Differentiating Multi-Infarct Dementia from Dementia of the Alzheimer Type

by

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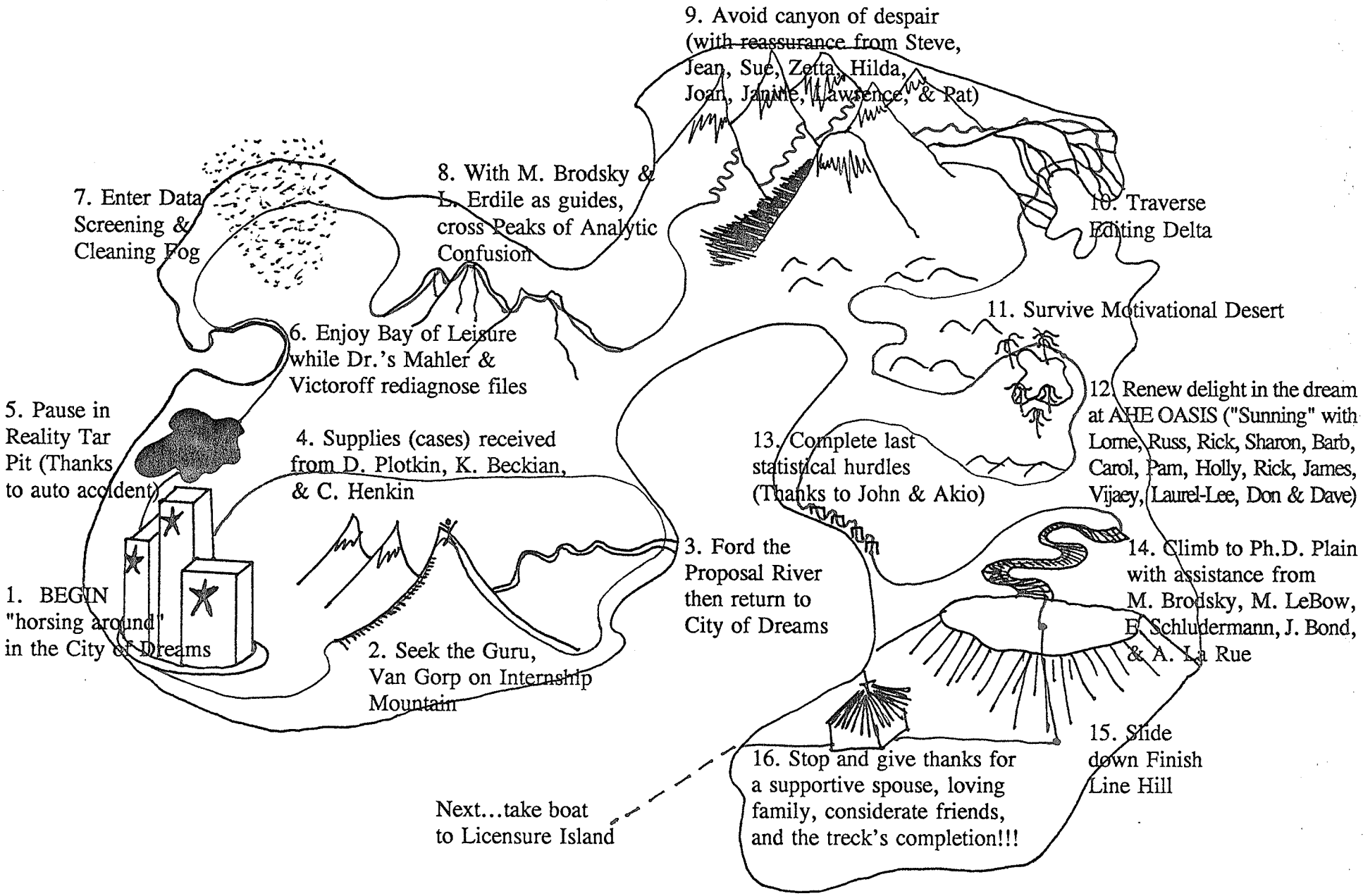
My Stay on Dissertation Island



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Abstract

The purpose of my study was to develop a comprehensive test battery for differentiating multi-infarct dementia (MID) from dementia of the Alzheimer type (DAT) in the elderly. In Phase 1, the files of 54 demented patients (23 with vascular dementia and 31 with dementia of the Alzheimer Type) were selected and evaluated from over 1200 files in the archives of the Dementia Clinic of the Neuropsychiatric Institute at UCLA in Los Angeles, California. Each subject was diagnosed as having MID or DAT by at least two of three independent raters (their clinic physician and two independent neurologists who were unaware of the original diagnosis). Each subject was also given a screening battery (the Mini-Mental State Examination) as well as a number of neuropsychological tests [Trail Making A & B, Boston Naming, the Fuld Object Memory Evaluation, the Visual Reproduction and delay subtest of the Wechsler Memory Scale, and three subtests from the WAIS-R (Vocabulary, Picture Completion, and Block Design)]. There were no sex or age differences between the two groups. However, level of severity of the dementia was a significant factor, with Alzheimer patients demonstrating a more severe form of dementia than Multi-infarct subjects ($p < .01$). A multivariate analysis of covariance with severity partialled out (MANCOVA) showed no single test significantly differentiated the two groups.

Concern was raised that the small sample size in Phase 1 might have led to erroneous

conclusions. Therefore, for the next six months, appropriate patients presented to either the Dementia Clinic at the Brentwood Division of the West Los Angeles Veteran's Administration Hospital or the Dementia clinic at UCLA's Neuropsychiatric Institute were tested with the same battery involved in Phase 1. Nine DAT and eight MID individuals who had been diagnosed as having dementia were classified as consistent with either multi-infarct dementia or dementia of the Alzheimer Type by at least two physicians; their primary physicians and two other neurologists. As in Phase 1, Phase 2 found no significant difference between DAT and MID patients on any demographic variable, however level of severity was significantly different between the two diagnoses. Subjects from Phase 1 were combined with those from Phase 2, and a multivariate analysis of covariance with severity partialled out (MANCOVA) was used to compare the groups on the relative discriminative power of the neuropsychological tests. No individual test significantly differentiated between these two groups after the effect of severity of the dementia was removed. However, two discriminant functions (one, including verbal tests and Mini Mental State scores, and the other including visuospatial tests and Mini Mental State scores) were found to significantly separate MID from DAT patients ($p < .01$, each). Discriminant functions based on the combined sample of 40 DAT and 31 MID subjects accurately classified 85% of DAT and 68% of the MID subjects.

Differentiating Multi-infarct Dementia from Dementia of the Alzheimer Type

Dementia is defined as "a syndrome of acquired intellectual impairment characterized by persistent deficits in at least three of the following areas of mental activity: memory, language, visuospatial skills, personality or emotional state, and cognition (abstraction, mathematics, judgment)" (Cummings, & Benson, 1983). Using this definition, approximately 5% of those persons over age 65 are severely demented, and an additional 10 - 15% are mildly to moderately demented (Cummings, 1985; Cummings & Benson, 1983).

Neuropathologists have recognized that the two most prevalent forms of dementia are: Dementia of the Alzheimer Type (DAT) and dementia secondary to multiple episodes of cerebral infarctions (Worm-Petersen & Pakkenberg, 1968), commonly referred to as multi-infarct dementia (MID) (Bucht, Adolfsson, & Winblad, 1984; Hachinski, Lassen, & Marshall, 1974). The difficulty with this differentiation is that there are at present no antemortem techniques that reliably distinguish between multi-infarct dementia (MID) and dementia of the Alzheimer Type (DAT) (Glen & Cristie, 1979; Liston & La Rue, 1983a; St. Clair, & Whalley, 1983).

Of those persons who are referred for the evaluation of dementia syndromes, most studies have determined that between 8% and 12% of the patients exhibited signs or

symptoms of cerebrovascular disease (Freemon, 1976), although in some studies as many as 35% of dementia patients had MID (Cummings, 1987; Marsden & Harrison, 1972; Smith & Kiloh, 1981). Further, these studies may underestimate the prevalence of MID in our society, since population surveys and autopsy investigations suggest that MID may often be misdiagnosed as DAT (Cummings, 1987; Todorov, Go, Constantinidis, & Elston, 1975; Tomlinson, Blessed, & Roth, 1970).

The prevalence of dementia increases sharply with advancing age, with approximately 3% of the persons between the ages of 65 and 74 years demonstrating probable Alzheimer's disease, while 19% of those 75 to 84 years old and 47% of those over age 85 exhibiting these same symptoms (Evans et al., 1989; Katzman, 1976). Through increasing longevity of the population, over time, the growth in the portion of the population over age 65 is creating a proportionately increasing group of demented adults (Benson, 1982). By the year 2030, 20 percent of the population in North America will be over age 65 (an estimated 60 million persons) (Plum, 1979). Therefore, between 3 and 6 million individuals will suffer from dementia (Barclay, Zemcov, & Blass, 1985; Beck, Benson, Spar, Rubenstein & Schiebel, 1982). Thus, as the number of aged persons increases, the number of dementia cases will correspondingly increase, and dementia will require an increasing share of the health care budget, health care work-hours, and hospital and nursing home beds (Cummings, 1982).

Williamson et al. (1964) noted that general practitioners recognized only 13% of the dementia cases amongst their patients. Roca, Klein, and Vogelsang (1982) reported that hospital physicians (perhaps better trained in diagnosing progressive cognitive

deterioration than general practitioners) still missed approximately 20% of the dementia among medical inpatients at a major teaching hospital. Further, because of time constraints, private practitioners (Chaifetz & Killian, 1983) and hospital staff often resort to using short screening procedures (e.g., orientation items such as orientation to person, place, and time) to classify individuals as demented. This practice fails to detect more than 40% of patients with moderate levels of cognitive deterioration (Klein et al., 1985).

The challenge of increasing numbers of demented elderly persons in our society demands an integrated, comprehensive, and systematic approach to accurate identification of dementing illnesses. Further, differentiation of the many etiologies of dementia, and continued research into the treatment of these various underlying etiologies must be achieved.

Value of Discriminating DAT from MID

The usefulness of discriminating the different forms of dementing disorders is exemplified by Seltzer and Sherwin (1978). In their study, patients who were previously assigned the non-specific diagnosis of organic brain syndrome could be reclassified into particular diagnostic categories with a reasonable degree of certainty using a "thorough neurological examination" that included evaluations involving a mental status test, description of thought processes (e.g., clear vs. loose associations, delusions, or hallucinations), abnormalities in mood, and alterations in psychomotor activity. Seltzer and Sherwin described each diagnosis as involving a relatively specific etiology with a characteristic clinical presentation. Through this differentiation process, they even revealed a few patients who had potentially treatable causes of dementia (e.g., tumors

or depression). The prospect of distinguishing forms of dementia which will respond positively to treatment is one major justification for developing test batteries which can clearly differentiate the different forms of cognitive deterioration in the elderly.

However, the principal hope is in prevention. This applies, most aptly, to cases of MID. Once established, the intellectual losses of MID cannot be reversed, although a limited amount of recovery may occur with lifestyle alterations. However, treatment of hypertension, control of diabetes, lowering of blood lipids and triglycerides, weight control, and abstinence from cigarette smoking will diminish the risk of MID, and, in established cases, these preventative measures may modify the progression of the disorder (Cummings, 1987). Also, less specific disease-related management including treatment of any associated psychosis, depression or seizures may occur. For instance, depression syndromes commonly associated with stroke have been shown to respond very positively to standard antidepressants (Lipsey, Robinson, & Pearlson, 1984; Redding, Haycox, & Blass, 1986).

From a practical standpoint, the serious danger of misdiagnosis lies in the clinician's failure to recognize vascular disorders (or psychiatric disorders) when they are important in the patient's symptomatology, not in the clinician's failure to make an early diagnosis of Alzheimer's dementia. The course of Alzheimer's disease will not be altered as a consequence of its early recognition and diagnosis, as at present, treatments are only useful for the management of symptoms, not for varying the course of the progressive degeneration (Cummings, 1985; Volicer, 1988). In contrast, the course of vascular disorders can be changed dramatically by early diagnosis and treatment of the

underlying etiology.

The danger of infarcts is so widely accepted that physicians counsel many elderly individuals with no history of cardiovascular disease to take daily doses of aspirin. This drug is known to inhibit platelet aggregation which might cause occlusion of small blood vessels in the brain, and is seen as "good preventative medicine" (Liston & La Rue, 1983; Volicer, 1988).

Raskin and Rae (1980) also point out that different types of dementing illness will probably respond better to different forms of treatment. For example, in their study, the depressed patients with apparent cognitive deterioration (Pseudodementia of depression) were agitated, restless, preoccupied with feelings of worthlessness and often engaged in suicidal ideation. The authors recommended an anti-depressant with sedative-hypnotic effects, such as amitriptyline, for these patients. In contrast, the Alzheimer's patients demonstrated few of those symptoms. The Alzheimer's patients were obsessed with concerns about their health and thoughts of death or dying. The authors recommended psychotherapy treatments for these individuals.

Volicer (1988) also noted that individuals at different stages of dementia present with different constellations of problems, and therefore require very different medications. For instance, attempts to treat early stages of DAT are usually directed at stabilizing mood. Therefore, antidepressants are frequently employed (Cook & James, 1981). Vasodilators, ergloid mesylates (Hydergine or Niloric), and cholinergic drugs are also used in an attempt to improve memory (Volicer, 1988).

However, behavioral problems are the hallmark of the middle stage(s) of DAT.

Thus, the drugs prescribed are used to alter symptoms of hyperactivity and restlessness, sleep disturbances, resistiveness, and assaultiveness. Hypnotics or neuroleptics are typically prescribed for this stage of DAT.

In the later stages of DAT, behavior problems decrease, and symptoms such as motor incoordination, seizures, constipation and incontinence escalate. At this point, medications are administered to keep the patient comfortable, and restraints are used to prevent him/her from injury through accidents (which might include just attempting to rise from a chair, unaided).

Thus, many medications are utilized during the course of intellectual deterioration associated with Alzheimer's disease. However, as later discussion will demonstrate (p. 17), all of the medications prescribed for the treatment of various stages of DAT merely alleviate problems specific to certain stages of the disease; the progress of the dementia remains unaltered (Volicer, 1988).

An additional interest regarding accurate diagnosis includes the possible genetic diathesis associated with Alzheimer's disease (Eisdorfer & Cohen, 1980). Substantiation of the diathesis hypothesis would make early diagnosis of Alzheimer's dementia in an elderly adult, and genetic counselling for family members of childbearing age, important considerations for future generations.

Counselling for family members at risk for vascular dementing illnesses may be even more effective in preventing their occurrence. Attention to underlying etiologies such as hypertension, diabetes, high blood lipids or triglycerides, obesity, and cigarette smoking, will diminish the risk of MID. Therefore, a swift and accurate method of

differentiating vascular dementia (MID) from a progressive deteriorating disease (such as DAT) would make significant contribution to both medical and psychological treatments.

