with circumscribed atrophy of the temporal, parietal, and frontal lobes and, thus, any kind of circumscribed slowly progressive cortical atrophy came to be diagnosed clinically as Pick's disease. Over the ensuing years the predilection of Pick's disease for anterior frontal and temporal zones has been recognized and cases of lobar atrophy with circumscribed neuropsychological

deficits have more recently tended to be included under the rubric of AD (Poeck & Luzzatti, 1988). Nevertheless, Pick's disease is often found to involve the cerebral hemispheres asymmetrically (Brun, 1987). In other cases of focal neuropsychological presentation, autopsy has revealed Creutzfeldt-Jakob disease (Brown, Cathala, Sadowsky, & Gadjusek, 1979; Shuttleworth, Yates, & Paltan-Ortiz, 1985).

The most frequently cited case of progressive focal neuropsychological deficit is that of progressive language disturbance. Since Wechsler's (1977) description of a 67-year-old man in whom progressive deterioration of behaviour and intellectual function was heralded by an aphasic disturbance, similar case reports have abounded in the literature (Basso, Capitani, & Laiacina, 1988; Casselli, Jack, Petersen, Wahner, & Yanagihara, 1992; Chawluck et al., 1986; Goulding, Northen, Snowden, MacDermott, & Neary, 1989; Heath, Kennedy, & Kapur, 1983; Kirshner, Tanridag, Thurman, & Whetsell, Jr., 1987; McDaniel, Wagner, & Greenspan, 1991; Mesulam, 1982; Pogacar & Williams, 1984; Sapin, Anderson, & Pulaski, 1989; Snowden, Neary, Mann, Goulding, & Testa, 1992).

Mesulam and coworkers have documented a number of cases in which progressive aphasia was unparalleled by generalized intellectual or functional decline, at least until the terminal stages of the disease, and contend that this syndrome, dubbed "primary progressive aphasia", is distinct from that of dementia of the Alzheimer type (Chawluck et al., 1986; Mesulam, 1982; Mesulam, 1987; Mesulam & Weintraub, 1983; Weintraub, Rubin, & Mesulam, 1990). They base this contention upon several lines of evidence. Firstly, although considerable heterogeneity in aphasic symptoms has been described in cases of primary progressive aphasia (e.g., Snowden et al., 1992), there do appear to be consistent differences in the nature of the language deficit typically

associated with AD and progressive aphasia. Whereas the language deficit in AD usually proceeds from early anomia to fluent paraphasic verbal output with marked comprehension deficits and intact repetition (reflecting primary impairment in the lexical and semantic aspects of language), primary progressive aphasia most often presents as word-finding difficulty, phonemic paraphasias, and verbal hesitancy progressing to a nonfluent Broca-like aphasia (reflecting primary impairment of morphosyntactic and phonological aspects of language) and eventually to a global aphasia (McDaniel et al., 1991; Weintraub et al., 1990). Secondly, PET studies reveal that hypometabolism in primary progressive aphasia tends to be restricted to left perisylvian regions in contrast to the bilateral hypometabolism seen in patients with the aphasic type of AD (Chawluck et al., 1986; Goulding et al., 1989; McDaniel et al., 1991; Snowden et al., 1992). Thirdly, pathology in most cases of primary progressive aphasia which have come to biopsy or autopsy has been characterized by nonspecific degenerative changes (neuronal loss, spongiosis, and astrocytic gliosis) in left frontal and temporal language zones and an absence of the histopathological features diagnostic of AD (Kirshner et al., 1987; Mehler, Horoupian, Davies, & Dickson, 1987; Mesulam, 1982; Snowden et al., 1992). Postmortem studies in a limited number of cases of primary progressive aphasia have moreover proved negative with respect to the depression in ChAT activity (Mehler et al., 1987) and the significant cell loss in the nucleus basalis of Meynert (Mehler et al., 1987; Snowden et al., 1992) so characteristic of AD.

Despite such findings, the clinical syndrome of primary progressive aphasia remains controversial. Sceptics counter that detailed neuropsychological assessment of such patients, especially when conducted serially, may reveal more widespread cognitive decline than suspected on clinical observation and thus that the distinction between progressive aphasia and primary

degenerative dementia is blurred (Foster & Chase, 1983; Gordon & Selnes, 1984; Green, Morris, Sandson, McKeel, & Miller, 1990; Kirshner, Webb, Kelly, & Wells, 1984; Poeck & Luzzatti, 1988). Language impairment may interfere with testing for other cognitive functions and thus, in such cases, characterization of deficits may rely on observation of nonverbal behaviour, rather than on formal testing of nonverbal cognition (Green et al., 1990; Kertesz, 1990). Poeck and Luzzatti (1988) found that standardized neuropsychological testing had been conducted in less than one third of 29 cases of progressive aphasia appearing in the literature to that time. On the basis of extensive neuropsychological follow-up of patients presenting with a predominant language disorder, they concluded that these patients most likely have a variant of AD with a long initial phase of language breakdown followed by the appearance of other neuropsychological deficits. This conclusion gains support from several other reports of patients who presented with focal neuropsychological deficits early in the course of the disease and who, with time, went on to meet clinical and/or histopathological criteria for a diagnosis of AD (Crystal et al., 1982; Green et al., 1990; Mayeux et al., 1985a; Neary et al., 1986; Pogacar & Williams, 1984; Shuttleworth, 1984). In several other cases of primary progressive aphasia, including that of Wechsler, pathological examination of postmortem brains has revealed Pick's disease (Caplan & Richardson, 1986; Cole et al., 1979; Kertesz, 1990). Kertesz (1990) provided the following breakdown of histopathological diagnosis in the 15 autopsied cases of primary progressive aphasia appearing in the literature up to 1990: AD in five cases, Pick's disease in three cases, and, spongiform changes and nonspecific neuronal loss with gliosis in the remaining seven cases. A more recent tally based on 20 autopsied cases revealed a similar distribution: About 50 percent of cases had nonspecific neuronal loss, gliosis, and spongiform change in the left perisylvian region; 25 percent had AD;

and the rest had either Pick's Disease, Creutzfeldt-Jakob disease, or neuronal achromasia (Black, 1994). Thus, it would appear that progressive aphasia is associated with a number of neurodegenerative conditions and that AD is a relatively common etiology of this syndrome. Indeed, "pseudo-focal" language disorders have been reported in as much as 23% of a sample of patients with a clinical diagnosis of mild AD (Capitani, Della Sala, & Spinnler, 1986).

Attempts have been made to characterize lateralized subtypes of AD according to both subject and disease characteristics. Celsis et al. (1990) reported a higher prevalence of pronounced functional asymmetry, as assessed by cognitive tests, SPECT scanning, and EEG, among male than among female AD patients. There is some suggestion that language disturbance may be more prominent in familial than in sporadic AD (Breitner & Folstein, 1984; Chui et al., 1985; Folstein & Breitner, 1982). However, several groups of investigators have not found any difference between familial and sporadic cases with respect to aphasic symptoms (Faber-Langendoen et al., 1988; Fitch et al., 1988; Heyman et al., 1983). Indeed, Knesevich and colleagues (Knesevich, Toro, Morris, & LaBarge, 1985) actually found a significantly lower prevalence of familial cases among aphasic AD patients after controlling for stage of dementia. Such negative findings may be due in some cases to a failure to control for whether or not relatives lived to the age of expression of AD (Huff et al., 1990).

Preponderant language disturbance has been frequently reported to predict a more malignant course (Berg et al., 1984; Huff et al., 1990; Kaszniak et al., 1978; Knesevich, LaBarge, & Edwards, 1986; Knesevich et al., 1985; Lopez et al., 1991). Indeed, among various EEG, CT, neurological, and neuropsychological variables, language deficits, and in particular anomia, have been reported to be the strongest predictor of cognitive decline and survival, even after

controlling for dementia severity (Boller et al., 1991; Huff et al., 1990; Kaszniak et al., 1978). Interestingly, left focal slowing on the EEG also predicts mortality at one year (Kaszniak et al., 1978). Moreover, language impairment is prognostic of deterioration in spheres of functioning that are largely or entirely independent of language, including difficulty in dressing, performing household tasks, and interpreting surroundings, suggesting that the aphasic disturbance is associated with more rapid progression of pathologic changes in both cerebral hemispheres (Huff et al., 1990). Huff et al. (1990) suggest that one explanation for this prognostic significance is that naming and associated lexical-semantic language processes may be particularly vulnerable to the widespread neuronal loss and disconnection that occurs in AD.

Others have found no differences in rate of progression of neuropsychological impairment (Burns et al., 1991a) or risk of death or institutionalization between AD patients with and without aphasic disturbances (Becker et al., 1988; Berg et al., 1988). Still others report dissociation of these outcomes, with more rapid progression of dementia but no associated decrease in survival duration (Faber-Langendoen et al., 1988; Knesevich et al., 1985).

Numerous reports have attested to more profound language disturbances in patients younger at onset of AD (Bayles et al., 1991; Chui et al., 1985; Faber-Langendoen et al., 1988; Filley et al., 1986; Seltzer & Sherwin, 1983). In view of their concurrent finding of a disproportionate number of left-handers among their early-onset cases, Seltzer and Sherwin (1983) postulated that there may be a greater vulnerability of the left hemisphere in presenile AD. However, others have found no such relationship between age-at-onset and either sinistrality (Chui et al., 1985; Faber-Langendoen et al., 1988; Filley et al., 1986) or aphasia (Appell, Kertesz, & Fisman, 1982; Becker et al., 1988; Capitani et al., 1990; Huff & Growdon, 1986; Huff et al.,

1990; Martin et al., 1986; Price et al., 1993; Selnes, Carson, Rovner, & Gordon, 1988). In fact, Bayles (1991) found older age-at-onset to predict a greater degree of language deficit after controlling for the effects of dementia severity on a subject-by-subject basis. She criticized the more common practice of controlling for disease duration in an effort to control for dementia severity as invalid in view of the wide variation in rate of progression among AD patients. Findings that the prevalence of aphasia is clearly dependent upon severity of dementia (ranging from 36% in mild AD to 100% in severe AD) emphasize the need for careful staging of dementia when studying the prognostic significance of language dysfunction in this disorder (Faber-Langendoen et al., 1988).

The nature of the relationships among aphasic disturbance, age at onset of AD, and disease progression may depend upon the specific linguistic function being considered (Bayles, 1991; Filley et al., 1986; Seltzer & Sherwin, 1983). There are findings to suggest that lexical/semantic deficits affecting word production may be a generic symptom in AD that is unrelated to age at symptom onset or rate of disease progression whereas impairment in auditory comprehension and, perhaps, written expression is more common in presenile AD and may bode more rapid cognitive decline (Becker et al., 1988; Filley et al., 1986; Lopez et al., 1991).

As with language deficits, there is also inconsistency with regard to the relationship between age at onset and degree of visuoconstructive disturbance, with some investigators reporting greater impairment in patients with senile onset (Filley et al., 1986) and others finding no such relationship (Becker et al., 1988).

Celsis et al. (1990) observed a complex interaction between age-at-onset and haemodynamic, neuropsychologic, and electroencephalographic asymmetry. A higher prevalence

of disproportionate left-sided impairment was observed in the 55 to 65 year age range whereas greater right deficiencies were more frequent in those over 65. They also identified a third subgroup of patients with predominant right-sided impairment, early-onset, and high overall severity of dementia.

Intrahemispheric Variability in Neuropsychological and Neurophysiological Profile

There is evidence to suggest the validity of subgrouping AD patients along an anterior/posterior as well as a left/right axis. There have now been several reported cases of probable and definite AD patients who presented with early and prominent visual associative deficits such as alexia, visual agnosia, prosopagnosia, environmental agnosia, visuoconstructive deficits, and Balint's syndrome (oculomotor apraxia, optic ataxia, simultanagnosia) associated in several instances with pronounced cerebral atrophy and/or decreased glucose metabolism in the posterior hemispheres (Benson, Davis, & Snyder, 1988; Berthier, Leiguarda, Starkstein, Sevlever, & Taratuto, 1991; Casselli et al., 1992; Cogan, 1985; De Renzi, 1986; Hof, Bouras, Constantinidis, & Morrison, 1990; Kertesz, 1990; Kiyosawa et al., 1989). Many of these patients sought ophthalmologic examination before cognitive deficits became manifest (Kiyosawa et al., 1989) and, in a number of cases, memory function, personality, and insight were relatively preserved until late in the course of the disease (Benson et al., 1988; Cogan, 1985). Maintenance of a selective posterior hypoperfusion into the late stages of the disease in histologically-confirmed cases of AD has also been observed (Neary et al., 1987). Pathology in seven cases of posterior cortical atrophy followed prospectively was distributed as follows: five cases of AD;

one case of nonspecific neuronal loss, spongiosis, and gliosis; and one case of Creutzfeldt-Jakob disease (Black, 1994). In a retrospective autopsy series of 2500 dementia cases, 8 AD patients with Balint's syndrome were differentiated from those with more typical Alzheimer dementia by a greater abundance of neurofibrillary tangles and senile plaques in visual association areas 17, 18, and 19, superior parietal cortex, posterior cingulate cortex, and the superior colliculus and by less AD pathology in the prefrontal cortex (Hof et al., 1990).

Several investigators (e.g., Binetti et al., 1996) have called attention to the existence of a subgroup of patients meeting diagnostic criteria for AD who are distinguished by prominent signs of frontal lobe dysfunction. These features, which include changes in personality, social comportment, and executive cognitive functions such as planning, organization, monitoring, and flexibility of behaviour (Blumer & Benson, 1975; Stuss, 1987; Stuss & Benson, 1983, 1984, 1986, 1987), stand in rather marked contrast to the relatively preserved social graces and severe anterograde amnesia of the typical Alzheimer patient (Coblentz et al., 1973; Cummings & Benson, 1986; Ingvar et al., 1978; Neary et al., 1986; Price et al., 1993; Sjögren et al., 1952).

Although pathological changes are seen in the frontal lobes of AD patients who were severely demented prior to death (Lishman, 1978), functioning in anterior brain regions, as revealed by metabolic rate, is usually spared until late in the course of the disease relative to the disturbance in temporoparietal areas (Chase, Burrows, & Mohr, 1987; Chase et al., 1984; Foster, et al., 1983, 1984; Frackowiak et al., 1981; Geaney & Abou-Saleh, 1990). This typical progression of AD from more posterior to more anterior association cortices as demonstrated by PET and SPECT is consistent with the early impairment of memory, language, and visuoconstructive skills which characterizes the Alzheimer patient and with findings of normal

neuronal and synaptic densities in frontal cortex in even severely demented subjects (Paula-Barbosa, Saraiva, Tavares, Borges, & Verwer, 1986).

The notion of "frontal sparing" in AD may be somewhat of an overgeneralization. PET findings suggest considerable regional variation in the involvement of frontal association cortex (Haxby et al., 1988; Kuhl et al., 1985) and, among moderately to severely demented patients, hypometabolism in premotor areas has been observed to equal that in the parietal lobes (Haxby et al., 1988). However, even within premotor cortex, metabolic reductions appear to develop later, failing to reach significance in mildly demented patients as do the changes in parietal and temporal regions.

Functional brain-mapping studies using PET and SPECT also demonstrate considerable heterogeneity in intrahemispheric patterns of cerebral hypometabolism among presumed Alzheimer patients, thus lending support to the notion of a frontal variant of AD. Subgroups of AD patients with disproportionate frontal or temporoparietal hypometabolism have been identified and these metabolic patterns have been found to correspond with the profiles of behavioral and neuropsychological deficits (Haxby et al., 1988). Conversely, anterior and posterior subgroups identified on clinical grounds have been shown to have compatible metabolic profiles (Chase et al., 1987; Kumar et al., 1990). These corresponding metabolic and neuropsychological profiles have been found to be quite stable over time in a given patient despite overall worsening of dementia severity (Haxby et al., 1988), arguing against an explanation of these differences in terms of variability among patients in the stage of the disease.

Again, in the absence of pathologically-confirmed diagnosis, it is unclear whether dementing patients presenting with prominent frontal-lobe involvement suffer from a variant of

AD or from a distinct pathological entity. Early and prominent frontal signs, most notably changes in personality and social comportment, have come to be recognized as hallmarks of Pick's disease which has a predilection for the frontal and anterior temporal lobes (Lishman, 1987). It is not surprising, then, that a number of cases of progressive dementia with prominent frontal lobe signs is found at autopsy to have the classical gross pathological features (circumscribed knife blade atrophy, especially in basofrontal regions) and histological changes (balloon cells and Pick bodies) of Pick's disease (Gustafson et al., 1990). A "frontal dementia" has also been observed in cases of Creutzfeldt-Jakob disease (Brun, 1987), bilateral thalamic infarction involving the dorsomedial nuclei (Brun, 1987), motor neuron disease, including amyotrophic lateral sclerosis (Gustafson, 1987; Neary et al., 1990) and a variant of spinal progressive muscular atrophy (Morita, Kaiya, Ikeda, & Namba, 1987), progressive supranuclear palsy (Albert, Feldman, & Willis, 1974; Maher, Smith, & Lees, 1985), and progressive subcortical gliosis (Brun, 1987).

Two independent groups of investigators, Neary and colleagues (1986) in Manchester, England, and Gustafson, Brun, and Risberg (Brun, 1987; Englund & Brun, 1987; Gustafson, 1987; Gustafson et al., 1990; Risberg, 1987) in Lund, Sweden, have described what appears to be a distinct form of frontal dementia. This "dementia of the frontal lobe type" (DFT), or "frontal lobe dementia of the non-Alzheimer type" (FLD), as respectively termed by the British and Swedish groups, is characterized clinically by disinhibition, loss of social and personal awareness, diminished insight and concern, hyperorality, utilization behaviour, stereotyped behaviour, distractibility and impersistence, dynamic (versus linguistic) aphasia, and mental inflexibility and impaired executive cognitive functions in the face of preserved instrumental cognitive abilities. Pathologically, FLD is characterized by fronto-temporal atrophy in the absence of specific

morphological abnormalities. Postcentral cortical areas, the amygdala and hippocampus, and the nucleus basalis of Meynert, areas significantly involved in AD, are only minimally affected and those brain areas that are attacked show only neuronal loss, slight gliosis and spongiosis (Brun, 1987). This condition has stronger familial aggregation than AD suggesting autosomal dominant inheritance (Gustafson, 1987) and accounts for approximately 10 to 20 percent of cases of primary degenerative dementia (Brun, 1987; Neary, 1994). The Swedish group has noted a short duration of illness relative to AD whereas the English group suggests that FLD is associated with a relatively long survival duration. In some cases, FLD is associated with motor neuron disease and it has been suggested that FLD and classical motor neuron disease may form a spectrum of the same disorder (Neary, 1994).

It is noteworthy, however, that the original Swedish patient series included two patients presenting with prominent manifestations of frontal lobe dysfunction who were found at necropsy to have AD (Brun, 1987). In a study by Haxby et al. (1988), autopsy confirmed the diagnosis of AD in 10 of 11 patients with prominent frontal hypometabolism during life (only one patient had FLD). Such findings suggest that frontal dementia may be a manifestation of both Alzheimer and non-Alzheimer pathology. It would appear that an important distinction between AD and FLD lies in whether or not there is concomitant involvement of more posterior cortical regions.

Whereas FLD patients present with *exclusive* frontal lobe deficits, the frontal variant of AD is characterized by prominent frontal lobe disturbance *in addition to* the more typical posterior temporoparietal dysfunction (Binetti et al., 1996; Delay & Brion as cited in Gustafson, 1987; Tariska, 1970). This distinction between frontal AD and FLD is substantiated by functional imaging studies which indicate that, in clinically-diagnosed and autopsy-proven cases of FLD,

decreases in cerebral blood flow are generally restricted to the anterior cerebral hemispheres (Neary, Snowden, Northen, & Goulding, 1988; Neary et al., 1987) whereas, in the frontal variant of AD, significant hypometabolism is usually evident in both frontal and parietal cortex (Chase et al., 1987; Haxby et al., 1988; Mann, Mohr, Gearing, & Chase, 1992; Risberg, 1987; Waldemar et al., 1994). Waldemar et al. (1994) found the co-presence of frontal hypometabolism in AD patients to be unrelated to disease duration or scores on a mental status examination, suggesting that it more likely reflects a variant than a stage of disease. Furthermore, variation in the regional distribution of dysfunction within the frontal lobes may differentiate the two groups. Whereas the greatest reduction in metabolism in frontal AD patients was observed in the premotor region (Haxby et al., 1988), depression of rCBF was found to be most pronounced in the prefrontal cortex in autopsy-confirmed cases of FLD (Gustafson et al., 1990).

Mann and colleagues (Mann, Mohr, & Chase, 1989; Mann et al., 1992) have recently reported that AD patients with rapidly progressive dementia can be differentiated from more slowly deteriorating patients by greater severity of frontal lobe dysfunction, as evident in cerebral glucose metabolism and neuropsychological test performance. Greater frontal lobe involvement has been observed in AD patients with earlier age at onset and longer disease duration (Gustafson, 1987). However, these factors could not account for the observed differences in frontal lobe involvement as the slowly and rapidly progressing patients were equivalent in terms of both age at symptom onset and age at testing. It might also be argued that the differences in progression rate were an artifact of group differences in stage of illness, in so far as rate of progression of AD may vary according to stage of disease (Burns et al., 1991a; Rasmusson et al., 1994, Thal & Grundman, 1986; but see Teri, Hughes, & Larson, 1990). However, the fact that the groups

were equivalent in terms of overall dementia severity, performance on tests of verbal, visuospatial, and memory functions, and metabolic activity in parietal, temporal, occipital and subcortical brain regions argues against such an interpretation. Furthermore, the finding that the frontal group in this sample was as impaired as the nonfrontal group on tests of instrumental cognitive abilities localized to more posterior brain regions serves to differentiate them from FLD patients.

Indirect support for a positive relationship between frontal lobe dysfunction and progression rate comes from several sources. Psychotic features, which have been associated with a faster rate of progression of AD (Drevets & Rubin, 1989; Jeste et al., 1992; Lopez et al., 1991; Mortimer, Ebbitt, Jun, & Finch, 1992; Stern et al., 1987), have also been shown to be particularly prominent in frontal dementia (Gustafson, 1987), to be associated with a greater density of senile plaques and neurofibrillary tangles in the middle frontal cortex in histologically-confirmed AD patients (Zubenko et al., 1991) and, in the case of idiopathic psychoses, to be accompanied by a selective decrease in blood flow and glucose metabolism in the frontal cortex (Ariel et al., 1983; Buchsbaum et al., 1982, 1984; Weinberger, Berman, & Zec, 1986). Kotrla and colleagues (Kotrla, Chacko, Harper, Jhingran, & Doody, 1995) found that AD patients with delusions had hypoperfusion in the left frontal lobe relative to the right. In prospective studies of AD patients, Miller (1994) found that those who developed delusions had a more profound decrease over time in right frontotemporal perfusion while Binetti et al. (1995) observed that the occurrence of delusions was related to the presence of white matter lesions in the frontal lobes. Furthermore, delusional AD patients have been found to perform more poorly than nondelusional ones on putative neuropsychological tests of frontal dysfunction (Jeste et al., 1992). Similarly, extrapyramidal motor signs, which have been associated with a more malignant form of AD, have

been shown to correlate with behavioral features of frontal lobe dysfunction (Bakchine et al., 1989; Girling & Berrios, 1990). In their postmortem study, Förstl et al. (1993) identified a subsample of pathologically-confirmed AD patients with Lewy bodies in the brainstem and cortex, a higher incidence of Parkinsonian features during life, and a frontal accentuation of cerebral atrophy. The correlation between parkinsonism and disease progression has led to speculation that a more malignant frontal variant of AD may be related to greater dysfunction in dopamine systems. Morris et al. (1989) have speculated that, in some cases, parkinsonism in AD may be related to AD pathology in the prefrontal terminal fields of the mesocortical dopaminergic system. That dopaminergic dysfunction can affect cognition is suggested by the frequent occurrence of cognitive impairment or dementia in patients with Parkinson's disease and by findings that this can be ameliorated to some degree with l-dopa treatment (Delis, Direnfeld, Alexander, & Kaplan, 1982; Marsh, Markham, & Ansel, 1971; Taylor, Saint-Cyr, & Lang, 1987). Alternatively, Mohr et al. (1990) have suggested that the greater frontal lobe involvement of their fast progressing group may be mediated by greater noradrenergic dysfunction in view of observations that the frontal lobe is the only cortical area with functionally significant reductions in NE in AD and that this decrease correlates with antemortem dementia severity (Adolfsson, Gottfries, Roos, & Winblad, 1979). Frontal release signs (such as palmomental, glabellar, snout, sucking, and grasp reflexes) have been associated with a more severe disease course (Bakchine et al., 1989). Finally, Becker, Bajulaiye, and Smith (1992) observed a more rapid decline in memory functioning over a one-year follow-up period among those early AD patients with a focal dysexecutive syndrome at baseline.

This putative relationship between degree of frontal lobe dysfunction and rate of cognitive deterioration has many important implications, not least of which is the promise of improvement in our ability to provide prognostic information to families and caregivers. However, in that support for such a relationship is based largely on retrospective data, it demands further validation. In the studies of Mann et al. (1989; 1992), rate of progression was determined retrospectively by dividing deviation from the normal range on a mental status measure by the estimated duration of symptoms. Determinations of disease duration are notoriously error-prone due to the insidious nature of the disease onset and the great variability in threshold for symptom detection among significant others. Furthermore, there is reason to suspect that the margin of error in estimations of disease duration might differ systematically according to the nature of the early symptoms. For example, subtle changes in personality and social comportment may be more readily dismissed than memory impairment as eccentricities associated with normal aging. Denial of illness is a hallmark of frontal dysfunction and, thus, it may be less likely that frontal symptoms will lead to subjective complaints on the part of the patient.

PREDICTION OF DEMENTIA PROGRESSION IN NONDEMENTED INDIVIDUALS AT RISK FOR AD

Recent evidence suggests that frontal lobe dysfunction may also predict conversion to dementia in preclinical AD. It is likely that Alzheimer pathology is present in the brain for many years prior to the appearance of obvious memory decline and dementia (Hardy & Allsop, 1991).

Assuming that future treatments for AD will be most efficacious when administered prior to the evolution of irreversible brain pathology, it would be highly desirable to be able to detect the presence of AD in its prodromal stages. Given that memory decline is typically the initial manifestation of the disease, measures of memory functioning would seem particularly well-suited to the detection of preclinical AD. Indeed, an increased frequency of the ApoE ϵ 4 allele (a known risk factor for AD) has been observed among individuals with age-related memory decline (Blesa et al., 1996). However, changes in memory functioning are a very common result of the normal aging process and, in the majority of cases, are quite benign. Thus reliance on memory changes alone in identifying preclinical AD may yield an unacceptably high false positive rate.

There is considerable debate concerning the prevalence of age-related memory decline and its etiologic and prognostic implications. This derives in large part from differences in how age-related memory decline is conceptualized and defined. Some investigators regard memory decline as an almost universal consequence of aging and define it in terms of diminished memory performance relative to a younger cohort. This position is reflected in the diagnostic criteria for "age-associated memory impairment" (AAMI) developed by the National Institute of Mental Health (NIMH; Crook et al., 1986). According to the NIMH criteria, AAMI can be diagnosed in intellectually normal individuals of at least 50 years of age who complain of gradual memory loss as reflected in such everyday problems as difficulty remembering names of new acquaintances or misplacing objects and who score at least one standard deviation below the mean for young adults on a standardized test of secondary memory.

The NIMH criteria have been criticized on the grounds that they fail to differentiate the larger proportion of elderly individuals with relatively benign, nonprogressive memory problems

from that minority in which the memory loss is a forerunner to dementia (Blackford & La Rue, 1989; Smith et al., 1991). This criticism is borne out by findings of a slightly elevated incidence of dementia among individuals with AAMI (Hänninen et al., 1995). One approach towards differentiating benign from malignant age-associated memory decline has been to search for features of the neuropsychological profile which might discriminate these two respective groups. In prospective cohort studies, both Albert and colleagues (Albert, 1997) and Hänninen et al. (1995) have found that neuropsychological tests of executive functions, considered to reflect the functioning of frontal brain systems, are useful in predicting progression of memory problems in elderly patients with cognitive impairment but no dementia. Although Albert (1997) did not find that perfusion differences in frontal neocortical regions on SPECT scanning discriminated those subjects who converted to dementia from those who did not, differences between these groups were observed in the anterior cingulate and the anterior thalamus (as well as in the hippocampus and posterior thalamus).

ASSESSMENT OF FRONTAL LOBE FUNCTIONING IN DEMENTIA

Yesavage and Brooks (1991) have stressed the fact that longitudinal research in AD demands better ways of quantifying decline and advocate the development of new tests that will allow for the valid assessment of abilities throughout the course of AD. They, like others (Galasko et al., 1991), have emphasized the need for instruments which are resistant to "floor effects". In that the validity of prospective studies aimed at identifying prognostic factors in AD

depends on the ability to dissociate these factors from overall dementia severity, it is equally important that the instruments used to measure such factors retain their specificity even at the lower end of the functional range.

The suitability of standard neuropsychological tests of frontal lobe function for studying frontal dysfunction in dementia patients is severely limited by the lack of specificity of these instruments as well as by their susceptibility to floor effects. Whereas the functions of the frontal lobes are considered to be of a supramodal, executive nature (e.g., Stuss & Benson, 1986), the validity of the neuropsychological tasks designed to measure them usually depends on the integrity of more posterior, modality-specific functions. Thus, failure on such tests may be due, not to frontal dysfunction *per se*, but to declining mnesis, gnosis, praxis, or language. This reasoning is supported by evidence that some of the most commonly-used neuropsychological indices of frontal lobe function (e.g., perseverative responding on the Wisconsin Card Sorting Test [WCST]) are as sensitive to diffuse brain damage as to focal frontal lobe lesions, even after controlling for overall level of psychological impairment (Robinson, Heaton, Lehman, & Stilson, 1980). The great range of variability among normal healthy elderly individuals on neuropsychological tests of frontal lobe function and the fact that many normal elderly adults are incapable of some of these tasks further attests to their limited specificity (Collins, Stuss, & Labelle, 1991). Clearly, attempts to evaluate the extent and significance of frontal dysfunction in AD will depend on the availability of tests which are both sensitive and specific to frontal lobe dysfunction across the wide range of cognitive capacity represented in a dementing population. Otherwise, putative frontal lobe tests become no more than another marker of overall dementia severity.

An alternative to existing psychometric methods for assessing frontal lobe functioning is the use of paradigms proven reliable and valid in studying the behaviour of infrahuman species, an approach referred to as "comparative neuropsychology" (Freedman & Oscar-Berman, 1986a, 1986b, 1986c; Oscar-Berman & Zola-Morgan, 1980a, 1980b; Oscar-Berman, Zola-Morgan, Oberg, & Bonner, 1982). Proponents of this approach maintain that, in holding performance requirements constant for humans and infrahuman species, assessment of psychological functions will be measured more analogously, thus allowing the wealth of behavioural and anatomical data generated in experimental studies to be brought more directly to bear on the issue of brain-behaviour relationships in humans. The use of animal models would appear to offer a particular advantage in work with dementia patients in that the relative simplicity of the tasks makes them manageable even for patients with quite severe cognitive impairment. Furthermore, the fact that these tasks can be administered nonverbally circumvents the potential problem that language impairment will confound interpretation of performance, as is the case on many standard neuropsychological tests. Two experimental paradigms, delayed alternation (DA) and delayed response (DR), shown to be both sensitive and specific to frontal lobe lesions in animals, may therefore have an application in the study of frontal lobe functions in dementia.

DA and DR Paradigms

The DR task was designed by the comparative psychologist Walter Hunter (as cited in Goldman-Rakic, 1987) in the early part of this century to study the abilities of different species to learn and respond to situations on the basis of stored information. In the classic version of the DR

task, a food reward is placed in one of two adjacent food wells in full view of the subject. An opaque screen is then lowered between the subject and the containers for a variable period of delay. The subject's initial response upon lifting of the screen is recorded (i.e., whether to the baited or the unbaited food well). The number of trials and errors necessary to establish consistently correct performance and the duration of delay which can be successfully bridged serve most often as the dependent variables.

The DA task is similar in many respects. However, the subject does not observe the baiting of the food wells in this paradigm. Rather, the respondent must learn that the location of the bait is alternated to the previously unbaited well following each correct response. Thus, the cue for each response is the location of the bait on the previous trial.

DA and DR are conducted in much the same way with human subjects as they are with infrahuman primates except that general verbal instructions are provided and the wells are baited with pennies rather than a food reward. The Wisconsin General Test Apparatus, used to conduct DA and DR in animal research, has been modified for use with human subjects by Oscar-Berman and Zola-Morgan (1980a, 1980b) and is illustrated in Appendix 2.

