Errors of Omission and Commission in Distinguishing Patients with Dementia of the Alzheimer-type and Patients with the Dementia Syndrome of Depression

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We accept this thesis as conforming to the required standard

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ABSTRACT

Dementia is characterized by a progressive decline in intellectual, memory and other cognitive functions. Alzheimer's disease (DAT) is the most prevalent cause of dementia in later life. Memory impairment may be the first symptom to herald the onset of the disease. The dementia syndrome of depression (DEP) may also be associated with a memory impairment which may masquerade as dementia in the elderly. Thus both types of patients may present with memory problems; DAT patients may also experience concomitant depression, and the distinction between DAT and DEP patients may be a difficult one. The current criteria for the diagnosis of DAT are generally exclusionary, that is, other possible causes of the dementia need to be ruled out before making the diagnosis. Therefore, the identification of a neurobehavioral marker for DAT could increase diagnostic accuracy by reducing the overall error rate. Alterations in neurotransmitter systems have been found in neurologic and psychiatric conditions Decreased cholinergic functioning has been associated with DAT while disruption of the noradrenergic system has been postulated in depression. Recurrent perseverations, the inappropriate repetition of a previous stimulus or response into a current response, have been associated with cholinergic system dysfunction (Fuld, 1982). Continuous perseverations, the inappropriate repetition of aspects of the current response, have been associated with noradrenergic functioning (Sandson & Albert, 1987). Thus, a qualitative scoring of memory tasks for the presence and types of perseverative errors may serve to increase diagnostic accuracy. In particular, we hypothesized that scoring errors of commission as well as errors of omission could be used to classify subjects into diagnostic groups. Additionally, we hypothesized that the DAT group would make a higher proportion of recurrent perseverations than the DEP group, while

the DEP group would make a higher proportion of continuous perseverations. Data from one verbal and one visual subtest of the Wechsler Memory Scale (WMS, Wechsler, 1945) from 49 DAT patients and 39 DEP patients were rescored for the presence of both errors of omission and errors of commission. These error scores were used in a discriminant function analysis with 85 percent correct classification overall. Commission errors were also scored for the type of error, i.e. recurrent or continuous. Proportion scores were derived for the number of each type of perseverative error to the total number of perseverative errors. A multivariate analysis of variance on the proportion scores demonstrated that the DAT group produced a higher proportion of recurrent perseverative errors than did the DEP group. Further, the DEP group produced a higher proportion of continuous perseverations than did the DAT group. Results were discussed in relation to possible underlying mechanisms.

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Dedication

This dedication is intended to honour someone who holds a special place in my heart. Although it is difficult to express in words, my heartfelt gratitude belongs to my father. He has continually inspired me to strive to achieve my goals and has always provided encouragement to do so. I will be eternally grateful.

Introduction

Dementia is defined as an acquired progressive impairment in two or more areas of cognitive function (Moss & Albert, 1988). Cummings and Benson (1984) report that mild to moderate dementia affects between 2.6 to 15.4 percent of the population over the age of 65. The definition does not imply a specific etiology and indeed, there may be many causes of dementia including Alzheimer's disease (AD) and depressive disorders (depressive pseudodementia, Caine, 1981). AD is thought to account for between 50 percent to 70 percent of all dementias (Kaszniak, 1986). As such, it accounts for the greatest proportion of dementia in old age. Depression is estimated to affect an estimated 3 to 7 percent of the population over a lifetime (King & Caine, 1990), and the "incidence and prevalence (of depression) is highest in the age group 55-70" (Lipton, 1976, p. 293). It is the major affective disorder in the elderly (Schatzberg, Liptzin, Satlin & Cole, 1984). Folstein and McHugh (1978) estimated that approximately half of depressed elderly patients exhibit cognitive impairments similar to patients with an organic dementia. Similarly, Reynolds, Perel and Kupfer (1987) found that in more than one third (6/16) of their patients with both symptoms of depression and cognitive impairment, effective treatment of the depression resulted in resolution of the cognitive impairments as well. Thus, a large proportion of the elderly population may experience cognitive difficulties due to dementia of the Alzheimer type, depression, or both.