Diagnostic Criteria for Discriminating Multi-Infarct Dementia from Dementia of the Alzheimer Type

Currently, DSM III-R (American Psychiatric Association, 1987) provides three criteria for MID, to distinguish it from DAT: (i) stepwise deterioration during the illness, resulting in a "patchy" distribution of deficits (i.e., affecting some functions but not others), especially early in the course; (ii) focal neurological signs and symptoms (e.g, exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity, etc.), which are associated with the particular location of the ischemic areas in the brain; and (iii) evidence, essentially from any source, of cerebrovascular disease judged to have a causal relationship to the dementia syndrome. Liston and La Rue (1983) point out that although these criteria for dementia have existed in the literature for more than half a century, the question remains whether this set of clinical features can, in fact, be employed antemortem to distinguish validly and reliably between DAT and MID. Further, although the diagnoses of MID and DAT are considered to only be certain if confirmed at autopsy, even then, only approximately 80% of the cases are accurately diagnosed (McKhann, Drachman, & Folstein, 1984).

Various antemortem methods have been employed to attempt to distinguish these two forms of dementia. The following is a review of the major techniques which have been employed.

Ischemic Score

Hachinski et al. (1974) were the first to present an overview of the interrelationship between atherosclerosis and dementia, concluding that atherosclerosis results in dementia only by virtue of its role in the causation of multiple cerebral infarcts. Thus, Hachinski and his co-workers introduced the term "multi-infarct dementia". Subsequently, Hachinski and other co-workers (Hachinski, Iliff, & Zihka, 1975) devised an Ischemic score (IS) based on the criteria in a textbook by Slater and Roth (1969) (see Appendix A). Hachinski et al. (1975) found a bimodal distribution of patients' Ischemic scores, with MID patients purportedly attaining scores of 7 or greater, and DAT patients having fewer than 4 points on this scale.

The Ischemic score is based on the different presentation and clinical course between DAT and vascular disease. It weighs factors that are thought to be more typical of a stroke-like illness compared with the insidious development of dementia in DAT. This approach presents fewer problems in younger patients (< 70 years of age), where "strokes are strokes and DAT is a clear clinical entity" (O'Brien, 1988, p. 798).

Hachinski et al.'s (1975), patients had an average age of 62 years, which describes a relatively young group of dementia patients. Further, the IS rating did not divide patients into a vascular group and an Alzheimer group. Instead it divided them into a large infarct group and an "everything-else" group. The "everything-else" group might have included patients with Binswanger's disease (hypertensive patients with multiple white matter lucencies presumed to be related to arteriosclerosis involving the penetrating arterioles that reach the white matter from the cerebral cortex) (Funkenstein,

1988). It might also have included dementias caused by neoplasms, trauma, hydrocephalus, toxicity or demyelinating disorders. Similarly, dementias produced by viruses or other infectious diseases (e.g., Jakob-Creutzfeldt's disease, syphilis, or chronic meningitis) as well as all the other vascular dementias that did not produce clinically evident strokes (O'Brien, 1988), could have been included in this group.

Harrison, Thomas, Du Boulay, and Marshall (1979) studied 52 patients referred for investigation of dementia using the Ischemic score. Although diagnostic criteria for dementia and level of severity were not included in their description of subjects, the authors noted that none of their subjects was severely demented and that the degree of intellectual involvement was the same in the two clinical groups.

Liston and La Rue (1983) reevaluated the data presented by the previous authors regarding the IS. They came to the following conclusions:

1. Critical issues exist in that Harrison et al. (1979) had no pathological confirmation of the diagnosis of MID or DAT, no stated diagnostic criteria for dementia, and no measure of severity of dementia for any of their subjects. 2. One of the bases on which Harrison et al. concluded that their sample had MID was "focal EEG abnormalities"; however more than 60% of the patients with high scores on the IS in Harrison et al.'s sample did not have abnormal EEG's.

3. The authors stated that visible disease in pial segments of the anterior, middle and posterior cerebral arteries was significantly more common in the high-IS than in the low-IS group. However, this difference was not significant at the 0.05 level of confidence by Liston and La Rue's (1983) re-analysis of the data.

4. There was also no significant difference in regional cerebral blood flow between the high- and low-IS subjects, which casts doubt on the assumption that the high-IS subjects had more cerebral infarcts than the low-IS individuals. Moreover, the numbers of brain regions with cerebral blood flow abnormalities did not differ between the two groups - with each demonstrating "very patchy" patterns of flow.

5. Finally, the two groups did not differ significantly with respect to either systolic or diastolic blood pressure. Liston and La Rue (1983) concluded that even if one could assume that Harrison et al.'s (1979) sample were actually comprised of two distinct groups of patients - one with dementia due to vascular cause and the other with dementia due to nonvascular processes - the parameters of cerebrovascular status employed in Harrison et al.'s study did not correlate with the IS. Thus, although Hachinski et al. (1974, 1975) and Harrison et al. (1979) thought otherwise, Liston and La Rue's (1983) reevaluation of their data suggests that the IS's clinical usefulness in the differentiation of DAT from MID has not been demonstrated.

Loeb (1980) also attempted to validate the Hachinski et al. Ischemic score. In his study, significantly higher frequencies of abrupt onset, history of strokes, focal signs, focal symptoms, depression, emotional lability, and arteriosclerotic signs were observed in the high-IS (proposed MID) group, compared to the low-IS (proposed DAT) group. However, frequencies of other IS features (stepwise deterioration, fluctuating course, nocturnal confusion, relative preservation of personality, somatic complaints, and hypertension) did not differ significantly between the high- and low-IS groups. Further, discrepancies between clinical diagnoses and IS groupings were frequent, with clinical

diagnosis being corroborated by the IS in only 52% of the DAT patients and 55% of the MID patients.

Difficulties in differentiating DAT from MID with Hachinski et al's (1975) Ischemic score have caused many investigators to seek clearer diagnostic criteria for separating these two forms of dementia. One popular method has been to enlist the aid of brain imaging techniques, with the most common form of neuroimaging being computed tomography (Rutledge, 1989).

Computed Tomography (CT Scans)

Computed tomography was developed by Hounsfield in 1973. It revolutionized the field of neuroimaging by allowing direct but non-invasive evaluation of brain parenchyma. It uses thinly calibrated beams of x-rays, passed through a person's head and variously attenuated, depending on the type of tissue through which they pass (Rutledge, 1989; Ramsey, 1987). As the x-rays emerge from the skull, they enter an image receptor (scintillation crystal) and are recorded. The x-rays are rotated around the person, and a computer algorithm reconstructs the attenuation changes into a two-dimensional image.

Even when studies attempt to use "clear diagnostic criteria" such as computerized tomography (CT scans) to separate the varieties of demented subjects, there are difficulties. Several studies have reported contradictory results.

Loeb (1980) described relatively sharp distinctions between MID and DAT with CT scans. Evidence of diffuse atrophy, typically accompanied by ventricular enlargement, was reported for all 20 DAT cases on which CT scans were performed.

Further, atrophy was observed in only 2 of the 14 MID cases, and there were no reported cases of MID with ventricular enlargement. However, a CT scan study conducted in India found significant atrophy in the brains of 93% of MID patients in comparison to age-matched controls (Jayakumar, Taly, Shanmugam, Nagaraja, & Arya, 1989). Thus, the presence or absence of atrophy cannot accurately classify a demented individual as having DAT or MID.

Glatt and his colleagues (Glatt, Lantos, Danziger, & Katzman, 1983) examined CT evidence of low attenuation zones (indicative of structural dysfunction) and symmetrical tissue loss in the brains of patients with probable DAT or MID. Although there was a correlation between the above characteristics and the clinical suspicion of MID, they concluded that the CT scan did not discriminate between patients with vascular dementia and those with degenerative brain disease (such as DAT).

Kohlmeyer (1982) and Molsa, Paljarvi, and Rinne (1985) concluded in separate studies that the CT scan can differentiate between DAT and MID in most cases. However, this differential diagnosis was correct in only about 70% of patients in each of their studies, leaving 30% of patients incorrectly classified. Further 7% of Kohlmeyer's subjects had normal scans, even though they were functionally impaired.

Jacoby, Levy, and Dawson (1980) also reported difficulty in differentiating DAT from MID patients using CT scans. In a carefully selected group of Alzheimer's type patients, they found that only 10 of 40 (25%) had low attenuation areas on CT scans, compared with 4 of 91 controls.

Subsequent investigators (e.g., London et al., 1986) have determined that white

matter periventricular lucencies are a common finding in the CT scans of the elderly. Further, improved brain imaging techniques have resulted in greater association of white matter lucencies with a diagnosis of multi-infarct dementia (Wallin, Blennow, Uhlemann, Langstrom & Gottfries, 1989).

For example, recently, a study of 233 consecutively admitted dementia patients was conducted (68 DAT, 79 MID and 46 possible vascular dementia) (Erkinjuntti, 1987). The presence of white matter low attenuation (WMLA) was found in 70% of MID, and in only 1% of DAT CT scans. Conversely, two other studies (London et al., 1986; and Wallin et al., 1989) found that periventricular lucencies did not substantially differentiate between DAT and MID.

Furthermore, in studies which test the hypothesis that WMLA is indicative of diminished cognitive functions, conflicting evidence has been also gathered. Steingart, Hachinski and Lau (1987) discovered deficits in oral fluency, memory for two sentences, and orientation to time for a small sample of healthy subjects with WMLA's when compared to subjects without WMLA's. However, in two separate studies Brant-Zawadzki and his colleagues (Brant-Zawadzki, Fein, & Van Dyke, 1985) and Rao and his associates (Rao, Mittenberg, Bernardin, Haughton, & Leo, 1989) found no differences in neuropsychological test scores for elderly individuals with or without WMLA's on CT scan. Thus, although numerous attempts have been made to identify reliable CT characteristics that aid in the differential diagnosis of DAT from MID, valid criteria for distinguishing these two groups have not yet been established (Aharon-Peretz, Cummings, & Hill, 1988).

Several notable problems exist with attempts to differentiate these two disorders using CT examinations: (a) CT has limited resolution in the posterior fossa and basal ganglia, so that small infarctions may be overlooked (Harrel et al. 1987); (b) cortical atrophy (demonstrated by increasing ventricular size and cortical sulcal prominence) is notable in the brains of normal elderly individuals, as well as Alzheimer-afflicted elderly (Blessed, Tomlinson, & Roth, 1968; Eisdorfer & Cohen, 1980), such that the existence of cortical atrophy is not an accurate means of defining DAT; (c) Leukoariosis (LA), defined as areas of increased lucency in the white matter of the cerebral hemispheres, has also been noted in demented and non-demented patients with cerebrovascular disease, in patients with DAT, and in normal elderly individuals (Aharon-Peretz et al., 1988; Erkinjuntti, Ketonen, & Sulkava, 1987; London, 1986; Steingart et al., 1987); (d) depression is commonly used to define MID (Cummings et al., 1987), however CT scans of Alzheimer patients are more similar to those of depressed elderly persons, in terms of brain tissue density, than they are to normals (Jacoby, Dolan, Levy, & Baldy, 1983); and (e) although a CT scan provides safe and accurate visualization of cerebral structures, this does not provide the practitioner with definitive information regarding functional cognitive deterioration (Eisdorfer & Cohen, 1980).

Problems in Differential Diagnosis

One difficulty in most of the literature attempting to differentiate MID from DAT is that the sureness of diagnosis is suspect. This is partially due to the fact that the diagnosis of DAT is not presently achieved by positive criteria and confirmative steps but, rather, by a process of exclusion of other identifiable causes of the dementia

syndrome (Cummings, 1985; Liston & La Rue, 1983). Unfortunately, "diagnosis by exclusion results in the inclusion of all unrecognized dementias as DAT and renders DAT a nonspecific diagnosis" (Cummings, 1985, p. 76).

The DSM III-R (APA, 1987) criteria for diagnosing MID have drawn heavily upon the work of Slater and Roth (1969) as well as Hachinski and his colleagues (1975). As noted in previous discussion, these clinical diagnostic criteria are not as accurate as we have been led to believe (Liston & La Rue, 1983).

Another difficulty in most studies attempting to differentiate DAT from MID is that there is seldom a control for (or even a description of) the stage or severity of the dementing illness (La Rue, Dessonville, & Jarvik, 1985; Liston & La Rue, 1983). This occurs even though the determination of the severity of the disorder is central to any clinical study of dementia (Hughes, Berg, Danziger, Coben, & Martin, 1982). Level of severity effects which measures are best suited to identifying one stage of dementia from another. For example, the tests which separate cases of early or mild dementia may differ from those that are diagnostically useful at later stages (e.g., Vitaliano, Breen, Albert, Russo, & Prinz, 1984). Investigations also typically report outcomes in mean differences, without describing or interpreting individual variations. Even when individual differences are reported, they are viewed as merely increasing concerns about the utility of diagnostic indicators (e.g., Fuld, Katzman, Davies, & Terry, 1982; La Rue, D'Elia, Clark, Spar, & Jarvik, 1986). However, without this information, it is difficult to know the sensitivity (correct inclusion rate) and specificity (correct exclusion rate) of the various features of test performance.

Few studies describe their findings in terms of cut-off scores which might be used to guide clinical judgments on the presence or absence of dementia. This omission is understandable, given the small samples and unstandardized procedures involved, but it does little to resolve the current diagnostic quandary (La Rue et al., 1985).

Value of Psychological Tests in Discriminating DAT from MID

There is strong evidence that psychological test performance may be extremely useful in screening potentially demented individuals. Many authors note the necessity of psychometric testing as part of the evaluation of a potentially demented patient (Chaifetz & Killian, 1983; Eastwood, Lautenschlaeger, & Corbin, 1983; Eisdorfer & Cohen, 1980; Hagberg & Gustafson, 1985; Hughes et al., 1982; Gustafson & Hagberg, 1978). In fact, in light of the failure of medical diagnostics [e.g., CT Scan (Eisdorfer & Cohen, 1980), and EEG (Duffy, 1985)] to distinguish between these two disorders, some authors have suggested that psychometric testing is the most specific diagnostic procedure presently available (e.g., Gustafson & Nilsson, 1982; Rabins, Merchant, & Nestadt, 1984).

To illustrate, Kaszniak, Fox et al. (1979) demonstrated that scores on memory and language tests were better at predicting survival than are either EEG or CT Scan findings. Survival, in turn, was highly correlated with severity, or stage, of the dementing illness (e.g., an individual with Stage 1 dementia may show few outward signs of this deteriorative disorder, and probably has 7 to 10 years to live, whereas an individual in Stage 6 dementia may be incontinent, unable to feed himself/herself, etc., and probably has only a couple of years to live, Reisberg, 1983). Thus, psychological

tests are accepted as being more valid predictors of dementia and its stages than are other forms of medical and neurological evaluation (La Rue, 1985). This is not surprising since psychological tests involve functional, rather than structural, analyses. As noted earlier, even a highly advanced structural analysis (i.e., CT Scan) can only provide evidence as to whether cortical atrophy and visible infarcts exist. Further, diminishing brain size is present in normal elderly persons as well as those with progressively dementing illnesses (Blessed, 1954; Kaufman, 1985); thus the presence of structural changes are not indicative of cognitive deterioration.

The most common symptom of the early stage of any dementing illness is deterioration of overall cognitive functioning (or, I.Q.) (e.g., Benson, 1982). Thus, it is not surprising that the most common psychological tool used thus far to assess and differentiate these two disorders has been the Wechsler Intelligence Scale (WAIS and WAIS-R).