DA and DR Following Frontal Lobe Lesions in Infrahuman Primates

In his early studies of the effects of circumscribed experimental brain lesions in nonhuman primates, Jacobsen (1935, 1936) demonstrated that frontally-lesioned monkeys were particularly impaired on acquisition and retention of tasks involving delay. This deficit appeared to be permanent and to be specific to frontal association cortex, in that it was not observed after

extensive bilateral lesions to parietal (Jacobsen, 1936; Butters, Pandya, Stein, & Rosen, 1972), temporal (Jacobsen & Elder, 1936), motor or premotor (Jacobsen & Haslerud, 1936), or postcentral (Breslau, Barrera, & Warden, 1934) cortical areas. Moreover, the deficit was task-specific in that monkeys with complete bilateral extirpation of frontal cortex were unimpaired in retention or new associative learning of simple problem box or visual discrimination habits. In so far as DR differs from these latter tasks in that reward contingencies are constantly changing and the differential cues governing response selection are eliminated from the testing situation, Jacobsen attributed the deficit in DR to impairment of immediate memory. His subsequent finding that performance on DA tasks, which also requires that differential response cues be recalled from recent experience, was equally vulnerable to ablation of frontal association cortex in monkeys was consistent with this interpretation (Jacobsen & Nissen, 1937).

Debate has since ensued as to the mechanism of the DA and DR deficits, with various investigators attributing these deficits to increased distractibility (Malmo, 1942; Wade, 1947), locomotor hyperactivity (Wade, 1947), perseveration (Mishkin, 1964; Stanley & Jaynes as cited in Numan, 1978), alterations in motivation and response to reinforcement (Finan, 1942), impairment in the ability to shift directed attention (Konorski & Lawicka, 1964), inability to use recently-acquired information (Gross & Weiskrantz, 1964), inability to effectively utilize proprioceptive and spatiovestibular feedback information for the regulation of response patterns (Numan, 1978), and deficiencies in the ability to reprogram and reorganize responding in the face of changing problem-solving demands (Pribram, Ahumada, Hartog, & Roos, 1964). However, the bulk of evidence favours Jacobsen's initial speculation that the deficit is indeed one of immediate memory. It has been shown, for example, that allowing prefrontally-lesioned monkeys to orient to the

correct side during the delay, thereby eliminating memory demands, serves to ameliorate the DR deficit (Kojima, Kojima, & Goldman-Rakic, 1982). Frontal lesions produce similar impairment on both visual and auditory DA tasks, indicating that the deficit is supramodal (Blum, 1952).

Sophisticated electrophysiological studies conducted over the past two decades (Funahashi, Bruce, & Goldman-Rakic, 1989, 1990; Fuster, 1973; Fuster & Alexander, 1971; Kojima & Goldman-Rakic, 1982, 1984; Kojima, Matsumura, & Kubota, 1981; Kubota, Iwamoto, & Suzuki, 1974; Kubota & Niki, 1971; Niki, 1974a, 1974b, 1974c) have demonstrated the existence of a class of prefrontal neurons that respond with significant changes in firing rate during the delay period of DR and DA trials. A small subclass of these delay-sensitive prefrontal neurons are spatially discriminative, changing discharge rate during the delay period of DA (Niki, 1974b, 1974c) or DR (Kojima et al., 1981; Kojima & Goldman-Rakic, 1984; Kubota et al., 1974; Niki, 1974a) according to the location of the cue or the spatial position of the impending behavioural response (Niki & Watanabe, 1976). Contentions that this small group of "delay-related spatial discriminative" neurons, constituting only about 5% of the neuronal population of the prefrontal cortex (Kojima & Goldman-Rakic, 1984), subserve a fundamental spatial mnemonic function are further supported by findings that spatial differential unit activity observed during the delay of a DA (Niki, 1974b) or DR (Kojima & Goldman-Rakic, 1984) trial disappears if the monkey is not required to remember the spatial position of the cue over this period.

Use of an elegant oculomotor DR paradigm in conjunction with single-cell recording techniques has lent further corroborating evidence to the spatial memory hypothesis (Funahashi et al., 1989, 1990). Results of such studies have shown that the vast majority of delay-sensitive prefrontal neurons respond selectively to visual cues in specific spatial locations (i.e., have a

"memory" field, usually for the contralateral visual field) and, in concert, subtend the full perimetry of visual space. Thus, these neurons appear to hold visuospatial information "on-line" when the stimulus goes out of view. Such findings have led to the currently prevailing view that the DR and DA deficits following lesions of prefrontal cortex result from impairment in a spatial-mnemonic function and, in combination with findings obtained using other behavioural paradigms both with monkeys (e.g., Passingham, 1985) and with humans (Milner, 1982; Petrides, 1991; Petrides & Milner, 1982), suggest that a cardinal function of the intact prefrontal cortex is to subserve working memory and hence permit temporal organization of behaviour (Fuster, 1990, 1991a, 1991b; Goldman-Rakic, 1987, 1990; Kolb, 1990).

While the controversy regarding mechanism has waged in the half century since Jacobsen's initial observations, the phenomenon itself has been consistently replicated in a variety of species, from rats (Kolb, Nonneman, & Singh, 1974) to humans (Freedman & Oscar-Berman, 1986a, 1986b, 1986c) using various functional and structural lesioning techniques (Blum, 1952; Finan, 1942; Fuster & Alexander, 1970; Goldman & Rosvold, 1970; Goldman, Rosvold, Vest, & Galkin, 1971; Gross & Weiskrantz, 1962; Kojima et al., 1982; Lawicka & Konorski, 1963; Mishkin, 1957; Orbach & Fischer, 1959; Oscar-Berman, 1975; Pribram, Mishkin, Rosvold, & Kaplan, 1952; Stamm, 1969; Wade, 1947). More recently, Goldman-Rakic and her colleagues (see Goldman-Rakic & Friedman, 1991 for a review), using the 2-deoxyglucose method, have demonstrated significant and specific enhancement of metabolic activity in prefrontal cortex and in cortical and subcortical areas with which it is densely interconnected in primates performing delayed response tasks.

DA and DR Deficits following Frontal Lobe Lesions in Humans

The effects of frontal lobe lesions in humans on DA and DR tasks are somewhat less robust than those in monkeys. However, deficits in DA have been observed after gunshot wounds of the frontal lobes in the acute phases after injury (Teuber, unpublished findings cited in Pribram et al., 1964) as well as in patients with frontal lobe damage secondary to lobotomy (Pribram et al., 1964). Although Chorover and Cole (1966) did find the DA task wanting in sensitivity and specificity as a test of frontal dysfunction in humans, failure rate on this task was considerably higher among patients with frontal as opposed to nonfrontal lesions. Furthermore, among those patients who were able to acquire the task, nonfrontal patients required considerably fewer trials to reach criterion than did those with focal frontal lesions. Ghent, Mishkin, & Teuber (1962) found no evidence of DR deficits in patients with penetrating wounds localized to the frontal lobes. However, these particular patients had sustained nondebilitating injuries 8 to 10 years prior to testing. Freedman and Oscar-Berman (1986a) found neurological patients with bilateral frontal lobe damage, as documented on CT scanning, to be impaired on both DA and DR tasks. Whereas error rate on these tasks was found to be unrelated to a measure of anterograde memory, it did correlate with a measure of perseveration derived from the WCST, a widely-used and well validated test of frontal lobe dysfunction in humans (Drewe, 1974; Milner, 1963; Robinson et al., 1980). Freedman and Oscar-Berman attributed the failure of other investigators to observe DA and DR deficits in frontal lobe patients to several factors including: 1) inclusion in the experimental group of patients with unilateral frontal lesions (Jacobsen [1935, 1936; Jacobsen & Nissen, 1937] had demonstrated that bilateral lesions were necessary to abolish the capacity for

DA and DR in monkeys); 2) inclusion in the control sample of patients with tumour, which may have affected the frontal lobes through mass effects; and 3) deviations from the classic paradigm in the procedure used to study DR performance.

The greater inconsistency of DA and DR deficits in humans may also stem from the variability in accidental lesions in comparison to the relative precision of surgical ablation. Results of lesion and stimulation studies in primates have clearly demonstrated that all regions within the frontal lobes are not equipotential in terms of their capacity to give rise to DA and DR deficits (Blum, 1952; Brutkowski, Mishkin, & Rosvold, 1963; Goldman et al., 1971; Goldman & Rosvold, 1970; Gross & Weiskrantz, 1962; Mishkin, 1957; Oscar-Berman, 1975; Pribram et al., 1952). The rather precise localization of the functions subserving DA and DR within prefrontal cortex may well explain the variability with which such deficits are found following accidental frontal lobe lesions in humans. The issue of localization of DA and DR functions within the frontal lobes will now be considered in more detail.

Anatomical Subdivisions of the Frontal Lobe

The frontal lobes are divided into two principle regions, the precentral and the prefrontal. The precentral region is delimited posteriorly by the central sulcus. From here, it extends rostrally to occupy approximately one-half of the frontal lobe in the monkey, and about one-tenth of the lobe in man. Microscopically, the precentral area is composed of essentially five layers since the internal granular layer (cortical layer IV) is absent or greatly reduced. The precentral region is, in

turn, subdivided into the motor and premotor areas (areas 4 and 6 of Brodmann, respectively).

The outstanding characteristic of primary motor cortex is the presence of the gigantic pyramidal cells of Betz. The premotor area lies anterior to the motor area and superior to the arcuate sulcus and the corresponding part of the superior gyrus on the medial aspect. Architecturally, this area is similar to area 4 except that the large Betz cells are absent. However, large pyramidal cells are found in the third and fifth cortical layers throughout area 6.

The prefrontal region is distinguished from the precentral region in primates by the presence of an internal granular cortical layer which is formed largely of stellate cells. The axons of stellate cells form intrinsic or local connections within the cortex in contrast to pyramidal cells which send their axons out of the cortex to distant structures (Goldman-Rakic, 1987). This area has been subdivided into the frontal eye fields (area 8 of Brodmann), which lie anterior to the premotor region on the convexity of the hemisphere, the remainder of the dorsolateral convexity, the medial surface lying between the hemispheres, and the orbital region lying on the underside of the lobe. Areas 44, 45, and 46 of Brodmann in the third frontal gyrus and the middle portion of the second frontal gyrus, are the speech areas in the human brain.

Localization of DA and DR Functions within the Frontal Lobes

Experimental studies comparing the effects of subtotal lesions in various regions of monkey prefrontal cortex have demonstrated that excisions of the dorsolateral surface and, in

particular, of the middle one third of the sulcus principalis in the midlateral part of this region, give rise to the greatest impairment on both the DA and the DR tasks (Blum, 1952; Brutkowski et al., 1963; Butters et al., 1972; Goldman et al., 1971; Goldman & Rosvold, 1970; Gross & Weiskrantz, 1962; Mishkin, 1957; Oscar-Berman, 1975; Pribram et al., 1952). Cortical lesions elsewhere on the lateral frontal surface result in a milder deficit (Oscar-Berman, 1975) which disappears with time and training (Gross & Weiskrantz, 1962; Pribram et al., 1952). However, lesions of the entire lateral granular cortex do produce a greater deficit on these two tasks than do ablations restricted to the sulcus principalis (Gross & Weiskrantz, 1964). Sulcus principalis is thus regarded as the cortical "focus" of the DA and DR deficits with the surrounding tissue on the lateral aspect of the frontal lobe considered the "field" (Gross & Weiskrantz, 1964). Localized disruption of function in sulcus principalis by means of electrical stimulation (Stamm, 1969) and cryogenic depression (Alexander & Goldman, 1978; Fuster & Alexander, 1970) also gives rise to DR and DA deficits and electrophysiological studies have revealed a preponderance of "delay-sensitive" neurons in the region of the sulcus principalis (Funahashi et al., 1989, 1990; Kojima & Goldman-Rakic, 1982; Niki, 1974a, 1974b, 1974c), particularly the middle third (Kubota & Niki, 1971). Compelling evidence for the specialization of sulcus principalis for DA and DR comes from demonstrations of double dissociation of function following focal prefrontal lesions. Performance on go/no-go problems (including go/no-go delayed response and go/no-go delayed alternation), object alternation, delayed matching to sample, and discrimination tasks, impaired by lesions elsewhere in prefrontal cortex, is relatively unaffected by lesions of sulcus principalis (Mishkin & Manning, 1978; reviewed by Rosenkilde, 1979). Goldman and colleagues observed that arcuate sulcus lesions produced much greater impairment of conditional position responding

(a spatial task without delay; Goldman & Rosvold, 1970) and go-no go alternation (a delay task without a spatial component; Goldman et al., 1971) than did sulcus principalis lesions. Such subtle dissociation of function confirms that both spatial and delay parameters are critical to eliciting the DA/DR deficit and provides strong support for the prevailing hypothesis that dorsolateral prefrontal cortex mediates short-term spatial memory and localizes this function more specifically to the sulcus principalis. Whereas monkeys with lesions of sulcus principalis exhibit deficits only on spatial DR tasks (Goldman & Rosvold, 1970; Goldman et al., 1971), leaving memory for the features of objects unaffected, monkeys with lesions of the inferior convexity exhibit deficits on tasks requiring working memory for visual features (e.g., colour, shape) of objects rather than their location, suggesting that different subdivisions of prefrontal cortex may be specialized for working memory in different informational domains (Goldman-Rakic, 1987).

DA and DR may themselves be dissociable. Although deficits in both functions are most prominent following dorsolateral lesions, orbitofrontal damage is more disruptive of DA than of DR (see Oscar-Berman et al., 1982; Oscar-Berman, McNamara, & Freedman, 1991). This has been attributed to the greater sensitivity of DA to the perseverative tendencies which follow lesions to more ventral regions in both subhuman primates (Mishkin & Manning, 1978) and humans (Oscar-Berman et al., 1991). Within dorsolateral prefrontal cortex, both the focus and the field for DR appears to be larger than that for DA (see Rosenkilde, 1979).

Electrophysiological studies have shown that the locations of units related to DA are circumscribed to the midprincipalis areas, whereas units responsive during DR task performance are more widely scattered in the midprincipalis, arcuate (Kubota et al., 1974) and anterior cingulate (Fuster, 1973) cortex. Further supporting the dissociability of these tasks are findings of

DA but not DR deficits following medial temporal lobe lesions in monkeys and of differential extent and rate of recovery in these functions following brain damage (see Oscar-Berman et al., 1982, 1991). Moreover, these capacities appear at different stages in development, as evident in the fact that ablations (Kling & Tucker, 1968) and cooling (Alexander & Goldman, 1978) of dorsolateral prefrontal cortex in immature monkeys impair performance on DA but not on DR. These deficits have also been dissociated in humans. The work of Freedman, Oscar-Berman and colleagues (see Oscar-Berman et al., 1991 for review) has demonstrated a number of dissociations between severity of deficits in DA and DR in various neurological conditions involving prefrontal cortex.

This functional specificity within prefrontal cortex is undoubtedly mediated by regional differences in neural circuitry. Dorsolateral and orbital subregions of the prefrontal cortex, which have been clearly distinguished on functional grounds, have been shown to have distinct patterns of subcortical projections (Johnson, Rosvold, & Mishkin, 1968). For example, those loci within dorsolateral prefrontal cortex which give rise to the most severe deficits in DR result in distinctive patterns of retrograde degeneration in the thalamus (largely confined to the lateral half [parvocellular region] of the dorsomedial nucleus; Pribram et al., 1952). Goldman-Rakic (1987) has summarized the functional connectivity of the sulcus principalis, the cortical focus of DR and DA. The major cortical input to the posterior two-thirds of the principal sulcus originates in the posterior parietal cortex, the cortical centre for spatial information processing. This connection provides access to the visuospatial information necessary to register the location of the food reward. Multiple direct and indirect connections link the principal sulcus with the hippocampus, a critical subcortical structure for many forms of memory, and undoubtedly play a major role in the

mnemonic requirements of DR. Projections from the sulcus principalis to the caudate nucleus, the motor thalamus, and the deep "motor" layers of the superior colliculus permit the sulcus principalis a role in motor control, including the selection or inhibition of responses. Emergence of the capacity for DR in both monkeys and humans during the course of development corresponds to a period of synaptic excess, indicating its dependence on establishment of the appropriate neural circuitry (Goldman-Rakic, 1987).

In support of this idea that function is supported by neural systems are findings that DR and DA deficits can also be produced in monkeys by lesions of the dorsomedial nucleus of the thalamus (Isseroff, Rosvold, Galkin, & Goldman-Rakic, 1982; Schulman, 1964) and by surgical lesions (Battig, Rosvold, & Mishkin, 1960; Divac, Rosvold, & Szwarcbart, 1967; Goldman & Rosvold, 1972), cryogenic depression (Krauthamer, Liebeskind, & Salmon-Legagneur, 1967), and electrical stimulation (Stamm, 1969) of the head of the caudate nucleus, areas which, as has just been reviewed, have extensive interconnections with dorsolateral prefrontal cortex (Goldman-Rakic, 1987; Nauta, 1972). Consistently, changes in neuronal firing rate during the delay period of DR have been observed in these as well as other cortical and subcortical areas with reciprocal connections with prefrontal cortex (Funahashi et al., 1989; Fuster & Alexander, 1971). Studies with primates using the 2-deoxyglucose method (as reviewed by Goldman-Rakic & Friedman, 1991) have demonstrated specific enhancement of metabolic activity, not only of dorsolateral prefrontal cortex, but of cortical and subcortical brain regions with extensive prefrontal interconnections, including the mediodorsal and anterior thalamic nuclei and hippocampus, during performance of tasks requiring delayed response. The head of the caudate appears capable of sustaining normal DR in monkeys following lesions to the prefrontal cortex in infancy. Monkeys

with prefrontal lesions demonstrated sparing of DR whereas those with combined lesions of prefrontal cortex and head of the caudate nucleus did not (Kling & Tucker, 1968). Moreover, there appears to be functional heterogeneity within the head of the caudate which corresponds to topographical projections from the prefrontal cortex (Divac et al., 1967). Lesions of the anterodorsal head of the caudate mimicked those of dorsolateral prefrontal cortex, which projects preferentially to this area, in producing deficits on DA but not object reversal. In contrast, lesions of the ventrolateral sector of the head of the caudate impaired object reversal but not DA. This latter syndrome is compatible with that observed following lesions to the orbitofrontal cortex, which projects to the ventrolateral area. The work of Rosvold and colleagues as well as others (as described in Rosvold, 1972) has demonstrated that projections from these functionally distinct areas within the caudate nucleus follow separate trajectories through successive subcortical relays. Thus, there appear to be at least two dissociable frontal systems: a "dorsal" system which projects from the dorsolateral prefrontal cortex, through the anterodorsal caudate and lateral pallidum to the subthalamic nucleus, and an "orbital" system which finds its way from the orbital cortex through the ventrolateral caudate and medial pallidum to the dorsal thalamus.

Specialization of function within subregions of the prefrontal cortex may also be related to the terminal distribution of various neurotransmitter systems. Biochemical studies have revealed marked regional differences in the endogenous concentrations and in the turnover rates of catecholamines in different cytoarchitectonic areas of the monkey cerebral cortex (see Goldman-Rakic, 1987). Rat prefrontal cortex is innervated by the three aminergic systems, dopamine, NE, and 5HT, all of which appear to modulate the responsiveness of efferent prefrontal neurons to afferent synaptic inputs (Thierry, Godbout, Mantz, & Glowinski, 1990). There is evidence to

suggest that the catecholamines at least (dopamine and NE) may be vital to normal DA and DR performance. Toxin-induced depletion of dopamine and NE in the principal sulcal region of monkeys has been observed to produce a deficit in DA almost as severe as that resulting from surgical ablation, while having no effect on visual discrimination tasks (Brozoski, Brown, Rosvold, & Goldman, 1979). This behavioural deficit was most strongly correlated with the extent of dopamine depletion in the affected area and could be reversed by the catecholamine precursor, L-dopa, and, in half of the animals, by the specific dopamine agonist, apomorphine. Clonidine, an α_2 -adrenergic receptor agonist, produced a moderate enhancement of DA performance in all animals, both before and after chemical lesioning. Clonidine has also been shown to reverse the age-related decrement in DR in monkeys (Arnsten & Goldman-Rakic, 1985). Conversely, the α -adrenergic receptor antagonist, yohimbine exaggerated the DR deficit when administered alone and, when co-administered with clonidine, negated the facilitating effect of this latter compound. In contrast, the beta-adrenergic receptor antagonist, propranolol, and the selective α_1 antagonist, prazosin, either alone or in combination with clonidine, failed to exert significant effects on DR. Neither clonidine nor yohimbine affected performance on a visual pattern discrimination task. In support of their findings implicating the α -adrenergic system in DR, Arnsten and Goldman-Rakic (1985) cite findings of dense clonidine binding in primate principal sulcal cortex and reports that the prefrontal cortex contains the highest concentration of postsynaptic α_2 receptors in the rodent brain. That the foregoing effects were mediated through receptors in the principal sulcal region was evident in the failure of these various compounds to affect DA or DR performance of monkeys with bilateral surgical ablation of the dorsolateral prefrontal cortex surrounding the principal sulcus.

Based on their observations of differential impairment of DA and DR in various neurological conditions with known neurotransmitter abnormalities, Oscar-Berman and colleagues (1991) have speculated that DR may be more susceptible to disturbances in catecholaminergic function, due to extensive interconnections between the dorsolateral prefrontal system and brainstem aminergic nuclei, whereas DA is more sensitive to disruption of cholinergic systems which densely innervate ventral (including orbital) prefrontal cortex and which, more importantly, are under descending control from ventral prefrontal regions.

The distribution of Alzheimer pathology within the brain is far from random and regional variation in vulnerability corresponds to a great degree with anatomical connectivity and neurotransmitter characteristics (Katzman & Jackson, 1991). In that anatomical and chemical neural networks also determine functional specificity, it is possible that the clinicopathological relationships observed in AD may be "purer" than those observed in patients who have sustained accidental neurological lesions. Local differences in neuronal loss within brainstem aminergic nuclei, thought to reflect topographical differences in projection patterns, have been documented (e.g., Zweig et al., 1988). For example, degeneration in the locus coeruleus in AD patients is particularly pronounced in the anterior portion which is innervated by the medial and lateral aspects of prefrontal cortex (but not orbitofrontal cortex; Arnsten & Goldman-Rakic, 1984; Zweig et al., 1988). Thus, paradigms such as DA and DR which appear to reflect activity within specific neural networks, may prove more sensitive and selective in neurodegenerative diseases than in cases of accidental cerebral lesions which do not respect functional anatomical boundaries.

Oscar-Berman and colleagues have adopted these experimental paradigms in investigating the involvement of frontal systems in various neurological conditions including Korsakoff disease

(Oscar-Berman et al., 1982), Huntington's disease (Oscar-Berman et al., 1982), AD (Freedman & Oscar-Berman, 1986b, 1986c), and Parkinson disease (Freedman & Oscar-Berman, 1986b, 1986c). Their demonstration of reliable differences among these neurological groups and between neurological patients and normal control subjects on several experimental paradigms used with animal models contradicts the assumption that the "comparative neuropsychological" approach will be insensitive in human subjects due to their ability to use language-based mnemonic strategies (Oscar-Berman et al., 1982). Freedman and Oscar-Berman (1986c) found performance of AD patients to be significantly worse than that of nondemented control subjects on both DA and DR tasks, while demented patients with Parkinson's disease were selectively impaired on DA. On the basis of these findings, they speculated that both orbitofrontal and dorsolateral frontal system dysfunction may be involved in AD whereas the dementia associated with Parkinson's disease may more selectively involve dorsolateral frontal systems (perhaps at the level of the caudate nucleus). Subsequent findings that AD patients were more impaired than Parkinson's patients on an object alternation task, which is most sensitive to lesions in the orbitofrontal cortex in non-human primates, was consistent with this reasoning (Freedman, 1990). Furthermore, error analysis revealed that the Alzheimer patients made more perseverative errors (repetition of a previously incorrect response) than did the Parkinson patients. This type of perseverative responding has been strongly associated with orbitofrontal lesions and is presumed to mediate the poor performance of orbitally lesioned monkeys on the object alternation task.

PURPOSE OF THE CURRENT STUDY

The results of numerous studies spanning more than half a century indicate deficits in DA and DR to be reliable behavioural markers of frontal system dysfunction in nonhuman primates and in man. In that failure on DA following frontal lobe damage in man appears to be unrelated to the presence or absence of dementia or mild dysphasia (Chorover & Cole, 1966), these paradigms may be much better suited than standard neuropsychological tests of frontal lobe function to the longitudinal study of the relationship between frontal lobe dysfunction and rate of progression of AD. If, as has recently been suggested, frontal system involvement predicts rate of disease progression in AD (Mann et al., 1989, 1992), and may even predict conversion to dementia in elderly patients with preclinical AD (Albert, 1997; Hänninen et al., 1995), such a reliable and valid index of frontal function may be a valuable prognostic guide. Moreover, in that performance decrements on DA and DR may be mediated by distinct neural, and perhaps neurochemical, systems within the prefrontal cortex, these models may have a potential application in monitoring the effects of neurotransmitter replacement in experimental drug trials and, ultimately, in guiding the selection of pharmacologic agents for symptomatic treatment of a given patient.

The purpose of the current study was threefold: 1) to validate DA and DR as measures of frontal lobe dysfunction in AD and AAMI and to investigate whether they are more effective markers of frontal lobe dysfunction in these populations than are standard neuropsychological tests of frontal lobe function; 2) to investigate the prognostic significance of disproportionate frontal lobe dysfunction in early AD and, thereby, to further explore the validity of a frontal

subtype of AD; and 3) to determine whether frontal lobe dysfunction might serve to predict progressive cognitive decline in AAMI subjects.

HYPOTHESES OF THE CURRENT STUDY

I Validity of DA and DR as Measures of Frontal Lobe Dysfunction in AD and AAMI

1. Performance on DA and DR tasks will be significantly correlated with that on standard neuropsychological measures of frontal lobe functioning.
2. Performance on DA and DR tasks will not correlate with performance on neuropsychological measures of parietal lobe functioning.
3. Performance on DA and DR tasks will correlate positively with frontal perfusion among subjects with AAMI and mild AD.
4. Performance on neuropsychological measures of nonfrontal function will not correlate with frontal perfusion among the AD and AAMI subjects.

5. DA and DR will be more specific markers of frontal lobe dysfunction than will clinical frontal neuropsychological tests as evident in their stronger correlations with frontal perfusion.

II Prognostic Significance of Frontal Lobe Dysfunction in AD and AAMI

6. Among AD and AAMI subjects, those with greater frontal dysfunction at initial testing will show greater negative change in overall mental status over a one-year test-retest interval. In addition, degree of frontal hypoperfusion at intake to the study will predict the deterioration on follow-up memory testing among the AAMI subjects.
7. DA and DR will be more predictive of change in overall mental status over a one-year follow-up period than will clinical neuropsychological measures of frontal lobe function which, in turn, will be more predictive than clinical neuropsychological measures of parietal lobe functioning.

METHOD

SUBJECTS

Two groups of subjects were included in the present study, AD patients and AAMI subjects. The AD group was comprised of individuals seen in memory clinics at the Ottawa General Hospital (OGH) and the Elisabeth-Bruyère Health Centre (CHEB). The AAMI group consisted of community-residing volunteers who had responded to an advertisement (posted in a senior's magazine and in the newsletter of the local Alzheimer Society), appealing to older individuals who had noticed their memory to be slipping.

The protocol was approved by the ethics committees of both OGH and CHEB. Informed consent was obtained from all subjects (See Appendix 3 for study information sheet and consent form). In the case of the AD patients, consent was also obtained from their power of attorney for personal care (where available) or from a family member (usually the spouse or child accompanying the patient to the clinic). In the case of nondemented subjects, proxy consent was not sought. The protocol required that, for all subjects, a collateral familiar with the subject's day-to-day functioning complete a functional rating scale. In the case of most of the AD subjects, this scale was completed by the same family member providing proxy consent. In one instance, this questionnaire was completed by a paid caregiver (the subject was living in a senior's residence) and, in another case, the rating scale was completed by a close friend who was residing with the patient.

Subjects were fluent in English with the exception of one francophone individual in the AD patient group who was tested in French. Language of testing was not considered particularly

important in so far as most of the tests used in this study tap visuospatial and nonverbal reasoning skills and involve neither verbal stimuli nor responses. Indeed, in that the DA and DR paradigms were developed with primates, they can be carried out in the absence of verbal communication. Therefore, there seems no reason to assume any systematic difference in performance as a function of language of testing so long as test instructions are clearly understood by the respondent.

Among the tests in the battery on which language of testing might be expected to systematically affect performance are the dementia screening tests (used to determine eligibility for the study and to calculate the Dementia Severity Index) and the letter fluency task. Few normative data from French-speaking samples have been published for these tests and anglophone and francophone subjects have never been compared in the same study. In order to investigate the equivalence of these tests in francophone and anglophone individuals, a multivariate analysis of covariance was performed on scores from the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), Dementia Rating Scale (DRS; Coblenz et al., 1973; Mattis, 1976, 1988), and "F" fluency test obtained by French- and English-speaking patients assessed in the OGH Memory Disorders Clinic over the past two years. French translations of these tests have been developed by the neuropsychology service of the OGH and have been in regular clinical use for a number of years. French ($n = 19$) and English ($n = 20$) subjects (defined according to preferred language of testing) were compared. The groups did not differ with respect to age but mean years of education was significantly greater in the English group (11.8 [$SD = 2.29$] for the English subjects versus 7.9 [$SD = 3.23$] for the French subjects; $F = 19.16$, $p < .001$). Subjects were equated for dementia severity by including only those individuals with a Clinical Dementia

Rating (CDR; Hughes, Berg, Danziger, Coben, & Martin, 1982) of 0.5 or 1.0, the range of dementia severity represented in the current study. There was no main effect of language in the multivariate analysis after controlling statistically for differences in level of education between the two language groups (Wilk's Lambda = 0.859, $p > 0.15$). Neither were the univariate analyses of covariance significant for any of the three variables (DRS: $F = 0.69$, $p > 0.79$; MMSE: $F = 1.42$, $p > 0.24$; "F" Fluency: $F = 2.30$, $p > 0.13$). These preliminary findings corroborate our clinical experience that performance on these tests has similar clinical implications in both French- and English-speaking individuals.

General Exclusion Criteria

- 1) A score of 10 or greater on the Geriatric Depression Scale (GDS; Yesavage et al., 1983). The GDS was selected as a screening measure for depression as it was specifically designed for sensitivity to depressive symptoms and ease of administration in an elderly population. Due to the limited availability of subjects, this criterion was relaxed in the case of one AD patient who scored 14 but who did not appear to be suffering from a syndromic depression. A cut-off of 14 on this scale still yields 80% sensitivity and 100% specificity for clinically-diagnosed depression (Brink et al., 1982). A cut-off score of 12/13 was recommended by Blackford and La Rue (1989) in their adaptation of diagnostic criteria for AAMI.

- 2) **History of prior or intercurrent neurological disorder including any of the following:**
Evidence on CT scan of tumour, infarction, or normal pressure hydrocephalus; history of major head trauma, Parkinson's disease, Huntington's disease, or supranuclear palsy.
Some degree of low attenuation in the periventricular white matter on CT scanning (presumably reflecting chronic ischemia) was acceptable provided that i) there was no clear-cut infarction; ii) the clinical presentation and the results of other investigations were compatible with a diagnosis of AD; and iii) the score on the Hachinski Ischemia Scale was less than four. Such mild leukoencephalopathy, noted in three subjects, is a common finding in patients diagnosed with AD and has led to hypotheses that there is considerable overlap between cerebrovascular disease and neurodegenerative conditions (Breteler, 1996; Brun, 1996; Brun & Englund, 1986; Leys et al., 1991a, 1991b; Sawada, Naritomi, Shimizu, Miyashita, & Kinugawa, 1996).
- 3) **Significant hepatic, renal, gastrointestinal, pulmonary, endocrine, metabolic, or haematologic conditions, unstable ischemic heart disease, or current malignancy.**
- 4) **Uncorrectable visual or hearing impairment.**
- 5) **Past or present DSM III-R (American Psychiatric Association, 1987) diagnosis of major psychiatric illness, including drug or alcohol abuse.**

- 6) Use of any drug that might significantly affect cognitive function during the month prior to psychometric testing.
- 7) Known allergy to potassium perchlorate, technetium-99m-hexamethyl-propyleneamine oxime (^{99m}Tc -HMPAO), or technetium-99mTc-ethyl-cysteinate-dimer (^{99m}Tc -ECD). Such allergies are very rare.
- 8) Age less than 50.