Additionally, the symptoms of dementia and depressive pseudodementia may overlap substantially (Post, 1975; Siegfried, 1989;

Teri & Wagner, 1992). Both groups of patients may present for a neuropsychological evaluation with reported memory impairments. Also, AD patients may concomitantly experience depressive symptoms (Cummings & Victoroff, 1990; Lopez, Boller, Becker, Miller, & Reynolds, 1990), and the severity of the depressive symptomatology may be inversely related to the degree of dementia (Fischer, Simangi, & Danielczyk, 1990). Differentiating dementia syndrome of depression patients from patients with dementia of the Alzheimer type may pose a difficult diagnostic challenge. According to Reynolds and Hoch (1987) it is "one of the central clinical and experimental problems of geriatric psychiatry" (p.743).

The differentiation of patients with dementia of the Alzheimer type from patients with the dementia syndrome of depression through an examination of errors of omission and comission is the focus of this research project. Therefore, a brief review of the literature pertaining to the neuropathology and neurochemistry associated with Alzheimer's disease and depression will be highlighted. Additionally, the cognitive deficits associated with these disorders will also be reviewed. However, the main emphasis of the literature review will be on the proposed classification of perseverative errors and the production of these types of errors in the patient groups.

Alzheimer's Disease

Alzheimer's disease (AD) is a degenerative disorder characterized by a progressive decline in intellectual, memory and other cognitive functions. At present, a diagnosis of Alzheimer's disease is based on "elimination of all other known causes of intellectual impairment" (Moss & Albert, 1988, p.

152). That is, a gradual decline in memory and other cognitive functions must be documented with possible causes other than AD ruled out. The diagnosis can then be designated as "Probable"; a "Definite" diagnosis requires histopathological confirmation (McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984).

A major problem with the diagnostic process is that undetected causes of dementia may still be classified as Alzheimer's disease. Follow up studies have shown that the incidence of erroneous diagnosis may be as high as 31 percent (Ron, Toone, Garralda & Lishman, 1979). "A variety of reasons account for this difficulty, but the presence of functional psychiatric illness can be a principal source of error" (Ron, et al., 1979, p. 161). Indeed, in a three year prospective study of patients referred to a dementia clinic, 44 of 225 patients were found not to be demented. Of these nondemented patients, 31, or 70 percent, were diagnosed as depressed (Reding, Haycox, & Blass, 1985). Since the diagnosis of AD is primarily one of exclusion, the introduction of positive signs or symptoms might increase diagnostic accuracy. "Studies of DAT could profitably concentrate on delineating clinical functions that would allow positive identification rather than depending on current exclusionary criteria" (Cummings & Benson, 1984, p. 878). Therefore, a noninvasive, neurobehavioral marker for AD would be beneficial in reducing errors and increasing diagnostic accuracy (Tierney, Reid, Zorzitto, Snow, Fisher, Campbell-Taylor, & Lewis, 1986). The aim of the current investigation is to identify such neurobehavioral markers for dementia of the Alzheimer-type (DAT) and the dementia syndrome of depression (DEP).

Neuropathology

AD is considered a "cortical" dementia, with the characteristic presence of neurofibrillary tangles, plaques and granuovacuolar degeneration (Chui, 1989). Neurofibrillary tangles are contorted neurofibrils which preferentially occur in the pyramidal cells of the neocortex, the hippocampus and the amygdala (Cummings & Benson, 1983). Neurofibrillary plaques are "minute areas of tissue degeneration consisting of granular deposits and remnants of neuronal processes.... The plaques are concentrated in the cerebral cortex and hippocampus but also occur in the corpus striatum, amygdala, and thalamus" (Cummings & Benson, 1983, p. 50). The primary sensorimotor cortex is generally spared, but the "multimodal association cortex is highly prone to neurofibrillary degeneration" (Chui, 1989, p. 808). Granuovacuolar degenerations are clusters of intracytoplasmic vacuoles. The degeneration is "highly selective for the pyramidal neurons of the hippocampus" (Cummings & Benson, 1983, p. 51). Additionally, there is neuronal loss and astrocytic hyperplasia within the cortex (Cummings & Benson, 1983). The preponderance of degenerative changes within the hippocampus may be responsible for the initial symptom of memory disturbance seen in DAT.