WAIS or WAIS-R Performance Studies

Perez et al. (1975) examined WAIS findings in an attempt to determine whether scores on this test could be used to differentiate degenerative from vascular dementia. Their sample was comprised of 42 demented patients, with a mean age of 66 years, classified into 10 with DAT, 16 with MID, and 16 with vertebrobasilar insufficiency (VBI - An insufficiency in blood supply to the brainstem and posterior portions of the brain). Subjects were selected from "over 100" demented patients, however reasons for excluding the majority of these patients in the study were not elucidated. Diagnostic classification was based on examination of history, clinical evaluation, and laboratory

study.

Clinical criteria for MID included a history of hypertension, a course "characterized by episodic strokes with cumulative worsening of mentation plus associated transient cerebral ischemic episodes," evidence of arteriosclerotic disease elsewhere in the body, and multiple signs, evident on neurological examination, "of diffusely represented cerebral deficits attributable to multiple vascular lesions." Arteriography was used to rule out cerebrovascular disease in the AD group and to confirm the diagnosis in MID and VBI cases by demonstrating arteriosclerotic plaques or stenosed or occluded cerebral vessels. The possibility of mixed cases of DAT and MID or VBI was not addressed, and pathological verification of the presence of cerebral lesions was confirmed in only 2 of the 42 cases, both of whom had DAT.

The three diagnostic groups were compared in their performance on six subtests of the WAIS; verbal, performance, and full-scale IQ scores were prorated from these subtests. Significant differences were observed on each of these measures, with the DAT group consistently obtaining lower scores than either of the vascular dementia groups. Discriminant function analyses were also performed with the WAIS scores, age, and education entered as predictor variables. Correct classification was reported for 90% of the DAT subjects, and for 81% of the VBI cases, but for only 56% of the MID group. Perez et al. (1975) concluded that they could differentiate between the three groups on the basis of WAIS scores, and noted that it was easier to classify patients who were "either maximally disordered (DAT) or minimally disordered (VBI) from a cognitive viewpoint".

Liston and La Rue (1983) note that Perez et al.'s (1975) conclusions from these data are confusing. Liston and La Rue contend that the possibility that the DAT patients were simply at a more advanced stage in the dementing process was not addressed by Perez and his colleagues.

Statistically, it is important to note that with a sample the size of that in Perez et al.'s (1975) study, only 3 variables should have been entered into the discriminant equation at any one time in order to produce reliable discriminant function coefficients (Morrison, 1990). From the description given by Perez and his colleagues, it is difficult to know whether they actually used 5 independent variables (VIQ, PIQ, FSIQ, age and education) or 11 (The previous five plus each of the six WAIS subtest scores). Equations with these numbers of predictor variables would require sample sizes of 75 and 165, respectfully, to produce reliable discriminant coefficients (Montgomery, 1976; Morrison, 1990).

Perez and other co-workers (Perez, Stump, Gay, & Hart, 1976) reported on a similar study of WAIS performance among patients classified as having DAT or MID. Two samples were examined separately - the first consisting of 10 DAT and 16 MID cases, and the second including 17 DAT and 14 MID cases. These cases were selected from "over 160" demented patients; however, again, the reasons for exclusion of the bulk of the original sample were not given. The diagnoses were established by "clinical and laboratory study", and cases of vertebrobasilar insufficiency were included under the MID category.

The authors concluded that their replication research "provides additional support

for the potential clinical and practical application of neuropsychological and behavioral procedures in identifying the psychological changes associated with the various diseases producing dementia". However, their conclusion is puzzling as their 1976 results conflicted with those of 1974. With the exception of Performance IQ in one of the sub-samples, there were no significant differences between the DAT and MID groups in the second (1975) study. Moreover, diagnostic classification rates based on discriminant function analyses were no better than chance in one of the sub-samples, and educational level was reported the best single predictor of DAT versus MID status. Thus, in their review of the area, Liston and La Rue concluded that the Perez et al. studies (1975, 1976) did not demonstrate how the WAIS might be profitably used to distinguish among subtypes of dementia.

Fuld (1984) had more success in developing a neurobehavioral marker of DAT based on a particular WAIS subtest profile. She derived her profile formula from Drachman and Leavitt's (1974) results. The formula is: $A > B > C \leq D$, with $A > D$, in which "A" is the mean of the Information and Vocabulary subtest scores, "B" is the mean of the Similarities and Digit Span subtest scores, "C" is the mean of the Digit Symbol and Block Design, and "D" is the Object Assembly subtest score. All subtest scores are age-corrected.

Fuld (1984) applied the formula to WAIS scores from several different studies [young normal adults with drug-induced cholinergic deficiency (scopolamine), young normal controls, DAT patients, and MID patients] with consistent results across samples. Approximately half of both the scopolamine and DAT cases revealed this

WAIS pattern, as opposed to less than 7% in the non-DAT groups, including the normal young controls.

In a replication comprising a group of DAT and MID cases (Brinkman & Braun, 1984), similar results were reported. The Fuld (1984) WAIS pattern, while characteristic of 56% of the DAT subjects, was observed in less than 5% of the MID subjects.

When normal elderly subjects were examined, Tuokko and Crockett (1987) found a very low frequency of this WAIS pattern ($< 1\%$) in a sample of 74 normal elderly subjects. Satz, Van Gorp, Soper, and Mitrushina (1987) found similar results testing a sample of 149 normal elderly subjects using the WAIS-R Satz-Mogel (1962) abbreviation of the WAIS-R (a short-form administration which uses every second or third item on each subtest, except Digit Span and Digit Symbol, which are given completely).

Satz et al. (1987) found that the profile pattern occurs relatively infrequently in the normal population. Thus, they concluded the WAIS-R marker is extremely useful in differentiating DAT from MID patients, even though only half of DAT patients show this profile. Further, they discovered that many sections of the Fuld WAIS-subtest pattern were observed in normal elderly (namely $A > B > C$). However, in their healthy elderly sample, C was not $\leq$ D. In fact, values were in the opposite direction. Thus, future research may address the use of Digit Symbol and Block Design scores in relation to Object Assembly scores, as a tool in the differential diagnosis of DAT from MID. Although these results still only discriminate half of the DAT sample, they provide optimism for the use of neuropsychological tests in differentiating DAT from MID, as they are both economical and non-invasive.

Studies Using Other Neuropsychological Tests

Few studies have been published which attempt to differentiate DAT patients from MID patients using neuropsychological tests other than the WAIS or the WAIS-R. However, a small amount of research exists in which other types of neuropsychological tools have been used to investigate dementia, more generally.

Whitehouse (1986) and Mayeux, Stern, Rosen, and Benson (1983) found no cognitive differences in their attempts to differentiate cortical versus subcortical dementia. Pillon, Dubois, and Lhermitte (1986) used a variety of tests to describe the heterogeneity of cognitive impairment in progressive supranuclear palsy, Parkinson's disease and Alzheimer's dementia. However, they did not clearly delineate what they used for a definition of dementia in their study.

Two other investigations used neuropsychological tests when attempting to separate cortical versus subcortical dementias, but each failed to control for level of severity of dementia among their subjects (Gainotti, Caltagirone, Massullo, & Micelli, 1980; Huber, Shuttleworth, Paulson, Bellchambers, & Clapp, 1986).

Differentiating DAT from Pseudodementia of Depression

La Rue et al. (1989) attempted to discover a test (or set of tests) which could accurately discriminate demented and depressed elderly individuals. Their article reported the results of two studies. The first study compared elderly individuals diagnosed as having either primary degenerative dementia, major depression, or no significant mental or medical disorder. The diagnostic utility of three memory tests was evaluated, as the acquisition of new information is generally the first and most salient

symptom to emerge in Alzheimer patients (Albert & Moss, 1988). Two discriminant functions were obtained from the best classifiers of the three memory tests. The first discriminant function accurately classified all of the demented patients and 9 of the 10 depressed patients (from their 10 person sample) as depressed, and not demented. The second discriminant function accurately classified 9 of the 10 patients in both the depressed and healthy elderly groups. The strongest predictor in these functions was the Object Memory Evaluation (Fuld, 1981).

In the second study, La Rue et al. (1986) applied the classification rules derived in the first investigation (i.e., the discriminant functions) to several geropsychiatry inpatients referred for neuropsychological evaluation. There was agreement between memory test classification and general categories of clinical discharge diagnosis (organic vs. functional) for 21 of 25 patients. Furthermore, the agreement between memory test classification and discharge diagnosis was substantiated approximately 18 months later, during follow-up by the patients' physicians.

Although La Rue et al. (1986) contributed to our understanding of the differentiation of dementia from depression, many questions still remain to be answered. For instance, did the limited sample size used by La Rue et al. effect the generalizability of their discriminant functions? Would classifying dementia patients on the basis of severity of symptoms affect which tests discriminated between the groups, and with what accuracy such a discrimination was possible? Might tests other than those oriented toward learning and memory aid in discriminating two groups of apparently demented patients? The present research attempted to address these issues.

In summary, various methods have been used to attempt to differentiate between MID and DAT. The methods range from a checklist of symptoms thought to most often delineate multi-infarct patients from those with Alzheimer's-type dementia (Hachinski et al., 1975), to Computerized Tomography (e.g., Glatt, 1983; Jacoby et al., 1980; Loeb 1980), to tests of intelligence (e.g., Fuld, 1984; Perez et al., 1975; Perez et al., 1976). The most successful of these attempts has been Fuld's (1984) WAIS profile differentiation process. However, the methodology employed by La Rue et al. (1986) in attempting to differentiate DAT from the pseudodementia of depression may be extended to separating the diagnoses of MID and DAT, as well.

Present Research

The present study was based on the hypothesis that patients with DAT would be differentiable from those with MID on the basis of their neuropsychological test scores. It was also expected that some tests might better separate the two diagnostic categories than others, at differing levels of severity. Further, DAT patients with greater severity were expected to perform more poorly on all neuropsychological tests than MID or DAT patients with mild or moderate levels of severity, thus making the groups of DAT and MID readily identifiable at the later stage.

Although the contribution of neuropsychological test information to the differential diagnosis of dementia is widely accepted (e.g., Eisdorfer & Cohen, 1980; McKhann et al., 1984), the question of which neuropsychological tests best facilitate this differentiation process is still unclear.

The nature of the dementia patient population (i.e., individuals who tire and

frustrate easily) also necessitates development of a brief test battery which will answer research questions accurately without overtaxing the patient. Thus, my research was designed to produce a battery which would be efficient as well as thorough in its sampling of a broad range of deficit areas. It was also designed to be sensitive to the relationship between disease severity and test performance and accurate in its discriminating power.

Purpose of the Research

Phase 1. The present study sought to expand on the research La Rue et al. (1986) by continuing the development of a comprehensive neuropsychological test battery for differentiating MID from DAT. La Rue et al. (1986) attempted to develop a neuropsychological test battery to differentiate between DAT and the pseudodementia of depression. Their research design was extended in my study in order to develop a comprehensive neuropsychological test battery for differentiating DAT from MID.

As the present study sought to develop a battery to distinguish DAT from MID, it was also an extension of Fuld's (1984) research. Fuld's (1984) investigation involved a very small sample of demented elderly individuals (12 DAT and 15 MID). The present study addressed this issue by obtaining a larger sample of demented elderly subjects.

The modest sample of dementia patients available to Fuld (1984) did not enable her to observe differences in test performance based on level of severity of the dementing illness. Berg et al. (1982) and Hughes et al. (1982) have noted the importance of differentiating the stages of dementia within a sample of dementia subjects. For example, an individual who is in the earliest stage of a dementing illness will display

different symptoms or manifest different levels of impairment than one who is in a later stage of the disease. Certainly, then, the tests which distinguish an individual at an early stage of the dementing process may be quite different from those which differentiate one at a later stage.

The present research addressed this issue by including subjects who were mildly, moderately, and more severely, impaired. It also evaluated the importance of level of severity in the differential diagnosis. This enabled a more accurate comparisons of elderly individuals with more varied symptomatology than previously possible. Since this situation is common clinically, the present study should have greater applicability to natural settings than previous research.

The patient population selected for the study was clearly delineated, as was the population used in the Fuld (1984) investigation, and every attempt was made to include only patients with Alzheimer dementia in the DAT group and only those with vascular dementia in the MID group. Assignments to the DAT and MID groups were originally made on the basis of psychiatric and neurological examinations, after medical evaluation and comprehensive laboratory screening (including EEG, EKG, CT or MRI, blood studies of thyroid, renal and hepatic functions, B-12 and folate levels, electrolytes and glucose, and urinalysis) ruled out specific medical causes of memory impairment.

The research recognized that accurate differentiation hinges on accurate diagnoses in the sample. Therefore, unlike any previous research, my investigation required an independent rating of each case by two neurologists who were blind to the patients' identities and previous diagnoses. These neurologists made their evaluations from file

information (containing all reports of medical, neurological, psychiatric and laboratory examinations, with conclusions from the test results deleted). These files also included neuropsychological test scores but not interpretations.

At least two of the three physicians (original clinic physician and two later raters) had to be consistent in their diagnosis of MID or DAT before the file was included in the research. This "triple-checking" of diagnosis allowed for more confidence in the interpretation of the results as reflecting the performance of individuals with a specific type of cognitive disorder than had been previously possible without histopathological evidence.

Although clinicians have to distinguish between many forms of dementia (e.g., Pick's Disease, Huntington's Chorea, Jacob-Creuzfeld's Disease, etc.) it is beyond the scope of the present research to classify all of the different forms of dementing illnesses. However, several files with diagnoses of dementing illnesses other than DAT or MID were included in the study so that the neurologists making the rediagnoses would have had to consider other possible causes for the dementia, as they must in a clinic.

Another manner in which the present study differed from that of most other investigations of this nature, (e.g., Anthony, Le Resche, Niaz, Van Koff, & Folstein, 1982; Berg et al., 1982; Eisdorfer & Cohen, 1980; Hughes et al., 1982; La Rue et al., 1986; La Rue, 1989) is that the present study sought to control for experimenter bias. Although most research groups have more than one physician involved in diagnosis, previous conclusions and opinions of other evaluators are commonly available to the next observers. The present study withheld knowledge of the patient's hospital diagnosis from

the two subsequent diagnostic raters until after all analyses were completed.

The first study also differed from that of Fuld (1984) by increasing the comprehensive nature of the independent variables used in the discriminative equation. Fuld compared the usefulness of one test (the WAIS) in discriminating MID from DAT patients. The present study included a screening instrument, two tests of learning and memory, a test of concentration/attention, 3 subtests from the WAIS-R, and a naming task.

Thus, the tests used in Phase 1 included all of the basic areas of psychometric testing noted by Hagberg and Gustafson (1985) as being necessary to diagnose dementia: (a) verbal ability, (b) reasoning ability, (c) verbal memory, (d) spatial memory, (e) intellectual ability, and (f) motoric speed.

Phase 2. The second investigation was an extension of Phase 1, in which sample size of MID and DAT patients was increased by assessing additional patients recently referred for evaluation, and combining these patients' data with that obtained in Phase 1. The two samples were compared on the same tests for differences in demographic features and level of severity, thus validating the inter-subject differences observed in Phase 1.