AD Patients

Nineteen patients assessed in the memory clinics at OGH and CHEB participated in the study. Two of these subjects withdrew consent to undergo SPECT scanning after having completed all other aspects of testing. The data from these subjects were used in all analyses not involving the SPECT variables. In the case of one AD subject, valid follow-up data could not be obtained as the patient had begun taking tacrine over the inter-test interval. Tacrine (available commercially in the US by the name of Cognex) is a drug which inhibits the reuptake of acetylcholine from the synaptic cleft and which has been shown to temporarily slow the progression of cognitive dysfunction in AD. Another AD patient was lost to follow-up due to acute health problems affecting her higher mental functioning and resulting in institutionalization. She was deemed untestable by health care workers and family members one year after intake to

the study. Data from these subjects were not included in any of the analyses involving dementia progression.

Inclusion Criteria for AD Patients

- 1) Satisfaction of DSM III-R (American Psychiatric Association, 1987) criteria for a diagnosis of dementia (see Appendix 1) as determined by a dementia workup including medical and neurological examination, CT scan, EEG, blood work, functional rating by a primary caregiver (using the scale of Lawton and Brody, 1969), as well as administration of a neuropsychological screening battery comprised of a modified version of the MMSE, the DRS, a 20-item version of the Boston Naming Test (Goodglass, Kaplan, & Weintraub, 1983), the Trail Making Test (parts A and B; Army Individual Test Battery, 1944), drawing subtests from the Boston Diagnostic Aphasia Examination (BDAE; Goodglass & Kaplan, 1987), and brief tests of ideomotor praxis, calculation, judgement in hypothetical circumstances, and word-list generation following letter cuing.
- 2) A history of dementia, as reported by the patient or a collateral source, of at least six months.
- 3) Satisfaction of NINCDS-ADRDA criteria for a diagnosis of probable AD (McKhann et al., 1984; Appendix 1) as determined by the same assessment protocol as that described for the determination of dementia.

- 4) CDR of 0.5 (questionable dementia) or 1.0 (mild dementia) and a score greater than 100 on the DRS. It was considered important to restrict the range of dementia severity in the sample in that many of the tests in the neuropsychological battery lose their specificity in moderately to severely demented patients and in that rate of dementia progression may vary as a function of stage of illness. The CDR is a global measure of dementia severity made by the clinical team by applying a simple algorithm to ratings (on a five-point scale) of the patient's level of functioning in the following cognitive and behavioural spheres: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. The foregoing information is derived from a semistructured clinical interview with the patient and an appropriate collateral source. Previous work has shown the inter-rater reliability of the CDR to be high (0.89 or better) and has demonstrated highly significant correlations between the CDR and popular mental status scales (Hughes et al., 1982). Furthermore, the CDR has been shown to accurately predict the subsequent rating obtained at 6 to 9 months after enrolment into a longitudinal study. Among patients with a CDR of 0.5 or 1 in the OGH Memory Disorder Clinic in the past two years, scores on the DRS ranged from 82 to 139.
- 5) A score of four or less on the Hachinski Ischemia Scale (Hachinski, 1978; Hachinski et al., 1975; see Appendix 4). This scale, which rates individuals according to risk factors for and indications of cerebrovascular disease, has been shown to reliably differentiate between AD and multi-infarct dementia in patients with known histological diagnoses (Rosen, Terry, Fuld, Katzman, & Peck, 1980).

AAMI Subjects

A sample of 18 AAMI subjects was derived from approximately 40 individuals responding to the appeal for volunteers. All respondents underwent a screening assessment comprised of a social and medical history, the Subjective Memory Questionnaire (SMQ; Bennett-Levy & Powell, 1980), the GDS, the MMSE, and memory screening measures (see Inclusion Criteria for details). Those individuals who were not eliminated on the basis of the general exclusion criteria listed above, who met the following inclusion criteria, and who were agreeable, were enrolled into the study. One of the AAMI subjects was unavailable for the one-year follow-up mental status and memory testing due to family crisis. Thus, only 17 AAMI subjects were considered for analyses involving the follow-up measures.

Inclusion Criteria for AAMI Subjects (From Crook et al., 1986)

- 1) Complaints of memory loss reflected in such everyday problems as difficulty remembering names of individuals following introduction, misplacing objects, difficulty remembering multiple items to be purchased or multiple tasks to be performed, problems remembering telephone numbers or postal codes, and difficulty recalling information quickly or following distraction (established by means of spontaneous self-report and responses to the SMQ). Onset of memory loss must be described as *gradual*, without sudden worsening in recent months.

- 2) Memory test performance that is at least one standard deviation below the mean established for young adults on a standardized test of secondary memory (recent memory) with adequate normative data. The specific tests and cutoff scores recommended by Crook et al. (1986) were used for this study. These measures included Administration A of the Benton Visual Retention Test (BVRT; Benton, 1974) and immediate and delayed versions of the Logical Memory and Verbal Paired Associates subtests of the Revised Wechsler Memory Scale (WMS-R; Wechsler, 1987). In keeping with the practice of Crook's group (e.g., Youngjohn, Larrabee, & Crook, 1992), this criterion was satisfied if performance on any one of these measures fell one standard deviation below the mean of a younger cohort.
- 3) Evidence of adequate intellectual function as determined by a scaled score of at least 9 (raw score of at least 32) on the Vocabulary subtest of the Wechsler Adult Intelligence Scale--Revised (WAIS-R; Wechsler, 1981).
- 4) Absence of dementia as determined by a score of 24 or higher on the MMSE.

ASSESSMENT SCHEDULE

Initial behavioural testing was typically carried out over two to three sessions conducted on separate days, depending upon the subject's tolerance for such testing. Testing was conducted either at the OGH or in the subject's home at the discretion of the subject.

Part I—Cognitive and Memory Screening: The first stage of behavioural testing involved screening for cognitive impairment and memory loss. This type of testing was required both to determine eligibility for the study and to monitor changes in overall cognitive status and/or memory function over a one-year follow-up interval. For most of the AD patients referred from the OGH, the cognitive screening tests (which included the MMSE, the DRS, and brief measures of naming, ideomotor praxis, calculation, visual memory, and judgment) had already been conducted as part of the diagnostic workup in the Memory Disorder Clinic prior to their enrollment into the study and were not readministered (provided there was a reasonably short interval between such mental status screening and enrollment into the study). In the case of those AD subjects referred from other memory clinics, this mental status testing was conducted during an initial screening session. Scores on the DRS were used in determining eligibility of AD patients for the study (it was required that they score greater than 100 on this test in an effort to limit the AD sample to those with mild dementia). Likewise, potential AAMI subjects were administered the MMSE as part of an initial screening examination to determine their eligibility for the study (i.e., it was necessary that they score at least 24 on this measure to rule out dementia). For AAMI subjects, the remaining portions of the dementia screening evaluation were given during subsequent testing sessions, after their eligibility for the study had been determined.

During the initial screening examination, potential AAMI subjects were also administered a number of memory screening tests (BVRT, Logical Memory I and II and Verbal Paired Associates I and II subtests from the WMS-R) in order to detect those individuals meeting inclusion criteria for the diagnosis of AAMI. Initial screening of potential AAMI subjects also included a semi-structured interview probing medical and social history, a questionnaire pertaining to symptoms of AAMI, and the SMQ, to ensure that they met other exclusion and inclusion criterion of AAMI.

As early as possible in the assessment process, a significant other (family member, cohabitant, or paid caregiver) was asked to complete the Lawton Scale (Lawton & Brody, 1969), a multiple-choice scale which requires the respondent to rate the individual's level of functioning in important spheres of day-to-day living such as feeding, dressing, and toileting.

Part II: The second phase of testing involved the administration of a neuropsychological assessment battery. This was generally completed within one month of most recent administration of the DRS.

Part III: The third phase of behavioural testing involved administration of the DR and DA tasks. Testing of DR always preceded that of DA in order that the same shift of mental set was required of all subjects.

Part IV: The dementia screening battery was readministered in its entirety approximately one year following initial administration of the DRS. In the case of many of the AD subjects referred from the OGH, these data were gathered as part of the routine annual follow-up provided by this clinic. At the time of follow-up, the significant other was again asked to complete the Lawton Scale in order to determine changes in the subject's level of day-to-day functioning. In the case of

the AAMI subjects, the memory screening tests used in determining eligibility for the study were readministered on the assumption that they would be more sensitive than global mental status scales to any decline in cognitive functioning over the inter-test interval.

SPECT scanning was carried out in the Department of Nuclear Medicine at the Ottawa General Hospital within one month of behavioural testing.

TESTS AND INVESTIGATIONS

Overall Mental Status

An index of overall mental status, representing a composite of scores on the mental status measures and functional rating scale, was calculated from initial screening data and from follow-up data, respectively. Change in overall mental status was determined by subtracting the follow-up score from the intake score.

In the case of AAMI subjects, a second index was computed to determine change in performance on tests of recent memory. As in the case of the overall mental status measure, this memory index, a composite of scores on the memory screening tests, was calculated at initial screening and follow-up assessment and the difference between the two scores was computed.

Clinical Neuropsychological Tests

The neuropsychological assessment battery was comprised of tests selected according to their sensitivity and specificity to neurological damage in the frontal and parietal lobes, respectively. Frontal and posterior measures were included to allow determination of both the sensitivity and the specificity of DA and DR as measures of frontal dysfunction.

Frontal Measures

1) Wisconsin Card Sorting Test (Berg, 1948; Grant & Berg, 1948). The WCST was administered and scored according to Heaton's protocol (Heaton, 1981). Performance on the WCST and, in particular, the tendency to make perseverative errors, has been repeatedly shown to be sensitive to lesions of the frontal lobes while focal lesions outside the frontal lobes produce no comparable effect (Bornstein, 1986; Drewe, 1974; Milner, 1963; Robinson et al., 1980; Rosvold and Mirsky [unpublished findings as cited in Milner, 1963]; Taylor, 1979).

2) Weigl Colour-Form Sorting Test (CFST; Weigl, 1941). Patients with bilateral prefrontal lobotomy were found by Kisker (1944) to be impaired in their ability to shift sorting strategy on this test.

3) Controlled Oral Word Association Test (COWA; Spreen & Benton, 1969). Performance on this task is highly sensitive to frontal lobe lesions, particularly those impinging on the left dorsolateral region (Benton, 1968; Milner, 1964; Perret, 1974; Ramier & Hécaen, 1970; Tow, 1955; Yeudall, 1985). SPECT activation studies with normal control subjects have revealed

an 8 to 12 percent increase in blood flow to frontal lobe regions during performance of this task (George et al., 1991).

4) Porteus Mazes (Porteus, 1959). A significant and persistent postoperative decline in scores on the Porteus Maze Test has been demonstrated in frontal psychosurgery patients, particularly those having undergone superior (versus orbital) topectomy (Smith, 1960; Smith & Kinder, 1958; Tow, 1955).

Posterior Measures

1) Parietal lobe battery of the BDAE (PLB; Goodglass & Kaplan, 1987). The PLB includes tests of right-left orientation, finger gnosis, topographical (map) orientation, representational drawing (spontaneous and copy), clock setting, stick construction memory, calculation, and three-dimensional block construction. All of these tasks tap spatial orientation which is disturbed following lesions of the posterior hemisphere, particularly those in the right hemisphere (McFie, 1969; Weinstein, 1964). Right-left orientation has been reliably shown to be disrupted by lesions of the left posterior hemisphere (Kolb & Whishaw, 1985; McFie & Zangwill, 1960; Sauget, Benton, & Hécaen, 1971; Semmes, Weinstein, Ghent, & Teuber, 1960). Right-left disorientation, finger agnosia, and acalculia are among the cluster of symptoms and signs comprising the Gerstmann syndrome which is a strong indicator of a lesion of the left angular gyrus at the posterior temporoparietal junction (Gerstmann, 1940; Goodglass & Kaplan, 1987). Severe and relatively selective loss of number sense and of the principles of arithmetic operations are indicative of selective parietal lesions (Goodglass & Kaplan, 1987). Drawing to command, stick construction memory, and three-dimensional block construction are all measures of

constructional abilities which are most severely disorganized following parietal lobe, especially right-sided or bilateral parietal lobe, damage (Goodglass & Kaplan, 1987). Clock-drawing requires a sense of number relations as well as geometric representation, both of which are disrupted by parietal lobe damage (Goodglass & Kaplan, 1987). Stuss and colleagues (Stuss, Benson, Kaplan, Della Malva, & Weir, 1984) found no differences between good recovery schizophrenic patients after frontal leucotomy and normal control subjects on subtests of the PLB. Hécaen and Albert (1978) likewise found that topographical orientation is not impaired after frontal lobe damage.

2) Judgement of Line Orientation Test (JOLO; Benton, Varney, & Hamsher, 1978).

Defective performance on this test is virtually exclusive to patients with right hemisphere and, particularly, right posterior lesions (Benton, Hamsher, Varney, & Spreen, 1983; Benton et al., 1978; Fontenot & Benton, 1972). Benton et al. (1978) observed that none of their patients with focal frontal or perirolandic lesions was impaired on this task. Split-half reliability of the test has been found to be in the range of 0.91, while test-retest reliability in a group of neurological patients with intertest intervals ranging from 6 hours to 21 days was 0.90 (Benton et al., 1978).

3) Block Design Subtest of the WAIS-R (Wechsler, 1981): Black and Strub (1976)

studied patients with missile wounds restricted to single quadrants of the brain and found that those with anterior lesions significantly outperformed those with posterior lesions. A subsequent study carried out by Stuss et al. (1984) revealed no differences between the performance of good recovery schizophrenic patients with frontal leucotomy and that of normal control subjects on this test. Shallice (1982) demonstrated a double dissociation between performance on the Block Design test and the Tower of Hanoi problem, considered to be more of a planning than a spatial

processing task, such that two left anterior patients scored below any normal subject on the Tower of London (25% and 42%) but well on Block Design (scaled scores 10 and 17) whereas two right posterior patients scored well on the Tower of London (67% and 84%) but below any control on Block Design (scaled scores 4 and 5).

DA and DR

DA and DR were administered according to the protocol described by Oscar-Berman and colleagues (Freedman & Oscar-Berman, 1986a; Oscar-Berman et al., 1982) in a modified version of the Wisconsin General Test Apparatus adapted for use with human subjects by Oscar-Berman and Zola-Morgan (1980a, 1980b) (see Appendix 2). The experimenter and the subject sat across a table from each other, separated by a wooden frame approximately 54 cm wide and 65 cm high. A black curtain was anchored to the frame such that the experimenter could raise the curtain enough to reveal the stimulus board when a response was required. This stimulus board, measuring approximately 54 cm by 30 cm, contained two reinforcement wells positioned side by side about 24 cm apart from centre to centre and covered by identical round white stimulus plaques.

On DA and DR tasks, the subject was seated opposite the experimenter with the curtain lowered between them. The experimenter explained to the subject in very general terms the requirements of the tasks. The subject was instructed that he or she would be shown two white plaques and that a dime would be hidden beneath one of them. He or she was instructed to try to get the dime every time the curtain was raised. The first trial was administered by raising the

curtain to expose the stimulus board with a reminder to the subject that he or she was to try to get the dime every time. In the current study, dimes rather than pennies were used as rewards.

DA

On the first trial of the DA problem, both plaques were baited with dimes such that the subject was rewarded regardless of his or her choice. On the second trial, the well not chosen on the initial trial was baited with the dime. A correction procedure was employed such that the dime remained on the same side until the subject correctly chose that side. The position of the dime was alternated on each trial following a correct response. Initially, there was a five-second intertrial interval, measured from the completion of the previous response to the presentation of the stimulus tray. This procedure was then repeated with intertrial intervals of 30 and 60 seconds, respectively. At each intertrial interval, the learning criterion was 12 consecutive correct responses and the failure criterion was 45 trials. If a subject failed at an intertrial interval of less than 60 seconds, he or she was not tested at longer delay intervals.

DR

There were four DR problems with delays of 0, 10, 30, and 60 seconds, respectively. With the curtain raised, the experimenter explained to the subject that a dime would be placed in one of the wells and that, as soon as the wells had been covered with the plaques, the curtain would be lowered. The subject was further instructed that, when the curtain was raised again, he

or she was to retrieve the dime by moving the plaque covering the baited well. The left and right wells were baited according to a modified Gellerman schedule (as per Oscar-Berman et al., 1982) in full view of the subject. On the initial, 0-second delay problem the curtain was lowered following placement of the dime and then immediately raised again.

On the delay trials, the experimenter explained to the subject that he or she would have to wait a few moments before taking the dime. Again, one of the wells was baited according to a modified random schedule in full view of the subject. However, the stimulus board was then withdrawn and the curtain lowered for the designated delay. After the delay, the curtain was raised to expose the stimulus board and the subject was allowed to retrieve the dime. A noncorrection procedure was used for all DR problems. In all cases, the learning criterion was 9 correct responses in a block of 10 trials and the failure criterion was 40 trials. As with DA, once the subject failed at a given delay, DR testing was terminated.

Performance on both the DA and the DR tasks was measured in terms of number of trials to criterion.

SPECT

SPECT scanning has been used in the study of dementia since the mid-1980s. Consistent with PET findings, SPECT studies of AD patients most commonly reveal maximal perfusion deficits in the temporoparietal cortex bilaterally (Bonte, Ross, Cheham, & Devous, 1986; Burns, Philpot, Costa, Ell, & Levy, 1989; Cohen et al., 1986; Geaney, Soper, Shepstone, & Cowen, 1990; Gemmell et al., 1987, 1989; George et al., 1991; Holman et al., 1992; Hunter et al., 1989;

Jagust, Budinger, & Reed, 1987; Johnson, Mueller, Walshe, English, & Holman, 1987; Neary et al., 1987; Perani et al., 1988; Sharp et al., 1986). SPECT has been shown to be more sensitive to cerebral abnormalities in cases of AD than magnetic resonance imaging, a high-resolution measure of cerebral structure (Sharp et al., 1986), and evidence is rapidly accumulating to suggest its usefulness in the differential diagnosis of dementia (Geaney & Abou-Saleh, 1990; Gemmell et al., 1987; George et al., 1991; Holman et al., 1992; Hunter et al., 1989; Neary et al., 1987). Several studies have demonstrated correlations in AD between rCBF as measured by SPECT and neuropsychological function in AD patients (Burns et al., 1989; Geaney et al., 1990; Hunter et al., 1989; Perani et al., 1988).

^{99m}Tc -HMPAO is a relatively new radiopharmaceutical developed for use with SPECT which is able to cross an intact blood brain barrier and is trapped inside functioning cells in proportion to cerebral blood flow. Brain uptake of ^{99m}Tc -HMPAO occurs over the first two minutes following intravenous injection and has a stable distribution for many hours thus enabling conventional equipment to be used to detect the radiation emitted from the brain and allowing generation of high resolution images. In animals the uptake of ^{99m}Tc -HMPAO is linearly related to rCBF. Comparative studies with PET in humans show a tendency for underestimation of flow in areas of high rCBF but a good correlation with areas of low and medium rCBF (as reviewed by Geaney & Abou-Saleh, 1990).

In the midst of the current study, the Nuclear Medicine Department at the OGH began using ^{99m}Tc -ECD rather than ^{99m}Tc -HMPAO as the tracer for cerebral perfusion imaging. Among the advantages of ^{99m}Tc -ECD over ^{99m}Tc -HMPAO are 1) faster blood clearance providing more favourable radiation dosimetry and a higher signal-to-noise ratio and 2) much longer chemical

stability *in vitro* after reconstitution (HMPAO must be used within 30 minutes of reconstitution; Ichise et al., 1997). The timing of the change was such that 9 of the 17 AD patients who underwent SPECT scanning were given HMPAO while the remaining 8 scanned AD patients, as well as all of the AAMI subjects, were given ECD. According to the product monograph, ECD is a neutral lipophilic complex which, like HMPAO, is rapidly taken up and selectively retained in the brain in a pattern consistent with regional cerebral perfusion. The brain distribution pattern is unchanged for at least six hours post-injection and is similar to that seen with the cerebral blood flow standard Xenon Xe 133 Gas (considered the gold standard in the measurement of rCBF). Whereas initial reports stressed the similarity of ECD and HMPAO in terms of their *in vivo* cerebral kinetics and initial distribution (Léveillé, Demonceau, & Walovitch, 1992), characteristic differences in the distribution patterns of these two nuclides have been more recently described. Koyama et al. (1997), in studies with normal subjects, found relatively high radioactivities in the basal ganglia and cerebellum in HMPAO-SPECT images versus relatively high values in the medial aspect of the occipital lobe in ECD-SPECT images. They attributed these variations in distribution pattern to the different mechanisms responsible for the cerebral accumulation of these compounds (de-esterification to polar complexes in the case of ECD versus reaction with glutathione for HMPAO).

Although absolute quantification of rCBF is not yet possible with HMPAO or ECD, uptake of these radiolabelled pharmaceuticals can be expressed semiquantitatively by comparing the counts of radiation emitted in the brain region (or regions) of interest (ROI) to a reference area (usually the cerebellum or occipital cortex in studies of AD patients, since blood flow to

these regions is relatively unaffected by AD). Thus, in semiquantitative SPECT studies, rCBF is expressed as a ratio, or percentage.

Data from PET studies suggest that proportional measures of rCBF may be more sensitive and reliable than absolute values. For example, Bartlett et al. (1988) observed a mean change of 7% (and individual changes of up to 22%) in two PET measurements of whole-brain glucose metabolism taken within a 24-hour period in normal subjects. In contrast, when metabolism in each region was expressed as a ratio of the whole-brain metabolism, the resulting average regional changes were less than 1%. Cutler et al. (1985) reported that while PET revealed no major reductions in absolute regional cerebral metabolic rates in patients with mild to moderate AD, consistent and significant reductions in the parietal lobe were apparent in ratios of regional to whole brain metabolism due to the much smaller variability in the latter values. Miller et al. (1991a) found the proportional data obtained from HMPAO scans to be very effective in differentiating among groups of patients with frontal lobe dementia, probable AD, and no cognitive impairment.

In the current study, SPECT scanning was conducted with a multi-headed camera system Prism 3000 Picker. Subjects received intravenous injection of 25 mCi of either ^{99m}Tc -HMPAO or of ^{99m}Tc -ECD. Injection of HMPAO was preceded by administration of 500 mg of potassium perchlorate to reduce background facial activity. SPECT scanning began 15 minutes following the standard injection protocol. Ambient light and noise were kept low. Patients were positioned in the gantry using the line from the orbit to the external auditory meatus as the reference plane.

Uptake of HMPAO or ECD in frontal and nonfrontal areas is expressed as a proportion of cerebellar uptake (which is relatively unaffected in AD; Kiyosawa et al., 1989; Pearson & Powell,

1989). The data used in calculation of these ratios was obtained from the brain imaging device and analysed in a fast processing computer. ROIs (as illustrated in Appendix 5) were manually drawn on the computer-generated image using a brain atlas for reference. The counts per pixel of all constituent pixels within a given ROI (or collection of ROIs) were summed and this sum compared to that obtained in the reference region.

DATA ANALYSES

Bivariate and canonical correlation were used to assess relationships between: 1) scores on the DA and DR tasks and scores on clinical neuropsychological tests of frontal and parietal function; 2) frontal and parietal perfusion on SPECT and performance on clinical neuropsychological measures of frontal and parietal function; and 3) frontal and parietal perfusion and performance on DA and DR. The relative effectiveness of two sets of variables (e.g., frontal and parietal neuropsychological measures) in predicting a dependent or outcome variable (e.g., change in overall mental status) was determined by using the z test of the difference between correlation coefficients (Steiger, 1980; Tabachnick & Fidell, 1996).

The degree to which frontal and parietal function (measured in terms of blood flow, performance on clinical neuropsychological tests, and DA/DR) predicted change in overall mental status over the test-retest interval was assessed by means of multiple linear regression techniques. The relative effectiveness of DA/DR and standard clinical neuropsychological tests of frontal lobe

function in predicting change in overall mental status over the test-retest interval was investigated with hierarchical regression analysis.

RESULTS

SUBJECTS

Group means on age and education, together with the numbers of males and females in both the AD and AAMI groups are presented in Table 1. The AD and the AAMI subjects differed significantly with respect to mean age ($t[34] = 3.75, p < .001$) but were equivalent with respect both to years of education ($t[32] = 0.01, p > .990$) and the proportion of males and females in the group ($\chi^2[1, N = 37] = .021, p > .885$).

MENTAL STATUS MEASURES

Table 2 presents mean scores of the AD and AAMI groups on general measures of cognitive and functional status at or prior to enrollment into the study (time one) and on retesting approximately one year later (time two). The two groups differed significantly on all of these measures at follow-up, and on all but praxis and calculation at intake, with the AD group scoring consistently lower than the AAMI group. Most of these group differences on the mental status measures persisted even after controlling for age. A multiple analysis of covariance (MANCOVA), with age serving as the covariate, revealed a significant difference between AD

Table 1**Demographic Data for AD and AAMI Groups**

	GROUP		
	AD Subjects n = 19	AAMI Subjects n = 18	All Subjects n = 37
DEMOGRAPHIC VARIABLE	Mean(SD)	Mean(SD)	Mean(SD)
Age*	75.79(6.93)	66.67(7.80)	71.35(3.86)
Education (Years)	13.74(4.45)	13.72(3.14)	13.69(8.61)
Gender	M:F = 8:11	M:F = 8:10	M:F = 16:21

Note. AD = Alzheimer disease; AAMI = Age Associated Memory Impairment; M = male; F = female

* $p < .05$, 2-tailed

Table 2

Scores on Mental Status Measures at Intake and One-Year Follow-Up in AD and AAMI Subjects

MENTAL STATUS MEASURE	GROUP			
	AD		AAMI	
	Intake n = 19	Follow-Up n = 17	Intake n = 18	Follow-Up n = 17
	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)
OGH Exam	31.37(3.79)	27.35(6.38)**	38.50(0.86)++	38.00(1.41)++
DRS	117.58(8.44)	111.59(13.97)	138.78(5.96)++	137.88(5.35)++
Lawton	49.74(8.96)	44.06(11.58)**	58.50(1.04)++	58.59(0.71)++
Naming	17.21(2.10)	16.47(3.36)	19.67(0.69)++	19.71(0.59)++
Praxis	8.79(0.54)	8.00(1.22)*	8.83(0.51)	8.94(0.24)+
Calculation	6.26(1.33)	6.06(1.43)	7.11(0.83)	7.29(0.77)+

OGH = Ottawa General Hospital

DRS = Dementia Rating Scale

* * Different from score at Intake at $p < .05$, two-tailed, after Bonferroni correction* Different from score at Intake at $p < .01$, two-tailed, after Bonferroni correction+Different from equivalent score in AD group at $p < .001$, two-tailed++Different from equivalent score in AD group at $p < .005$, two-tailed

and AAMI groups on the time-one mental status measures ($F[6,29] = 11.155, p < .001$). The two groups differed significantly on the following measures according to univariate F tests:

OGH1 ($F[1,34] = 62.904, p < .001$); DRS1 ($F[1,34] = 54.96, p < .001$); Lawton1 ($F[1,34] = 5.717, p < .022$); Naming1 ($F[1,34] = 14.876, p < .001$), and Calculation1 ($F[1,34] = 5.838, p < .021$).

Age was a significant covariate in the case of OGH1 and Lawton1. A second MANCOVA revealed that the groups also differed significantly on the time-two mental status measures ($F[6,26] = 8.472, p < .001$). Univariate F tests were significant for all time two measures (OGH2: $F[1,31] = 41.672, p < .001$; Naming2: $F[1,31] = 16.145, p < .001$; Praxis2: $F[1,31] = 7.169, p < .012$; Calculation2: $F[1,31] = 8.404, p < .007$; DRS2: $F[1,31] = 47.835, p < .001$; Lawton2: $F[1,31] = 14.09, p < .001$). Age was not a significant covariate in any instance.

Table 2 further illustrates that, whereas scores on many of the mental status measures declined significantly over the follow-up period for AD subjects (OGH: $t[16] = 3.58, p < .002$; Lawton: $t[16] = 3.13, p < .006$; Praxis: $t[16] = 2.63, p < .018$), as would be expected in the case of a neurodegenerative disorder, there was no such change in any of the mean scores for the AAMI group. However, the average intertest interval was only 353.941 days ($SD = 23.437$) for the AAMI subjects compared to 388.211 days ($SD = 28.617$) for the AD subjects, a significant difference ($t[33.76] = 3.95, p < .001$). In an effort to mitigate any confounding effects of delay and to control experiment-wise error rate, a series of repeated measures analyses of covariance (ANCOVAs) were conducted (with delay serving as covariate) to compare the change in performance of the two groups from intake to follow-up on the various mental status measures. These analyses yielded significant group by time interaction effects after Bonferroni correction for the number of analyses conducted (6) in the case of OGH Exam ($F[1,32] = 9.19, p < .005$) and

the Lawton Scale ($F[1,32] = 10.11, p < .003$), as well as a trend towards significance in the case of praxis ($F[1,32] = 6.35, p < .017$). These interaction effects indicate that there is a group difference in the change on these scores from intake to follow-up that cannot be fully accounted for by the discrepancy in the intertest interval. The group by time interaction effects did not reach significance in the case of Naming ($F[1,32] = 1.59, p > .216$), Calculation ($F[1,32] = 1.51, p > .229$), or DRS ($F[1,32] = 3.72, p > .063$). The covariate, delay, was nonsignificant in all of these analyses.

CLINICAL NEUROPSYCHOLOGICAL MEASURES

Table 3 summarizes the performance of the AD and AAMI groups on the neuropsychological measures generally associated with frontal lobe functioning. Considering raw test scores, it is evident that the AD subjects performed more poorly than the AAMI subjects on virtually all of the neuropsychological measures. Univariate t-tests comparing groups on the frontal variables listed in Table 3 revealed that the only difference to reach significance after Bonferroni correction for the number of comparisons being conducted was that on WCST Categories ($t[31] = -3.17, p < .003$). Group differences on WCST-Perseverative Responses ($t[31] = 2.77, p < .009$) and Porteus Mazes ($t[35] = -2.75, p < .009$) approached significance (i.e., $p < .10$ after Bonferroni correction). Due to marked heterogeneity of variance between the two groups on CFST (Levene's $F = 16.242, p < .001$), a t-test was not considered appropriate for testing the group difference on this variable. This heterogeneity of variance reflects the lack of

Table 3

Scores on Frontal Neuropsychological Tests for AD and AAMI Groups

FRONTAL MEASURE	GROUP	
	AD n = 19	AAMI n = 18
	Mean(SD)	Mean(SD)
CFST	2.89(1.29)	3.89(0.32)+
COWA	27.53(10.38)	36.22(11.04)**
Porteus Mazes	11.47(3.27)	14.39(3.17)*
WCST		
Categories	2.47(2.09)	5.11(2.89)
Perseverative responses (%)	37.63(25.78)	18.00(16.48)*
Nonperseverative errors (%)	15.89(6.73)	18.94(6.50)
Losses of set	1.53(2.17)	1.22(1.56)

Note. AD = Alzheimer disease; AAMI = Age Associated Memory Impairment; CFST = Colour Form Sorting Test; COWA = Controlled Oral Word Association Test; WCST = Wisconsin Card Sorting Test

** Group differences significant at $p < .05$, two-tailed, after Bonferroni correction and controlling for age

* Group differences significant at $p < .10$, two-tailed, after Bonferroni correction and controlling for age

+ Significant difference in frequency of nonperfect score in two groups ($p < .05$)

variability in AAMI subjects, who all performed near ceiling on this simple task. Therefore, for the purposes of subsequent regression and discriminant function analyses, CFST was recoded into a nominal dichotomous variable, with one level representing a perfect score on the task, and the other level representing a less than perfect score. The AD and AAMI groups were found to differ significantly in terms of the relative frequency of perfect and nonperfect scores on the CFST ($\chi^2[1, N = 37] = 8.877, p < .003$).

In order to control for possible confounding effects of age (AD and AAMI subjects differed significantly in terms of mean age) and experiment-wise error rate, a MANCOVA, with age serving as the covariate, was conducted with a subset of the frontal neuropsychological variables listed in Table 3. Only one error score from the WCST was included in the MANCOVA in order to prevent multicollinearity and singularity (given generally high correlations among the various WCST error scores). Perseverative responses was chosen as it has been shown to be particularly sensitive to frontal lobe dysfunction. Losses of set on the WCST was retained in the analysis as its correlations with other WCST measures are quite modest. CFST was excluded from the MANCOVA due to the heterogeneity of variance problem described earlier. This MANCOVA was significant ($F[4,31] = 2.856, p < .040$). However, despite the fact that the covariate, age, was not significant in any of the analyses, COWA ($F[1,34] = 10.128, p < .003$) was the only measure to attain significance in univariate tests after controlling for age. WCST-Perseverative Responses ($F[1,34] = 2.870, p < .099$) and Porteus Mazes ($F[1,34] = 3.321, p < .077$) approached significance.