Neurochemistry

Although it is considered a cortical dementia, it has also been shown that the neuronal population of the nucleus basalis of Meynert (NbM) is reduced by "70 percent" in AD and by "47 percent" in Korsakoff's syndrome. On the other hand, there is no marked loss of these neurons in Huntington's disease (HD) (Arendt, Bigl, Arendt, & Tennestedt, 1983). Thus, the NbM neuronal population is not reduced in all demented groups.

The NbM is the main source of cholinergic input to the cortex. Acetylcholine and choline levels are reduced in AD (Coyle, Price, & DeLong, 1983), "whereas enzymes involved in the synthesis or metabolism of other transmitters are relatively unaffected" (Cummings & Benson, p. 53). Postsynaptic acetylcholine receptors are not diminished in AD, suggesting the alterations reflect the dysfunction of the cholinergic projections from the NbM. The rather selective involvement of the cholinergic system has also been hypothesized to be a cause of the cognitive deficits of AD. "The degeneration of this discrete cholinergic neuronal population ... is probably directly related to the progressive deterioration of memory and other cognitive processes in affected patients" (Arendt et al., 1983, p. 101). Due to the preferential involvement of the cholinergic system in AD, some attempts to find a cognitive marker for AD have been based on cognitive impairments associated with cholinergic dysfunction in healthy control subjects. This literature will be reviewed in the following sections.

Experimental Studies

Drug studies have shown that anticholinergic drugs produced memory deficits in normal subjects for both verbal (Drachman, 1977; Drachman & Leavitt, 1974) and nonverbal (Meador, Moore, Loring, Zamrini, & Allen, 1991) material. In an early study, Drachman and Leavitt (1974) demonstrated a significant decrement in the cognitive performance of young normals treated with scopalamine, a cholinergic blocking agent. Subjects were assessed with the Wechsler Adult Intelligence Scale (WAIS, Wechsler, 1955), a verbal fluency task, and experimental measures of memory. For the verbal fluency task, subjects were asked to list orally as many words as

possible from a specific category, such as fruits. One memory measure, the supraspan digit storage test, used repeated presentations of three sequences of 15 digits until a perfect recall was achieved or for a maximum of five trials per sequence. Another measure, the free recall word storage test, used one of two equivalent 35 word lists for three learning trials; recall was written.

Scopolamine alone produced profound impairments of storage of digits and words, despite normal immediate span. Moderate impairment of semantic word retrieval was also observed on the verbal fluency task. Interestingly, the scopalamine treated subjects "often retrieved items from a different category after a brief time" (p.116). Additionally, Performance IQ (PIQ) and Full Scale IQ (FSIQ) were significantly impaired. Treatment with either methscopalamine (a peripherally acting scopalamine analog) or physostigmine (which allows acetylcholine to persist at synaptic sites) did not produced any significant changes.

Drachman (1977) replicated the previous results and further delineated a specific role for the cholinergic system in memory and intellectual functions. Young normals were administered scopolamine; some subjects were also administered physostigmine, or d-amphetamine, which interferes with the re-uptake of dopamine and norepinephrine but does not affect the cholinergic system. With the addition of physostigmine, there were significant improvements in word storage as well as PIQ and FSIQ. The addition of d-amphetamine, however, produced further impairments in word storage and a non-significant improvement in PIQ. These findings suggest that it is <u>specifically</u> the cholinergic system which is involved in the production of these cognitive and verbal memory deficits. Scopalamine has

also been shown to disrupt immediate and delayed visual memory in young normals on a complex figure test (Meador et al., 1991).

Neuropsychological Studies

Based on the findings of Drachman and colleagues, Fuld (1984) re-examined the data (Drachman & Leavitt, 1974) and developed a dementia profile for the WAIS, based on the performance of the young controls who had received scopolamine. The pattern developed was: A > B > C < = D, and A > D, where:

A (Information + Vocabulary)/2

B= (Digit Span + Similarities)/2

C= (Block Design + Digit Symbol)/2

D= Object Assembly

Substituting age corrected scaled scores into the formula, Fuld found that 10 of 19 (53%) drug subjects showed this profile while only 4 of 22 controls showed this pattern. In a clinical validation study, Fuld examined the occurrence of the profile in patients with a research diagnosis of AD, multi-infarct (MID) or mixed MID-AD dementia. She found that 9 of 15 testable AD patients (60%) exhibited the profile while only 1 of 15 non-AD patients exhibited the profile.