Discriminant analysis was applied to the combined samples, to assist in categorizing future patients as being consistent with DAT or MID.

METHOD - Phase 1

Subjects

Approximately 1200 files of patients seen from September 1, 1986 through August 31, 1988 were reviewed. These cases were drawn from the Dementia Clinic of the Neuropsychiatric Institute at the University of California in Los Angeles, California. Seventy-four files were found where patients over the age of 58 carried a firm diagnosis of one form of dementia (e.g., MID or DAT but not the two combined), who had also completed neuropsychological testing.

Obviously, many patient's files could not be included in the study. Patients with active major psychotic symptoms at the time of testing (i.e., hallucinations, delusions, schizophrenia, psychotic mania or psychotic depression), toxic or metabolic deliria, or a major systemic disease (e.g., infection, hypothyroidism, myocardial disease, hepatic disease, or insulin dependent diabetes mellitus) were excluded (Kaszniak, Garron, & Fox, 1979). There was also an exclusion of patients with other disorders which might effect cognition (e.g., alcohol abuse) and neurological diseases, such as Huntington's disease, communicating hydrocephalus, and seizure disorders (Hughes et al., 1982). Patients with a history of head injury were also removed from the sample. Finally, patients noted to have had a severe loss of vision or hearing, or damage (or loss of) a shoulder, arm, hand or fingers, were eliminated from the study. Seven files from patients with firm diagnoses of dementia, but with forms other than MID or DAT (angular gyrus syndrome, pseudodementia of depression, dementia of Parkinson's disease, and Pick's disease) were also included as dementia files, necessitating a

differential diagnosis that involved more than a choice between two possibilities.

Procedure

Each subject's file was extracted from the archives by hand by the experimenter, after she found the file to contain: (a) a firm diagnosis of one form of dementia; (b) neuropsychological testing; and (c) no history of alcohol abuse, uncontrolled hypertension at the time of testing, or any other criteria for exclusion (as noted above). The selection of appropriate files was accomplished by first, searching for cases with diagnoses of MID or DAT which did not contain multiple diagnoses (e.g., "mixed vascular and Alzheimer's type dementia"), statements modifying the diagnosis (e.g., "possible" dementia), or other potential etiologies for the disorder (e.g., "Rule out affective disturbance"). Cases which had carried modifiers or had noted the necessity to check other origins for the cognitive decline were included if these issues had been successfully addressed through subsequent laboratory, physical, and neurological examinations, such that a firm diagnosis of DAT or MID was attached to the patient. No cases of potentially mixed forms of dementia (according to the original clinic diagnosis) were incorporated into the study sample.

The histories of persons whose files contained a firm diagnosis of a single form of dementia, who also had received a neuropsychological workup, were then perused by the experimenter for potential exclusion criteria. Any patient with a history of alcohol abuse (or even notation of frequent use), head injury, or neurological disorder (including seizures limited to childhood) were excluded. Similarly, a search was made for notations regarding all other exclusion criteria in the results of laboratory, physical, and neurological examinations. Patients who had displayed major psychotic symptoms (e.g.,

hallucinations or delusions) or had contracted a major systemic disease at some point in their life (infection, myocardial disease) were not excluded if they had been symptom free for at least 6 months prior to neuropsychological testing (e.g., files of persons with hypertension were included if it had been successfully controlled through medication). None of the patients whose files were considered for the study by this point were physically or visually impaired.

All of the file material from the 74 cases selected by the investigator was then photocopied and all information regarding the patient's name was removed. Previous conclusions based on neuropsychological test findings were deleted from the experimental files, and all notations regarding a previous diagnosis were eliminated before the files were passed on to the neurologists for re-diagnosis.

The only definitive diagnosis of DAT is currently considered to be histopathological evidence of a specified number of plaques and tangles in brain tissue (Moss & Albert, 1988), gained at autopsy. Liston and La Rue (1983a; b) have critically questioned whether there exists an established set of clinical features that can be practically applied antemortem to distinguish between DAT and MID in a valid and reliable fashion. It was crucial that the patients be accurately separated into the diagnostic groups of DAT and MID in order to validate the use of neuropsychological testing to also perform this antemortem differentiation. However, this study did not have the resources to obtain histopathological evidence to substantiate the antemortem diagnoses. Thus, all attempts were made to separate the two diagnostic categories as accurately as possible without this postmortem evidence. To accomplish this, the

guidelines set forth by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) Work Group on the diagnosis of Alzheimer's disease (McKhann et al., 1984) were employed.

The strict exclusion criteria set forth in the previous section were employed as a first step in the process. Further, although files were selected for inclusion in the study only if the patients had been given a firm diagnosis of one form of dementia, each file was reevaluated by two independent neurologists using the NINCDS-ADRDA diagnostic criteria.

The neurologists involved in the re-diagnosis were given a checklist of NINCDS-ADRDA criteria for differentiating dementia cases (McKhann et al., 1984; See Appendix D). A blank checklist was attached to each patient's file, and each neurologist was asked to check the items which fit with their diagnosis of that case. When one neurologist had completed his diagnosis, the checklist was removed and another blank checklist was placed in the file, so neither neurologist was informed of the other's findings.

Differentiation Procedure

The experimental files were assigned numbers, and were given to each of the neurologists for evaluation and re-diagnosis. The neurologists were asked to consider each file a case of MID, DAT, or "other".

Raters were instructed to categorize the files in the following manner: DAT Patients. Using the NINCDS-ADRDA criteria, a clinical diagnosis of probable Alzheimer's disease was made with confidence if there was an insidious onset of

dementia with progressive cognitive decline sufficient to affect social and occupational functioning. Further, it was necessary that there be no other systemic or brain diseases that could account for the progressive memory decline and other cognitive deficits (APA, 1987; McKhann et al., 1984). Each patient had to have demonstrated cognitive impairment in the presence of clear consciousness (i.e., no delirium or other conditions disturbing alertness or clouding of consciousness), and other possible disorders (e.g., Parkinson's disease, pernicious anemia, luetic brain disease, etc.) had to have been eliminated.

Cases with slightly aberrant presentation or course were also included as being possible Alzheimer's disease if, on clinical judgment, Alzheimer's disease was considered by the neurologist to be the most likely cause of the progressive dementia. This is also in keeping with the criteria set forth by the NINCDS-ADRDA work group (McKhann et al., 1984).

MID Patients. Diagnostic criteria for multi-infarct dementia were based primarily on the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised (DSM III-R) (APA, 1987) and consisted of: (a) The presence of dementia; (b) A stepwise deteriorating course (i.e., not uniformly progressive) with "patchy" distribution of deficits (i.e., affecting some functions, but not others) early in the course; (c) Focal neurological signs and symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity, etc.); and (d) evidence, from the history, physical examination, or laboratory tests of significant cerebrovascular disease that was judged to be etiologically related to the

disturbance. Exclusion criteria for major medical, neurological or psychiatric disorders (as noted for DAT patients, above), also applied.

Independent Rating of Subjects' Diagnostic Category. Two neurologists rated the files as being consistent with MID, DAT, or an "other" form of dementia. Through this re-diagnosis procedure, the neurologists found three files which did not contain adequate information regarding physical examination to accurately classify the patients, thus these files were eliminated from the study. The neurologists also found it necessary to create a fourth diagnostic category, "Mixed MID and DAT", for a small percentage of the cases (5 & 11 of the 71 cases from neurologist 1 and 2, respectively). This occurred even though the previous (file) diagnosis for each patient had been of only one form of dementia. The category of "Mixed MID and DAT" was not used in subsequent analyses in this study.

Neuropsychological Tests

The neuropsychological tests used in assessing these patients were selected by a neuropsychologist at the Neuropsychiatric Institute of UCLA on an a priori basis following Albert's (1981) guidelines for neuropsychological assessment of older adults. The tests assessed the domains of attention/concentration, intelligence, language, visuospatial ability, and memory. The specific tests were selected because they have been shown to be effective in detecting early changes in central nervous functioning (Lezak, 1983) and because they assess a broad range of intellectual and cognitive abilities. Thus, the battery was designed to briefly yet comprehensively assess a constellation of varied abilities in this sample (Van Gorp, Satz, Kiersch, & Henry, 1986;

Van Gorp, Satz, & Mitrushina, in press). Subjects in phase I of this research were tested by postdoctoral fellows specializing in Neuropsychology at the U.C.L.A. Neuropsychiatric Institute, in Los Angeles, California.

Attention and Concentration

Trail Making Test. The Trail Making Test (Reitan, 1955b; Reitan, 1958) has been widely used as an easily and quickly administered screening measure for organic impairment (Armitage, 1946; Gordon, 1972; Greenlief et al., 1985; Reitan, 1955b; Reitan, 1958; Spreen & Benton, 1965), although not previously applied to this specific differential diagnosis. It is objectively scored and very sensitive to the presence of cerebral dysfunction (Greenlief, Margolis, & Erker, 1985; Gordon, 1972; Reitan, 1955b; 1958), as it is a good measure of motoric speed, as well as visual tracking and scanning ability.

Both of the Trail Making tests (A and B) are timed tasks, where the subject is asked to complete the work as quickly as possible. Trail Making A involves connecting 25 numbered circles in numeric order. This is considered a measure of motor speed, visual scanning, visual tracking, and visual-motor integration. Trail Making B involves connecting 25 numbered or alphabetic circles alternating between numeric and alphabetic order (i.e., 1-A, 2-B, etc.). This test is purported to measure motor speed, visual scanning, visual motor integration, mental flexibility, sustained attention and logical sequencing (Dean, 1984).

Normative data for the elderly are limited for Trail Making A & B, and one of the more recent sets of norms has not yet been published in a journal of psychology (Van

Gorp, Satz, & Mitrushina, 1987). Davies (1968) noted that in the absence of such normative data, normal adults are more likely to be misclassified as brain-damaged as their age increases. This claim was further substantiated by Goul and Brown (1970), who found Reitan's (1958) cutoff scores to misclassify half of their control patients (ages 20-72). However, Greenlief et al. (1985) tabulated the mean number of seconds necessary for their samples of mildly, moderately, and severely cognitively impaired elderly subjects, and found that the combined scores from Trail Making A + B differentiated among all three of their groups. Their findings suggest that this combined score provides an excellent means of discriminating over-all level of neuropsychological impairment.

Intelligence

Wechsler Adult Intelligence Scale - Revised (Wechsler, 1981). This test was originally developed by Wechsler (1955) and is widely used as a measure of adult intelligence. The entire test involves 11 subtests, three of which were used: Vocabulary, Block Design, and Picture Completion.

Vocabulary is the verbal subtest which is most highly correlated with overall IQ on the WAIS-R. It is the subtest which demonstrates the least change with normal aging, and is often used as a measure of premorbid intelligence in individuals referred because of cognitive deficits. It involves asking the subject to give the definition of various words of increasing difficulty.

Block Design is the performance subtest which is most highly correlated with overall IQ on the WAIS-R. This subtest demonstrates considerable change with normal

aging. However, this is usually ascribed to the timed component of the task. In this test, subjects are asked to put together colored blocks to make figures like the ones with which they are presented in a booklet. This task is seen as a measure of visuospatial perception as well as a test of constructional skills.

Picture Completion is a task in which several cards with drawings are presented to the subject. Each of the drawings has an important element missing, and the subject's assignment is to discover what is missing. The task involves concentration (to discover the inconsistency), attention to detail, and a visual perception component (Rapaport, Gill, & Schafer, 1968).

The WAIS-R is used ubiquitously in clinical evaluation settings. Its reliability is relatively well investigated (Franzen, 1989), and much of this information is documented in the WAIS-R manual (Wechsler, 1981). For example, the split-half reliability for each of the subtests used here are reported as: .87 for Block Design, .81 for Picture Completion, and .96 for Vocabulary. Test-retest reliabilities for each of the subtests were computed from the results of two administrations to a group of 48 subjects between the ages of 45 and 54 years, and 71 subjects ages 25 to 34. The intertest interval ranged from 2 to 7 weeks, and the test-retest reliability coefficients ranged from .91 for Vocabulary to .80 for Block Design, with Picture Completion at .89 (Wechsler, 1981).

The validity of the three subtest short form used in the present study was documented by Margolis, Taylor and Greenlief (1986). Their study was performed on elderly subjects who had diagnoses of dementia (DAT, Mixed, and Pseudodementia), and it was recommended for use on this type of subject to reduce testing time and stress.

They demonstrated that the Full Scale IQ prorated from the combination of Block Design, Picture Completion, and Vocabulary [using Silverstein's (1982) method] was not significantly different from Full Scale IQ's from the entire battery. Although the author's cautioned against the use of the three subtest short form when precise IQ measurements are necessary, they considered it a valid method for monitoring the intellectual functioning of an elderly patient with dementia, especially given the stable retest reliability coefficients, noted above.

Although the three subtest short form is recommended for use with dementia patients, it is unfortunate for the purposes of the present research that the neuropsychologist at the Neuropscyhiatric Institute of UCLA did not give more of WAIS-R. A reexamination of Fuld's (1984) WAIS profile findings could not be performed in the present research, as five of the seven subtests used in her profile were not administered.

Hamilton Rating Scale for Depression

The Hamilton Rating Scale for Depression (Hamilton, 1967) was developed to measure the severity of depression in patients already diagnosed as suffering from depressive illness and has become a standard measure in clinical studies of depression (Albert & Moss, 1988). The scale consists of 17 items rated on a 3 or 5 point scale of severity , depending on the type of symptom. There are an additional four items relating to common symptoms (paranoia, depersonalization and obsessive-compulsive behavior). It is administered by a trained rater, and thus, interviewer skills are an important component in it's reliability and validity in a clinical setting (Melville & Blazer, 1985).

However, a structured interview guide has been developed which should alleviate the variability previously observed between raters (J. P. Abrahams, personal communication, March, 1988; Williams, 1988).

Mini Mental Status Examination

The Mini Mental Status examination (MMS) is a very brief test of gross cognitive functioning. The scale assesses a subject's orientation to time and place, instantaneous recall, short-term memory, and the ability to perform serial subtractions or reverse spelling (Folstein et al., 1975; Folstein, 1983; see Appendix E). The MMS usually requires no more than 10 minutes for completion, and may be properly administered by either clinical or lay personnel with little specialized training (Folstein, 1983). The MMS has proven reliable in samples of both psychiatric and neurological patients with test-retest reliability at or above .89, and interrater reliability at or above .82 (Folstein et al., 1975; Folstein & McHugh, 1979). Further, the sensitivity (valid positive rate) and specificity (valid negative rate) of the MMS have been demonstrated.

Various studies have demonstrated the usefulness of the MMS in elderly populations, and have demonstrated a cutoff score of 24 out of 30 possible points separates intellectually impaired persons from those without such impairment. For instance, Folstein et al. (1975) reported that all 63 normal elderly community residents in their investigation scored at least 24 points on the MMS. In a later study, DePaulo and Folstein (1978), reported that none of 26 neurological patients with spinal cord injury, peripheral nerve damage, or neuromuscular disorder in the absence of cerebral disturbance scored fewer than 24 points on this test. Finally, in a paper by Anthony, Le

Resche, Niaz, Van Koff, and Folstein (1982) this instrument was used on a general medical ward. The MMS was shown to be 61% sensitive (i.e., correctly positive in including cases) and 95% specific (correctly negative in excluding cases) in categorizing persons with apparent intellectual impairment as having dementia or delirium when scores of less than 24 were obtained.