Table 4 depicts the scores of the AD and AAMI subjects on neuropsychological measures generally associated with parietal lobe functioning. Levene's test revealed significant

Table 4

Scores on Parietal Neuropsychological Tests for AD and AAMI Groups

PARIETAL MEASURE	GROUP	
	AD n = 19	AAMI n = 18
	Mean(SD)	Mean(SD)
PLB		
TOTAL SCORE	95.04(13.24)	112.28(10.16)*
3D Block Construction	6.50(2.53)	8.72(1.60)*
Calculation	25.47(4.86)	29.50(2.12)*
Clock Setting	8.32(2.87)	10.39(1.94)*
Drawing	9.32(2.84)	10.56(2.04)
Finger Gnosis	14.15(1.11)	14.87(0.29)
Map	10.26(5.12)	12.28(3.79)
R-L Orientation	14.03(2.30)	15.31(1.11)
Stick Design	6.89(2.02)	10.67(2.47)*
JOLO	18.16(6.11)	22.33(4.80)
WAIS-R Block Design	12.84(6.23)	21.22(8.85)*

Note. AD = Alzheimer disease; AAMI = Age Associated Memory Impairment; PLB = Parietal Lobe Battery; JOLO = Judgement of Line Orientation Test; WAIS-R = Wechsler Adult Intelligence Scale-Revised.

*Group differences significant at $p < .05$, two-tailed, after Bonferroni correction, in univariate F tests with age as covariate

heterogeneity of variance between the groups on PLB Finger Gnosis ($F = 17.409$, $p < .001$), PLB Right-Left Orientation ($F = 4.134$, $p < .050$), and PLB Calculation ($F = 8.906$, $p < .005$).

However, unlike the CFST, there was considerable variability in these scores in either group.

Given that F_{Max} (the ratio of the variances in the two groups) was relatively small in all cases (between 2 and 4) and that the sample sizes were almost equal, this was not considered too great a threat to the validity of the statistical tests employing these variables and they were left untransformed. A series of t-tests revealed significant group differences on the following parietal variables appearing in Table 4: PLB Total Score ($t[33.6] = -4.46$, $p < .001$); PLB Block Design ($t[31.13] = -3.24$, $p < .003$); PLB Calculation ($t[24.91] = -3.30$, $p < .003$); PLB Stick Design ($t[32.91] = -5.06$, $p < .001$); WAIS-R Block Design ($t[30.39] = -3.31$, $p < .002$).

A MANCOVA involving the parietal measures shown in Table 4 (excluding total score on the PLB to avoid singularity and including age as a covariate) only approached significance ($F[10,27] = 2.13$, $p < .061$). In univariate ANCOVAs, PLB Stick Design ($F[1,34] = 11.692$, $p < .002$), PLB Calculation ($F[1,34] = 12.322$, $p < .001$), PLB Clock Setting ($F[1,34] = 9.341$, $p < .004$), and PLB Total score ($F[1,34] = 15.048$, $p < .001$) were significant after controlling for the number of comparisons and for age. It is clear that parcelling out group differences on age somewhat altered the pattern of significant comparisons, despite the fact that age itself was not significant in any of these univariate analyses.

DA AND DR

The performance of the AD and AAMI subjects on the DR and DA tasks is summarized in Table 5. Inspection of the means for the AAMI subjects reveals that they had very little difficulty with the DR task and that their performance was near-optimal at all delay intervals (the criterion being 9 out of 10 correct responses and, hence, the minimum score being 9). There was no significant effect of delay on trials to criterion among the AAMI subjects. In contrast, performance of the AD subjects was near optimal on the no-delay condition but declined with lengthening of the delay interval. This group difference in sensitivity to delay was tested in a repeated measures analysis of variance (ANOVA), with delay condition on DR as a within-subjects factor and group as a between-subjects factor. The group by delay interaction was significant ($F[3,105] = 3.30, p < .023$). Although a univariate t-test did indicate that AD patients required more trials to reach criterion on DR60 than on DR0 ($t[18] = -2.58, p < .019$), this difference fell short of significance after Bonferroni adjustment for the number of post-hoc comparisons being conducted (6).

The frequency distribution of the DR60 variable in the AD subjects was bimodal: Subjects either met criterion in the minimum number of trials ($n = 14$) or they failed the task entirely and received the maximum score ($n = 5$). The frequency of failure was significantly higher in the AD subjects than in the AAMI subjects ($\chi^2[1, N = 37] = 5.477, p < .019$). In view of the relative lack of variability in both groups on DR measures other than DR60, only DR60 was considered in further analyses involving DR. Given the non-normal distribution of scores on DR60, it was

Table 5

Means and Standard Deviations of Delayed Response and Delayed Alternation Measures in AD and AAMI Groups

DR/DA MEASURE	GROUP	
	AD n = 19	AAMI n = 18
	Mean(SD)	Mean(SD)
DR		
DR0	9.26(0.45)	9.00(0.00)+
DR10	13.47(10.39)	9.00(0.00)
DR30	12.95(9.80)	9.06(0.24)
DR60	17.37(13.90)	9.06(0.24)*
Total	53.05(29.67)	36.11(0.32)*
DA		
DA5	44.06(13.75)	31.68(14.47)
DA30	43.67(14.57)	22.78(17.40)+
Total	87.72(28.28)	54.46(30.46)+

Note. DR = Delayed Response; DA = Delayed Alternation

* Groups significantly different at $p < .05$, two-tailed, after Bonferroni correction

+ Groups significantly different at $p < .10$, two-tailed, after Bonferroni correction

recoded into a nominal dichotomous variable (failure/non-failure) for use in regression and discriminant function analyses.

The distribution of scores on the DA task was somewhat different. Eighty-three percent of the AD subjects failed to meet criterion in the allotted 50 trials on DA5 as compared to only twenty-eight percent of the AAMI subjects. This group difference in the frequency of failure is highly significant ($\chi^2[1, N = 36] = 11.25, p < .001$). The scores were again bimodally distributed in the AD group while there was a considerable range of scores among the AAMI subjects. Those subjects who failed to meet criterion on DA5 (the majority of the AD subjects) were not administered DA30 but, instead, were automatically assigned the maximal score on this task. Those subjects (whether AD or AAMI) who succeeded in meeting criterion on DA5 (and, hence, were administered DA30) went on to meet criterion on DA30 in a minimal number of trials. As a result, the differences between the groups on DA30 have been artificially inflated and really provide little information over and above that gleaned from their respective performance on DA5. Thus, DA5 was the only variable from the DA task to be used in further statistical analyses. Given the non-normal distribution of this variable, particularly in the AD subjects, DA5 was also recoded into a nominal-dichotomous variable (failure/non-failure) for use in regression or discriminant function analyses involving all subjects.

BLOOD FLOW MEASURES

Given that the two radionuclides used in SPECT scanning (ECD and HMPAO) may differ in terms of brain distribution pattern and were not equally represented across groups in the present study (i.e., none of the AAMI subjects had HMPAO scans), there was a concern that differences attributable to type of tracer used would contaminate group comparisons on blood flow variables. In an effort to address this issue, a series of t-tests was conducted in order to compare perfusion ratios in the various cerebral ROIs in those AD patients given HMPAO and those given ECD. Table 6 contains the results of these comparisons, which were nonsignificant in all cases, even prior to Bonferroni correction of alpha for the number of comparisons in the series. Thus, the SPECT data from all AD patients were pooled for subsequent analyses.

Table 7 summarizes the SPECT findings in AD and AAMI subjects. Values in this table represent ratios of average radioactivity counts per pixel in the respective ROIs referenced to the cerebellum. Although there was a strong correlation between blood flow in the various ROIs and age ($R = .902$), this failed to reach significance in a multiple regression due to the large number of predictor (SPECT) variables relative to the number of subjects ($F[26,8] = 1.351, p > .344$). Bivariate correlations between age and perfusion were significant for several ROIs, including cingulate ($r = -.5342, p < .001$), right superior occipital region ($r = -.5083, p < .002$), left superior occipital region ($r = -.5047, p < .002$), right white matter ($r = -.4127, p < .014$), and left anterior temporal region ($r = -.3387, p < .047$). Older age was associated with lower blood flow in all cases. Older age was also associated with lesser total blood flow (i.e., sum of perfusion ratios in

Table 6

Comparison of Cerebral Blood Flow Values in AD Patients Given ^{99m}Tc -HMPAO and those Given ^{99m}Tc -ECD as the Radionuclide for SPECT Brain Imaging

ROI ON SPECT	RADIONUCLIDE		t	df	p
	HMPAO n = 9	ECD n = 8			
	Mean(SD)	Mean(SD)			
R Superior Frontal	.9522(.107)	.8838(.060)	1.66	12.80	.121
L Superior Frontal	.9322(.104)	.8863(.066)	1.10	13.69	.289
R Midfrontal	.9100(.113)	.8512(.068)	1.31	13.34	.212
L Midfrontal	.9067(.105)	.8413(.058)	1.61	12.71	.131
R Inferior Frontal	.9198(.106)	.8750(.074)	1.00	14.31	.336
L Inferior Frontal	.8778(.109)	.8363(.072)	0.94	13.92	.365
R Association (Parietal)	.8500(.153)	.8413(.050)	0.16	9.85	.875
L Association (Parietal)	.8200(.128)	.7862(.077)	0.67	13.25	.517
R Parietal	.8844(.126)	.8550(.033)	0.68	9.19	.514
L Parietal	.8367(.128)	.8013(.064)	0.73	12.08	.477
R Anterior Temporal	.8756(.109)	.8112(.111)	1.21	14.71	.247
L Anterior Temporal	.7989(.096)	.7625(.088)	0.82	14.97	.427
R Posterior Temporal	.8722(.149)	.8575(.061)	0.27	10.90	.791
L Posterior Temporal	.8444(.096)	.7850(.084)	1.36	15.00	.194
R Superior Occipital	.9578(.142)	.9700(.113)	-0.20	14.84	.847
L Superior Occipital	.9511(.123)	.9338(.123)	0.29	14.77	.776
R Inferior Occipital	.9256(.133)	.9875(.094)	-1.12	14.37	.282
L Inferior Occipital	.9522(.131)	.9575(.089)	-0.10	14.13	.923
Brainstem	.8489(.064)	.7962(.114)	1.15	10.74	.274
Cingulate	.8033(.130)	.8175(.080)	-0.27	13.45	.788
R Thalamus	.8856(.088)	.8263(.070)	1.54	14.88	.143
L Thalamus	.8889(.088)	.8225(.047)	1.96	12.48	.073
R Basal Ganglia	.9322(.101)	.8850(.088)	1.03	15.00	.319
L Basal Ganglia	.9011(.095)	.8650(.073)	0.88	14.72	.392
R White Matter	.4744(.067)	.4663(.081)	0.23	13.70	.824
L White Matter	.4900(.056)	.4688(.077)	0.64	12.68	.532

Note. AD = Alzheimer disease; SPECT = single photon emission computed tomography; ROI = region of interest; ^{99m}Tc -HMPAO = ^{99m}Tc -hexamethylpropylene amine oxime; ^{99m}Tc -ECD = ^{99m}Tc -ethylcysteinate dimer; R refers to right; L refers to left

Blood flow values represent perfusion ratios in ROI referenced to cerebellum

Table 7

Means and Standard Deviations of Cerebral Blood Flow in Various Regions of Interest (ROI) in AD and AAMI Groups

ROI ON SPECT	GROUP	
	AD n = 17	AAMI n = 18
	Mean(SD)	Mean(SD)
R Superior Frontal	.9200(.092)	.9139(.125)
L Superior Frontal	.9106(.088)	.9067(.139)
R Midfrontal	.8824(.097)	.8806(.119)
L Midfrontal	.8759(.090)	.8672(.117)
R Inferior Frontal	.8982(.092)	.8772(.104)
L Inferior Frontal	.8582(.093)	.8561(.108)
R Association (Parietal)	.8459(.113)	.8761(.080)
L Association (Parietal)	.8041(.105)	.8389(.074)
R Parietal	.8706(.093)	.9256(.099)
L Parietal	.8200(.101)	.8778(.095)
R Anterior Temporal	.8453(.111)	.8267(.092)
L Anterior Temporal	.7818(.091)	.8150(.095)
R Posterior Temporal	.8653(.113)	.8939(.088)
L Posterior Temporal	.8165(.093)	.8522(.081)
R Superior Occipital	.9635(.126)	1.0394(.119)
L Superior Occipital	.9429(.120)	1.0050(.123)
R Inferior Occipital	.9547(.117)	.9911(.096)
L Inferior Occipital	.9547(.110)	.9783(.094)
Brainstem	.8163(.089)	.7206(.060)*
Cingulate	.8100(.106)	.8483(.107)
R Thalamus	.8576(.083)	.8383(.077)
L Thalamus	.8576(.078)	.8261(.090)
R Basal Ganglia	.9100(.095)	.8561(.073)
L Basal Ganglia	.8841(.085)	.8401(.075)
R White Matter	.4706(.071)	.4939(.090)
L White Matter	.4800(.066)	.4811(.091)

Note. AD = Alzheimer disease; AAMI = Age Associated Memory Impairment; SPECT = single photon emission computed tomography; R refers to right; L refers to left

Blood flow values represent perfusion ratios in ROI referenced to cerebellum

* Group difference significant at $p < .05$ level, two-tailed, after Bonferroni correction

all ROIs; $r = -.370$, $p < .029$). Given the significant difference in mean age between AD and AAMI groups, age was thus included as a covariate in analyses comparing perfusion in these two diagnostic groups (although age differences in blood flow were not noted in the ROIs of greatest interest to this study, namely, frontal and parietal regions). Univariate ANCOVAs revealed a significant difference in brainstem perfusion between AD and AAMI subjects ($F[1,32] = 12.191$, $p < .001$). However, when radiopharmaceutical condition was included as a second covariate in the analysis ($F[1,31] = 5.090$, $p < .031$), or when HMPAO subjects were omitted from the analysis ($F[1,23] = 4.787$, $p < .039$), the group difference in brainstem perfusion no longer met the adjusted criterion for significance. A MANCOVA including all ROIs was nonsignificant ($F[26,7] = 1.143$, $p > .460$) but, given the large number of dependent variables relative to sample size, the power of this analysis was extremely low (.27). However, neither did the AD and AAMI subjects differ on the total blood flow measure (i.e., the sum of perfusion ratios in all ROIs) when age was treated as a covariate in an ANCOVA ($F[1,32] = 0.788$, $p > .381$).

Table 8 depicts group means and standard deviations on a number of SPECT summary measures, including total frontal blood flow (a sum of the perfusion ratios in the three cortical frontal ROIs in each of the two hemispheres), total parietal blood flow (sum of the perfusion ratios in the two cortical parietal ROIs in each of the two hemispheres), the sagittal anterior/posterior ratio (sum of four frontal sagittal ROIs divided by sum of four posterior sagittal ROIs), and the frontal/parietal ratio (average of six frontal perfusion ratios divided by average of four parietal perfusion ratios). Although age was not significantly correlated with any of these

Table 8**Means and Standard Deviations of Summary Cerebral Blood Flow Measures in AD and AAMI Groups**

SPECT SUMMARY MEASURE	GROUP	
	AD n = 17	AAMI n = 18
	Mean(SD)	Mean(SD)
Total Frontal	5.3453(0.464)	5.3017(0.688)
Total Parietal	3.3406(0.377)	3.5183(0.323)
Frontal/Parietal Ratio	1.0745(0.114)	1.0027(0.066)+
Sagittal A/P Ratio	0.9076(0.183)	0.9328(0.125)

Note. AD = Alzheimer disease; AAMI = Age Associated Memory Impairment; SPECT = single photon emission computed tomography; A/P = anterior/posterior

+ Groups significantly different at $p < .10$, two-tailed, after Bonferroni correction

summary perfusion measures, it was nonetheless included as a covariate in comparisons between diagnostic groups in an effort to reduce extraneous variability.

A MANCOVA including total frontal perfusion, total parietal perfusion, and the sagittal anterior/posterior ratio as dependent variables (frontal/parietal ratio was excluded given that it is a combination of other variables in the set) and age as a covariate, was nonsignificant ($F[3,30] = 2.176, p > .112$), as were respective univariate ANCOVAs with total frontal perfusion ($F[1,32] = 1.618, p > .213$), total parietal perfusion ($F[1,32] = 0.505, p > .482$), and sagittal anterior/posterior ratio ($F[1,32] = 0.001, p > .970$) serving, in turn, as the dependent variable. However, a univariate ANCOVA revealed a group difference in the anterior/posterior ratio ($F[1,32] = 6.579, p < .015$) which approached significance even after Bonferroni correction of alpha for the four univariate comparisons being conducted. From inspection of Table 8, it is evident that the sensitivity of the anterior/posterior ratio is due to an additive effect of higher frontal flow and lower parietal flow in the AD compared to the AAMI subjects. The net result is that the anterior/posterior ratio is significantly higher in the AD than in the AAMI subjects.

HYPOTHESIS 1: DEGREE OF FRONTAL DYSFUNCTION AT INTAKE WILL PREDICT DEMENTIA PROGRESSION OVER A ONE-YEAR TEST-RETEST INTERVAL.

The first step toward analysing the ability of frontal dysfunction to predict dementia progression was determination of the mental status measure which would be used to quantify such progression. In constructing this index, an effort was made to find the combination of scores

derived from the mental status assessment (conducted at intake and follow-up) that would be optimally sensitive to change over the test-retest interval. As noted in Table 2, scores on the OGH Mental Status Examination, ideomotor praxis testing, and the Lawton Scale all declined significantly from time one to time two in AD patients. Scores on these three measures were therefore summed to obtain a general measure of mental status. Change in overall mental status was calculated by subtracting this mental status score at time two from the mental status score at time one and dividing this difference by the number of days in the follow-up interval. The mean daily change, as determined in this way, was $-.026$ points ($SD = .025$) for AD patients and $-.001$ points ($SD = .005$) for AAMI subjects. This difference was statistically significant ($t[32] = -4.09$, $p < .001$).

In the case of the AAMI subjects, change in mental status was further assessed by comparing their scores at intake and follow-up on the various memory tests used to establish the initial diagnosis of AAMI (Logical Memory I and II and Paired Associates I and II from the WMS-R and immediate reproduction score from the BVRT). These scores appear in Table 9. Inspection of the table reveals that scores consistently improved from time one to time two, in keeping with a positive practice effect. The improvement on Logical Memory I was significant ($t[16] = -3.57$, $p < .003$), while the increase in total memory score approached significance ($t[16] = -2.93$, $p < .10$) after Bonferroni correction for the number of comparisons (5). An overall "memory change" score (the difference between memory scores at time one and time two divided by the number of days in the delay interval) was considered as a dependent (outcome) variable in some of the following analyses involving AAMI subjects.

Table 9

Scores on Memory Tests at Intake and One-Year Follow-Up in AAMI Subjects

MEMORY MEASURE	TIME OF TESTING	
	Intake n = 18	Follow-Up n = 17
	Mean(SD)	Mean(SD)
Wechsler Memory Scale-Revised		
Logical Memory I	17.89(6.17)	21.00(5.66)*
Logical Memory II	14.06(6.79)	16.00(5.35)
Verbal Paired Associates I	15.89(3.56)	16.88(4.40)
Verbal Paired Associates II	6.56(1.29)	6.65(1.32)
Benton Visual Retention Test	5.83(1.20)	6.29(1.61)
TOTAL MEMORY SCORE	60.22(15.56)	66.82(15.20)+

Note. AAMI = Age Associated Memory Impairment

* p < .05 after Bonferroni correction

+ p < .10 after Bonferroni correction

Blood Flow Measures

A standard linear regression analysis revealed that frontal perfusion at the time of intake, calculated as the sum of perfusion ratios across six frontal ROIs (three frontal ROIs in each hemisphere) on SPECT, did not predict cognitive decline over the follow-up interval in AD subjects (R for the regression = .100, $F[1,13] = 0.130$, $p > .723$), AAMI subjects (R for the regression = 0.365, $F[1,15] = 2.308$, $p > .150$), or in the sample as a whole (R for the regression = .039, $F[1,30] = 0.045$, $p > .834$). The same negative results obtained if total frontal perfusion was regressed on mental status at follow-up with mental status at intake treated as a covariate by forcing it to enter the regression equation first (β for frontal perfusion = -.001, $T = -0.028$, $p > .986$ in combined sample; β for frontal perfusion = .071, $T = 0.463$, $p > .652$ in AD sample; β for frontal perfusion = -.346, $T = -1.647$, $p > .122$ in AAMI sample). These ANCOVAs did show, as would be expected, that mental status at time one (the covariate) was a highly significant predictor of mental status at time two in AD subjects (R for the regression = .843, $F[1,13] = 31.844$, $p < .001$) and AAMI subjects (R for the regression = .512, $F[1,15] = 5.328$, $p < .036$) considered separately, as well as in the combined sample (R for the regression = .935, $F[1,30] = 210.120$, $p < .001$).

Left and right frontal perfusion (sum of three frontal ROIs in left and right hemisphere, respectively) were also examined for their ability to predict change in mental status. Neither proved to be a significant predictor. Right frontal perfusion did not predict mental status change in AD patients (R for the regression = .181, $F[1,13] = 0.439$, $p > .519$), AAMI subjects (R for the regression = .356, $F[1,15] = 2.178$, $p > .161$), or the combined sample (R for the

regression = .001, $F[1,30] = 0.000$, $p > .997$). Neither did right frontal perfusion predict mental status at time two residualized on mental status at time one, whether in AD patients (β for right frontal perfusion = .098, $T = 0.640$, $p > .534$), AAMI subjects (β for right frontal perfusion = -.350, $T = -1.667$, $p > .118$), or the combined sample (β for right frontal perfusion = .009, $T = 0.140$, $p > .890$). Similarly, left frontal perfusion did not predict either mental status change (R for the regression with AD subjects = .001, $F[1,13] = 0.000$, $p > .997$; R for the regression with AAMI subjects = .368, $F[1,15] = 2.356$, $p > .146$; R for the regression with all subjects = .075, $F[1,30] = 0.168$, $p > .685$) or mental status at time two residualized on mental status at time one (β for left frontal perfusion in AD sample = .035, $T = 0.227$, $p > .824$; β for left frontal perfusion in AAMI sample = -.339, $T = -1.601$, $p > .131$; β for left frontal perfusion in combined sample = -.011, $T = -0.174$, $p > .863$).

Similar analyses were then conducted to determine whether parietal lobe perfusion (the sum of perfusion ratios across two parietal ROIs in each hemisphere) at intake to the study predicted change in mental status. Parietal lobe perfusion at time one was found to predict change in mental status for AD patients (R for the regression = .587, $F[1,13] = 6.841$, $p < .021$) and for the combined subject group (R for the regression = .420, $F[1,30] = 6.439$, $p < .017$), but not for the AAMI group (R for the regression = .352, $F[1,15] = 2.125$, $p > .166$). When parietal lobe perfusion was used to predict mental status at time two with initial mental status serving as a covariate, none of the analyses attained statistical significance, although a trend toward significance ($p < .10$) was noted in the AD group (β for total parietal perfusion = .277, $T = 2.004$, $p < .068$).

Right and left parietal perfusion were also considered separately in terms of their ability to predict change in mental status over the follow-up interval. Both right and left parietal perfusion predicted mental status change in AD patients (R for the regression = .525, $F[1,13] = 4.954$, $p < .044$ for right perfusion; R for the regression = .592, $F[1,13] = 6.997$, $p < .020$ for left perfusion) and in the combined subject group (R for the regression = .379, $F[1,30] = 5.047$, $p < .032$ for right perfusion; R for the regression = .421, $F[1,30] = 6.460$, $p < .016$ for left perfusion), whereas neither right nor left parietal flow predicted change in mental status in the AAMI subjects (R for the regression = .307, $F[1,15] = 1.565$, $p > .230$ for right perfusion; R for the regression = .362, $F[1,15] = 2.260$, $p > .154$ for left perfusion). When left and right parietal perfusion were regressed on mental status score at follow-up, with initial mental status score serving as a covariate, none of the analyses attained statistical significance. However, a trend toward significance ($p < .10$) was observed when left parietal perfusion was regressed on time two mental status scores in the AD group ($\beta = .275$, $T = 1.969$, $p < .073$). The relationships between frontal and parietal blood flow, respectively, and change in mental status over the follow-up interval in AD, AAMI, and combined groups are shown graphically in Figures 1 through 4.

When, rather than looking at frontal perfusion or parietal perfusion separately, the frontal/parietal ratio was regressed on mental status change, the regression analysis was highly significant for the sample as a whole (R for the analysis = 0.585, $F[1,30] = 15.591$, $p < .001$). The correlation between the frontal/parietal ratio and mental status change was significantly greater than that between parietal flow and mental status change ($Z^* = 5.441$, which exceeds the critical value of $z = \pm 1.96$). While the frontal/parietal perfusion ratio also predicted mental status change in the AD subjects (R for the regression = .586, $F[1,13] = 6.791$, $p < .021$), it did