Brinkman and Braun (1984) found that 13 of 23 AD-type patients (57%) had a positive profile. In contrast, only 2 of 39 MID subjects had the profile. In both of these studies, however, the AD group was older than the MID group. Nevertheless, Satz, Van Gorp, Soper, and Mitrushina (1987) found that only 19 of 149 normal elderly subjects (12.8%) showed the pattern, and there was no correlation with increasing age.

The Fuld profile thus appeared to show some promise as a positive

marker for AD. Unfortunately, although the profile has generally been shown to have good specificity (few false positives), it has low sensitivity (few true positives). In a more recent study which used more rigorous criteria for the diagnosis of AD, only 13 of 53 AD-type subjects (24%) had a positive profile (Goldman, Axelrod, Giordanni, Foster, & Berent, in press). With continued progression of the intellectual decline, only 4 of the original 13 subjects who initially showed a positive profile, continued to show this profile. Five new subjects also showed the profile (17% altogether on retest). The authors concluded that the profile was not useful for accurate identification of AD. They state, "perhaps, a marker based on global intellectual functioning does not offer sufficient precision in detecting specific cholinergic mechanisms and their effects on cognition" (p.10).

Memory Testing

The memory impairments associated with cholinergic dysfunction may offer more precision in the early detection of AD. The earliest phase of AD has been termed the "forgetfulness phase" (Kaszniak, 1986) as memory disturbance is the most common symptom to herald the onset of the disease. "Difficulty with the acquisition of new information is generally the first and most salient symptom to emerge in the patient with AD" (Moss & Albert, 1988, p. 154).

AD patients have been shown to have a diminished immediate memory span relative to age matched controls for both verbal and nonverbal material (Corkin, 1982). They evidence poorer performance on free recall measures (Delis, Massman, Butters, Salmon, Cermak & Kramer, 1991) with a higher percentage of responses from the recency region of a list than

normals (Delis et al., 1991; Poitrenaud, Moy, Girousse, Wolmark, & Piette, 1989). Recall and recognition is also impaired in the nonverbal domain (Moss & Albert, 1988). AD subjects have also been shown to have higher forgetting rates after a delay, even if storage capacity is equated first (Dannenbaum, Parkinson, & Inman, 1988). These findings have led Dannenbaum and colleagues to conclude "performances of DAT patients suggest multiple deficits including registration and in storage maintenance or/and retrieval" (Dannenbaum et al., 1988, p. 230).

Dementia Syndrome of Depression

While memory disturbance often heralds the onset of AD, an impaired ability to learn new information has also been found in depressive patients (Weingartner, Cohen, Murphy, Martello, & Gerdt, 1981; Caine, 1986). In elderly depressive patients, the associated memory impairment may masquerade as dementia (Post, 1975). Caine (1981) characterized pseudodementia as follows: (1) an intellectual impairment in a patient with a primary psychiatric disorder; (2) the features of the neuropsychological abnormality resemble, at least in part, the presentation of a neuropathologically induced cognitive deficit; (3) the intellectual disorder is reversible; and (4) the patient has no apparent primary neuropathological process leading to the genesis of the disturbance. It has been estimated that one third (Reynolds, et al., 1987) to one half (Folstein & McHugh, 1978) of elderly depressed patients exhibit severe cognitive impairment due to their affective state. Although Bieliauskas (1993) recently questioned the concept of pseudodementia, he stated that "if there is a history of primary depression..., cognitive symptoms may indeed have a depressive

component" (p.132). However, LaRue, Goodman, and Spar (1992) found that length of current illness, rather than previous history was associated with significant memory impairments in depressed patients, relative to age matched controls. Thus, the variables necessary to produce a dementia syndrome of depression picture have not yet been fully delineated.