However, while brief mental status tests such as the MMS are suggestive of the level of performance of a patient, they are not definitive (Albert & Moss, 1988). Some subjects who are in the early stages of a dementing process still do well on brief examinations of cognitive functioning, while many individuals who are not dementing can do poorly on such a test. Thus, such a screening test is useful as part of a standard battery to give a quick overview of the patient's functioning, or in following a patient's changes over time.

Language

The Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) was developed as a confrontational naming task, consisting of 60 line drawings of objects, ordered from easiest to most difficult. The pictures are presented in order, allowing up to 20 seconds for a response. If the subject misperceives the drawing, a stimulus cue is provided (which is printed in brackets on the scoring sheet). For example, if the response to the picture of a mushroom is given as, "umbrella", the tester says, "No - it's something to eat." The subject is allowed up to 20 seconds to name the picture after the stimulus cue has been given.

Phonemic cues are also available, and are to be given "after every failure to

respond or after any incorrect response." They consist of the sound of the first part of the name for the picture, and are underlined on the tester's score sheet.

Adults begin with item 30 and continue forward unless they encounter a failure before item 38. In the event of such a failure, the tester administers item 29, and continues backwards until 8 consecutive pictures are correctly named without assistance. Testing is discontinued after six consecutive failures.

This test was originally developed in 1972, and was standardized on a new normative sample of 242 aphasics between 1976 and 1982 (Goodglass & Kaplan, 1983). Two studies have also provided normative data using this test on normal, english-speaking adults. The first involved men ranging from 25 to 85 years in age (Borod, Goodglass, & Kaplan, 1980). The second involved a sample of 78 normal, healthy, elderly persons (aged 59 - 80), who were living independently (Van Gorp et al., 1986).

In the original study reported in the manual (Goodglass & Kaplan, 1983), the Kuder-Richardson reliability coefficient was found to be .96. Borod and his colleagues (Borod, Goodglass, & Kaplan, 1980) recommend the use of the Boston Naming Test on the basis of its content and face validity, which Franzen (1989) describes as "considerable". However, empirical validation is still lacking on this test.

Visuospatial Ability

The Block Design subtest of the WAIS-R (described above) as well as the Visual Reproduction of the WMS (described below) were used to assess visuospatial abilities in each subject.

Memory Tests

One test of verbal learning and memory, the Object Memory Evaluation (Fuld, 1981; Appendix B) was administered to each of the patients. The Visual Reproduction portion of the Wechsler Memory Scale (Wechsler, 1945) was also included as a test of nonverbal learning and memory.

Object Memory Evaluation. The Object Memory Evaluation (OME) (Fuld, 1981; Appendix B) was developed for use in distinguishing different types of dementing and amnestic disorders. Normative data exist for use with aged populations whether they are residing in the community or in nursing homes (Fuld, 1980, 1981, 1983; La Rue et al., 1986). The OME is administered according to instructions provided by Fuld (1981). The stimuli to be remembered are 10 common objects that the individual identifies tactually and visually before the first attempt at recall. These items are easily recognized, even by blind, deaf or language handicapped individuals (Fuld, 1983). Five recall trials are employed because multiple trials have been demonstrated to provide better discrimination between impaired and unimpaired elderly subjects (Fuld, 1980). On each trial the experimenter tells the subject which of the 10 items were not correctly recalled on the previous trial. The recall trials are alternated with 30 or 60 seconds of a distracter task (naming words rapidly from a familiar category). Because of the distracter, all recall on the Fuld test is assumed to consist of items encoded for long-term storage.

Mean scores on the Object Memory Evaluation, averaged across trials, were calculated for each of the following measures (c.f. Fuld, 1981; La Rue et al., 1986):

retrieval (number of items correctly recalled), storage (cumulative retrieval), consistent retrieval (number of items recalled on two consecutive trials), and recall failure (number of times when there was failure to recall an item on two consecutive trials, in spite of intervening reminding), free recall (number of items recalled spontaneously after a 30 minute delay, and "hits" (number of items not recalled spontaneously but recognized using a multiple-choice format after the recall task).

Wechsler Memory Scale - Visual Reproduction and Delay. This portion of the Wechsler Memory Scale was developed to delineate the nature of a patient's memory disorder. The memory deficit noted in the DAT patients was expected to be consistent for both verbally presented material, and nonverbally (pictorially) presented material (Wilson et al., 1983). However, the patients with MID were expected to demonstrate more difficulty on memory tasks in which nonverbal stimuli, as opposed to verbal, were used in the test (Orsini, Van Gorp, & Boone, 1988). Moss and Albert (1988) consider the most useful type of memory test for identifying DAT to be one which assesses the loss of information over a delay interval (Eslinger & Damasio, 1985; Gordon, 1984; Moss & Albert, 1988). The Wechsler Memory Scale was administered according to instructions provided by Wechsler (1945). In the Visual Reproduction portion of the Wechsler Memory Scale, the patient is presented with three sets of geometric designs (see Appendix C) and asked to copy them. The first two presentations are of a single design, and the third is of two geometric figures. The patient is allowed to view each presentation for only 10 seconds (including the card with two figures), during which time no copying is permitted. After this brief viewing period, the patient is allowed to draw

whatever he/she recalls of the design (termed, "Immediate Recall"). Thirty minutes later, "Delayed Recall" occurs.

Originally, Wechsler saw the Wechsler Memory Scale as a test of organic impairment. It was supposed to represent the memory ability of an individual in comparison to the memory ability of other people of roughly the same age (Franzen, 1989). Although it was supposed to measure memory as a whole, it is weighted toward the assessment of verbal memory, with six of the seven subtests depending heavily on verbal abilities. However, there are no tests of delayed memory (save the one subtest involving Visual Reproduction) or of memory with interference.

Further, the original standardization sample was small (200 normal subjects), and did not include elderly individuals (Wechsler & Stone, 1973). Therefore, another test of verbal memory (with higher reliability and validity regarding an elderly population) was also used in my research. The Visual Reproduction subtest was utilized as it is a simple and brief visuospatial test, it has the highest reliability of any of the Wechsler Memory Scale subtests, and normative data have been collected on an elderly population (Van Gorp et al., in press).

Reliability information on the Wechsler Memory Scale is scarce (Franzen, 1989). One test-retest study was conducted which included both normal subjects and a mixed psychiatric-neurological inpatient sample (Ryan, Morris, Yaffa, & Peterson, 1981). Pearson Product Moment correlation coefficients were calculated separately for the two groups, resulting in values of .75 for normals and .89 for the inpatients. The internal consistency of the Visual Reproduction subtest was examined using Cronbach's

coefficient alpha values and was found to be .64 (Hall & Toal, 1957).

RESULTS - Phase 1

Table 1 displays diagnosis by rater (file, neurologist 1, and neurologist 2) for the 71 files. Although care was taken to include files with a firm diagnosis of one form of dementia, the neurologists who reevaluated these files found it necessary to include a category of "mixed DAT and MID" in their diagnoses. Those files which received the same rating by at least two of the evaluators were accepted as holding that diagnosis (see Table 2). Sixty-four (90%) of the cases were in this category. Of these, 69% were cases where all three diagnoses (file, and two independent neurologists) were in complete concordance. Chi-square analyses (9 d.f.) demonstrated significant agreement between the two neurologists' ratings and the file diagnoses for both the DAT and the MID determinations ($p < .05$). Those files in which no two diagnoses agreed were noted as holding "no match," and were excluded from the subsequent analyses. Ten percent of the cases ($N = 7$) fell into this category, thus subsequent analyses were conducted using a sample size of 64.

Table 3 presents the means and standard deviations of demographic information (age and Hollingshead rating of Socioeconomic Status) for the two groups of interest (DAT and MID) and for the entire sample. No significant differences between groups existed on these variables. The mean age of the sample population was 76.2 years, with a range from 58 to 93 years. The average education level was high school graduate, and the mean occupational level was clerical, sales, or technical work (combined Hollingshead score of 47).

Table 1

Number of Cases by Diagnosis
(N = 71)

	DAT	MID	Mixed DAT & MID	"Other"
File Diagnosis	34	30	0	7
Neurologist 1 Diagnosis	32	24	5	10
Neurologist 2 Diagnosis	37	16	11	7

Table 2

Number of Cases with Concordant Diagnoses
by Raters
(File, Neurologist 1, & Neurologist 2)
In Phase 1
(N = 71)

	DAT	MID	Mixed	Other
3 Diagnoses Match	28	13		3
2 Diagnoses Match: File and 1 Neurologist	2	8		2
2 Neurologists	1	2	4	1

(Note: "No Match" occurred in 7 cases:
3 involved 1 diagnosis each of DAT, MID, and Other
3 involved 1 diagnosis each of DAT, MID, and Mixed
1 involved 1 diagnosis each of MID, Mixed, and Other)

Table 3

Age and SES of Phase 1 Subjects
(N = 54)

	DAT			MID			Entire Sample		F
	Range	M	SD	Range	M	SD	M	SD	
Age (in years)	58-93	76.1	7.7	61-87	76.5	7.0	76.2	7.2	0.218
SES (Hollingshead Rating)[1]	15-77	48.7	19.0	11-77	46.5	20.4	46.9	19.2	0.899

($p > .05$ for either variable)

[1]Greater Hollingshead rating implies higher socioeconomic status (as assessed through occupational and educational attainment).

Gender differences have been observed in previous studies. Commonly, male predominance in the multi-infarct dementia group, and female predominance in the Alzheimer's dementia group is reported (e.g., Hachinski et al., 1974; Roth, 1978). In my sample, women outnumbered the men, 56 to 15, but were equally distributed in both the DAT and MID groups.

Analyses of Variance

Screening information (Hamilton Rating Scale for Depression and Mini Mental Status exam) for the DAT and MID groups is presented in Table 4. No large or statistically significant differences exist between the two diagnoses for level of depression on the HAM-D. This is an unusual finding in light of previous research, where depression is a common complication of MID: Hachinski and his colleagues included depression in their Ischemia Scale as a feature supportive of the diagnosis of MID (Hachinski et al., 1975). Further, Gustafson and Nilsson (1982) confirmed that depression was more common in MID than DAT. Also, Brucht et al. (1984) and Redding and his associates (1985) found a higher incidence of depression amongst MID patients, in relation to DAT patients.

An ANOVA was performed which demonstrated that the level of depression (measured by the HAM-D scores) did not differ by diagnosis or gender of the subjects (see Table 5).

However, statistically significant variation does arise on the MMS score (see Table 4). An analysis of variance (ANOVA) was performed which demonstrated that, as expected, a significant difference existed between DAT and MID groups on the MMS

Table 4

Screening Information

Phase 1

(N = 54)

	DAT			MID			Entire Sample		F
	Range	M	SD	Range	M	SD	M	SD	
HAM-D[1]	0-22	7.9	5.2	3-21	8.3	5.5	7.9	5.5	1.63
MMS[2]	8-25	16.0	4.5	10-28	21.3	5.2	18.6	4.7	6.47*

* $p < .001$

[1]Greater HAM-D scores correspond to more severe depression.

[2]Higher MMS scores correspond to more intact gross cognitive functioning.

score (see Table 6). Further, when an ω^2 (omega^2) was calculated, the amount of variance in MMS scores accounted for by diagnosis was almost 80%, which is considered a strong association (Hays, 1981; Kirk, 1982). Still, men and women did not differ on MMS, and no interaction between gender and diagnosis was observed. As this score is an accepted measure of level of severity of dementia (Folstein et al., 1975; Huber et al., 1986; Jagust, Budinger, & Reed, 1987), a method of controlling for the severity of the dementia had to be found.

Controlling for level of severity. Where a "concomitant" or "nuisance" variable exists (such as level of severity) which may be linearly related to the variables of interest (neuropsychological test scores) which cannot be controlled by the experimenter, an analysis of covariance may be performed (Montgomery, 1976). The analysis of covariance involves adjusting the observed neuropsychological test scores to account for the effect of the level of severity. Without such an adjustment, the level of severity might inflate the error mean square in the MANOVA and cause true differences in the neuropsychological test scores due to diagnosis, to be harder to detect (Morrison, 1990).

A correlation matrix of the various neuropsychological tests and MMS scores is shown in Table 7. From this it is possible to observe that various tests (i.e., Trail Making A, Boston Naming, Fuld Object Memory Evaluation recall, WAIS-R Vocabulary, WAIS-R Picture Completion, and WAIS-R Block Design)

Table 5

2-Way Analysis of Variance
for Hamilton Rating Scale for Depression (HAM-D)
by
Gender and Diagnosis
(N = 54)

	Sum of Squares	D.F.	Mean Square	F
Gender	28.9	1	28.9	1.122
Diagnosis	1.9	1	1.9	0.075
Interaction (Diagnosis x Gender)	114.62	1	114.62	4.44*
Error	954.27	3	25.79	

* $p < .05$

are highly correlated with level of severity of the dementia (Mini Mental Status Exam).

Thus, a Multivariate Analysis of Covariance (MANCOVA, SPSS-X, 1984) was performed. This procedure is a combination of multivariate analysis of variance and regression analysis (Montgomery, 1976; Morrison, 1990). A multivariate approach was taken in this phase because of the need to examine the effects of level of severity on the specific diagnostic utility of each of the tests. [Using individual ANOVA's would have greatly increased the possibility of misclassification due to Type I error (Morrison, 1990,)].

The noncentrality parameter in multivariate analysis requires knowledge of the covariant matrix in order to calculate the power of the test. Since that matrix was not readily available, I attempted to achieve a reasonable estimate of power based on the example in Morrison's (1990) text on multivariate statistical methods. This procedure assumes a common variance, covariance, and population mean differences for each neuropsychological test score. Given the sample size of 54 (23 MID and 31 DAT cases - with 17 files rated as having "other" or "mixed" forms of dementia being excluded from these analyses), I concluded that only four variables should be entered into the equation at one time. This would enable a test at level $\alpha = 0.01$ to have a power between 0.60 and 0.95 of detecting certain minimal differences between mean vector components. Therefore, neuropsychological tests were divided into two groups of three or four tests each, based on a priori assumptions regarding the primary domain each test evaluates. On this basis, two groupings were formed: Verbal and Visuospatial tasks.