Figure 1: Mental Status Change as a
Function of Total Frontal Perfusion

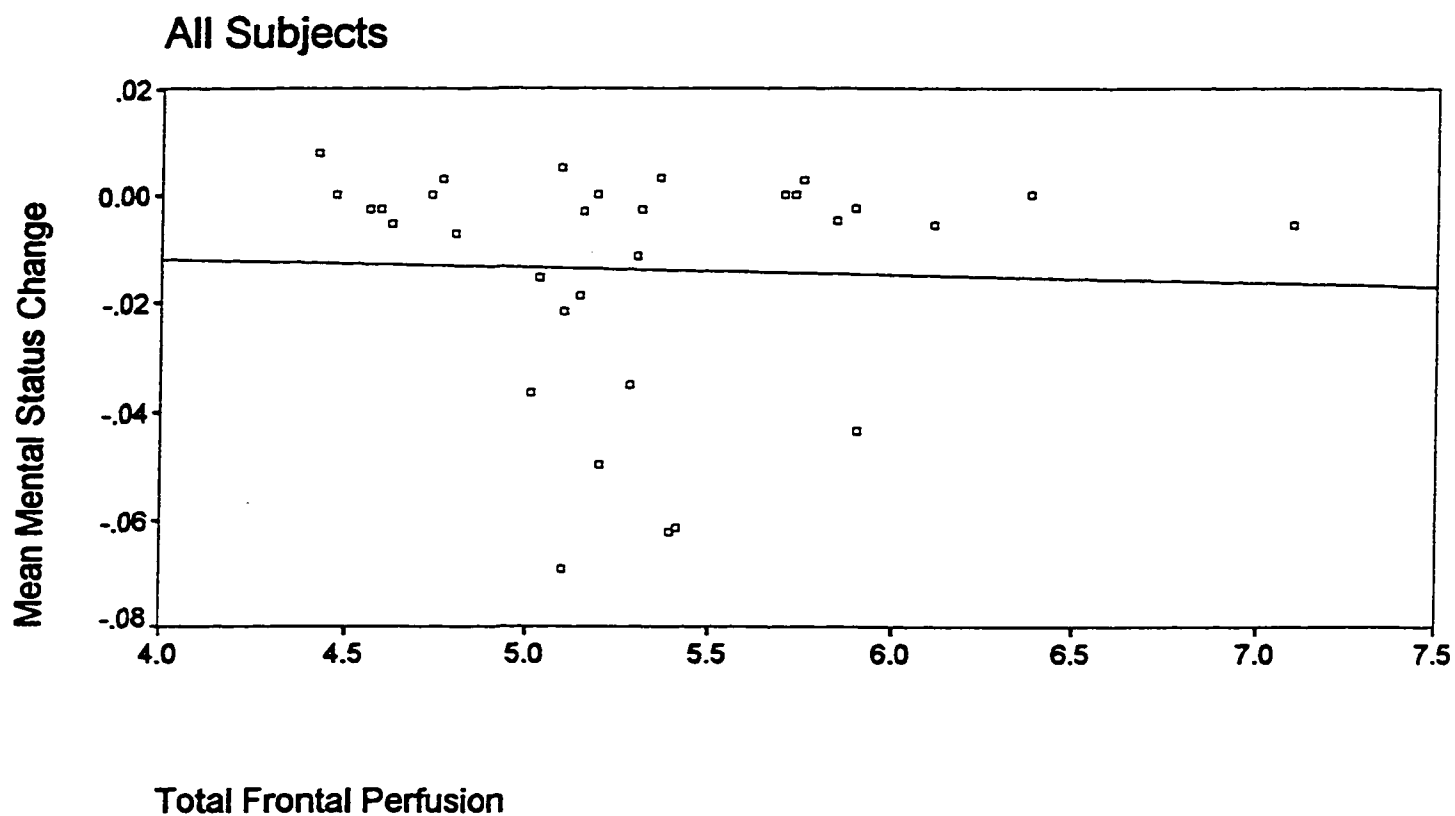


Figure 2: Mental Status Change as a
Function of Total Frontal Perfusion

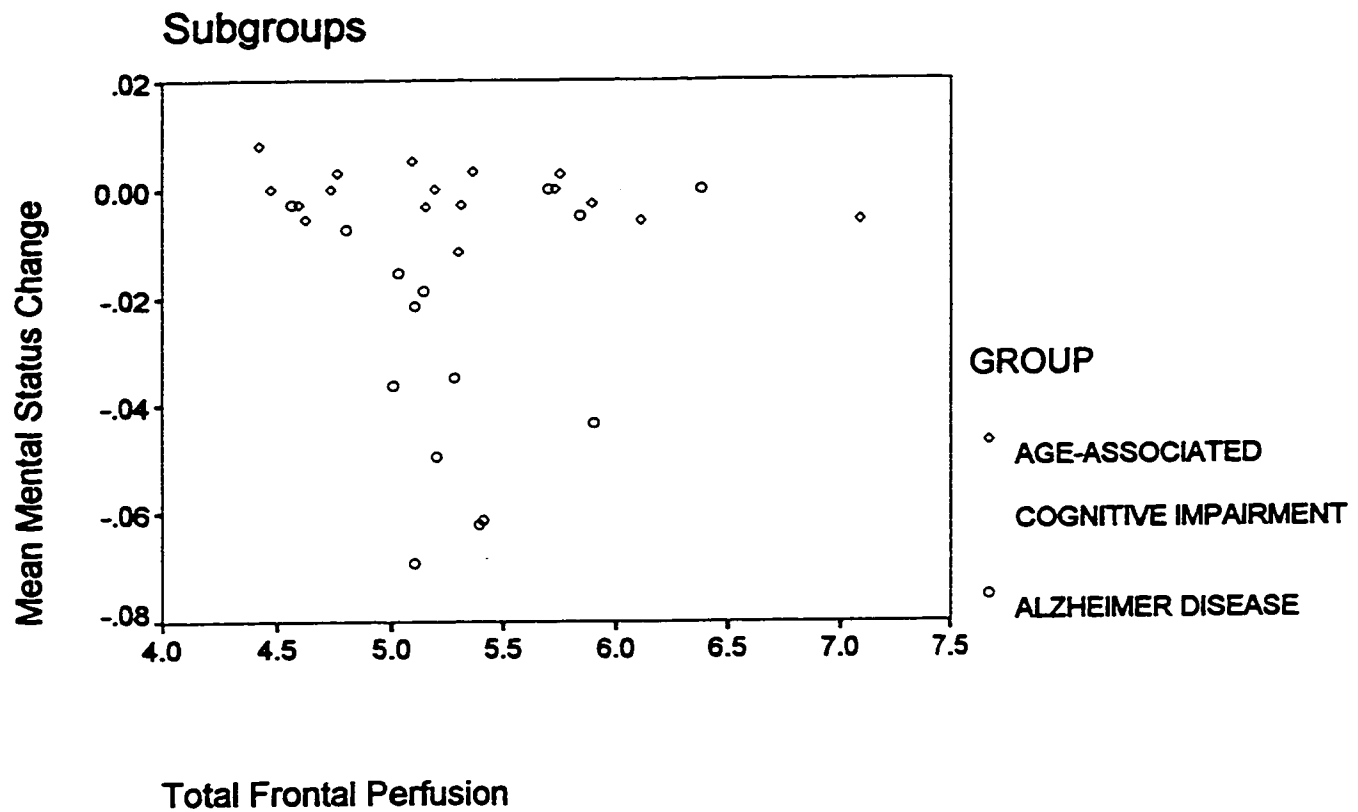


Figure 3: Mental Status Change as a
Function of Total Parietal Perfusion

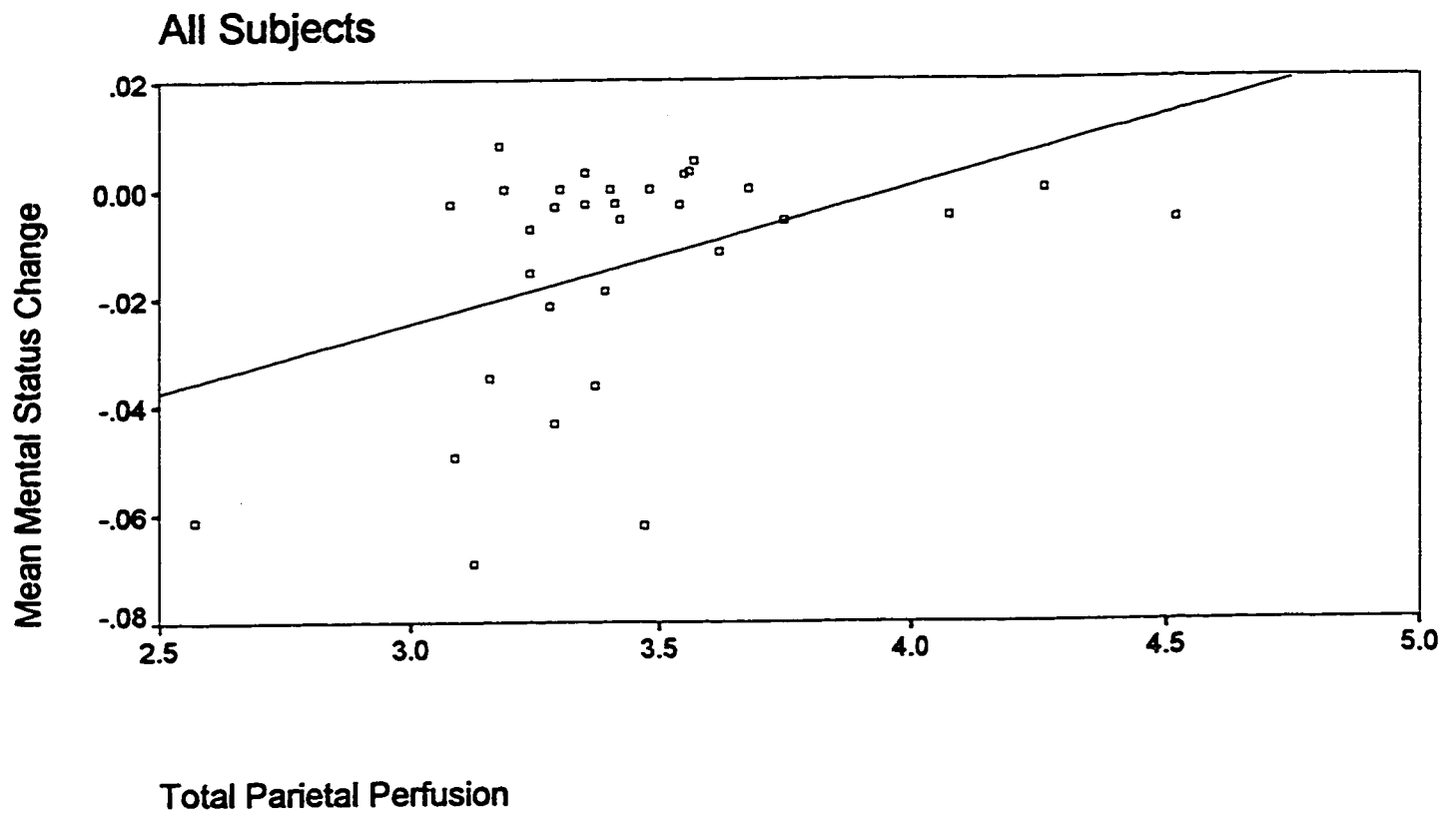
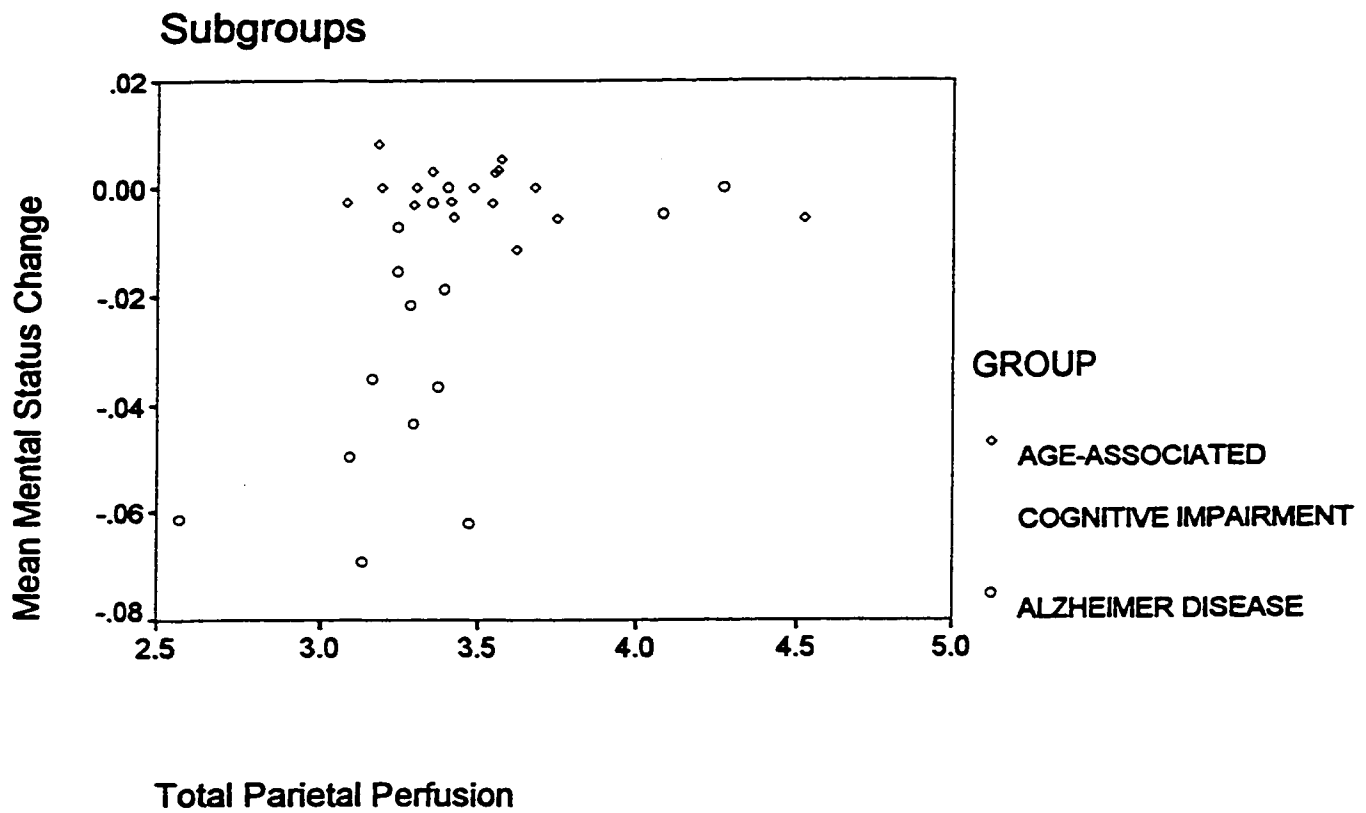


Figure 4: Mental Status Change as a
Function of Total Parietal Perfusion



not do so in the AAMI subsample (R for the analysis = .234, $F[1,15] = .871$, $p > .364$). When the frontal/parietal ratio was regressed on mental status at time two with time-one mental status as a covariate, the frontal/parietal ratio again proved a significant predictor in the group as a whole ($\beta = -.158$, $T = 2.439$, $p < .021$), but only approached significance in the AD group ($\beta = -.261$, $T = -1.842$, $p < .090$). The regression was again nonsignificant in the case of the AAMI subjects ($\beta = -.298$, $T = -1.375$, $p > .190$). As evident in Figures 5 and 6, the nature of the relationship between the frontal/parietal ratio and mental status change was opposite to prediction: The lower the frontal relative to parietal flow in AD subjects, the lesser the change in mental status over the one-year follow-up interval.

The relationship between blood flow and mental status change in the AD patients was alternatively examined by dividing the AD subjects into "fast" and "slow" progressors at the median of the mental status change measure. A series of univariate t-tests was then conducted in order to determine whether these two groups differed at intake in terms of various blood flow measures of interest. The difference in frontal/parietal ratio between the fast and slow progressors did not meet the criterion for significance after Bonferroni correction for the 8 comparisons being tested ($t[8] = 2.33$, $p > .047$). Neither did the fast and slow progressors differ in terms of total frontal perfusion ($t[10] = 0.03$, $p > .973$), left frontal perfusion ($t[12] = 0.21$, $p > .837$), right frontal perfusion ($t[11] = -0.13$, $p > .896$), total parietal perfusion ($t[13] = -2.08$, $p > .058$), left parietal perfusion ($t[13] = -1.79$, $p > .096$), right parietal perfusion ($t[13] = -2.09$, $p > .058$), or sagittal anterior/posterior ratio ($t[13] = -0.77$, $p > .457$).

The ratio of frontal to parietal perfusion as determined from mid-sagittal sections (sum of four frontal sagittal ROIs divided by sum of four posterior sagittal ROIs) did not predict mental

Figure 5: Mental Status Change as a
Function of Frontal/Parietal Ratio

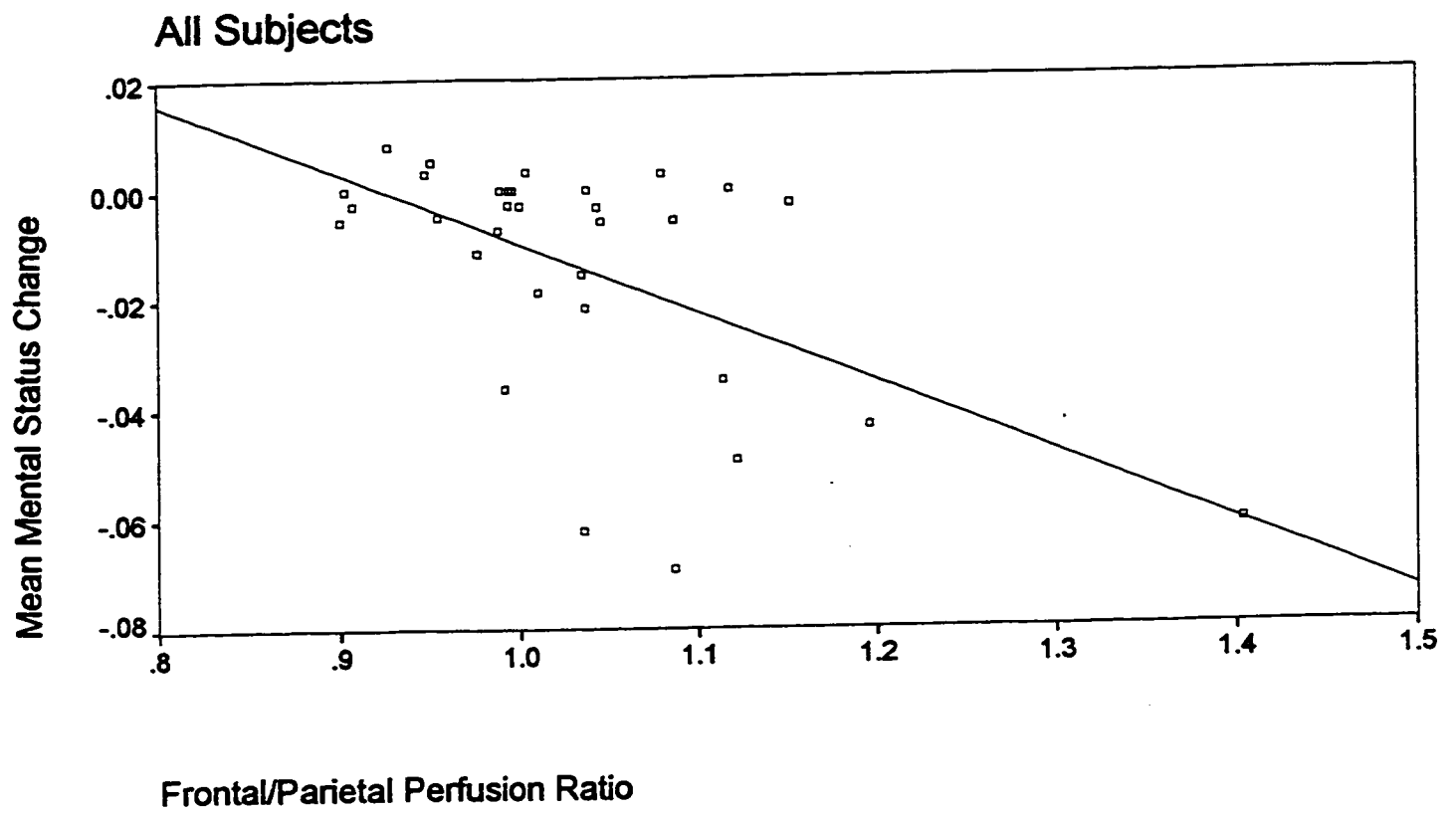
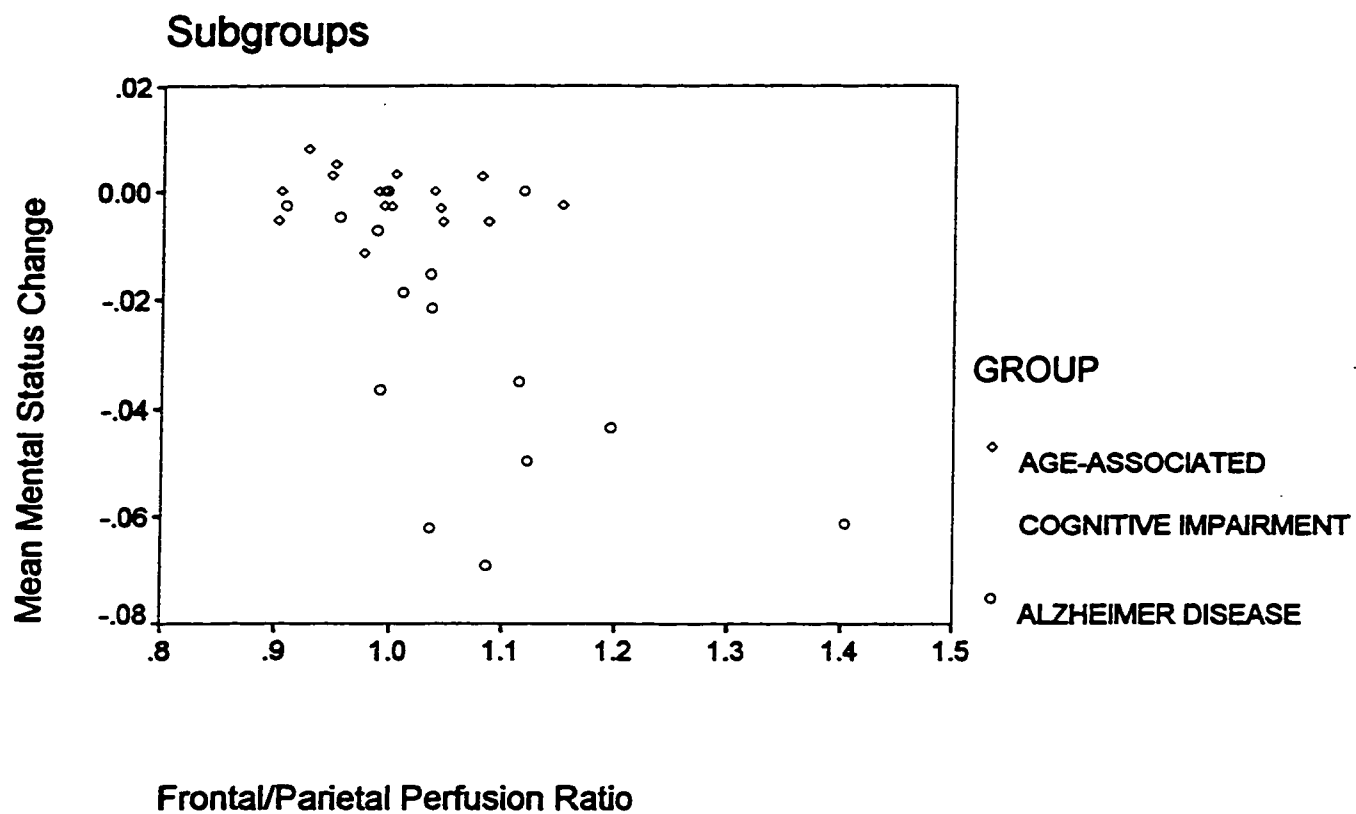


Figure 6: Mental Status Change as a
Function of Frontal/Parietal Ratio



status change over the follow-up interval, either in the sample as a whole (R for the regression = .087, $F[1,30] = .229$, $p > .636$) or in the AD (R for the regression = .043, $F[1,13] = .024$, $p > .880$) and AAMI (R for the regression = .138, $F[1,15] = .291$, $p > .597$) subgroups. Comparable analyses involving regression on mental status at time two residualized on mental status at time one were even less significant (β for anterior/posterior ratio in combined sample = -.009, $T = -0.134$, $p > .894$; β for anterior/posterior ratio in AD sample = -.030, $T = -0.186$, $p > .855$; β for anterior/posterior ratio in AAMI sample = -.071, $T = -0.289$, $p > .777$).

In order to better examine any possible relationships between blood flow measures and mental status change in the AAMI subjects, various blood flow measures of interest were regressed on the memory change score. None of the resultant correlations was significant (r with total frontal flow = .002, $p > .994$; r with total parietal flow = -.053, $p > .841$, r with frontal/parietal ratio = .112, $p > .669$; r with sagittal anterior/posterior ratio = -.083, $p > .753$). As noted above, mean scores of the AAMI subjects on most of the memory tests improved on retesting such that the sum of these scores was significantly higher at time two than at time one. However, in 5 of the 17 AAMI subjects who underwent follow-up assessment, a decrement was noted at time two in the sum of memory test scores. These 5 subjects were compared to the remaining 12 AAMI subjects who improved on retesting in terms of blood flow in several ROIs or combinations thereof. None of these comparisons even approached significance ($t[4.49] = 0.69$, $p > .522$ for total frontal flow; $t[4.48] = 0.79$, $p > .468$ for left frontal flow; $t[4.51] = 0.58$, $p > .588$ for right frontal flow; $t[4.44] = 0.96$, $p > .385$ for total parietal flow; $t[4.68] = 1.06$, $p > .339$ for left parietal flow; $t[4.38] = 0.81$, $p > .460$ for right parietal flow; $t[6] = -0.10$,

$p > .927$ for frontal/parietal ratio; $t[12.87] = 1.43$, $p > .176$ for sagittal anterior/posterior ratio).

Interestingly, there was no correlation between change in memory test scores and change in mental status test scores ($r = -.094$, $p > .721$) and there was no difference in mental status change scores between those AAMI subjects who declined overall on memory testing and those who improved ($t[6.32] = 0.18$, $p > .862$).

Clinical Neuropsychological Measures

Scores summarizing performance on frontal and parietal neuropsychological measures, respectively, were computed by standardizing scores on the relevant variables, summing the standardized scores, and dividing by the number of scores in the index. Frontal measures included in the composite score were perseverative responses on the WCST, losses of set on the WCST, total score on COWA, and Test Age on Porteus Mazes (the first two error scores were negatively weighted in the equation). CFST was not included due to the virtual absence of variability on this measure in the AAMI group. Only one error score from the WCST was included in the composite measure due to the high intercorrelations among the various WCST error variables. Loss of set on the WCST was included, however, as its correlations with other WCST measures are much more modest (in the .3 to .4 range). Parietal measures included in the summary score were the JOLO score, the score on BD, and the total score on the PLB. Although regressions of these neuropsychological summary scores on the mental status change measure in the combined sample approached significance for both the frontal measure (R for the regression = .338,

$F[1,32] = 4.121, p < .051$) and the parietal measure (R for the regression = .334, $F[1,32] = 4.017, p < .054$), these marginal effects were eliminated by including age as a covariate in the regression model (β for the frontal neuropsychological summary score = .295, $T = 1.687, p > .102$; β for the parietal neuropsychological summary score = .291, $T = 1.654, p > .108$), despite the fact that age itself was not a significant predictor of mental status change ($R = .231, F[1,32] = 1.799, p > .189$). Regressions of the neuropsychological summary scores on mental status change were nonsignificant in AAMI subjects (R for frontal neuropsychological measure = .269, $F[1,15] = 1.168, p > .297$; R for the parietal neuropsychological measure = .411, $F[1,15] = 3.054, p > .101$) and in AD subjects (R for frontal neuropsychological measure = .037, $F[1,15] = 0.020, p > .889$; R for the parietal neuropsychological measure = .022, $F[1,15] = 0.007, p > .933$).

In the alternative regression model in which mental status at time two served as the outcome variable with mental status at time one included in the regression model as a covariate, neither the frontal nor the parietal neuropsychological summary measure was significant. In the combined sample, beta for the frontal neuropsychological summary measure was -.001 ($T = -0.011, p > .991$) and beta for the parietal neuropsychological summary measure was .029 ($T = 0.318, p > .753$). When AD subjects were considered separately, beta for the frontal neuropsychological summary measure was -.061 ($T = -0.351, p > .731$) and beta for the parietal neuropsychological summary measure was -.053 ($T = -.310, p > .762$). When AAMI subjects were considered separately, beta for the frontal neuropsychological summary measure was .336 ($T = 1.582, p > .138$) and beta for the parietal neuropsychological summary measure was .06

($T = 0.272$, $p > .790$). These effects were little influenced by including age as a second covariate in the regression model. Age was highly significant as a predictor of mental status at time two ($F[1,32] = 7.940$, $p < .009$), but not after controlling for the mental status score at intake ($\beta = .032$, $T = .372$, $p > .712$).

Individual frontal and parietal neuropsychological measures were also assessed, by means of successive stepwise regression analyses, for their ability to predict mental status change. Regardless of the regression model used (i.e., whether the mental status change variable or mental status at time two residualized on mental status at time one was considered as the dependent variable) and the nature of the sample analysed (AD subjects, AAMI subjects, or all subjects), none of the frontal measures met the criterion ($p = .05$) for entry into the regression equation. However, the PLB total score did predict mental status change in the combined group (i.e., did seem to predict the progressive from the nonprogressive subjects), even when age was included in the analysis as a covariate (β for PLB Total = .392, $T = 2.379$, $p < .024$).

Additional stepwise multiple regression analyses were therefore conducted using the individual subtest scores from the PLB rather than the PLB total score. When the parietal neuropsychological measures were regressed on the mental status change measure in all subjects combined, 2 of the 10 variables entered the final regression model (PLB Finger Gnosis and PLB Right-Left Orientation). The multiple R for this regression equation was .720 ($F[2,31] = 16.703$, $p < .001$). When this same regression model was tested in the AD sample, only the PLB Right-Left Orientation score qualified for entry to the equation (R for the regression = .634, $F[1,15] = 10.060$, $p < .006$). None of the parietal measures was significant when this model was tested in the AAMI subjects alone. In all cases, poorer performance on the parietal lobe measures

was associated with greater cognitive decline. The parietal neuropsychological measures were then regressed on mental status at time two residualized on mental status at time one. In this model, PLB Right-Left Orientation was the only variable to meet the .05 criterion for entry to the regression equation in the case of the combined sample ($\beta = .249$, $T = 3.749$, $p < .001$). PLB Right-Left Orientation also predicted time two mental status in the AD group ($\beta = .392$, $T = 2.959$, $p < .010$), but none of the parietal measures qualified for entry into the regression equation when AAMI subjects were considered separately. All of the foregoing regression analyses involving subtest scores from the PLB were replicated with age as a covariate. The pattern of results was identical.

Analyses were then conducted in order to determine whether the frontal and parietal neuropsychological measures, either individually or combined in respective summary indexes, predicted change in memory test performance among the AAMI subjects. In stepwise multiple regression analyses, none of the individual parietal neuropsychological measures qualified for entry to the equation, whether the variable being predicted was change in memory test performance or memory test performance at time two residualized on memory test performance at time one. Neither did the parietal neuropsychological summary score predict memory change (R for the regression = .052, $F[1,15] = 0.040$, $p > .843$) or time-two memory test scores ($\beta = .227$, $T = 1.236$, $p > .237$). Although the frontal neuropsychological index did not significantly predict change in memory test performance ($R = .400$, $F[1,15] = 2.854$, $p > .112$), it did emerge as a significant predictor of memory performance at time two after covarying out the influence of initial memory test performance (β for frontal summary score = .382, $T = 2.755$,

$p < .016$). This effect persisted even when age was entered into the regression equation first as a covariate (β for frontal summary score = .391, $T = 2.814$, $p < .015$). Age itself was not predictive of memory test performance at time two ($\beta = -.136$, $T = -1.018$, $p > .327$). Although those AAMI subjects who failed to improve on the overall memory measure from time one to time two ($n = 5$) did not significantly differ from AAMI subjects who did improve ($n = 12$) in terms of their overall score on the frontal neuropsychological summary measure, there was a trend toward lower frontal neuropsychological scores in the no-improvement subgroup ($t[13.46] = -1.83$, $p < .090$).

In subsequent stepwise multiple regression analyses in which the various neuropsychological measures contributing to the frontal neuropsychological index were considered separately, Test Age on Porteus Mazes consistently qualified for entry into the equation ($p < .05$), whether change in memory score or memory score at time two was considered as the dependent variable, and whether or not age was included in the regression model as a covariate. This effect was particularly strong in the case where the maze score was regressed on the memory score at time two, with memory score at time one and age included as covariates (β for maze score = .486, $T = 4.085$, $p < .001$). Poorer performance on Porteus Mazes was associated with less improvement on memory testing at time two. Although mean Test Age on Porteus Mazes was only 11.900 ($SD = 4.037$) in those AAMI subjects who failed to improve on memory retesting, as compared to 15.208 ($SD = 2.330$) in those who did show a positive practice effect, this difference did not reach significance ($t[5] = -1.72$, $p > .145$) due to the highly unequal sample sizes ($n = 5$ and $n = 12$, respectively).

DA/DR

Standard multiple regression was used to determine whether the ability to perform DA and DR tasks predicted change in mental status (or memory functioning in the AAMI subjects) over the follow-up interval. Trials to criterion on DR60 and DA5, converted to dichotomous variables (pass/fail), were included as predictors in the analyses involving the combined sample and the AD subjects. As there was no variability on the DR60 variable in the AAMI subjects (they all met criterion on this task in the minimum number of trials), this variable was not used in analyses involving AAMI subjects only. Rather, the raw trials to criterion score on DA5 was used as a predictor, as there was reasonable variability on this measure among the AAMI subjects. When mental status change was considered as the dependent variable, the regression was nonsignificant, both in the combined sample (R for the regression = .351, $F[2,30] = 2.105$, $p > .139$) and in the AD subjects considered separately (R for the regression = .114, $F[2,13] = .086$, $p > .919$). Negative results were also obtained when mental status at time two (rather than mental status change) was used as the outcome variable with mental status at time one included in the regression as a covariate, whether the AD subjects were considered separately (β for DR60 = .158, $T = 0.747$, $p > .469$; β for DR5 = -.005, $T = -0.026$, $p > .980$) or combined with the AAMI subjects (β for DR60 = .118, $T = 1.239$, $p > .225$; β for DR5 = .004, $T = .046$, $p > .963$). In the AAMI subjects, raw trials to criterion on DA5 did not predict mental status change ($R = .301$, $F[1,15] = 1.497$, $p > .240$) or change in memory test scores ($R = .321$, $F[1,15] = 1.720$, $p > .209$), nor did it predict the residualized mental status time two measure ($\beta = .172$, $T = 0.728$, $p > .479$) or the residualized memory time two score ($\beta = -.196$, $T = -1.249$, $p > .232$).

HYPOTHESIS 2: DA AND DR WILL BE MORE PREDICTIVE OF CHANGE IN OVERALL MENTAL STATUS OVER THE FOLLOW-UP PERIOD THAN WILL STANDARD NEUROPSYCHOLOGICAL MEASURES OF FRONTAL LOBE FUNCTION WHICH, IN TURN, WILL BE MORE PREDICTIVE THAN NEUROPSYCHOLOGICAL MEASURES OF POSTERIOR FUNCTIONS.

In an effort to gauge which, if any, of the neuropsychological and experimental measures best predicted dementia progression, a series of stepwise multiple regressions was performed with the following predictor variables: DA5 (coded dichotomously as pass/fail), DR60 (coded dichotomously as pass/fail), the frontal neuropsychological summary score, and the parietal neuropsychological summary score. None of these variables qualified for entry to the regression equation ($PIN = .05$), whether mental status change or mental status at time two (with mental status at time one as a covariate) served as the outcome variable, or whether AD subjects were considered separately or all subjects were considered together.

The raw score on DA5, rather than the dichotomized DR60 and DA5 variables, was used together with the neuropsychological summary scores in similar analyses with the AAMI sample. None of these variables predicted either mental status change or change in memory test scores in the AAMI subjects (i.e., none qualified for entry to the regression equation). Both the frontal neuropsychological summary score ($\beta = .698$, $T = 3.423$, $p < .005$) and the raw score on DA5 trials to criterion ($\beta = .504$, $T = 2.486$, $p < .027$) predicted mental status at time two residualized on mental status at time one. However, neither qualified for entry when preceded by age as a covariate, despite the fact that age itself did not significantly predict the residualized time two

mental status variable (β for age = .017, $T = .072$, $p > .943$). Even with age included as a covariate, the frontal neuropsychological variable did predict memory scores at time two residualized on memory scores at time one, as was seen in previous regressions involving the frontal neuropsychological variable alone ($\beta = .391$, $T = 2.814$, $p < .015$).

HYPOTHESES 3 AND 4: PERFORMANCE ON DA AND DR TASKS WILL BE SIGNIFICANTLY CORRELATED WITH THAT ON STANDARD NEUROPSYCHOLOGICAL MEASURES OF FRONTAL LOBE FUNCTIONING AND WILL NOT CORRELATE WITH PERFORMANCE ON NEUROPSYCHOLOGICAL MEASURES OF NONFRONTAL FUNCTIONING.

Correlations between DA and DR measures and the various frontal and parietal neuropsychological measures for the combined sample and for AD and AAMI subjects considered separately appear in Tables 10 to 15. In the case of the combined sample and the AD sample, DR60 and DA5 trials to criterion scores were recoded dichotomously as pass-fail and the values in Tables 10 and 11 (pertaining to frontal neuropsychological variables) and 13 and 14 (pertaining to parietal neuropsychological variables) represent point-biserial correlations. When the AAMI subjects were considered separately, DR values were not used as they did not vary in this group. Rather, the raw number of trials to criterion on DA5 was used in this sample and thus the values in Table 12 (pertaining to frontal neuropsychological variables) and Table 15 (pertaining to parietal neuropsychological variables) represent Pearson Product Moment correlation coefficients.