Table 6

2-Way Analysis of Variance
for MMS Score
by
Gender and Diagnosis
(N = 54)

	Sum of Squares	D.F.	Mean Square	F
Gender	0.71	1	0.71	0.029
Diagnosis	329.74	1	329.74	13.22**
Interaction (Diagnosis x MMS)	6.94	2	6.94	0.28
Error	24.95	3	24.95	

**$p < .01$

**$\omega^2 = .79$

Table 7 - Correlation of Independent Variables

	MMS	TMA	TMB	BNS	OME R	OME H	VREPI	VREPD	VOC	PC
MMS										
TMA	-.52**									
TMB	-.08	.46								
BNS	.45**	-.18	.04							
OME R	.39**	-.19	.08	.28						
OME H	.26	.03	-.16	.20	-.09					
VREPI	.36	-.24	-.30	-.04	.51**	-.02				
VREPD	.19	-.13	-.36	.37*	.42*	-.08	.43*			
VOC	.56**	-.32	.09	.64**	.20	.20	.09	.24		
PC	.43**	-.39*	-.38	.29	.16	.08	.35	.37	.33*	
BD	.33*	-.27	-.51	.38*	.12	.21	.34	.28	.37*	.62**

Where MMS = Mini Mental Status Exam
TMA = Trail Making A score
TMB = Trail Making B score
BNS = Boston Naming Score
OME R = Fuld Object Memory Evaluation Recall
OME H = Fuld Object Memory Evaluation "Hits" on Recognition
VREPI = Wechsler Memory Scale Visual Representation Immediate
VREPD = Wechsler Memory Scale Visual Representation Delay
VOC = WAIS-R Age Scaled Vocabulary score
PC = WAIS-R Age Scaled Picture Completion score
BD = WAIS-R Age Scale Block Design score

* ($p < .01$)
**($p < .001$)

Mean performance on the neuropsychological measures for the DAT and MID groups are noted in Tables 8 and 9. When the effect of severity level was eliminated, as observed in the MANCOVA (Tables 10 and 11) analyses, no differences were observed between the groups of DAT and MID patients. The test for significance (Wilks lambda) was converted to an F, and was found to be highly significant for the effect of the covariate (MMS) for both verbal and visuospatial tasks [Verbal $F(4,58) = 11.67$, $p < .001$, Visuospatial $F(3,47) = 6.93$, $p < .01$]. However, the null hypothesis - that the neuropsychological test scores did not differ across the two diagnoses - had to be accepted, for both verbal and visuospatial tests [Verbal $F(4,58) = 1.21$ $p > .05$, Visuospatial $F(3,47) = 1.27$ $p > .05$]. Thus, removing the effect of severity of the dementia also removes the variations between the two groups on neuropsychological tests.

This finding is contrary to the original hypotheses of the research, where differences were expected to exist between the two diagnoses even after the effect of severity level was eliminated. It was recognized that certain constraints had been placed on the analyses of Phase 1, due to original small sample size and inclusion of a diagnostic category of "Mixed DAT and MID", which decreased the analyzable sample even further (from 71 to 64). For example, many DAT and MID persons were unable to complete Trail Making B and WMS Visual Reproduction. Therefore, concerns regarding the power of the MANCOVA test for mean comparisons were raised. The multivariate analysis of covariance is a conservative measure, and lacks power when an

Table 8

Means of Verbal Tests[1] and MMS

by Diagnosis

(N = 47)

	DAT			MID		
	Range	M	SD	Range	M	SD
Boston Naming	0-38	21.2	10.3	0-59	30.3	13.7
Fuld OME Recall	0- 6	1.0	1.5	0- 9	2.5	2.8
Fuld OME "Hits"	0-10	4.2	2.6	0- 9	4.0	2.5
WAIS-R Vocabulary	1-12	7.4	2.5	2-16	8.5	3.1

($p > .05$ for any comparison)

[1]Higher scores reflect better performance on all these tests of verbal abilities.

Table 9

Means of Visuospatial Tests and MMS

by Diagnosis

(N = 37)

	DAT			MID		
	Range	M	SD	Range	M	SD
Trail Making A[1]	42-330	153.5	99.5	49-257	135.8	70.0
WAIS-R Picture Completion[2]	1- 11	5.1	2.6	2- 15	4.9	3.3
WAIS-R Block Design[3]	2- 10	5.0	2.1	1-14	5.1	3.1

($p > .05$ for any comparison)

[1]Higher scores reflect longer (more impaired) performance time.

[2]Higher scores reflect better performance.

[3]Higher scores reflect better performance.

Table 10

Multivariate Analysis of Covariance
for
Verbal Neuropsychological Tests
(N = 47)

Source	D.F.	Wilks λ	Significance
Covariate (MMS)	4, 41	F = 7.64	$p < .001$
Diagnosis	4, 41	F = 1.36	$p > .05$

Table 11

Multivariate Analysis of Covariance
for
Visuospatial Neuropsychological Tests
(N = 37)

Source	D.F.	Wilks λ	Significance
Covariate (MMS)	3, 32	F = 3.06	$p < .05$
Diagnosis	3, 32	F = 0.89	$p > .05$

extremely small sample is used.

For example, 25 (of the 54) cases were eliminated from the analysis of visuospatial abilities due to some form of missing data. [Missing data typically took the form of key tests not being administered by the neuropsychologist (16 of 25 cases). However 2 cases were eliminated because of the patients' refusal to perform some of the neuropsychological tests, and 7 others were eliminated because of the patients' inability to attempt one or more of the tasks]. The example in Morrison's (1990) text on which my power calculation was conducted was based on a sample size of 60. Since the investigator did not wish to overlook effects which might have been masked in Phase 1 by virtue of the small sample size, a second sample of DAT and MID patients was collected. An investigation was undertaken to ascertain whether this second sample was equivalent to the first, in demographic distribution. If no differences existed, the two samples could be combined and the analyses of Phase 1 could be repeated.

METHOD - Phase 2

Subjects

Participants in the second portion of the investigation were 17 individuals (8 DAT and 9 MID) attending the dementia clinics at either the Brentwood Division of the Los Angeles Veteran's Administration Hospital or the Neuropsychiatric Institute for evaluation and treatment between September 1, 1988 and March 1, 1989. Each of these patients was referred for neuropsychological testing because of reports of memory problems by themself, relatives or their physician.

Procedure

Neuropsychological testing was ordered by the primary physician for any patient who presented with what appeared to be either DAT or MID. One of three persons doing postdoctoral studies in neuropsychology administered the neuropsychological tests without having any information regarding the test information needed for this study. However, he/she was aware of the physician's diagnosis when testing was conducted.

Patients files were reviewed by two neurologists who reportedly diagnosed each case independently from one another, using the same inclusion criteria as outlined in the first portion of the study. Also, at least two of these cases were discussed as part of clinical rounds at the hospitals, at which time each neurologist was able to hear the diagnostic opinion of the other. Further, the neurologists did not complete the checklist (Appendix D) for these cases, as they had in the first portion of the investigation, due to time constraints. However, the neurologists' diagnoses matched in 100% of these cases.

RESULTS - Phase 2

Demographic and Screening Information

Table 12 displays the means and standard deviations of demographic and screening information (age, Hollingshead rating of Socioeconomic status, MMS, and Hamilton Rating Scale for depression scores) for the two samples. No significant differences between samples existed on these variables. The mean age of the combined sample was 74.2 years. The average education level was high school graduate, and the mean occupational level was clerical, sales, or technical work (combined Hollingshead score of 47).

A multivariate analysis of variance was conducted to compare the homogeneity of the samples from Phase 1 and Phase 2. Socioeconomic status (Hollingshead SES), level of depression (HAM-D) and mental status scores (MMS) were compared across the two groups. Table 13 displays these findings. No significant variations occurred across the two samples due to level of depression or level of socioeconomic status. Further, MMS scores did not differ significantly across these two groups. This indicates that similar levels of severity were observed in both samples. Since age was a binary variable, it was not included in the MANOVA. Instead, age was compared across the two samples using a students t-test for independent means, and was not found to be statistically significant [$t(14) = 1.4$].

Table 12

Demographic & Screening Information
for
Combined Sample in Phase 2

	DAT			MID			All Subjects	
	Range	M	SD	Range	M	SD	M	SD
Age (in years)	58-93	75.5	7.1	60-87	69.2	6.6	74.2	7.4
SES[1]	15-77	47.3	17.9	11-77	47.2	20.3	47.3	18.2
HAM-D[2]	0-22	8.0	5.5	3-21	9.5	3.5	8.3	3.1
MMS[3]	8-25	18.5	5.6	10-29	19.0	5.8	18.6	5.6

[1]Higher Hollingshead rating corresponds to higher socioeconomic status (as assessed through occupational and educational attainment).

[2]Higher HAM-D scores correspond to more severe depression.

[3]Higher MMS scores correspond to more intact gross cognitive functioning.

Table 13

Multivariate Analysis of Variance
for
Gender, SES, HAM-D, and MMS
by Sample

Source	D.F.	Wilks λ	Significance
Group (Sample I or II)	4, 60	F = 2.41	$p > .05$
Constant	4, 60	F = 12.75	$p < .001$

Therefore, the two samples were pooled, and subsequent analyses were conducted using this combined sample.

Multivariate analyses

In the original sample in Phase 1, multivariate analyses of covariance were conducted on the sample of DAT and MID subjects, to remove the effects of severity. This was also done on the combined sample, removing the effect of MMS score for verbal and visuospatial tests. These analyses are displayed in Tables 14 and 15. Wilks lambda was converted to an F, and when the effect of severity level was eliminated, no differences were observed between the groups of DAT and MID patients.

According to calculations from Morrison (1990), the power of these MANCOVA's should have been at least .95, as the combined sample size of Phase 1 and Phase 2 of this study was 64. Therefore, it can be said with confidence that DAT subjects were undifferentiable from MID subjects on the basis of any one of these neuropsychological tests.

Discriminant Analyses

The next statistical procedure consisted of stepwise discriminant analyses (SPSS-X, 1984). Discriminant analysis allows us both to observe whether the MID and DAT groups differ significantly from one another on some combination of measures and, if they do differ, also to understand the nature of these differences. Further, they can be used to determine group membership of unclassified individuals at some point in the future, based on those subjects' neuropsychological test scores (which are considered to be affected by the group to which each individual belongs) (Sitgreaves, 1973).

Table 14

Multivariate Analysis of Covariance
for
Verbal Neuropsychological Tests
on Combined Sample

Source	D.F.	Wilks λ	Significance
Covariate (MMS)	4, 58	$F = 11.67$	$p < .001$
Group Effect (Combination of Samples I and II)	4, 58	$F = 1.21$	$p > .05$
Constant	4, 58	$F = 1.89$	$p > .05$

Table 15

Multivariate Analysis of Covariance
for
Visuospatial Neuropsychological Tests
on Combined Sample

	D.F.	Wilks λ	Significance
Covariate (MMS)	3, 47	$F = 6.93$	$p < .01$
Group Effect (Combination of Samples I and II)	3, 47	$F = 1.27$	$p > .05$
Constant	3, 47	$F = 22.92$	$p < .01$

As the number of tests (or other independent variables) increases, so does the difficulty in interpreting differences between MID and DAT groups. Discriminant analysis allows a linear combination of the set of tests to be constructed that maximally differentiates between the groups. This, in turn, eases the interpretation of the relationship between the various independent variables to the dependent measure, of interest. Furthermore, linear functions have been demonstrated to be quite appropriate in medical applications such as this one, where no theoretical reason exists for using a curvilinear model (Breiman, Friedman, Olshen, & Stone, 1984). A Fisher linear discriminant function was used for the following analyses (SPSS-X, 1984).

Discriminant exclusion criterion were set at $\underline{f} < 1.0$ to determine the relative usefulness of the test measures in diagnostic group classification. Stepwise discriminant analyses were performed with both forward and backward selection of variables. Thus, at each step the variable which added the most to the separation of the groups was entered into (or the variable that added the least was removed from) the discriminant function.

According to Tatsuoka (1970), when one performs a discriminant analysis, "the total sample size should be **at least** two or (preferably) three times the number of variables used...[and] the size of the smallest group [must] be no less than the number of variables used". (p. 38). This combined sample included 29 MID cases and 35 DAT cases, and might have allowed for the introduction of 9 independent variables, using Tatsuoka's criteria. However, I decided to follow the more cautious recommendations of Morrison (1990), who demands only 1 variable be used for each 15 subjects' data.

This was done to ensure that the discriminant coefficients, which are strongly effected by sample size, would be consistent when applied to future samples. Thus, only 3 - 4 variables were included in each discriminant analysis.

The two discriminant functions included variables assessing verbal skills and visuospatial skills, as in Phase 1. Further, in Phase 1, level of severity of the dementia was found to be an extremely important aspect of DAT and MID patients' behavior. Therefore, MMS score was also entered into each of the discriminant equations.

Verbal Tests. One criterion of discriminant analysis is that predictor variables not be highly correlated with one another (Montgomery, 1976). I was curious regarding two of the variables I intended to include in the analysis: Fuld O.M.E. recall score and Fuld O.M.E. hits on recognition. Logically, these two variables should be highly negatively correlated, as the subject is only asked to recognize ("hit") items he/she has not been able to recall spontaneously after a 30 minute delay.

Closer inspection of the data revealed that many patients in the combined sample neither recalled any items nor recognized any from a multiple-choice format. Thus, a distribution skewed towards zero was created within the data for the Fuld O.M.E. delay tasks. The nine subjects with scores of zero on both Fuld O.M.E. Recall and Fuld O.M.E. hits on recognition were removed, and a normally-shaped distribution was observed in the data. Therefore, these 9 subjects' data were removed from subsequent analyses.

These two variables were then found to be related (with a Pearson Product moment correlation of -.44). Since this relationship did not explain more than 20% of

the variance between the Fuld O.M.E. Recall and Fuld O.M.E. hits on recognition, it was deemed acceptable to simultaneously enter both variables into the discriminant equation (Morrison, 1990).

The discriminant function for the combined sample using MMS and four verbal tests was highly significant at $p < .001$ [$\lambda_{(5)} = 21.9$], with Y = (0.19 x Mini Mental State score) + (0.006 x Boston Naming score) + (0.021 x Fuld O.M.E. Recall score) - (0.007 x Fuld "hits" on recognition) - (0.18 x WAIS-R Vocabulary Age Scaled Score) - 2.65. This function correctly classified 74% of the subjects in this sample. Eight of the 29 MID and 7 of the 35 DAT patients were misclassified.

Standardized canonical discriminant function coefficients demonstrated the relationship between these variables and the diagnostic classification of DAT and MID patients (compensating for the different test scales) to be as follows: (0.89 x MMS) + (0.46 x Fuld O.M.E. recall score) + (0.82 x Boston Naming Score) - (0.51 x WAIS-R Vocabulary Age Scaled score) - (0.02 x Fuld hits on recognition).

These functions indicate that a low score on the Mini Mental Status examination, recalling few items after a 30 minute delay on the Fuld Object Memory Evaluation, having difficultly naming objects on the Boston Naming test, and high scores on the WAIS-R Vocabulary test were all related to being diagnosed as DAT instead of MID. The Fuld O.M.E. hits score (recognizing Fuld O.M.E. items not recalled after the delay), did not add a significant amount of new information to this differential equation.

Visuospatial Tests. The discriminant function for the combined sample using MMS and three visuospatial tests was statistically significant, as well, at $p < .01$ [$\lambda_{(4)}$

= 17.7], with Y = (0.26 x Mini Mental State score) + (0.0071 x Trail Making A score) + (0.0046 x WAIS-R Picture Completion Age Scaled score) + (0.068 X WAIS-R Block Design Age Scaled score) - 6.57. This function correctly classifies 78% of the subjects in this sample, with 5 of the 25 DAT and 5 of the 21 MID cases being misclassified.