Table 10

Point-Biserial Correlations among Neuropsychological Measures of Frontal Lobe Functions and Delayed Response (DR) and Delayed Alternation (DA) Measures in All Subjects Combined

Frontal Neuropsychological Variables	DR/DA Variables	
	DR60 $n = 37$	DA5 $n = 36$
WCST-PR	-.334 $p = .022$	-.418* $p = .006$
WCST-SET	.209 $p = .107$	-.260 $p = .063$
CFST	.520** $p = .001$	.180 $p = .147$
COWA	.307 $p = .032$	.344 $p = .020$
MAZES	.365 $p = .013$	.581** $p = .001$

Note. DR60 = total trials to criterion on 60" delay condition of DR task scored dichotomously as pass/fail; DA5 = trials to criterion on 5" delay condition of DA task scored dichotomously as pass/fail; WCST-PR = number of perseverative responses on Wisconsin Card Sorting Test (WCST); WCST-SET = number of set losses on WCST; CFST = total score on Colour Form Sorting Test; COWA = total score on Controlled Oral Word Association Test; MAZES = Test Age on Porteus Maze Test

$n = 37$ for correlations with DR60; $n = 36$ for correlations with DA5

** $p < .05$, one-tailed, after Bonferroni correction

* $p < .10$, one-tailed, after Bonferroni correction

Table 11

Point-Biserial Correlations among Neuropsychological Measures of Frontal Lobe Functions and Delayed Response (DR) and Delayed Alternation (DA) Measures in AD Subjects

Frontal Neuropsychological Variables	DR/DA Variables	
	DR60 n = 19	DA5 n = 18
WCST-PR	-.242 p = .159	-.238 p = .171
WCST-SET	.319 p = .092	-.337 p = .086
CFST	.427 p = .034	-.216 p = .195
COWA	.268 p = .134	-.183 p = .233
MAZES	.333 p = .082	.533 p = .011

Note. AD = Alzheimer disease; DR60 = trials to criterion on 60" delay condition of Delayed Response task scored dichotomously as pass/fail; DA5 = trials to criterion on 5" condition of Delayed Alternation task scored dichotomously as pass/fail; WCST-PR = number of perseverative responses on Wisconsin Card Sorting Test (WCST); WCST-SET = number of set losses on WCST; CFST = total score on Colour Form Sorting Test; COWA = total score on Controlled Oral Word Association Test; MAZES = test age on Porteus Maze Test

Probabilities are one-tailed

Table 12

Pearson Product-Moment Correlations among Neuropsychological Measures of Frontal Lobe Functions and Delayed Alternation (DA) in AAMI Subjects

	Frontal Neuropsychological Variables				
	WCST-PR	WCST-SET	CFST	COWA	MAZES
DA5	.419 p= .042	-.002 p= .497	-.001 p= .498	-.236 p= .173	-.512 p= .015+

Note. AAMI = Age Associated Memory Impairment; WCST-PR = number of perseverative responses on Wisconsin Card Sorting Test (WCST); WCST-SET = number of set losses on WCST; CFST = total score on Colour Form Sorting Test; COWA = total score on Controlled Oral Word Association Test; MAZES = Test Age on Porteus Maze Test; DA5 = trials to criterion (raw score) on 5" delay condition of DA task

n = 18 for all correlations

+p < .10, one-tailed, after Bonferroni correction

Table 13

Point-Biserial Correlations among Neuropsychological Measures of Parietal Lobe Functions and Delayed Response (DR) and Delayed Alternation (DA) Measures in All Subjects

Parietal Neuropsychological Variables	DR/DA Variables	
	DR60 n = 37	DA5 n = 36
PLB SUBTEST		
DRAWING	.383 p = .019	.323 p = .055
STICK DESIGN	.373 p = .023	.496* p = .002
BLOCK DESIGN	.376 p = .022	.387 p = .020
FINGER GNOSIS	.350 p = .034	.318 p = .059
R-L ORIENTATION	.367 p = .026	.386 p = .020
CALCULATION	.305 p = .067	.197 p = .250
CLOCK SETTING	.564* p = .001	.064 p = .713
MAP	.232 p = .168	.225 p = .186
PLB TOTAL SCORE	.536* p = .001	.416 p = .012
JOLO	.370 p = .024	.226 p = .185
WAIS-R BLOCK DESIGN	.303 p = .068	.362 p = .030

Note. DR60 = total trials to criterion on 60" delay condition of DR task scored dichotomously as pass/fail; DA5 = trials to criterion on 5" delay condition of DA task scored dichotomously as pass/fail; PLB = Parietal Lobe Battery; JOLO = total score on Judgement of Line Orientation Test; WAIS-R = Wechsler Adult Intelligence Scale-Revised
*p < .05, two-tailed, after Bonferroni correction

Table 14

Point-Biserial Correlations among Neuropsychological Measures of Parietal Lobe Functions and Delayed Response (DR) and Delayed Alternation (DA) Measures in AD Subjects

Parietal Neuropsychological Variables	DR/DA Variables	
	DR60 n = 19	DA5 n = 18
PLB SUBTEST		
DRAWING	.392 p= .097	.345 p= .161
STICK DESIGN	.271 p= .261	.186 p= .461
BLOCK DESIGN	.281 p= .243	.240 p= .338
FINGER GNOSIS	.236 p= .331	.166 p= .510
R-L ORIENTATION	.301 p= .211	.265 p= .288
CALCULATION	.161 p= .510	-.187 p= .457
CLOCK SETTING	.581 p= .009	-.298 p= .230
MAP	.200 p= .413	.261 p= .295
PLB TOTAL	.516 p= .024	.164 p= .516
JOLO	.337 p= .158	.268 p= .283
WAIS-R BLOCK DESIGN	.241 p= .321	.265 p= .287

Note. DR60 = total trials to criterion on 60" delay condition of DR task scored dichotomously as pass/fail; DA5 = trials to criterion on 5" delay condition of DA task scored dichotomously as pass/fail; PLB = Parietal Lobe Battery; JOLO = total score on Judgement of Line Orientation Test; WAIS-R = Wechsler Adult Intelligence Scale-Revised
Probability values are two-tailed

Table 15

Pearson Product-Moment Correlations among Neuropsychological Measures of Parietal Lobe Functions and Delayed Alternation (DA) in AAMI Subjects

Parietal Neuropsychological Variables	DA5
PLB SUBTEST	
DRAWING	-.155 ($p = .539$)
STICK DESIGN	-.220 ($p = .380$)
BLOCK DESIGN	-.357 ($p = .146$)
FINGER GNOSIS	.046 ($p = .857$)
R-L ORIENTATION	-.234 ($p = .350$)
CALCULATION	-.025 ($p = .921$)
CLOCK SETTING	.076 ($p = .764$)
MAP	-.094 ($p = .711$)
PLB TOTAL SCORE	-.191 ($p = .448$)
JOLO	.227 ($p = .366$)
WAIS-R BLOCK DESIGN	-.114 ($p = .652$)

Note. DA5 = trials to criterion on 5" delay condition of DA task; PLB = Parietal Lobe Battery; JOLO = total score on Judgement of Line Orientation Test; WAIS-R = Wechsler Adult Intelligence Scale-Revised
 $n = 18$ for all correlations
 Probability values are two-tailed

As the direction of correlations involving frontal lobe neuropsychological measures had been predicted, significance for tests of these correlations was one-tailed. Two-tailed significance testing was used in the case of correlations involving parietal measures.

Considering the sample as a whole, significant correlations (after Bonferroni correction for the number of correlations in the series) involving the frontal neuropsychological variables were observed between CFST and DR60 ($r_{pb} = .5195$, $p < .001$) and between Test Age on the Porteus Mazes Test and DA5 ($r_{pb} = .5805$, $p < .001$). The correlation between WCST perseverative responses and DA5 approached significance (i.e., $p < .10$ after Bonferroni correction; $r_{pb} = -.4184$, $p < .006$). These correlations were in the expected direction and so met the criterion for significance in these one-tailed tests. When the AD subjects were considered separately, none of the correlations between frontal measures and DA/DR measures reached significance after Bonferroni correction. However, the correlation between raw trials to criterion score on DA5 and Test Age on Porteus Mazes ($r = -.5117$, $p < .015$) approached significance in the AAMI sample.

In order to determine whether the foregoing correlations between frontal neuropsychological measures and DR/DA measures were simply attributable to the fact that all of these variables are general markers of dementia, their relationships were reassessed including the general mental status measure (at time one) as a covariate. In an analysis of covariance, those subjects who passed the DR60 task were found to differ significantly from those who failed the DR60 task in terms of CFST score, even after covarying out the general mental status measure ($F [1,34] = 7.017$, $p < .012$). Similarly, those subjects who passed the DA5 task were found to differ significantly from those who failed the DA5 task in terms of Test Age on the Porteus Maze

Test after covarying out the effects of general mental status ($F [1,33] = 6.068, p < .019$). The raw trials to criterion score on DA5 significantly predicted Test Age on Porteus Mazes in AAMI subjects when general mental status was controlled by including it as a covariate (β for DA5 = $-.434, T = -3.146, p < .004$; β for mental status = $.574, T = 4.09, p < .001$).

Among the 55 correlations involving DR/DA measures and the parietal neuropsychological measures, only three were significant after Bonferroni correction, all of these occurring in the combined sample: DR60 with PLB Clock Setting ($r_{pb} = .564, p < .001$), DR60 with PLB Total Score ($r_{pb} = .536, p < .001$), and DA5 with PLB Stick Design ($r_{pb} = .496, p < .002$). As can be seen, the correlations were positive in all cases, indicating that higher (better) scores on the PLB tests were associated with passing the DR or DA task. However, only the relationship between DR60 and PLB Clock Setting retained significance after controlling for general mental status at time one: In an analysis of covariance, those who passed DR60 were found to differ significantly from those who failed ($F [1,34] = 8.920, p < .005$). In other analyses of covariance (with mental status at time one serving as the covariate), PLB Total Score did not differ between those who passed and those who failed DR60 ($F [1,34] = 2.497, p > .123$) and PLB Stick Design did not differ between those who passed and those who failed DA5 ($F [1,33] = 0.567, p > .457$). None of the correlations involving parietal neuropsychological variables was significant when AD patients and AAMI subjects were considered separately and correction was made for the number of correlations computed in each series.

In an attempt to compare the relative strength of association between neuropsychological measures of frontal and parietal function, on the one hand, and the experimental tests (DA and DR) on the other, the frontal and parietal neuropsychological summary scores were correlated

with the dichotomized scores from DR60 and DA5. These point-biserial correlations appear in Table 16. Incidentally, the frontal and parietal neuropsychological summary scores were quite highly correlated with each other in both the AD group ($r = .513$, $p < .025$) and in the sample as a whole ($r = .569$, $p < .001$). The correlations presented in Table 16 did not provide an obvious answer as to the relative strength of relationships between frontal and parietal neuropsychological measures, on the one hand, and DR/DA on the other hand. Whereas the frontal neuropsychological summary score was highly correlated with DA5 ($r_{pb} = .6607$, $p < .001$), the parietal neuropsychological summary score was highly correlated with DR60 ($r_{pb} = .4508$, $p < .005$). Moreover, the correlation between the parietal neuropsychological summary score and DA5 approached significance after Bonferroni correction ($r_{pb} = .3735$, $p < .025$).

In a further effort to determine whether frontal or parietal neuropsychological measures correlated more strongly with the experimental DR/DA tasks, multiple regressions were performed in which the dichotomized DA and DR scores were regressed on the frontal and parietal neuropsychological summary scores, respectively. In a standard multiple regression with the frontal neuropsychological summary score as the dependent variable, R for the regression was .701 ($F[2,33] = 15.961$, $p < .0001$). The beta weight for DR60 (.237) fell just short of significance ($p > .067$), whereas that for DA5 (.628) was highly significant ($p < .0001$). This multiple regression analysis was repeated including mental status at time one as a covariate (by forcing it to enter the regression equation before the other predictors). Although the strength of the relationships between predictor and outcome variables was slightly attenuated by inclusion of the covariate, the overall pattern of results was the same, with the beta weight for DR60 (.140) being nonsignificant ($T = .877$, $p > .387$) and that for DA5 (.542) being highly significant

Table 16

Point-Biserial Correlations between Summary Scores of Frontal and Parietal Neuropsychological Function and Summary Measures of Delayed Response (DR) and Delayed Alternation (DA) in All Subjects

DR/DA VARIABLES	Neuropsychological Summary Scores	
	NP FRONTAL	NP PARIETAL
DR60 n = 37	.331 p = .046	.451* p = .005
DA5 n = 36	.661* p = .000	.374+ p = .025

Note. NP FRONTAL = sum of standardized scores on Porteus Mazes Test and Controlled Oral Word Association Test minus standardized values for perseverative responses and for losses of set on Wisconsin Card Sorting Test; NP PARIETAL = sum of standardized scores on Parietal Lobe Battery (total score), Judgement of Line Orientation Test, and Block Design Subtest of the Wechsler Adult Intelligence Scale-Revised; DR60 = total trials to criterion on 60" delay condition of DR task scored dichotomously as pass/fail; DA5 = trials to criterion on 5" delay condition of DA task scored dichotomously as pass/fail

*p < .05, two-tailed, after Bonferroni correction

+p < .10, two-tailed, after Bonferroni correction

($\beta = .542$, $T = 3.555$, $p < .001$). Mental status at time one was itself a highly significant predictor of the frontal neuropsychological summary score ($\beta = .558$, $T = 3.923$, $p < .001$). When these same variables were regressed in a stepwise fashion on the frontal neuropsychological summary score, DA5 entered the regression, whereas DR60 did not (whether or not mental status at time one was included as a covariate in the regression model).

A standard multiple regression with the parietal neuropsychological summary score as the dependent variable was also significant, although not to the same degree as when the frontal summary score was used (R for the regression = .532, $F[2,33] = 6.501$, $p < .005$). In this instance, both the DA and the DR variables had significant beta weights (β for DR60 = .382, $T = 2.566$, $p < .015$; β for DA5 = .321, $T = 2.154$, $p < .039$). However, in this case, including mental status at time one as a covariate (by forcing it to enter the regression equation in advance of the other predictors) eliminated any ability of DR60 ($\beta = .229$, $T = 1.221$, $p > .231$) or DA5 ($\beta = .186$, $T = 1.039$, $p > .306$) to predict parietal neuropsychological performance. When the DR and DA variables were regressed stepwise on the parietal neuropsychological summary score after forced entry of mental status at time one, neither qualified for entry to the equation.

As noted above, the multiple R from the regression involving the frontal neuropsychological summary score was somewhat greater than the respective multiple R from the regression on the parietal neuropsychological summary score. This difference between the multiple R s from the two regressions was statistically significant ($Z^* = 2.839$ which exceeds the critical value of $Z = \pm 1.96$).

Canonical correlation procedures were used in yet another approach to assessing whether parietal neuropsychological or frontal neuropsychological variables correlated more strongly with

DA and DR measures. Firstly, canonical correlation was performed between a set of frontal neuropsychological measures (perseverative responses on the WCST, losses of set on the WCST, COWA, and Test Age on Porteus Mazes) and the dichotomized DA5 and DR60 variables. The first canonical correlation was .670, while the second was effectively zero. With both canonical correlations included, Chi-square (8, $N = 36$) was 22.496 ($p < .004$). Subsequent tests of Chi-square were nonsignificant. Thus, the first pair of canonical variates accounted for the significant relationship between the two sets of variables. A second canonical correlation was then performed between a set of parietal neuropsychological measures (PLB Total Score, JOLO, and BD) and the same DA and DR variables. The first canonical correlation was .567, the second effectively zero. With both canonical correlations included, Chi-square (6, $n = 36$) was 13.572 ($p < .035$). Subsequent tests of Chi-square were nonsignificant, indicating that the first pair of canonical variates accounted for the significant relationship between these two sets of variables. This relationship, however, was not nearly as significant as that between the first pair of canonical variates in the correlation involving frontal neuropsychological variables.

HYPOTHESES 5 AND 6: PERFORMANCE ON DA AND DR TASKS WILL BE SIGNIFICANTLY CORRELATED WITH MEASURES OF FRONTAL PERFUSION.

HYPOTHESIS 7: PERFORMANCE ON EXPERIMENTAL TASKS (DA AND DR) WILL CORRELATE MORE STRONGLY WITH MEASURES OF FRONTAL PERFUSION THAN WILL SCORES ON STANDARD NEUROPSYCHOLOGICAL TESTS OF FRONTAL LOBE FUNCTION.

Table 17 depicts correlations between summary frontal perfusion measures and neuropsychological measures of frontal lobe functioning for the sample as a whole. The probability associated with the correlation between the score on CFST and the frontal/parietal ratio in the combined sample was less than alpha ($r = -.4515$, $p < .003$). However, the nature of the relationship was in the direction opposite to prediction (the higher the frontal relative to parietal perfusion, the lower the score on the CFST) and so was not significant in this one-tailed test. All other correlations between frontal perfusion measures and frontal neuropsychological measures in the combined sample were nonsignificant, even prior to Bonferroni correction for the number of correlations computed in each series. All correlations between the frontal lobe perfusion measures and frontal neuropsychological measures were nonsignificant in the AD and AAMI subgroups, as evident in Tables 18 and 19, respectively.

The point-biserial correlations between frontal perfusion measures and dichotomized measures of DR60 and DA5 are presented in Table 20 for all subjects combined and in Table 21 for the AD sample. None of these correlations was significant, even prior to correction for the number of correlations in the series. Neither did the raw trials to criterion score on DA5 correlate

Table 17

Correlations among Neuropsychological and SPECT Measures of Frontal Lobe Function in All Subjects

Neuropsychological Measures	SPECT Summary Measures		
	Total Frontal Perfusion	Sagittal A/P Ratio	Frontal/Parietal Ratio
WCST-PR	-.114 p= .257	.103 p= .279	.131 p= .226
WCST-SET	.175 p= .157	-.121 p= .245	.165 p= .172
CFST	.034 p= .423	-.067 p= .352	-.452 p= .003
COWA	-.090 p= .304	.029 p= .435	-.221 p= .101
MAZES	.025 p= .444	.026 p= .442	-.186 p= .142
NP FRONTAL	-.053 p= .382	.031 p= .431	-.238 p= .088

Note. SPECT = single photon emission computed tomography; Total Frontal Perfusion = sum of perfusion ratios in all frontal regions of interest; Sagittal A/P Ratio = ratio of total frontal to total posterior flow on sagittal section; Frontal/Parietal ratio = ratio of total flow in lateral frontal cortical regions to total flow in lateral parietal cortical regions; WCST-PR = number of perseverative responses on Wisconsin Card Sorting Test (WCST); WCST-SET = number of set losses on WCST; CFST = total score on Colour Form Sorting Test; COWA = total score on Controlled Oral Word Association Test; MAZES = Test Age on Porteus Maze Test; NP Frontal = Frontal neuropsychological summary score
 $n = 35$ for all correlations
 Significance values are one-tailed

Table 18

Correlations among Neuropsychological and SPECT Measures of Frontal Lobe Function in AD Subjects

Neuropsychological Measures	SPECT Summary Measures		
	Total Frontal Perfusion	Sagittal A/P Ratio	Frontal/Parietal Ratio
WCST-PR	.030 p = .455	.323 p = .103	.110 p = .337
WCST-SET	.002 p = .497	-.361 p = .078	.036 p = .445
CFST	.133 p = .306	-.158 p = .273	-.397 p = .057
COWA	-.302 p = .119	-.026 p = .461	-.171 p = .256
MAZES	-.063 p = .405	-.201 p = .220	-.168 p = .260
NP FRONT	-.165 p = .263	-.059 p = .411	-.210 p = .209

Note. SPECT = single photon emission computed tomography; Total Frontal Perfusion = sum of perfusion ratios in all frontal regions of interest; Sagittal A/P Ratio = ratio of total frontal to total posterior flow on sagittal section; Frontal/Parietal ratio = ratio of total flow in lateral frontal cortical regions to total flow in lateral parietal cortical regions; WCST-PR = number of perseverative responses on Wisconsin Card Sorting Test (WCST); WCST-SET = number of set losses on WCST; CFST = total score on Colour Form Sorting Test; COWA = total score on Controlled Oral Word Association Test; MAZES = Test Age on Porteus Maze Test; NP Frontal = Frontal neuropsychological summary score
 $n = 17$ for all correlations
 Significance values are one-tailed

Table 19

Correlations among Neuropsychological and SPECT Measures of Frontal Lobe Function in AAMI Subjects

Neuropsychological Measures	SPECT Summary Measures		
	Total Frontal Perfusion	Sagittal A/P Ratio	Frontal/Parietal Ratio
WCST-PR	-.341 p= .083	-.222 p= .188	-.379 p= .060
WCST-SET	.349 p= .078	.381 p= .059	.342 p= .083
CFST	-.034 p= .448	-.036 p= .444	.051 p= .420
COWA	.051 p= .420	.026 p= .460	.029 p= .455
MAZES	.121 p= .317	.243 p= .166	.237 p= .172
NP FRONTAL	.058 p= .410	.045 p= .430	.120 p= .317

Note. SPECT = single photon emission computed tomography; Total Frontal Perfusion = sum of perfusion ratios in all frontal regions of interest; Sagittal A/P Ratio = ratio of total frontal to total posterior flow on sagittal section; Frontal/Parietal ratio = ratio of total flow in lateral frontal cortical regions to total flow in lateral parietal cortical regions; WCST-PR = number of perseverative responses on Wisconsin Card Sorting Test (WCST); WCST-SET = number of set losses on WCST; CFST = total score on Colour Form Sorting Test; COWA = total score on Controlled Oral Word Association Test; MAZES = Test Age on Porteus Maze Test; NP Frontal = Frontal neuropsychological summary score $n = 18$ for all correlations
Significance values are one-tailed

Table 20

Point-Biserial Correlations among Delayed Response (DR) and Delayed Alternation (DA) Measures and Frontal Perfusion Measures in All Subjects

SPECT Measure	DR/DA Variables	
	DR60 n = 35	DA5 n = 34
TOTAL FRONTAL PERFUSION	-.058 p = .371	.214 p = .112
SAGITTAL A/P RATIO	.201 p = .124	.114 p = .261
FRONT/PARIETAL RATIO	-.157 p = .185	-.061 p = .365

Note. SPECT = single photon emission computed tomography; DR60 = total trials to criterion on 60" delay condition of DR task scored dichotomously as pass/fail; DA5 = trials to criterion on 5" delay condition of DA task scored dichotomously as pass/fail; Sagittal A/P ratio = ratio of total frontal to total posterior flow on sagittal section; Front/Parietal ratio = ratio of total flow in lateral frontal cortical regions to total flow in lateral parietal cortical regions. Significance values are one-tailed.

Table 21

Point-Biserial Correlations among Delayed Response (DR) and Delayed Alternation (DA) Measures and Frontal Perfusion Measures in AD Subjects

SPECT Measure	DR/DA Variables	
	DR60 n = 17	DA5 n = 16
TOTAL FRONTAL PERFUSION	-.085 p= .374	.111 p= .341
SAGITTAL A/P RATIO	.224 p= .193	.030 p= .456
FRONT/PARIETAL RATIO	-.001 p= .499	.147 p= .294

Note. SPECT = single photon emission computed tomography; DR60 = total trials to criterion on 60" delay condition of DR task scored dichotomously as pass/fail; DA5 = trials to criterion on 5" delay condition of DA task scored dichotomously as pass/fail; Sagittal A/P ratio = ratio of total frontal to total posterior flow on sagittal section; Front/Parietal ratio = ratio of total flow in lateral frontal cortical regions to total flow in lateral parietal cortical regions. Significance values are one-tailed.

with total frontal blood flow ($r_{pb} = -.2778$, $p > .132$), with the sagittal anterior/posterior ratio ($r_{pb} = -.1649$, $p > .257$), or with the frontal/parietal ratio ($r_{pb} = -.3073$, $p > .108$) in the AAMI sample.

In so far as frontal perfusion measures did not correlate in the expected direction with either frontal neuropsychological measures or with DA and DR variables, hypothesis 7 was not particularly relevant. Nevertheless, an effort was made to address the question as to whether DA/DR measures or neuropsychological measures correlated more strongly with frontal blood flow by comparing the R s from multiple regression analyses in which the dichotomous DR60 and DA5 measures and a subset of frontal neuropsychological test scores (WCST perseverative responses, COWA, and Mazes), respectively, were regressed on total frontal perfusion. The difference between these correlations was nonsignificant ($Z^* = .0752$, less than the critical value of $Z = \pm 1.96$).

COMPARISON OF "HIGH" AND "LOW" FRONTAL PERFUSION GROUPS IN TERMS OF NEUROPSYCHOLOGICAL AND DA/DR MEASURES OF FRONTAL FUNCTION

Subjects were divided into "high" and "low" frontal perfusion groups by separating the combined sample at the median of the total frontal perfusion measure (the sum of the perfusion ratios for all frontal ROIs). A discriminant function analysis was then conducted using all subjects to determine whether the dichotomous DA5 and DR60 measures would discriminate between the high and low frontal blood flow groups. The one discriminant function was not significant in either the combined sample ($\chi^2[2, N = 34] = 4.64$, $p > .098$) or the AD sample

($\chi^2[2, N = 16] = 2.699, p > .259$). In the case of AAMI subjects, the raw trials to criterion score on DA5 was assessed for its ability to discriminate the high and low perfusion subgroups. Again, the discriminant function was nonsignificant ($\chi^2[1, N = 18] = 2.229, p > .135$). Additional discriminant function analyses were then conducted with subjects divided, in turn, according to the median perfusion in specific frontal regions of interest (left and right superior frontal, left and right midfrontal, and left and right inferior frontal, respectively). The resultant discriminant functions were nonsignificant (even prior to correction for the number of analyses conducted), whether AD and AAMI subjects were considered separately or combined into a single sample. The results of statistical tests of these various discriminant functions are presented in Table 22.

High and low frontal perfusion groups were also compared in terms of their performance on neuropsychological measures of frontal lobe functioning. A series of discriminant function analyses was conducted in which a subset of individual frontal neuropsychological measures (perseverative responses on the WCST, losses of set on the WCST, Test Age on Porteus Mazes, and total score on COWA) served as the predictor variables and various frontal perfusion measures (total frontal perfusion, right and left superior frontal perfusion, right and left midfrontal perfusion, and right and left inferior frontal perfusion), in turn, served as the grouping variable. These discriminant functions were also nonsignificant. The results of statistical tests of these various discriminant functions are presented in Table 23.

Table 24 summarizes the results as they pertain to the various hypotheses tested in this study.

Table 22

Chi-Square Values for Discriminant Functions Summarizing Ability of Delayed Response (DR) and Delayed Alternation Variables to Classify Groups with High and Low Perfusion in Various Frontal Regions of Interest (ROI) in AD Subjects, AAMI Subjects, and All Subjects

FRONTAL ROI	SAMPLE		
	AD n = 16	AAMI n = 18	ALL SUBJECTS n = 34
L Superior Frontal	0.765 p = .682 (7/9)	1.155 p = .283 (10/8)	1.288 p = .525 (17/17)
R Superior Frontal	1.860 p = .395 (7/9)	1.451 p = .228 (10/8)	2.435 p = .296 (17/17)
L Midfrontal	0.000 p = 1.000 (8/8)	1.351 p = .245 (9/9)	1.015 p = .602 (17/17)
R Midfrontal	2.699 p = .259 (8/8)	2.229 p = .135 (9/9)	4.640 p = .098 (17/17)
L Inferior Frontal	0.351 p = .839 (6/10)	0.836 p = .361 (10/8)	0.015 p = .993 (16/18)
R Inferior Frontal	1.274 p = .529 (6/10)	1.065 p = .302 (11/7)	1.288 p = .525 (17/17)
Total Frontal	4.640 p = .098 (8/8)	2.699 p = .259 (9/9)	2.229 p = .135 (17/17)

Note. AD = Alzheimer disease; AAMI = Age Associated Memory Impairment; R = right; L = left
 Predictor variables in discriminant function analyses with combined sample and AD sample were: dichotomous (pass/fail) scores on 5" delay condition of DA task and dichotomous (pass/fail) scores on 60" delay condition of DR task (Chi-square has 2 degrees of freedom in these analyses). Predictor variable in discriminant function analyses with AAMI subjects was raw trials to criterion score on 5" delay condition of DA task (Chi-square has 1 degree of freedom in these analyses). Numbers in brackets represent number of subjects in "low" perfusion group/number of subjects in "high" perfusion group
 Significance values are two-tailed

Table 23

Chi-Square Values for Discriminant Functions Summarizing Ability of Frontal Neuropsychological Variables to Classify Groups with High and Low Perfusion in Various Frontal Regions of Interest (ROI) in AD Subjects, AAMI Subjects, and All Subjects

FRONTAL ROI	SAMPLE		
	AD n = 17	AAMI n = 18	ALL SUBJECTS n = 35
L Superior Frontal	1.859 p = .762 (8/9)	1.611 p = .807 (10/8)	3.812 p = .432 (18/17)
R Superior Frontal	2.208 p = .698 (8/9)	2.828 p = .587 (10/8)	5.277 p = .260 (18/17)
L Midfrontal	0.367 p = .985 (9/8)	4.515 p = .341 (9/9)	1.225 p = .874 (18/17)
R Midfrontal	2.048 p = .727 (8/9)	1.411 p = .842 (9/9)	1.231 p = .873 (17/18)
L Inferior Frontal	1.245 p = .871 (7/10)	3.382 p = .496 (10/8)	1.882 p = .757 (17/18)
R Inferior Frontal	1.111 p = .893 (6/11)	3.126 p = .537 (11/7)	1.375 p = .849 (17/18)
Total Frontal	1.618 p = .806 (8/9)	1.411 p = .842 (9/9)	0.810 p = .937 (17/18)

Note. AD = Alzheimer disease; AAMI = Age Associated Memory Impairment; R = right; L = left
 Predictor variables in all discriminant function analyses were: losses of set on Wisconsin Card Sorting Test (WCST);
 WCST perseverative responses; Controlled Oral Word Association Test; Test Age on Porteus Mazes
 Chi-square for 4 degrees of freedom
 Numbers in brackets represent number of subjects in "low" perfusion group/number of subjects in "high" perfusion
 group
 Significance values are two-tailed

Table 24

Summary of Results

Hypothesis	Results
1. Degree of frontal dysfunction at intake will predict dementia progression	
a) Blood flow measures	● Frontal perfusion <i>per se</i> not a significant predictor of dementia progression ● Parietal perfusion does predict dementia progression in combined sample and AD sample (largely by virtue of its association with initial overall mental status) ● Frontal/parietal perfusion ratio better predictor of dementia progression than parietal perfusion in AD and combined samples
b) Neuropsychological measures	● Frontal neuropsychological function not a significant predictor of dementia progression after controlling for age ● Some evidence that parietal neuropsychological function predicted dementia progression in combined sample and AD sample ● Frontal neuropsychological function did predict degree of positive practice effect on memory retesting in AAMI subjects ● Not a significant predictor of dementia progression
c) Experimental behavioural measures (DR and DA)	

Hypothesis	Results
2. DA and DR will be better than frontal neuropsychological measures which will be better than parietal neuropsychological measures in predicting change in overall mental status	● Not supported
3. DA and DR will be significantly correlated with frontal neuropsychological measures	● DA more correlated than DR with frontal neuropsychological measures
4. DA and DR will not correlate with parietal neuropsychological measures	● Overall, correlation of DA/DR with frontal neuropsychological measures stronger than that with parietal neuropsychological measures
5. DA and DR will be poorer in subjects with lesser frontal blood flow	● Not supported
6. Frontal neuropsychological measures will be significantly correlated with frontal perfusion whereas parietal neuropsychological measures will not	● Neither frontal nor parietal neuropsychological measures were correlated with frontal perfusion measures
7. DA and DR will be more strongly related to frontal blood flow than will frontal neuropsychological measures	● Not supported--neither behavioural measure was related to blood flow

DISCUSSION

Significant frontal lobe dysfunction early in the course of AD may portend a more malignant disease course. This is important for a number of reasons. First and foremost, such prognostic information could be vital to management planning. Secondly, early frontal lobe involvement and more rapid disease progression may mark a subtype of AD with different neurotransmitter involvement and, hence, different treatment requirements. Thirdly, such findings raise the possibility that frontal lobe dysfunction might differentiate benign age-related cognitive decline from the earliest stages of a neurodegenerative disease. If the extent of frontal lobe involvement should prove an important prognostic factor, the development of accurate ways to assess frontal lobe dysfunction in the dementia patient would assume a whole new importance. Neuropsychological assessment remains the *sine qua non* in the assessment of dementia and in differentiating dementia from normal age-related cognitive loss. However, the existing selection of frontal neuropsychological tests is somewhat lacking in specificity, particularly in elderly patients (Collins et al., 1991; Mittenberg, Seidenberg, O'Leary, & DiGiulio, 1989) and in cases of diffuse brain disease (Robinson, Heaton, Lehman, & Stilson, 1980). Thus, the purpose of the current study was twofold: 1) to investigate the prognostic significance of disproportionate frontal lobe dysfunction in early Alzheimer dementia and, thereby, to further explore the validity of a frontal subtype of AD; and 2) to assess the validity of DA and DR tasks as clinical markers of frontal lobe dysfunction in patients with AD and AAMI. The present findings do not support the hypothesis that frontal lobe dysfunction is associated with faster dementia progression, at least within the time-frame studied here (one year). On the other hand, extent of parietal lobe

dysfunction, as measured by SPECT and by neuropsychological testing, was of some prognostic value in AD patients. The current results also offer some validation of the DA task as a measure of frontal lobe dysfunction.

SUBJECTS

In interpreting the results of this study, the relatively small size of the AD and AAMI samples must be considered in so far as this may have masked subtle effects by limiting the power of statistical analyses. At the same time, it was intended that this study would yield clinically applicable results. For example, it was hoped that prognostic factors might be identified that would better equip the clinician to distinguish benign from malignant memory problems or to more accurately predict the rate at which dementia would progress in the *individual* patient on the basis of his or her neuropsychological test performance or perfusion pattern on a SPECT scan. It could be argued that if this effect were too small to be detected in a sample of this size, it would clearly be too subtle for any practical application to the individual patient in a clinical setting. Large-scale studies often yield results which, although statistically significant, are trivial from a clinical perspective. In order to enhance the power of this study, efforts were made to minimize the number of dependent or predictor variables in multivariate statistical procedures, either by rationally selecting the "best" measure from a series of similar variables, or by combining variables into a single score.

Given the difficulties inherent in recruiting a relatively pure clinical sample, some of the inclusion and exclusion criteria were relaxed slightly. One subject scored 14 on the GDS but did not appear to be suffering from a syndromic depression and quite clearly manifested clinical signs of a neurodegenerative disorder. It should be noted that the original exclusionary criterion calling for a score of 10 or less on the GDS was quite stringent. Binetti et al. (1995, 1996) used a score of greater than 20 on the GDS as the exclusion criterion in their recent studies with early AD patients. This may be a more reasonable practice in so far as depressive symptoms and depressed mood occur in 30 to 40 percent of AD patients (Allen & Burns, 1995; Jeste, 1994; Wragg & Jeste, 1989). Three subjects diagnosed with probable AD in the OGH Memory Disorder Clinic had patches of low density, presumably ischemic, change in the frontal white matter, in the context of more diffuse cerebral atrophy and a clinical picture and course compatible with AD. These subjects were still considered to meet criteria for a diagnosis of probable AD given increasing evidence that this type of white matter change constitutes primary AD pathology (Breteler, 1996; Brun, 1996; Brun & Englund, 1986; Leys et al., 1991a, 1991b; Sawada et al., 1996).

The main hypotheses of this study did not call for a direct comparison of AD and AAMI subjects (i.e., the AAMI subjects were not serving as a control group). Rather, the subjects were considered as separate diagnostic groups or were combined to represent a broader spectrum of cognitive impairment. Thus, subjects in the AD and AAMI groups were not matched on any particular variable. Nevertheless, it was of interest to compare these two samples on various dimensions and, where such comparisons were conducted, attempts were made to control statistically for the potentially confounding group differences on demographic variables by

including the latter as covariates. For example, the AD and AAMI groups differed significantly with respect to mean age (as might be expected, given the exponential increase in the prevalence of dementia after the age of 65; Canadian Study of Health and Aging Work Group, 1994). As age was found to be significantly related to perfusion in various cerebral ROIs, age was included as a covariate in analyses comparing blood flow in AD and AAMI samples.

GROUP DIFFERENCES ON CLINICAL NEUROPSYCHOLOGICAL, EXPERIMENTAL, AND SPECT MEASURES

Clinical Neuropsychological Measures

Differences between the AD and AAMI subjects on mental status measures (which endured after covarying out any effect of age) are hardly surprising, given that scores on various components of the mental status examination were among the inclusion and exclusion criteria used in subject selection. That the differences tended to be more pervasive and significant at time two (i.e., at the one-year follow-up assessment) reflects the fact that the AD patients were at an early stage of dementia at time one (and so scored within normal limits on some of the less sensitive tests of cognitive impairment such as calculation and praxis) and that there was deterioration in cognitive status over the one-year follow-up interval in this group. As would be expected, AD subjects generally performed more poorly than the AAMI subjects on the neuropsychological measures. That the groups did not differ significantly on all of the

neuropsychological measures is in keeping with the fact that various cognitive domains are differentially affected in the early stages of Alzheimer dementia. It is of some interest that the diagnostic groups differed more on frontal neuropsychological functioning than parietal neuropsychological functioning, given the reported predilection of early AD for temporo-parietal cortical areas. This finding may well be an artifact of the greater number of measures included in the MANCOVA comparing the groups on the parietal measures: On univariate comparisons, significant group differences were obtained on more parietal than frontal measures. These findings do suggest, however, that frontal neuropsychological measures, particularly very simple ones such as word-list generation and the CFST, may be a worthwhile addition to the neuropsychological assessment of dementia. Measures of executive functions are conspicuously absent from some of the most widely-used mental status scales, including the MMSE. The CFST deserves particular attention in this regard. Whereas virtually all (16/18) of the AAMI subjects obtained a perfect score on this simple task, nearly 60% of the AD subjects did not. Thus, using a perfect score/non-perfect score cutting point, this task has excellent specificity (though relatively limited sensitivity). This finding is particularly meaningful given the relatively mild degree of dementia in the AD group. It is at precisely this stage that many patients are first coming to medical attention and are undergoing initial diagnostic assessment of their cognitive impairment. Given the simplicity of administration and the brief time required (less than five minutes) for this task, it might well be considered as an addition to the dementia screening battery.

DA and DR

The DR task was also found to be quite specific in differentiating subjects with AD from those with AAMI. Whereas the AAMI subjects obtained near-perfect scores at all delay intervals (ranging from 0 to 60 seconds), the AD subjects could cope with the briefer delays but had increasing difficulty remembering the spatial location of the hidden stimulus as the delay period increased, such that there was a significant difference between the groups at the 60-second delay interval. This finding confirms earlier evidence (Freedman & Oscar-Berman, 1986b; Freedman & Oscar-Berman, 1986c) that performance on this task is disturbed in AD. The distribution on the DR and DA variables was generally bimodal: either subjects met criterion (9 out of 10 correct responses) in the minimum number of trials (9 or 10) or they failed the task and received the maximum score (40 in the case of DR). Freedman and Oscar-Berman (1986b, 1986c) have obtained similar results with these paradigms. The issue, then, was one of whether or not the subject was able to do the task. Whereas all of the AAMI subjects were able to bridge the 60-second delay on the DR task, 25 percent of the AD sample failed to do so, a highly significant difference. The segment of the AD sample failing the DR60 task was characterized by poorer overall mental status than their cohorts. A very simple version of this task could also be easily incorporated into a mental status examination. For example, the examiner could place a coin in either the right or left hand in view of the patient, and then proceed to hold his or her hands behind the back for 60 seconds before asking the patient to indicate the location of the hidden coin. Given the bimodal distribution of the test scores observed in this study, 50 trials would not be necessary. Rather, if the examinee has not met the criterion in the minimal number of trials, it

is unlikely that he or she will do so at all. Although an ability to perform the task could not be construed as ruling out cognitive dysfunction, abnormal performance would be strongly suggestive of cognitive impairment.

A somewhat different pattern was observed in performance on the DA task. The vast majority of AD subjects (83 percent) failed to meet criterion in the allotted 50 trials on DA5 whereas only 5 of the AAMI subjects completely failed this task, a difference which is again highly significant. However, while the distribution of scores in the AD group was bimodal as in the case of DR60, there was a considerable range of scores among the AAMI subjects. The problem inherent to this task, then, did not appear to be one of bridging the delay, but rather one of apprehending that the location of the stimulus was alternating from trial to trial (the subject is not apprised of this fact in task instructions but, rather, is left to discover it spontaneously). Typically, once this realization dawned on the subject, he or she went on to meet criterion (9 out of 10 correct responses) in very short order. Thus, the difference between the AD and AAMI subjects on this task appears to lie in the ability to deduce the underlying structure of the task. Although it is quite conceivable that an appreciation of the global organization of the task, in itself, relies on working memory (i.e., keeping in mind what has happened from one trial of the task to the next), it cannot be assumed that group differences in performance on the DA5 task reflect a greater frequency of spatial working memory impairment among the AD subjects, especially in so far as the AD patients had no difficulty bridging the shorter delays on the DR task. The extent to which the problems of AD patients on the DA task are related to working memory could be tested in future studies by advising subjects in advance of the alternation aspect of the task. Given the fact that most of the AD subjects failed to meet criterion on DA5, they were not

administered DA30 but, instead, were automatically given the maximal score on this task. Thus, the differences between the groups on DA30 may have been artificially inflated and thus may provide little information over and above that provided by DA5. It is worthy of note, however, that all subjects (whether AD or AAMI) who succeeded in meeting criterion on DA5 (and, hence, were administered DA30) went on to meet criterion on DA30 in a minimal number of trials. This lends further support to the notion that the primary problem in the DA task was not bridging the delay interval, but rather, appreciating the alternation aspect of the task.

SPECT Measures

Most of the perfusion ratios in the ROIs were less than one, a finding which is consistent with previous reports of relatively high cerebellar activity in the brain in the resting state (Lehtovirta et al., 1996; McKeith et al., 1993; Talbot, Lloyd, Snowden, Neary, & Testa, 1994). Given the relatively small number of subjects in each sample, the large number of ROIs in the SPECT analysis, and the early stage of AD in most patients, it is not particularly surprising that few of the group differences in regional blood flow retain significance after correcting the significance level for the number of comparisons being made. Although brainstem perfusion was found to be significantly higher in AD patients than in the AAMI subjects, this appeared to be an artifact of differences in distribution of the two radionuclides (HMPAO and ECD) used in the study. Controlling for type of tracer used (either by including this as a covariate in the analysis or by excluding those subjects receiving HMPAO from the analysis) served to eliminate the group difference in brainstem perfusion. AD subjects were also found to have higher perfusion in the

basal ganglia than AAMI subjects, a difference which, though not significant after controlling for experimentwise error rate, was significant in univariate tests. This difference also appeared to reflect confounding by type of tracer in so far as 1) relatively high radioactivity counts are noted in the basal ganglia with HMPAO (Koyama et al., 1997; half of the AD sample received HMPAO versus none of the AAMI subjects) and 2) the group difference in basal ganglia perfusion was eliminated by controlling for type of tracer.

Whereas the paucity of significant perfusion differences in specific ROIs can be attributed to the stringent significance criterion required to correct for the number of comparisons being conducted, it is somewhat more perplexing that AD and AAMI subjects did not differ on more global blood flow measures, such as total frontal and total parietal flow. Such negative findings raise questions as to the sensitivity of blood flow measures to neurodegenerative disease. Similar doubts have been expressed by Bergman et al. (1997), who concluded that the sensitivity and specificity associated with visual inspection of scans were too low for SPECT to be useful as a diagnostic test for AD. It should be noted, however, that the AD and AAMI groups did differ on a ratio of the aggregate frontal and parietal perfusion measures (presumably due to an additive effect of slightly higher frontal and slightly lower parietal flow in the AD compared to the AAMI subjects). Clinical readings of SPECT scan images may well be predicated on this type of contrast.

HYPOTHESES

Hypothesis 1: Degree of frontal dysfunction at intake will predict dementia progression over a one-year test-retest interval

Contrary to prediction, neither frontal blood flow nor performance on frontal clinical neuropsychological tests predicted change in mental status over the follow-up interval, even when the AD and AAMI subjects were combined into a single sample. However, while frontal blood flow also failed to predict change in memory test performance among the AAMI subjects, frontal neuropsychological functioning (in particular, performance on a measure of planning) did predict the extent to which AAMI subjects realized a positive practice effect on memory retesting. The ability to use past experience to modify behaviour has been imputed to the frontal lobes (Stuss & Benson, 1986). This could explain why those AAMI subjects with less efficient frontal functioning, and, in particular, poorer planning skills, also tended to show a less positive practice effect on readministration of the memory tests. This finding is consistent with the position that age-related declines in learning may reflect waning executive functions (e.g., Craik, Morris, Morris, & Loewen, 1990; Parkin & Lawrence, 1994; Parkin & Walter, 1992; Vanderploeg, Schinka, & Retzlaff, 1994). This, in turn, suggests that imparting new information to the elderly might be enhanced by supporting executive functioning (e.g., by providing learning strategies and by organizing the material which is to be learned). It is curious that frontal neuropsychological functioning only emerged as a significant predictor of memory retest scores when performance on memory retest was residualized on initial memory test performance and not when change in

memory test performance, *per se*, was treated as the outcome variable. This discrepancy suggests that pre-existing differences in memory test performance among the AAMI subjects were somehow obscuring the relationship between frontal lobe functioning and memory change (i.e., were serving as a suppressor variable). Some of the AAMI subjects in this sample may eventually develop dementia. It would be most interesting to follow this sample over a much longer period of time in order to determine whether the failure to show improvement on memory retesting might have been a very early cognitive sign of neurodegeneration. Such a finding would support the hypothesis that frontal dysfunction predicts cognitive deterioration in patients with preclinical degenerative dementia.

On the other hand, parietal lobe functioning, as reflected in both blood flow and performance on parietal neuropsychological tests, did predict mental status change, with poorer parietal function at intake to the study associated with greater cognitive decline. With regard to neuropsychological measures, the total score from the PLB was a significant predictor of mental status change in the combined sample, with the Finger Gnosis and Right-Left Orientation subtests being particularly good predictors in the sample as a whole. Only Right-Left orientation predicted progression rate in the AD subjects and none of the parietal neuropsychological measures predicted mental status or memory change in the AAMI subjects. These effects, when obtained in the combined sample, are quite readily interpretable. Although the difference in parietal flow between the AD and AAMI subjects does not meet the stringent criterion for statistical significance, mean parietal flow was lower in the AD group. In so far as bilateral temporoparietal perfusion on SPECT has been found to characterize AD, its association with cognitive decline is to be expected. However, lower parietal blood flow was also associated with greater mental

status change when the AD subjects were considered separately and so this effect cannot be totally dismissed as an artifact of the expected difference in progression rate between two different diagnostic groups. It may be that variability in parietal blood flow among AD patients is a reflection of stage or severity of disease which, in turn, could be related to progression rate (given findings that the rate of dementia progression is not linear throughout the course of the disease; Brooks, Kraemer, Tanke, & Yesavage, 1993; Morris et al., 1993). This interpretation receives some support from the fact that the predictive power of parietal flow is attenuated when mental status at time two, residualized on mental status at time one, serves as the outcome variable rather than mental status change, *per se*. Regressing mental status at time two on mental status at time one essentially removes any contribution of pre-existing mental status differences to the prediction. Even when this latter regression model is used, however, the ability of parietal blood flow to predict dementia progression approaches significance in the AD sample. This indicates that the degree of parietal perfusion in AD patients may predict mental status decline even after controlling for initial dementia severity. Perhaps progression of AD neuropathology is evident in increasing perfusion deficits prior to its manifestation in behaviour. If so, patients with more severe hypometabolism may be approaching transition to a more advanced stage of disease than other patients who score similarly on mental status measures but have milder perfusion deficits. However, in that performance on neuropsychological measures of parietal lobe function predicted progression rate in the same way as parietal perfusion, this is an unlikely explanation. Rather, it seems that the severity of parietal lobe dysfunction may be a marker of the malignancy of disease.

The ratio of frontal to parietal flow also predicted mental status change, both in the combined sample and in AD patients considered separately. However, the nature of the effect was opposite to that predicted, with lower frontal relative to parietal flow being associated with less dementia progression. To some extent, this is simply a replication of the foregoing findings that higher parietal flow is associated with a slower progression rate. Parietal flow is the denominator of the frontal/parietal ratio and an increase in the denominator serves to reduce the ratio. It is noteworthy, however, that the predictive power of the frontal/parietal ratio is considerably greater than that of parietal flow alone. Thus, it seems that an additive effect of lower parietal flow and greater frontal flow is predicting greater dementia progression.

Why greater frontal hypoperfusion should be associated with slower dementia progression is not immediately obvious. One possibility is that non-AD patients have been included in the AD sample. Martin (1990) has eloquently expressed the problem of diagnostic uncertainty in the study of AD subtypes:

...the issue of diagnostic uncertainty is a double-edged sword. On the one hand, it provides the central rationale for performing these studies and gives them their particular importance and relevance. On the other hand, however, one is forced to acknowledge that there is no way of knowing, short of brain tissue biopsy, how many of the patients in the AD group are in fact suffering from AD. As a result there is no way to determine to what extent the group profile is distorted by the inclusion of patients who do not have this disease (p. 145).

Mild, presumably cerebrovascular, changes were noted in the frontal white matter of three of the AD patients in the current study. Although such leukoencephalopathy is increasingly regarded as primary AD pathology (Breteler, 1996; Brun, 1996; Brun & Englund, 1986; Leys et al., 1991a,

1991b; Sawada et al., 1996), it could be that these patients actually suffer from vascular dementia, which is not associated with the inevitable cognitive deterioration which characterizes AD. Were this so, it could account for the relationship between lower frontal perfusion at intake and less dementia progression. The data do not bear out such an explanation, however. The three patients with frontal leukoencephalopathy were found to have dementia change scores of $-.02$, $-.04$ and $-.06$, indicating that, on average, they experienced slightly greater decline in mental status change than the mean ($-.03$) for the AD subjects. A second possibility is that, despite attempts to hold disease stage relatively constant, those AD subjects with lower frontal perfusion at intake were at a more advanced stage of disease and that this was associated with less change in mental status scores over the follow-up period. This explanation is somewhat lacking as well. Although there is evidence to suggest that the rate of dementia progression is not linear throughout the course of AD, more advanced disease has typically been associated with faster rates of decline (Morris et al., 1993). Brooks et al. (1993) have found that a trilinear model better describes the progression of AD than does a linear model. While this trilinear model does posit a final period of stability, due either to true disease stabilization or to a "floor" effect in the psychometric instruments used to measure cognitive decline, it is unlikely that any of the mildly demented subjects in the current AD sample had entered this end stage of disease. Furthermore, there was no evidence of floor effects in the measures being used to assess dementia severity.

In failing to demonstrate that frontal dysfunction predicts deterioration in mental status, the foregoing findings are inconsistent with those of Mann and colleagues (1992). There are several reasons why this might be so. Mann et al. identified groups of fast and slow progressors by dividing a sample of 21 AD patients at the mean of an index of disease progression. This

disease progression index was determined by 1) subtracting the patient's current score on the DRS from the lowest "normal" score on this test (in effect obtaining an index of the extent to which mental status has declined from normal) and then 2) dividing this difference by estimated symptom duration (as obtained from the history). The apparent relationship between frontal dysfunction and progression rate reported by Mann et al. may simply be an artifact of their reliance on DRS scores in the calculation of the disease progression index. The DRS, unlike most other mental status scales, is very sensitive to deficits in the initiation, maintenance, and sequencing of behaviour, disturbances which have been strongly associated with frontal lobe dysfunction (Stuss & Benson, 1986). Indeed, 20 of the total 144 points on this test are awarded for a word-list generation task, a task on which patients with frontal lobe dysfunction often perform very poorly. Thus, what were interpreted by Mann and colleagues as "fast" and "slow" progressors in their sample may actually have been those with "more" and "less" frontal lobe dysfunction. It is hardly surprising, then, that this distinction would be found to correlate with performance on neuropsychological and PET measures of frontal lobe dysfunction. For example, a nondemented patient with initiation impairment resulting from dysfunction in frontal-subcortical systems could quite easily lose 20 to 25 points on the initiation section of the DRS. Meanwhile, a more typical early AD patient whose cognitive disturbance affects primarily anterograde memory function might lose 5 points on the initiation section (due to diminished semantic fluency) and 10 points on the memory section due to problems with delayed sentence recall and temporal orientation. Assuming that reported disease duration were equal, Mann et al. would conclude that the former patient had declined more rapidly than the latter when the results would be better understood in terms of the greater sensitivity of the DRS to frontal lobe dysfunction. This problem arises in part

from the retrospective nature of the Mann et al. study and their resultant need to estimate progression rate. The current study was a prospective one in which patients were reassessed one year after intake, thereby allowing more accurate determination of the change in mental status. However, the prospective nature of the study may be its weakness as well as its strength in that the window of opportunity to detect mental status change was much more limited than in the Mann et al. study (an average of five years in Mann et al.'s slow progressors). It could be that one year is simply not time enough in which to detect differential progression rates in such a small sample, as has been suggested by Morris et al. (1993) and Mortimer et al. (1992). It is hoped that many of the AD subjects in this sample will be available for further study and that, with more extended follow-up, other significant prognostic factors may emerge.

None of the blood flow measures predicted change in either global mental status or in memory test performance among the AAMI subjects. This is hardly surprising, given the fact that this group showed no deterioration in either memory or general mental status. In fact, performance on the memory measures improved somewhat from intake to follow-up. A positive practice effect was also observed in the standardization sample for the WMS-R (Wechsler, 1987). The improvements in test performance observed in the standardization sample were considerably greater than those observed in the current AAMI sample, in keeping with a much shorter intertest interval (four to six weeks as compared to one year in the present study). For example, in those individuals aged 55 to 64 in the standardization sample, the mean score on Logical Memory I increased by 5.8 points from the first to the second testing, whereas an increase of 3.11 points was observed among the AAMI subjects in the current study. The mean score of the standardization sample on Verbal Paired Associates I improved by 2.2 points as compared to 1

point in the current AAMI sample. Wechsler considered the most likely explanation for these increments to be familiarization with testing procedures and the effects of learning.

There has been considerable interest in AAMI as a possible precursor to degenerative dementia. This study provided little evidence in support of this contention. As a group, the AAMI subjects showed no significant change in mental status over the one-year follow-up period and their performance on memory tests significantly improved. Although a minority of the AAMI subjects did not exhibit this positive practice effect, only two showed any real decline in the overall memory score and this was not associated with a similar decline on mental status testing and so was not particularly suggestive of an incipient dementia. None of the AAMI subjects was demented according to DSM III-R criteria at the time of follow-up and, indeed, none showed any evidence of significant cognitive deterioration. A different pattern of results may well have been obtained had this sample been selected for peer-referenced cognitive decline (as advocated by Blackford & La Rue, 1989). The latter method of sampling would have been expected to result in a higher prevalence of preclinical dementia and thereby to have increased the likelihood of detecting meaningful prognostic factors. AAMI as defined by NIMH criteria has been found to carry only a slight increase in risk for dementia (Hänninen et al., 1995).

The prevalence and dementia risk associated with age-related cognitive decline will not only depend on the criteria used for diagnosis, but also on the manner in which those criteria are operationalized. Application of the NIMH criteria for AAMI has not been standardized and estimates of the prevalence of AAMI vary enormously depending on the number and the nature of the memory tests used in diagnosis (Koivisto et al., 1995; Smith et al., 1991). Use of fewer or less sensitive measures of memory function in the current protocol might also have resulted in a

higher prevalence of preclinical dementia in the AAMI sample and thereby have led to different conclusions regarding the prognostic significance of various neuropsychological and blood flow parameters in this group.

Contrary to prediction, performance on the DR and DA tasks did not predict dementia progression. Nor did the ability to perform these tasks predict change in memory test performance in the AAMI subjects. The current results demonstrate that performance on these tasks tended to be all-or-nothing. Given this insensitivity to finer gradations of performance, it is perhaps not surprising that these tests were not effective in teasing out subtle differences within a given diagnostic group.

Hypothesis 2: DA and DR will be more predictive of change in overall mental status over the follow-up period than will standard neuropsychological measures of frontal lobe function which in turn will be more predictive than neuropsychological measures of posterior functions.

It is clear from the findings discussed thus far that there is no support for this hypothesis. DA and DR were not found to predict dementia progression at all and, with regard to the neuropsychological tests, parietal lobe measures were better at predicting mental status change than were frontal ones, which were also ineffective in this regard.

Hypotheses 3 and 4: Performance on DA and DR tasks will be significantly correlated with that on standard neuropsychological measures of frontal lobe functioning and will not correlate with performance on neuropsychological measures of nonfrontal functioning

There were very few significant correlations between the DR and DA measures on the one hand and the frontal neuropsychological measures on the other. This is undoubtedly due in large part to the general insensitivity of the DA and, in particular, the DR tasks to individual differences in cognitive functioning (i.e., a "ceiling" effect). Most of the subjects, including those with early AD, performed optimally across all delay conditions of the DR task. The DA task proved somewhat more challenging, for AAMI subjects as well as AD patients. Indeed, in the case of the latter group, most of the subjects failed the task entirely. Given the far from normal distributions on these measures, they were treated as dichotomous variables. Restricting the range in this manner would have further reduced the likelihood of detecting relationships with other, more normally distributed, variables.

Within the combined sample, performance on the CFST did correlate with the ability to perform the DR60 task. The fact that both of these tasks are very simple and easily achieved by most subjects suggests that they may be correlated because they are both markers of more advanced dementia, rather than because they measure a specific cognitive process or functioning in a focal neuroanatomical region. However, controlling for global mental status did not eliminate the relationship between DR60 and CFST. DR60 unquestionably places a demand upon spatial working memory. There is arguably a working memory component to the CFST as well. The CFST requires that a subject organize into meaningful groups an assortment of blocks, differing

along dimensions of shape and colour. Having done so, he or she is then required to rearrange the blocks according to a second principle. In order not to perseverate the previous response, the subject must bear in mind the first strategy employed. Both the CFST (Kisker, 1944) and the DA task (Freedman & Oscar-Berman, 1986c) are considered sensitive to perseverative tendencies. A relationship was also observed between the ability to solve the pencil-and-paper mazes on the Porteus Mazes Test and performance on the DA task. Interestingly, this relationship appeared to be stronger among the AAMI subjects than in the AD subjects and it, too, persisted after covarying out differences among subjects in overall mental status. As previously discussed, the problem on the DA task was not as obviously one of spatial working memory as in the case of the DR task (where performance only faltered on longer delay intervals). Rather, the challenge appeared to be recognition of the inherent pattern of the task, that is, appreciation of the fact that the location of the bait was alternating from trial to trial. Once a subject grasped this perspective on the task, without exception, he or she went on to meet criterion in very short order, even under conditions of longer delay. In other words, the problem in the DA task was to understand the global plan or organization of the task. Porteus Mazes is generally regarded as a measure of visuomotor planning. In order to solve the mazes successfully, the subject must first consider the entire maze, as to make an initial move without regard for the far-reaching consequences of that move is to court an error. Thus, both of these tasks can be seen as involving an element of planning and organization, skills that are included among the "executive abilities" ascribed to the frontal lobes (Stuss & Benson, 1986). The fact that DR and DA correlated with different neuropsychological measures supports the observation that the challenge in each of these tasks was quite different in nature.

Not only did DA and DR measures fail to correlate with many of the "frontal" neuropsychological measures, they did correlate with some of the "parietal" neuropsychological measures. Again, DR and DA do not correlate with the same neuropsychological measures, suggesting that they may be tapping different cognitive processes. Given this situation in which there were some significant correlations between DR/DA and frontal neuropsychological measures on the one hand, and between DR/DA and parietal neuropsychological measures on the other hand, the question arose as to which set of correlations was more significant. More sophisticated multivariate statistical techniques such as multiple regression and canonical correlation were used to address this issue. These multivariate analyses, which permitted more accurate adjustment of experimentwise error rate than did the Bonferroni technique, indicated that DR/DA variables correlated very highly with frontal neuropsychological measures, much more highly than with parietal neuropsychological tests. DA was found to be particularly sensitive to frontal lobe functioning as assessed neuropsychologically. That there was some degree of association between DR/DA measures and parietal neuropsychological tests in the combined sample was not surprising in so far as these tests are all sensitive to dementia. In the case of the parietal measures, the relationship with DR/DA can be totally accounted for in this manner: Removing variance related to general mental status served to eliminate any relationship between parietal neuropsychological variables and DR/DA measures. This was not so in the case of the frontal neuropsychological measures. DA was still very significantly correlated with frontal neuropsychological measures even after covarying out the influence of general mental status. In sum, then, there is evidence to validate DA as a specific measure of frontal lobe functioning.

The dissociation between performance on DA and DR tasks, with the former correlating more strongly than the latter with clinical neuropsychological measures of frontal lobe function, is interesting given that both of these tasks are considered to measure spatial working memory, that both are maximally disrupted by lesions of the sulcus principalis in the prefrontal cortex of monkeys, and that both tasks are associated with activation of the same population of neurons in the primate brain as demonstrated by electrophysiological studies. However, this is not the first study to demonstrate dissociability of these tasks. Oscar-Berman and colleagues have reported that orbitofrontal damage is more disruptive of DA than DR (Oscar-Berman et al., 1982) and have shown that, whereas DA is impaired in both Korsakoff patients and patients with bilateral frontal lobe damage, only the latter group is impaired on DR (Freedman and Oscar-Berman, 1986a). It could be argued that DA is simply more difficult than DR and, hence, more susceptible to disruption. However, in that performance on these two tasks showed different patterns of correlation with clinical neuropsychological measures of frontal function in the present study, a simple explanation in terms of task difficulty is unsatisfactory. Rather, it seems that the DR and DA tasks are tapping into qualitatively different cognitive processes. In the case of DR, an explanation in terms of spatial working memory is quite plausible. None of the nondemented patients had any difficulty meeting the immediate memory demands of this task, as would be expected given the fact that immediate memory is relatively unaffected in AAMI, which is rather more a disorder of secondary memory processing. The dementia patients, on the other hand, had increasing difficulty with the DR task as a function of delay interval, as would be predicted if the task were a pure measure of spatial working memory. As noted previously, the DA task posed difficulties for some AAMI subjects as well as for AD patients and the distribution of scores on

this task suggested an all-or-nothing quality to performance which was not as easily explained in terms of immediate spatial memory. Rather, performance on this task appears to reflect the ability to appreciate the implicit organization of a situation. Poor performance on the WCST seems, in many subjects, to be attributable to a similar failure. It is not that these subjects fail to recognize the relevant sorting dimensions of colour, shape, and number (as evident in the nature of their responses and their verbalizations), nor that they perseverate in the classic sense of committing the same erroneous response in an unbroken string. Rather, their performance is disorganized and suggests a failure to grasp the structure of the task as cycling through different contingencies. When this overarching structure is apprehended, the performance of such subjects immediately and dramatically improves, often to near-perfect levels. These findings, then, suggest that spatial working memory and appreciation of the organization of a problem-solving situation may be dissociable executive cognitive functions subserved by the frontal lobes. It has been suggested that DA is more sensitive than DR to the perseverative tendencies which tend to follow lesions to more ventral regions within prefrontal cortex (Mishkin & Manning, 1978). Interestingly, the correlation between DA and perseverative errors on the WCST approached significance in this study. Logic would dictate that the tendency for perseveration would be inversely proportional to the ability to comprehend the more global nature of a situation.

HYPOTHESES 5, 6, and 7: Correlations between DA/DR and frontal perfusion will be significant and will exceed correlations between frontal neuropsychological tests and frontal blood flow.

None of the foregoing predictions was borne out by the data. Correlations between frontal blood flow and DR/DA were uniformly nonsignificant. This is not particularly surprising given the lack of sensitivity and restriction of range in the DR and DA variables.

Even in the case of the neuropsychological variables, which are more sensitive to individual differences and more normally distributed, there were few significant correlations with blood flow measures. The single correlation of this nature that did attain significance (between the frontal/parietal ratio and COWA) was actually in the direction opposite to prediction. This result probably reflects the poorer performance on COWA in the AD group and elevation of the frontal/parietal ratio due to higher frontal and lower parietal flow in the AD subjects. "High" and "low" frontal perfusion groups did not differ on any of the neuropsychological or DR/DA measures.

In so far as frontal perfusion measures did not correlate in the expected direction with either frontal neuropsychological measures or with DA and DR variables, the question as to whether neuropsychological or DR/DA measures correlated more strongly with frontal blood flow lost its relevance. Nevertheless, an attempt was made to compare their respective strengths of correlation with blood flow. The clinical and experimental neuropsychological measures were not found to differ in this regard.

CONCLUDING COMMENTS

Despite the exploratory nature of this study, it did yield a number of clinically relevant findings. The current results have suggested economical means for enhancing dementia testing. A shortcoming of many widely-used dementia screening tests is their failure to address executive functions. Assessment of executive functions in the dementia patient is critical from the point of view of both diagnosis (differentiating AD from conditions such as Pick disease and frontotemporal degeneration which give rise to a frontal dementia) and management (understanding and modifying difficult behaviours). Certain simple executive tasks, such as CFST and DA, were observed in this study to be well tolerated by dementia patients. Moreover, though sensitivity to dementia was lacking, they had near-perfect specificity. Given that, in the most typical form of AD, temporoparietal functioning is predominantly affected in the early stages with relative preservation of frontal lobe functioning (Benson, 1982; Benson et al., 1983; Chase et al., 1983, 1984; Chawluck et al., 1990; Cutler et al., 1984; Duara et al., 1986; Fazekas et al., 1989; Foster et al., 1984; Frackowiak et al., 1981; Friedland et al., 1985; Gustafson et al., 1990; Haxby et al., 1985, 1986; Holman et al., 1992; Ingvar et al., 1978; Ingvar & Lassen, 1979; Kuhl et al., 1985; Kumar et al., 1990; Mielke et al., 1991; Neary et al., 1987; Nybäck et al., 1991), the variable ability of the AD subjects to perform simple executive tasks would be expected given the early stage of disease of the patients in this study.