Standardized canonical discriminant function coefficients demonstrated the relationship between these variables and the diagnostic classification of DAT and MID patients (accounting for the different test scales) to be as follows: (1.18 x MMS) + (0.62 x Trail Making A score) + (0.04 x WAIS-R Block Design Age Scaled score) - (0.033 X WAIS-R Picture Completion Age Scaled score).

These functions indicate that a low score on the Mini Mental Status examination and Trail Making A increased the likelihood that an individual's performance would be scored as consistent with DAT. The WAIS-R Block Design and Picture Completion test scores did not add a significant amount of new information to the discriminant function.

Probability of DAT Given These Discriminant Functions

The probability that an individual patient has DAT given the presence of this study's verbal and visuospatial markers, is possible to estimate. The patients involved in the present research were selected from a dementia clinic where the incidence of dementia in referrals is 70% (i.e., 7/10 new cases sent to this clinic are diagnosed as having some form (or forms) of dementia, and 3/10 new cases are diagnosed as having a non-dementing disorder, such as depression) (Satz et al., 1987). Further, the best estimate of DAT in this setting has been calculated (using Baye's theorem) to be .53 [P(DAT) = P(dementia) x P(DAT\dementia)].

Estimates of the prevalence of DAT in the general population range from 6% to 30% with a mean base rate of occurrence of approximately 25% (Cummings & Benson, 1983; Satz et al., 1987). The probability of a positive diagnosis, given DAT from this study is: P(+\DAT) = 34/40 = .85. (That is, 34 of the 40 patients previously diagnosed as having dementia of the Alzheimer's type were correctly classified by either the verbal or the visuospatial function). Further, the probability of incorrectly describing someone as having DAT, although that person has an MID diagnosis is P(+\MID) = 10/31 = .31. (That is, 10 of the 31 patients previously diagnosed as having Multi-infarct dementia were incorrectly classified by either the verbal or the visuospatial function as having DAT). These values permit the determination of the conditional (posterior) probabilities of the discriminant functions as follows:

$$P(DAT\backslash +) = \frac{P(DAT) \times P(+\backslash DAT)}{P(DAT) \times P(+\backslash DAT) + P(\text{non-DAT}) \times P(+\backslash \text{non-DAT})}$$

$$= \frac{(.15)(.53)}{(.15)(.53) + (.85)(.31)}$$

$$= 0.23$$

Thus, only 23% of individuals who have positive findings on the discriminant equations will be diagnosed as having DAT. This seems extremely low. However, this equation allows persons who have no diagnosis of dementia to be included in the analysis.

The ultimate test is whether these discriminant equations improve on the diagnostic classification using base rates alone. Further, if the battery is applied to only

cases of dementia with diverse though unknown etiologies, the probability of DAT [P(DAT\Dementia)] would be approximately .75 (Cummings & Benson, 1983; McKahn et al. 1984; Satz et al., 1987). This base rate of DAT is much higher than the empirical value from the Dementia Clinic at UCLA [P(DAT) = .53] because the incidence of dementia is 100% rather than 70%.

Thus, the probability of an individual case being correctly detected as DAT if that individual had positive discriminant function signs would be:

$$P(DAT\backslash +) = \frac{P(DAT) \times P(+\backslash DAT)}{P(DAT) \times P(+\backslash DAT) + P(\text{non-DAT}) \times P(+\backslash \text{non-DAT})}$$

$$= \frac{(.75)(.85)}{(.75)(.85) + (.25)(.31)}$$

$$= 0.89$$

The base rate of detection of DAT given a firm diagnosis of dementia is presently 0.80 (Satz et al., 1987). Thus, use of the neuropsychological tests performed in my study, and subsequent use of the discriminant functions derived from those tests, increases the accuracy of the differential diagnosis by approximately 10%.

DISCUSSION

The primary finding in my investigation is that when used together in a battery of either verbal or visuospatial tests (which includes a measure of severity), between 74% and 78% of patients with DAT can be differentiated from those with MID. However, not one of the neuropsychological tests used in this study could, independently, differentiate patients with Alzheimer-type dementia from those with multi-infarct dementia when the effects of severity were removed. If the results of the present study are applied to classifying patients known to suffer from dementia, 89% of the persons with Alzheimer's disease will be detected accurately as having DAT when using these discriminant functions.

These results are exciting, as these neuropsychological tests are both noninvasive, economical, and improve on clinical diagnoses by 10%. Thus, they may be used in various clinical settings where the risk of dementia is high, to augment other clinical laboratory techniques.

The present research used cases which were relatively clean of contaminants. In other words, only files in which stringent criteria were met which excluded patients with other disorders which might effect their dementia evaluation were used. Also, diagnoses must have been agreed upon by at least two of three highly skilled diagnosticians. Thus, it was expected that the results would exceed the precision of a typical antemortem clinical diagnosis in separating DAT from MID. Further, only cases where a unique diagnosis of either DAT or MID were included in the present study - even though the joint occurrence of these two disorders is relatively common (Cummings, 1985). Future

investigations of this sort are necessary to precisely define Alzheimer's disease, and aid in its early detection. [However, in the absence of autopsy information, the possibility of DAT (or mixed MID/DAT) cannot be ruled out].

These results have important implications for future clinical diagnoses and research. A relatively brief battery of tests (requiring less than an hour to administer to a demented individual, and including the Mini Mental State examination, Boston Naming, the Vocabulary subtest of the WAIS-R, the Fuld Object Memory Evaluation, and Trail Making A) provided a quantitative method for differentiating DAT patients from those with MID. Dawes, Faust and Meehl (1989) suggest that actuarial (or quantitative) methods are much more accurate than clinical judgment when attempting to label a specific case. Certainly, the battery of tests proposed to perform this task by the present research would be more time- and cost-efficient than the extensive examination regimens currently employed to differentiate MID from DAT patients, which involve extensive physical and neurological examination (and require anywhere from 2 days to 2 weeks to complete). However, the aim of this research is not to replace the thoroughness of the current diagnostic procedure, but rather, to assist physicians in making a decision between diagnoses of MID and DAT when the physical data are unclear.

If these results can be replicated on a larger sample, they offer special promise in the use of these measures in the early detection and differential diagnosis of DAT. A follow-up study involving the reapplication of the discriminant functions to a new sample of dementia patients is necessary to ensure the validity of the specific weights applied to each test score. Further, this type of reapplication would allow a calculation

of sensitivity and specificity of the differential diagnoses, using the discriminant equations.

My research did not achieve more accuracy than any previous method, in separating DAT from MID cases. Fuld's (1984) WAIS profile offers an even higher degree of precision (Satz et al., 1987) by accurately classifying half of the patients referred to the UCLA Dementia Clinic and 99% of patients diagnosed as having some form of dementia. However, Fuld's sample was not as stringently screened, nor was a control for severity level employed. Thus, her findings may reflect differences in severity of dementia, which was the most significant difference between groups in the present study. Other authors have also been less positive about the diagnostic utility of Fuld's WAIS profile for distinguishing these two groups (Filley, Koyabashi, & Heaton, 1987). Future research may wish to incorporate Fuld's important WAIS-R subtests as well as the tests shown in this study, and assess the relative utility of each in accurately differentiating between MID and DAT. However, even though the present study used tests of differential functioning, 11% of DAT cases were incorrectly classified as having MID.

Within Group Variability

One hypothesis which has been proposed by Whitehouse (1986) to account for the difficulty in differentiating DAT patients from those with MID, is that within group differences (e.g., between vascular dementias) are often just as significant as between group differences (i.e., between DAT and MID). Thus, he challenged the contention that dementias can be subdivided into the two categories of DAT and MID.

There has also been growing evidence to support the division of vascular dementia into at least two subgroups: Cortical atherosclerotic dementia (CAD), and Subcortical atherosclerotic dementia (SAD) (Chui, 1989). These distinctions are based on the size and location of infarcts observed on CT scans.

Cortical atherosclerotic dementia is associated with cerebral cortical infarction of the large feeding vessels (e.g., carotid and cerebral arteries). SAD, on the other hand, refers to infarction or ischemia due to atherosclerosis of the medium-sized and small penetrating intracerebral arterioles (i.e., lenticulostriate and deep medullary arteries). SAD also encompasses two syndromes known as lacunar state and Binswanger's subcortical arteriosclerotic encephalopathy, which are differentiated by virtue of discrete infarcts in the former and more diffuse incomplete infarctions in the latter; however, the two syndromes of SAD often coexist and share common pathogenetic features (Chui, 1989).

Liston and La Rue (1983) note there is no certainty regarding the pathogenesis, nor the size, number, and location of cerebrovascular lesions which cause dementia. Still, some authors have taken to sorting their samples of vascular dementia patients by size and location of infarcts (Rao et al., 1989). For example, Frackowiak et al. (1981) demonstrated that the frontal regions of MID patients consistently showed less pathological involvement than did the brains of DAT patients.

Thus, future studies attempting to accurately differentiate between MID and DAT might include evaluation of the CT or MRI scans of MID patients. Then these cases might be divided by the areas of greatest involvement (i.e., largest and/or most numerous

infarcts). Orsini, Van Gorp, and Boone (1988) note that multi-infarct dementia, by definition, varies in severity and clinical presentation - depending on where the infarctions occur - and remind future researchers that it will be very difficult to establish one neuropsychological pattern that characterizes MID, unless the size and location of infarctions are considered. Pawlik and Heiss (1989) believe that the distinction between MID and DAT can be achieved best if positron emission tomography (PET) is used in lieu of CT or MRI scanning.

Technological Advances

PET. Positron emission tomography permits the quantification and three-dimensional imaging of distinct physiological variables, and allows for a dynamic analysis of brain functioning. This is accomplished by using radioactive isotopes and observing the glucose metabolism or oxygen consumption, of various portions of the brain (Pawlik & Heiss, 1989). Thus, like neuropsychological testing, PET scans indicate brain function, as opposed to structure (as in CT scans).

However, PET scan technology is in its infancy, and very few units are now in operation (partly, because of their present high cost). Further, Pawlik and Heiss (1989) note there are a variety of problems with PET studies. One problem involves unstandardized anatomic localization on functional images, and little validity to permit quantification of results. Also, PET scans necessitate high procedural standards to assure interpretability of results, and have a large margin of error. Still, this apparatus may prove very useful in the future, for delineating dementias such as DAT and MID.

MRI. Various authors (e.g., Hachinski et al., 1975; Rosen, Terry, Fuld,

Katzman, & Peck, 1980) believe that MID and DAT can now be distinguished at a reasonably high level of accuracy when the patient's history, focal neurological and neuroimaging findings are put into proper perspective. For example, magnetic resonance imaging (MRI) scans are much more sensitive to white matter changes, than are CT scans (Pawlik & Heiss, 1989), and thus hold great promise (in Hachinski's and Rosen et al.'s opinions) in separating these two disorders.

However, as noted in the introduction to this research, great controversy surrounds the relationship between white matter lucencies [leukoariosis or white matter low attenuation (WMLA)] and MID. Although some authors contend WMLA's are strongly related to MID (e.g., Erkinjuntti, 1987; Kohlmeyer, 1982; Molsa et al., 1985), others have stated that periventricular lucencies do not substantially help in the differential diagnosis of MID from DAT (e.g., London et al., 1986; Wallin et al., 1989). Furthermore, cognitive deficits have not been found to be related to the presence or absence of WMLA's (e.g., Brant-Zawadzki et al., 1985; Rao, 1989).

Therefore, at present, advances in neuroimaging techniques may eventually help us better differentiate MID from DAT by better delineating the size, numbers and locations of the MID infarcts. However, the mere presence or absence of infarcts or WMLA's appear to be less strongly related to differential diagnosis.

Clinical Diagnoses

Much of the previous research in this area has relied upon clinical diagnoses to accurately categorize subjects for subsequent differential analyses. Liston and La Rue (1983b) argued that an established set of clinical features that can practically, reliably,

and validly be applied antemortem to distinguish between DAT and MID, does not yet exist. They go on to recommend histopathological verification of diagnoses, although they note that even those studies using pathological correlation have produced inconsistent and contradictory findings.

Given the lack of resources or time available to this investigator to perform a study using autopsy verification, the problem of questionable original categorization was addressed by having three independent evaluations of each of the cases (the original clinic physician, and two subsequent neurologists).

Given that the original sample was selected based upon stringent exclusion criteria, and the fact that each patient in that sample had a firm diagnosis of only one form of dementia, the correlation between our raters was expected to be extremely high.. However, on reexamination of the files, the neurologists disagreed with one another or the file diagnosis in 31% of the cases. Further, in 10% of the cases, each of the three diagnoses was completely different!

This is an especially remarkable finding when considering that the original file diagnoses were made at UCLA's Dementia clinic - a facility which specializes in the diagnosis and treatment of such patients. Thus, the level of expertise involved in these original diagnoses would have been higher than if subjects had been drawn from a general hospital or other facility in which fewer cases of DAT and MID are regularly seen.

Thus, the reliability of clinical diagnoses is questionable, even when these diagnoses are based on clinical, laboratory, and neuroimaging evidence, and are based

on cases with stringent exclusionary criteria. This concern is relevant when evaluating previous research in this area, and in planning future investigations. Moreover, it speaks to the need for an actuarial method such as attempted in the present research (as opposed to one involving clinical judgment) for differentiating MID from DAT. However, as noted by Cicchetti (1988), I am in a better position to report my data, statistical analyses, and interpretations with confidence, as diagnoses of the cases were agreed upon by independent raters.

Level of Severity

Although the necessity to control for level of severity is, by now, well documented (e.g., Liston & La Rue, 1983; Huber et al., 1989), studies involved in the differentiation of MID and DAT are still lacking in this very important area. The small sample sizes observed in most research of this nature is part of the problem (e.g., 10 or 12 cases of each form of dementia). In studies where control for severity exists, investigators have commonly matched subjects on the basis of certain clinical and demographic variables. The validity of such matchings is often suspect.

In one recent study which attempted to compare Alzheimer dementia with Parkinson's dementia (PD), Huber et al. (1989) found their sample of 144 DAT patients had mean MMS scores of 14.3, as compared to 22.8 for those with PD. Therefore, they selected patients with DAT whose scores were above the lowest score in the PD group (MMS = 11) and patients with PD whose scores were lower than the highest score for those with DAT (MMS = 23). Then, their sample included 9 DAT subjects with a mean MMS = 17.1 (s.d. = 1.5) and 10 PD subjects with mean MMS = 19.7 (s.d. = 1.3).

Huber et al. (1989) reported these two groups as "not significantly different". However, a reanalysis of their data using a t-test for independent means (J. Lind, personal communication, March 9, 1990), reveals them to be significantly different at $p < .05$ [$t(17) = 4.1$, as opposed to $t(17) = 1.4$, as they reported]!

Thus, the Huber et al. (1989) research recognized the need to control for level of severity in their small sample of dementia patients by matching subjects on their Mini Mental Status Exam scores. However, the results of Huber et al.'s study are erroneous, as the patients with Parkinson's dementia were significantly more severely debilitated than those with Alzheimer's disease. Future research in this area needs to carefully match dementia patients with similar severity, to elucidate variations due to differing etiologies of dementia from those due to different levels of progression of the disorder. Additionally, the greatest practical and clinical utility will be obtained if differentiation of mildly demented individuals can be accomplished. Thus, future studies might focus on this section of the dementia population.