Results of this study suggest that the ability of nondemented elderly individuals to learn from previous experience may be related to executive cognitive functions. This, in turn, has important implications for how we might enhance learning in older adults, many of whom

experience the loss of memory capacity, like the loss of visual acuity, as a very bothersome consequence of the aging process. This study has also raised the interesting question as to whether the absence of an expected positive practice effect on memory testing might be among the earliest cognitive manifestations of neurodegenerative disease.

Finally, this study suggests that the severity of parietal lobe dysfunction, whether assessed by means of functional neuroimaging or neuropsychological assessment, may forecast dementia progression rate. This type of prognostic information is vital to the clinician attempting to assist AD patients and their families in coping with this devastating illness.

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APPENDIX 1

CRITERIA FOR THE CLINICAL DIAGNOSIS OF ALZHEIMER DISEASE

DSM III-R Diagnostic Criteria for Primary Degenerative Dementia

A. Dementia.

- a. A loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning.
- b. Memory impairment.
- c. At least one of the following:
 - (1) impairment of abstract thinking, as manifested by concrete interpretation of proverbs, inability to find similarities and differences between related words, difficulty in defining words and concepts, and other similar tasks
 - (2) impaired judgement
 - (3) other disturbances of higher cortical function, such as aphasia (disorder of language due to brain dysfunction), apraxia (inability to carry out motor activities despite intact comprehension and motor function), agnosia (failure to recognize or identify objects despite intact sensory function), "constructional difficulty" (e.g., inability to copy three-dimensional figures, assemble blocks, or arrange sticks in specific designs)
 - (4) personality change, i.e., alteration or accentuation of premorbid traits
- d. State of consciousness not clouded (i.e., does not meet the criteria for Delirium or Intoxication, although these may be superimposed).
- e. Either (1) or (2):
 - (1) evidence from the history, physical examination, or laboratory tests, of a specific organic factor that is judged to be etiologically related to the disturbance
 - (2) in the absence of such evidence, an organic factor necessary for the development of the syndrome can be presumed if conditions other than Organic Mental disorders have been reasonably excluded and if the behavioral change represents cognitive impairment in a variety of areas.

B. Insidious onset with uniformly progressive deteriorating course.

C. Exclusion of all other specific causes of dementia by the history, physical examination, and laboratory tests.

NINCDS-ADRDA Criteria for Clinical Diagnosis of AD

I. The criteria for the clinical diagnosis of PROBABLE AD include:

dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;

deficits in two or more areas of cognition;

progressive worsening of symptoms;

no disturbance of consciousness;

onset between ages 40 and 90, most often after age 65; and

absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE AD is supported by:

progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

impaired activities of daily living and altered patterns of behaviour;

family history of similar disorders, particularly if confirmed neuropathologically; and

laboratory results of:

normal lumbar puncture as evaluated by standard techniques,

normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and

evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE AD, after exclusion of causes of dementia other than AD, include:

plateaus in the course of progression of the illness;

associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;

other neurological abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

seizures in advanced disease; and

CT normal for age.

IV. Features that make the diagnosis of PROBABLE AD uncertain or unlikely include:

sudden, apoplectic onset;

focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE AD:

may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variation in the onset, in the presentation, or in the clinical course;

may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and

should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE AD are:

the clinical criteria for probable AD and

histopathologic evidence of AD obtained from a biopsy or autopsy.

VII. Classification of AD for research purposes should specify features that may differentiate subtypes of the disorder, such as:

familial occurrence;

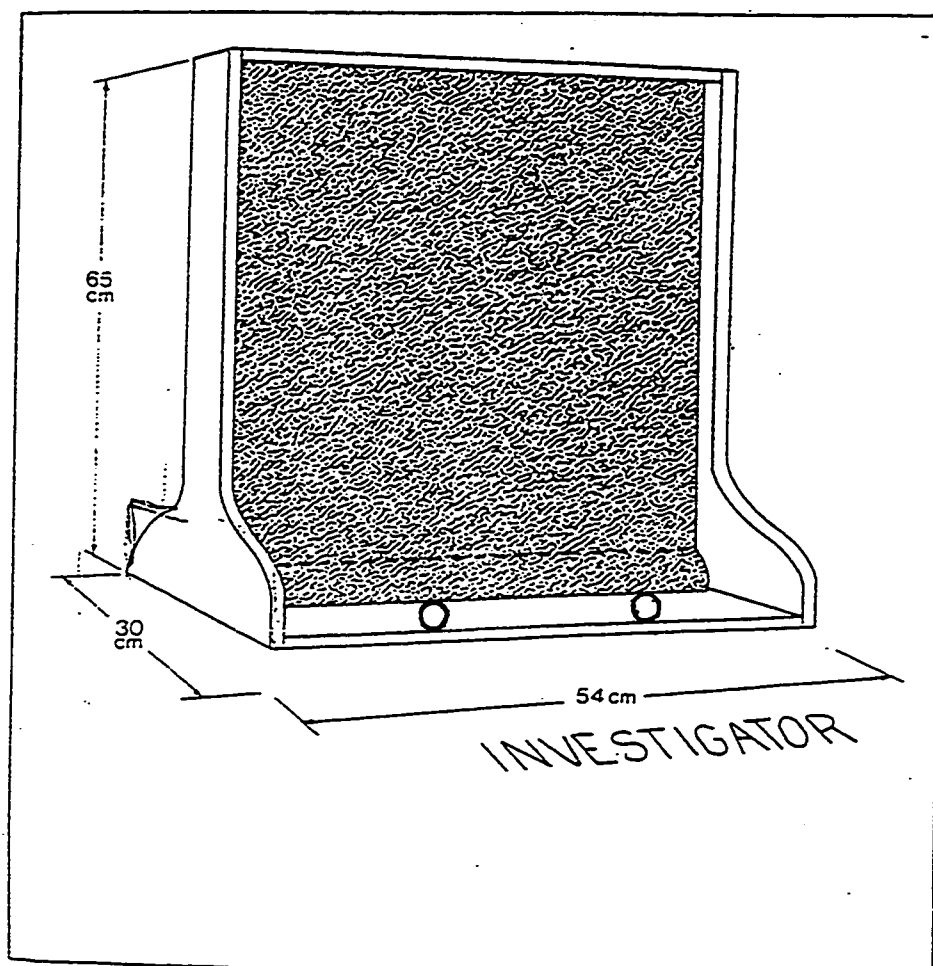
onset before age of 65;

presence of trisomy-21; and

coexistence of other relevant conditions such as Parkinson's disease.

APPENDIX 2

MODIFICATION OF THE WISCONSIN GENERAL TEST APPARATUS FOR USE WITH HUMAN SUBJECTS



APPENDIX 3
CONSENT FORMS

PREDICTORS OF CHANGE IN MEMORY IN OLDER ADULTS**INFORMATION SHEET****PURPOSE OF STUDY**

The study in which you are being asked to participate is being carried out in order to increase our understanding of different patterns of cognitive impairment in the elderly, to develop better ways of testing such cognitive impairment, and to allow us to be better able to predict the future course of the cognitive symptoms.

INVESTIGATIONS

Participation in this study will involve psychological testing, similar to that which you have already undergone in the Memory Disorder Clinic. It will also involve undergoing a SPECT (single photon emission tomography) scan, a type of scanning which allows us to see the activity of cells in various parts of the brain.

The psychological testing will be carried out on two separate days and will take about two to three hours on each day. The SPECT scan will be carried out at the Ottawa General Hospital on another day. A few minutes before the scan is done, you will be injected with approximately 25 mCi of a radioactive drug called Technetium 99m HM-PAO which allows us to visualize the blood flow to various parts of the brain and thereby to determine the level of activity in those brain areas.

RISKS

The psychological testing involves no risk to the participant. Neither are there any known hazards associated with SPECT scanning and it is a procedure carried out routinely with medical patients. It does involve exposure to some radiation as does any X-ray. It is impossible to guarantee that any radiation dose is safe. Estimated radiation dose from one treatment is 0.225 rad to the brain, 0.630 rad to the liver, and 0.225 rad to the whole body. This is less radiation than is associated with dental X-rays (0.750 rad). However, even this minimal exposure to radiation is contraindicated during pregnancy. The only other risk is some possibility of bleeding and/or clot formation at the site on the arm where the injection is made. Care will be taken to minimize side effects.

BENEFITS

There is no direct benefit to participants in this study other than the advantage of receiving a SPECT scan which may detect abnormalities in the brain not detected by other investigations. All SPECT scans will be reviewed by a physician specialized in nuclear medicine and the results will be made available, at the patient's request, to their primary physician in the Memory Clinic. The only other benefit to participants in this study is the knowledge that they have contributed to our understanding of cognitive impairment in the elderly and perhaps to the quality of care available to future patients.

COMPENSATION

This study is designed to be as safe as possible and every precaution will be taken to guard against harmful side effects. However, in the event that some injury does result from the pharmacological effects of the agents used in this study, there is no compensation available from the hospital for such injury. Any necessary medical care for injury resulting from participation in this study would be obtained in the same manner as any other medical care.

QUESTIONS, WITHDRAWAL, AND CONFIDENTIALITY

Participation in this study is entirely voluntary. Furthermore, participants are free to withdraw from the study at any time. Refusal to participate or decision to withdraw from the study will in no way interfere with your medical care at the Ottawa General Hospital.

The information collected from you as part of this study will be held in the strictest confidence. Psychological test forms will be identified by number and your name will not appear on them. Data from this study may be included in future publications but this data will not bear your name or any other identifying information.

If you have any questions or concerns about this research or should you desire further explanation during the course of the study, you are encouraged to contact Barbara Collins at 737-8634 or Dr. Andrée Tellier at 737-8039.

CHANGEMENTS AU NIVEAU DE LA MEMOIRE ADULTE: PARAMETRES DE PREDICTION

FEUILLE DE RENSEIGNEMENTS

BUT

L'étude à laquelle on vous demande de participer servira à améliorer nos connaissances en ce qui a trait aux différentes formes de troubles cognitifs chez la personne âgée. De plus, nous espérons pouvoir développer des mesures d'évaluation de tels troubles cognitifs plus adéquates et d'être plus en mesure de prédire le cours des problèmes affectant les fonctions cognitives.

INVESTIGATIONS

Votre participation consistera en premier lieu d'une évaluation neuropsychologique telle que celle que vous avez déjà eue à la Clinique des Troubles de la Mémoire. Vous aurez également à passer un test appelé le "SPECT" qui consiste essentiellement en une mesure du flot sanguin au niveau du cerveau.

L'évaluation neuropsychologique, qui durera environ de deux à trois heures, sera répartie sur deux jours différents. Le SPECT se fera lors d'une troisième journée. Quelques minutes avant que le SPECT commence, vous allez recevoir une injection de 25 mCi d'un produit radioactif appelé le "Technetium 99m HM-PAO" qui permet la visualisation du flot sanguin à travers différentes parties du cerveau.

RISQUES

L'évaluation neuropsychologique ne comporte aucun risque. Il n'y a également pas de risques connus avec l'utilisation du SPECT quoique cette procédure requière que vous soyez exposé à un certain taux de radiation comme n'importe quel rayon-X que vous avez pu passé auparavant. Quoiqu'il est impossible de garantir que le taux de radiation utilisé lors de cette procédure soit sans aucun danger, sachez que le taux de radiation est moins élevé que celui reçu chez le dentiste durant la prise d'un rayon-X. L'irradiation reliée à l'étude représente 0.25 rad au cerveau, 0.63 rad au foie, et 0.225 rad au corps entier. Le SPECT demeure une procédure qui est utilisé couramment en milieu hospitalier. Le seul autre risque, à part d'une contreindication chez les femmes enceintes, a trait à une certaine possibilité de saignement et/ou formation d'un caillot à l'endroit de l'injection. L'on prendra soin de minimiser une telle possibilité lors de l'injection.

BENEFICES

L'étude n'apportera aucun bénéfices directs aux participants autre que la certitude d'avoir contribué à améliorer nos connaissances en ce qui a trait aux troubles cognitifs de la personne âgée et à améliorer le soin que nous pourrions offrir à nos futurs patients.

COMPENSATION

Cette étude a été développée de façon à être des plus sécuritaires et afin d'éviter tout effet secondaire néfaste. Cependant, dans l'éventualité où une complication surviendrait suite à l'utilisation de l'agent radioactif, il n'existe pas de fonds de compensation à l'hôpital. Toute intervention médicale provenant d'une telle complication serait disponible selon les procédures usuelles de l'hôpital.

QUESTIONS, REFUS DE CONTINUER, ET CONFIDENTIALITE

Votre participation est à titre bénévole seulement. Vous avez le droit de cesser de participer en tout temps même avant la finition des procédures. Votre refus de participer à cette étude n'entravera en rien les soins futurs que vous pourrez obtenir à l'hôpital général d'Ottawa.

Les renseignements obtenus lors de l'étude seront sauvegardés avec le plus de soin possible. Les tests neuropsychologiques seront identifiés par un numéro et votre nom n'apparaîtra sur aucun des formulaires. Les données obtenues lors de cette étude pourront être publiées dans des revues scientifiques mais sans la publication d'aucuns noms ou autres renseignements pouvant vous identifier.

Si vous avez des questions au sujet de cette recherche, n'hésitez pas à contacter Barbara Collins 737-8634 ou le docteur Andrée Tellier au 737-8039.



**CONSENTEMENT DU PATIENT/
PROCURATION À DES RECHERCHES MÉDICALES**

PATIENT/PROXY CONSENT FOR MEDICAL RESEARCH

Nom de l'étude

PREDICTORS OF MEMORY CHANGE IN OLDER ADULTS

Name of research project

Je confirme que j'ai expliqué la nature ainsi que les complications
connues de ce projet de recherche/procuration du patient.

I confirm that I have explained the nature of and known
complications of the research project to the patient/proxy.

Barbara Collins

(chercheur)

(researcher)

Je consens à la participation de :

Nom du patient

N° de projet

I consent to the participation of :

Patient's name

Research no.

à l'étude précitée et j'autorise par la présente le(s) médecin(s) et
le(s) chercheurs(s) à procéder aux examens et/ou à dispenser les
traitements suivants :

in the above study and I hereby authorize the physician(s) and
investigator(s) to proceed with the following questionnaire,
examinations and/or to administer these treatments:

Cognitive testing and brain SPECT

J'ai lu la feuille d'explication détaillée approuvée par le Conseil
d'éthique en recherches et je suis au courant des effets secondaires
et des risques connus ayant trait aux examens et aux traitements.

I have read the detailed information sheet approved by the
Research Ethics Board and am aware of the known side effects
and risks related to the examinations and treatments.

J'ai également reçu une description de tous les avantages à
attendre de ces examens et de ces traitements. On m'a fait
connaître d'autres formes d'examen et de traitement.

I have also received a description of any benefits that may be
expected from these examinations and treatments. As well,
other forms of treatment and exams have been disclosed to me.

J'ai eu l'occasion de poser des questions au sujet de ces examens
et de ces traitements et on y a bien répondu.

I have been given an opportunity to ask questions concerning
the examinations and treatments involved and the questions
which I have asked have been adequately answered.

On m'a dit que je pouvais retirer le consentement et suspendre la
participation à l'étude à n'importe quel moment et pour quelque
motif que ce soit et que cette action n'affectera pas la qualité des
soins en cours et futurs.

I have been told that I can withdraw consent and stop
participation in the study at any time and for any reason, and
that such action will not affect the quality of ongoing and future
care.

Je reconnais qu'en agissant, comme procurateur, ce sera dans le
meilleur intérêt du patient.

I acknowledge that if I am acting as a proxy that I am acting in
the best interest of the patient.

En toute connaissance de cause, je consens volontairement à ce
que _____ participe à cette étude.

With full knowledge of this, I voluntarily consent to the
participation of _____ in the study.

Ce protocole a été approuvé par le Conseil d'éthique en recherches
de l'Hôpital général d'Ottawa. Ce conseil étudie les aspects éthiques
de tous les projets de recherche sur les humains. Si je le désire, je
peux contacter le président de ce comité.

This protocol has been approved by the Research Ethics Board
of the Ottawa General Hospital. This Board considers the ethical
aspects of all hospital research projects using human subjects.
If I wish, I may contact the Chairperson of the Board with
questions.

Nom (lettres moulées) - Name (print)

Signature

Lien de parenté - Relationship

PATIENT OU PERSONNE LÉGALEMENT RESPONSABLE (PROCURATION) - PATIENT OR PERSON LEGALLY RESPONSIBLE (PROXY)

Nom du témoin (lettres moulées) - Name of witness (print)

Signature

Date (j/d-m/m-a/y)

CONSENT FORM
Predictors of Change in Memory in Older Individuals

A. Patient Consent

I have read the description of the study or it has been read to me and I have had the opportunity to discuss it and to ask questions. I consent to take part in this study. I also consent to Barbara Collins having access to my Memory Disorder Clinic file. A copy of this consent form has been given to me.

Patient's Name (print)

Patient's signature

Date

B. Consent of Power of Attorney for Personal Care

I have read the description of the study or it has been read to me and I have had the opportunity to discuss it and to ask any questions. I consent to the participation of my ward _____ in this study. I also consent to Barbara Collins having access to my ward's Memory Disorder Clinic file. A copy of this consent form has been given to me.

Name of Power of Attorney
for Personal Care (print)

Signature of Power of Attorney
for Personal Care

Relationship to Patient

Date

Name of Investigator (print)

Signature of Investigator

Date

Name of Witness (print)

Signature of Witness

Date

FORMULAIRE DE CONSENTEMENT

Nom de l'étude: Changements au Niveau de la Mémoire Adulte: Parametres de Prédiction

A. Consentement du Patient

J'ai pris connaissance de l'information ci-haut ou celle-ci m'a été lue. J'ai également eu la chance de poser des questions. Je consens à participer à cette étude. Je consens également à ce que Barbara Collins ait accès à mon dossier de la Clinique de Mémoire. Une copie du formulaire de consentement m'a été donnée.

Imprimer le nom du patient

Signature du patient

Date

B. Consentement du Proche

J'ai pris connaissance de l'information ci-haut ou celle-ci m'a été lue. J'ai également eu la chance de poser des questions. Je consens à ce que _____, qui est sous ma tutelle, participe à cette étude. Je consens également à ce que Barbara Collins ait accès au dossier de la Clinique de Mémoire de _____. Une copie du formulaire de consentement m'a été donnée.

Imprimer le nom du proche

Signature du proche

Relation face au patient

Date

Imprimer le nom du chercheur

Signature du chercheur

Date

Imprimer le nom du témoin

Signature du témoin

Date

APPENDIX 4
HACHINSKI ISCHEMIA SCALE

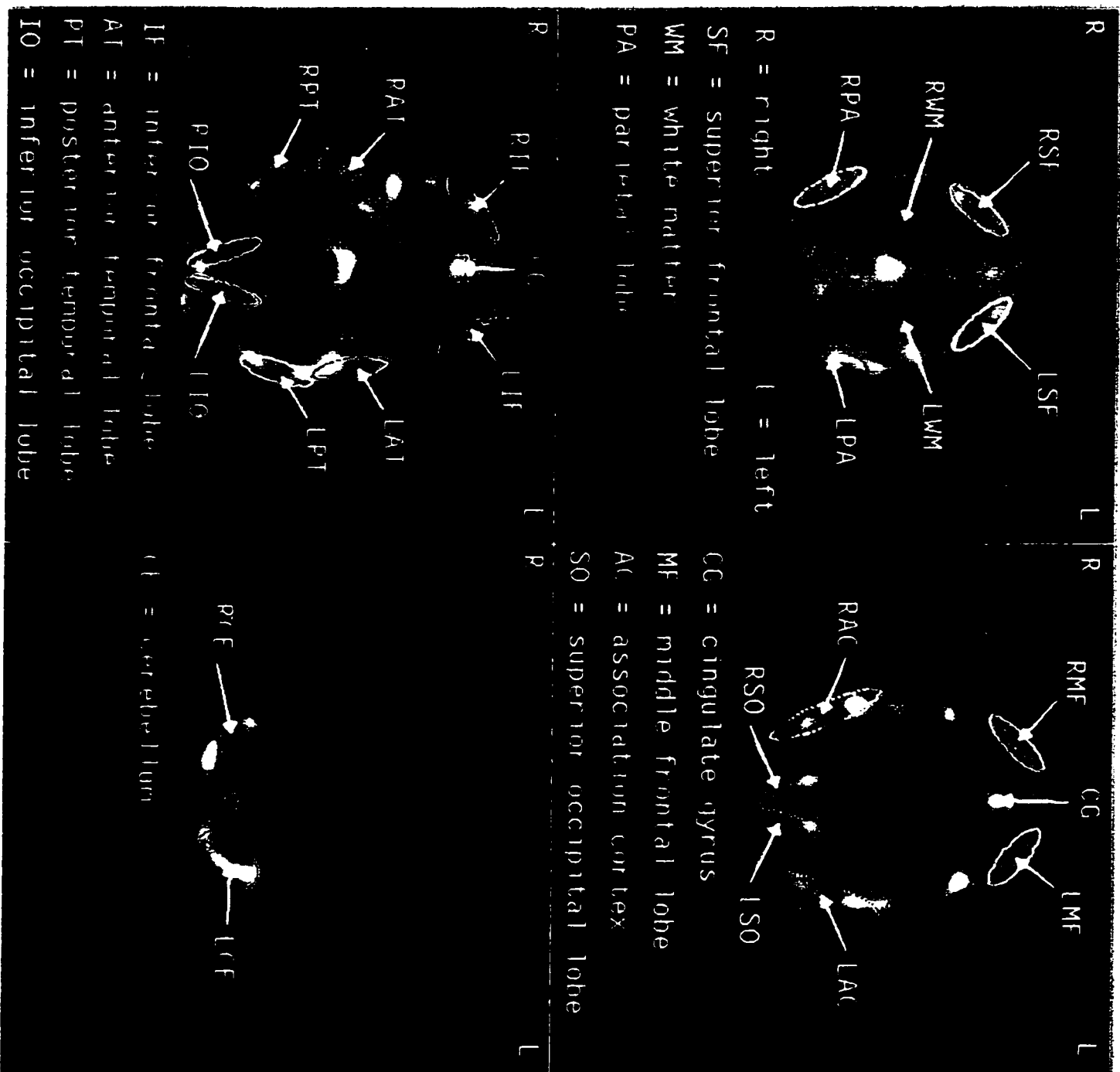
Hachinski Ischemia Scale
(Clinical Features of Multi-Infarct Dementia)

1. Abrupt onset	2
2. Stepwise deterioration	1
3. Fluctuating course	2
4. Nocturnal confusion	1
5. Relative preservation of personality	1
6. Depression	1
7. Somatic complaints	1
8. Emotional lability	1
9. History of hypertension	1
10. History of strokes	2
11. Evidence of associated atherosclerosis	1
12. Focal neurological symptoms	2
13. Focal neurological signs	2
MAXIMUM SCORE	18

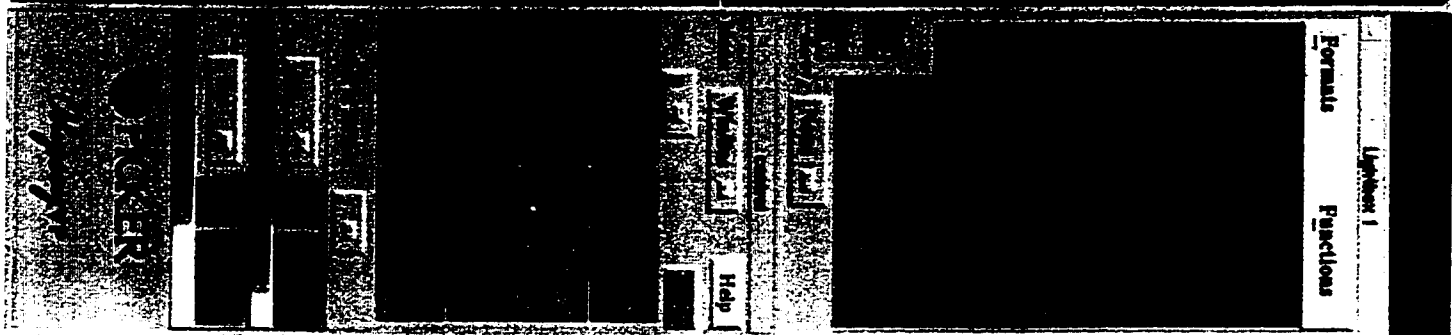
Score < 4 consistent with primary degenerative dementia
 Score > 7 consistent with multi-infarct dementia
 Scores between 4 and 7 and indeterminate

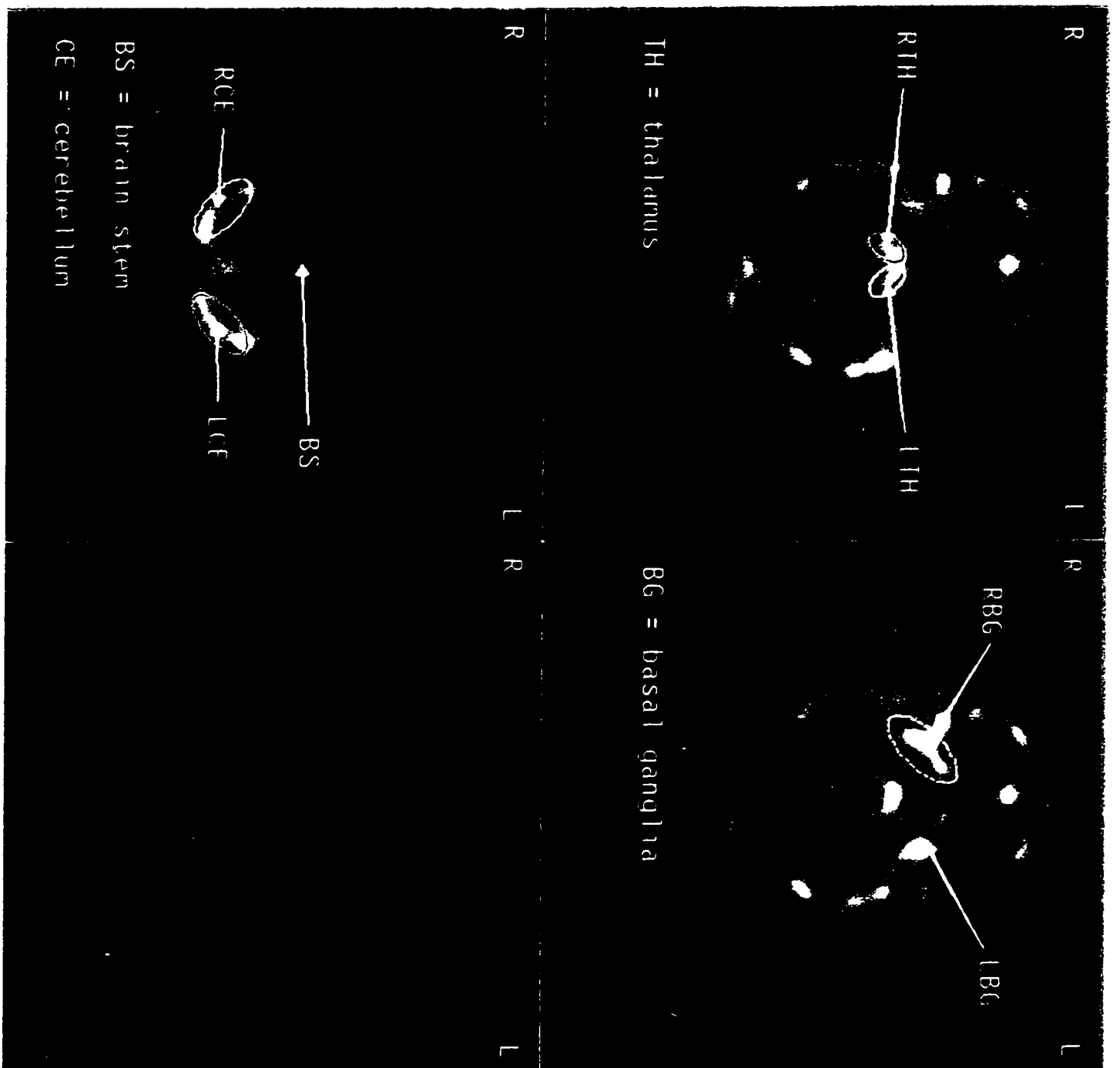
APPENDIX 5
REGIONS OF INTEREST ON SPECT BRAIN SCANS

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3 QUANTIF-1





3 QUANTIF - 2

APPENDIX 6
RESULTS OF POWER ANALYSES

POWER ANALYSES

ANALYSIS: Linear regression of total frontal blood flow on mental status change

Combined sample ($n = 32$), $L = 0.05$, power well beneath lowest tabled value

ANALYSIS: Linear regression of total parietal blood flow on mental status change

Combined sample ($n = 32$), $L = 6.43$, power = .69

AD subjects only ($n = 15$), $L = 6.85$, power = .75

AAMI subjects only ($n = 17$), $L = 2.12$, power = .29

ANALYSIS: Linear regression of frontal/parietal perfusion ratio on mental status change

Combined sample ($n = 32$), $L = 15.59$, power = .98

AD subjects only ($n = 15$), $L = 6.787$, power = .75

AAMI subjects only ($n = 17$), $L = 0.873$, power beneath lowest tabled value

ANALYSIS: Linear regression of frontal neuropsychological summary score on mental status change

Combined sample ($n = 32$), $L = 4.12$, power = .52

AD subjects only ($n = 15$), $L = 0.02$, power beneath lowest tabled value

AAMI subjects only ($n = 17$), $L = 1.16$, power beneath lowest tabled value

ANALYSIS: Linear regression of parietal neuropsychological summary score on mental status change

Combined sample ($n = 32$), $L = 4.04$, power = .52

AD subjects only ($n = 15$), $L = 0.01$, power beneath lowest tabled value

AAMI subjects only ($n = 17$), $L = 3.05$, power = .40

ANALYSIS: Z test of the difference between multiple correlations from regressions of dichotomized DA5 and DR60 scores on 1) frontal neuropsychological summary score and 2) parietal neuropsychological summary score

Combined sample ($n = 36$), $q = .276$, power = .30

ANALYSIS: Point biserial correlations between dichotomized scores on DAS and DR60 and frontal and parietal neuropsychological summary scores in combined sample

DR/DA VARIABLES	Neuropsychological Summary Scores	
	NP FRONTAL	NP PARIETAL
DR60 n = 37	.331 p= .046 Power = .53	.451* p= .005 Power = .98
DAS n = 36	.661* p= .000 Power = .80	.374+ p= .025 Power = .63

Correlations among Neuropsychological and SPECT Measures of Frontal Lobe Function in All Subjects

Neuropsychological Measures	SPECT Summary Measures		
	Total Frontal Perfusion	Sagittal A/P Ratio	Frontal/Parietal Ratio
WCST-PR	.114 p= .257 P = .03	.103 p= .279 P = .02	.131 p= .226 P = .04
WCST-SET	.175 p= .157 P = .07	-.121 p= .245 P = .03	.165 p= .172 P = .06
CFST	.034 p= .423 P < LTV	-.067 p= .352 P < LTV	-.452 p= .003 P = .58
COWA	-.090 p= .304 P < LTV	.029 p= .435 P < LTV	-.221 p= .101 P = .11
MAZES	.025 p= .444 P < LTV	.026 p= .442 P < LTV	-.186 p= .142 P = .07
NP FRONTAL	-.053 p= .382 P < LTV	.031 p= .431 P < LTV	-.238 p= .088 P = .29

Note. n = 35 for all correlations

Significance values are one-tailed

P = power

Power calculated at $\alpha_2 = .01$ for all correlations (to correct for number of comparisons) except those with NP Frontal which were calculated at $\alpha_1 = .05$ (i.e., less conservative)

LTV = lowest tabled value

Point-Biserial Correlations among Delayed Response (DR) and Delayed Alternation (DA) Measures and Frontal Perfusion Measures in All Subjects

SPECT Measure	DR/DA Variables	
	DR60 $n = 35$	DA5 $n = 34$
TOTAL FRONTAL PERFUSION	-.058 $p = .371$ $P < \text{LTV}$	.214 $p = .112$ $P = .14$
SAGITTAL A/P RATIO	.201 $p = .124$ $P = .12$	.114 $p = .261$ $P = .05$
FRONT/PARIETAL RATIO	-.157 $p = .185$ $P < \text{LTV}$	-.061 $p = .365$ $P < \text{LTV}$

Note. $n = 35$ for correlations with DR60, $n = 34$ for correlations with DA5

Significance values are one-tailed

P = power calculated at $\alpha = .01$ to correct for number of comparisons being conducted

LTV = lowest tabled value