Neuropsychological Testing and Dementia Patients

The idea of a simple scale to assist in differential diagnosis is an appealing one, partly because a numerical score gives the impression of quantitative measurement. However, despite many attempts at its creation (e.g., Hachinski et al., 1976; Fuld, 1980), such an instrument does not yet exist.

The present research is the best attempt to date in developing a brief, comprehensive battery involving a screening instrument, to detect severity and various other tests to assess relevant cognitive domains (e.g., memory, language, attention, and

motor skills). However, a more extensive battery might aid in the categorization of patients, still misclassified by this set of tests.

Frontal tests. For example, the present study did not include tests of organization, categorization, abstract reasoning or judgment. If, as purported by Frackowiak et al. (1981) the frontal regions of MID patients demonstrate much less pathology than do those of DAT patients on PET analyses, then neuropsychological tests which assess the function of the frontal lobes (i.e., organization and reasoning) might add a great deal to attempts at differential diagnosis.

Meeting the Assumptions of Statistical Analyses. The questions investigated by neuropsychological research often produce problems for the researcher such as small sample sizes, a wide range of variability on many of the measures, incomplete data, and skewed distributions (Lezak & Gray, 1984). These problems must be addressed if parametric statistical analyses are used. Unfortunately, few investigators report the distributions of their data. Rourke (1988) describes some investigators as acting as though computer programs were new toys, such that they "feel obliged to apply them to any data set that is available", regardless of the assumptions necessary to correctly employ such analyses.

The present study highlights the importance of including tasks on which normal distributions of patients' scores occur. Many subjects' data had to be eliminated from analyses in this study because of missing data. This was caused by MID and DAT patients' inability to perform certain tests (e.g., Trail Making B, WAIS-R Block Design, WAIS-R Picture Completion, and Wechsler Memory Scale Visual Reproduction). The

scores of subjects who did complete Block Design and Picture Completion formed normally shaped distributions.

Further, tests included in the present study which were originally developed for an elderly population, or had been administered to a normative sample of elderly persons, were found to produce a normally-shaped distribution of data from dementia subjects (e.g., Boston Naming, Fuld Object Memory Evaluation, Mini Mental State).

However, it is important to check the distributions of data on each neuropsychological test when evaluating dementia patients. In the present study, recall and recognition scores on the Fuld O.M.E. - logically - should have been negatively correlated. (Subjects were only offered the opportunity to recognize words they had not spontaneously recalled). When almost no correlation was found between these scores in the combined sample of Phase 2, the data from these tests were plotted, and closely scrutinized. A small percentage of subjects with scores of zero on each test greatly affected the correlation between these two subtests (i.e., zero scores included, $r = -0.9$; zero scores excluded, $r = -0.44$).

Using the uncorrected values of Fuld O.M.E. recall and recognition could have affected the discriminant function coefficients so extensively that certain tests which were actually especially useful in categorizing patients might have appeared insignificantly related to this differentiation. Or, conversely, tests which actually do not add much information to the differentiation of DAT from MID patients might have appeared quite significant.

Discriminant function coefficients are quite susceptible to problems in insufficient

sample size. Some previous research has allowed a large number of predictor variables to be applied to a small sample of subjects (e.g., Perez et al., 1975). Although easy to use computer programs make this kind of error a temptation, the validity and reliability of the results is almost certainly compromised by such an approach.

The present research was unable to examine the relative usefulness of verbal tests in relation to visuospatial tests, given the limited sample size in this study. However, relative certainty can be placed on the strong contribution of MMS, Boston Naming, Fuld O.M.E. Recall, Vocabulary, and Trail Making A scores in differentiating DAT from MID patients. Similarly, tests such as Block Design, Picture completion and "hits" on the Fuld O.M.E. recognition task, do not significantly separate these two groups.

There is no question that cases of dementia which are caused by multiple (small or large) areas of infarction may result in progressive intellectual impairment (Liston & La Rue, 1983). Neither, is there any debate regarding the insidious progressive cognitive decline of patients with Alzheimer's disease. However, debates do occur when attempting to assert that either of these disorders occurs in complete isolation from the other.

The present research points to the significant ability of neuropsychological tests to assist in differentiating these two diagnostic groups. Moreover, discrimination between MID and DAT will improve when controls are employed for level of severity; size, location and number of infarcts; and with assurance that original diagnoses are accurate (either through multiple independent diagnoses or histopathological confirmation). A neuropsychological battery which assesses domains demonstrated to

produce the greatest differences between MID and DAT patients, while also including tests that most dementia patients can perform, will further facilitate the differentiation process. Finally, accurate use of statistical analysis is imperative for accumulation of valid and reliable data regarding differences between MID and DAT.

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Appendix A

Ischemic Score

Finding	Score
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional lability	1
History of hypertension	1
History of strokes	2
Associated atherosclerosis	1
Focal neurological symptoms	2
Focal neurological signs	2

Appendix B

Fuld Object Memory Evaluation

Cat. No. 33925R Record Form
Form I, FULD OBJECT-MEMORY EVALUATION

Subject's name: _____ Date: _____

Hand Order	OBJECT-NAMING ORDER (record)	ITEM	NAMING Touch	NAMING Vision	Trial 1 __sec.	Trial 2 __sec.	Trial 3 __sec.	Trial 4 __sec.	Trial 5 __sec.
1-L		Ball							
2-R		Bottle							
3-R		Button							
4-L		Card							
5-L		Cup							
6-R		Key							
7-R		Matches							
8-L		Nail							
9-L		Ring							
10-R		Scissors							
(1) STORAGE									
(2) RETRIEVAL									
(3) REPEATED RETRIEVAL (+, +)									
(4) INEFFECTIVE REMINDER (−, −)									

INTRUSIONS:

Rapid Verbal Retrieval

	NAMES 60	FOODS 30	HAPPY 30	VEGETABLES 30	SAD 30
1	21	1	1	1	1
2	22	2	2	2	2
3	23	3	3	3	3
4	24	4	4	4	4
5	25	5	5	5	5
6	26	6	6	6	6
7	27	7	7	7	7
8	28	8	8	8	8
9	29	9	9	9	9
10	30	10	10	10	10
11	31	11	11	11	11
12	32	12	12	12	12
13	33	13	13	13	13
14	34	14	14	14	14
15	35	15	15	15	15
16	36	16	16	16	16
17	37	17	17	17	17
18	38	18	18	18	18
19	39	19	19	19	19
20	40	20	20	20	20
TOTALS					

Cat. No. 33925R
Stoelting Co., Chicago, IL 60623

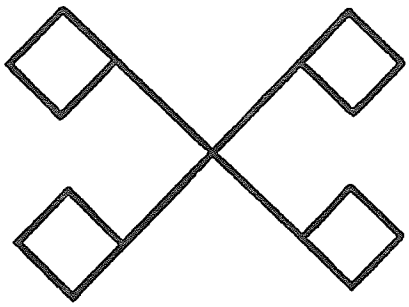
	RECALL		RECOGNITION	
Ball		Stone	Block	Ball
Bottle		Light Bulb	Bottle	Box
Button		Coin	Buckle	Button
Card		Photograph	Card	Stamp
Cup		Spoon	Saucer	Cup
Key		Key	Can Opener	Nail File
Matches		Lighter	Toothpick	Matches
Nail		Nail	Screw	Pencil
Ring		Bracelet	Ring	Thimble
Scissors		Scissors	Knife	Pliers

TOTAL RECALLED _____ + **TOTAL RECOGNIZED** _____ = **RETENTION ESTIMATE** _____

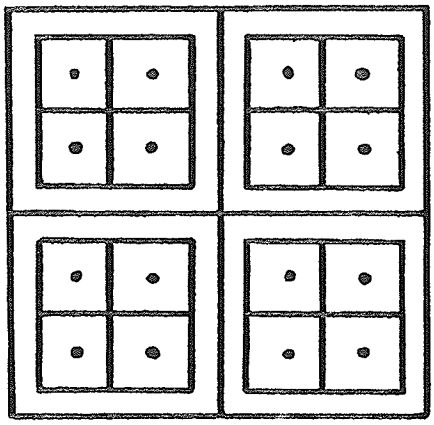
Appendix C

Wechsler Memory Scale

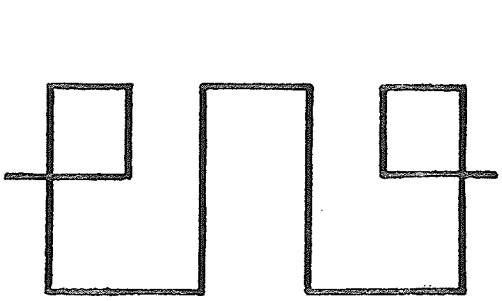
Visual Reproduction Designs

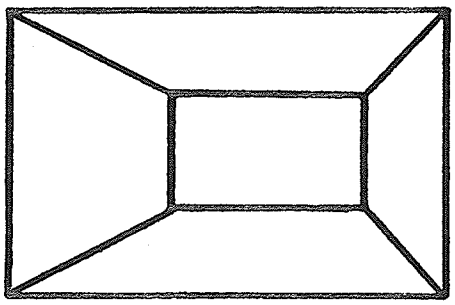


Card A
W-M-S I



Card B
W-M-S I





rd C
M-S I

Cut this sheet on the lines to make the three cards for the Wechsler Memory Scale Form I

50 51 52 53 54 55 56 57 58 59 60 A B C D E

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Appendix D

Neurologists' Checklist

Dementia of the Alzheimer Type

___Insidious onset
  ___Onset between ages 40 and 90

___No disturbance of consciousness

___Dementia present
  ___Established by clinical exam
  ___Documented by Folstein MMS, Blessed, or similar exam

___Progressive loss of memory and cognitive functions
  ___Progressive loss of specific cognitive functions
  ___Deficits in ≥ 2 areas of cognition
    ___Memory Difficulties
      ___Forgets events/conversations
      ___Repeats him/herself
      ___Unaware of deficits
    ___Word Finding difficulty
      ___paraphasias
      ___aphasic
      ___mute
    ___Visuospatial difficulties
      ___Perceptual misjudgment
      ___Difficulty driving/walking
      ___Becomes lost/disoriented in familiar places
  ___Plateaus in course of progression of illness

___Absence of systemic disorders or other brain diseases that in and of themselves, could account for deficits
  ___Normal LP
  ___Normal or nonspecific changes on EEG

___CT - progressive cerebral atrophy documented with serial observations
  ___CT normal for age
  ___Enlarged ventricles
  ___No focal lesions

___Cognitive decline sufficient to effect social & occupational functioning
  ___Impaired ADL's and altered behavior patterns
    ___Weight loss
    ___Nocturnal confusion
    Personality alterations:
    ___Apathy
    ___Depression
    ___Emotional incontinence
    ___Hallucinations
    ___Delusions

___Family history of similar disorders
  ___Confirmed by neuropathological evidence

Multi Infarct Dementia

___Abrupt onset

___Stepwise deterioration

___Fluctuating course

___Patchy distribution of deficits

___Personality alterations:
  ___Apathy
  ___Depression
  ___Emotional incontinence
  ___Hallucinations
  ___Delusions

___Focal neurological signs & symptoms
  ___Exaggeration of deep tendon reflexes
  ___Dysarthria
  ___Extensor plantar response
  ___Pseudobulbar palsy
  ___Gait abnormalities
  ___Weakness of an extremity
  ___Other:_____

CT
  ___Multiple lesions
  ___No unusual enlargement of ventricles

___Significant cerebrovascular disease
  ___from history
  ___from physical exam
  ___from laboratory tests

___Sudden appearance of new deficit
  Describe:_____

_____

Other form of dementia

___Evidence from laboratory tests or the history of a specific organic factor that is judged to be etiologically related to the disturbance

___Movement disorder present (e.g., Parkinsonian)

___Inappropriate/uncharacteristic behavior preceding onset of memory disturbance

___Dysphoric mood and/or anhedonia which is prominent & persistent

Appendix E

Mini Mental Status Exam

I. Orientation:

Ask: "What is today's date?" (Then ask specifically for parts omitted, e.g., "Can you also tell me what season it is?").

Ask: "Can you tell me the name of this clinic (hospital)?" "What floor are we on?" "What city (town) are we in?" "What country are we in?" "What state are we in"

II. Registration:

Ask the subject if you may test his/her memory. Then say, "ball", "flag", and "tree" clearly and slowly, about one second for each. After you have said all three, ask him/her to repeat them. This first repetition determines the patient's score (0 - 3) but keep saying them until he/she can repeat all 3. If after 6 trials, he/she does not learn all 3, recall cannot be meaningfully tested.

I. Orientation

1.Date....._____

2.Year....._____

3.Month....._____

4.Day....._____

5.Season....._____

6.Clinic....._____

7.Floor....._____

8.City (town).._____

9.County....._____

10.State....._____

II. Registration:

11.Ball....._____

12.Flag....._____

13.Tree....._____

III. Attention and Concentration:

Ask the subject to begin with 100 and count backwards by 7. Stop after 5 subtractions (93, 86, 79, 72, 65). Score the total number of correct answers. If the subject cannot or will not perform this task, ask him/her to spell the word "world" backwards. The score is the number of letters in correct order. For example: dlrow = 5, dlorw = 3. Record how subject spelled "world" backwards.

III. Attention and Concentration

15. 93....._____

16. 86....._____

17. 79....._____

18. 72....._____

19. 65....._____

20. "WORLD" backwards (DLROW)....._____

***Only score item 20 if items 15 through 19 are blank

IV. Recall:
Ask the subject to recall the 3 words you previously asked him/her to remember. Score 0 - 3.

V.Language:

Naming: Show the subject a wrist watch and ask what it is. Repeat for pencil.
Repetition: Ask the subject to repeat, "No ifs, ands, or buts".
3-Stage Command: Give the subject a piece of plain blank paper and say, "Take the paper in your right hand, fold it in half and put it on the floor."
Reading: On a blank piece of paper, print the sentence, "Close your eyes" in letters large enough for the subject to see clearly. Ask him/her to read it and do what it says. Score correct only if eyes are closed.

IV. Recall
21.Ball....._____
22.Flag....._____
23.Tree....._____

V. Language:

24.Watch....._____

25.Pencil....._____

26.Repetition.._____

27.Takes paper in right hand.._____

28.Folds paper in half....._____

29.Puts Paper on floor....._____

30.Closes eyes._____

V.Language (cont).

Writing: Give the subject a blank piece of paper and ask subject to write a sentence. It is to be written spontaneously. It must contain a subject and verb and be sensible. Correct grammar and punctuation are not necessary.

Copying: On a clean piece of paper, draw intersecting pentagons, each side about 1 inch, and ask subject to copy it exactly as it is. All 10 angles must be present and two must intersect to score 1 point. Tremor and rotation are ignored.

V. Language (cont).

31.Writes Sentence....._____

32.Draws pentagons....._____

TOTAL SCORE

All items except number 14 and 20 are each scored 1 if correct and 0 if incorrect. Item 20 is scored 0 - 5. The total score is the sum of items 1 through 32 excluding #14.

T O T A L

SCORE...._____