Neuropathology

By definition, no known neuropathology is associated with depressive pseudodementia. However, the neuroanatomical substrates underlying depression itself have been examined. In a large study of 80 patients with left sided hemispheric lesions and 80 patients with right hemispheric lesions, a depressive-catastrophic reaction, characterized by tearful outbursts or anxiety reactions, was observed more frequently in patients with left hemisphere than right hemisphere lesions (Gainotti, 1972). In more recent studies, patients with single hemisphere lesions, verified by computerized tomography, were examined for the presence of mood disorders. Patients with left anterior lesions had a significantly greater frequency and severity of depression. This relationship held for both cortical (Robinson, Kubos, Starr, Rao, & Price, 1984) and subcortical lesions (Starkstein, Robinson, & Price, 1987). On the other hand, right hemisphere lesioned patients had a significantly higher incidence of inappropriate cheerfulness (Starkstein, et al., 1987). In a positron emission tomography study of depressed patients, lower metabolism in the left prefrontal region was found, relative to the right (Martinot, Hardy, Feline, Huret, Mazoyer, Attar-Levy, Pappata & Syrota, 1990).

Although these findings have not always been replicated (Dam, Pederson, & Ahlgren, 1989), this may be due to a number of methodological differences including different sample characteristics, measures of depression, and timing of the assessment interview. Another possible confounding factor is the presence of a previous psychiatric history, as this may indicate a predisposition towards depression, prior to the onset of the stroke. In a recent study, Morris, Robinson, and Raphael (1992) studied 35 patients with a semistructured interview and the Montgomery and Asberg Depression Rating Scale. They found that the association of depression with anterior left hemisphere lesions held only after the influence of a pre-existing vulnerability to depression was removed. They interpreted these findings to suggest that lesion location is only one of the factors involved in post-stroke depression.

Neurochemistry

Schildkraut (1965) proposed the catecholamine hypothesis of affective disorders stating, "some, if not all, depressions are associated with an absolute or relative deficiency of catecholamines, particularly norepinephrine, at functionally important receptor sites in the brain". Depression can be caused by the monoamine antagonist reserpine (Sachar & Baron, 1979). Further support for the hypothesis comes from the observed therapeutic effect of antidepressant medications. Both monoamine oxidase inhibitors and tricyclic antidepressants are monoaminergic agonists. The disruption of aminergic input to the hemispheres may result in a "metabolic encephalopathy" producing both cognitive and emotional disorders (Brumback, 1993).

Different subtypes of depression have been associated with dysfunction of either the norepinephrinergic system or the serotonergic system (Maas, 1975). "Too little noradrenergic activity results in lethargic depression, and too little serotonergic activity results in agitated depression" (Carlson, 1986, p. 702).

A third hypothesis is that the ratio of acetylcholine to the catecholamines (dopamine and noradrenaline) is too high in depressive states (Liston, Jarvik & Gerson, 1987). The "relative prevalence of cholinergic over aminergic mediation due to an inverse correlation of their activities, plays an essential role in the genesis of depression in general..., and acquires a special meaning in old age, because functional imbalance of these two systems in the direction of activation of cholinergic effects is an important factor in aging of the brain" (Burchinsky, 1985, p. 10). While the exact mechanisms involved in the genesis of depression are not definitively known, it appears that disruption of aminergic functioning (catecholaminergic and/or indoleaminergic) is a primary consideration, with possibly increased cholinergic functioning. In contrast, decreased cholinergic functioning is associated with Alzheimer's disease.

Lateralization of Neurotransmitter Systems

It appears that different neurotransmitter systems are primarily involved in AD (cholinergic) and depressive pseudodementia (noradrenergic or serotonergic). Tucker and Williamson (1984) reviewed evidence to suggest that these neurotransmitter systems control different aspects of cognitive behaviour and are also differentially lateralized. According to the authors, the cholinergic and dopaminergic neurotransmitter systems

reciprocally regulate cortical activation, while the noradrenergic and serotonergic systems reciprocally regulate arousal. The dopaminergic/cholinergic system is involved in the activation system which maintains "tonic readiness for action" (p. 188). The noradrenergic/serotonergic system is involved in the arousal system which orients to novel informational input. Dopaminergic activation is thought to increase informational redundancy, while noradrenergic arousal is thought to promote orienting to novelty.

The authors further reviewed evidence to suggest that these systems are asymmetrically lateralized, with the cholinergic and dopaminergic systems exhibiting relatively greater left lateralization, and the noradrenergic and serotonergic systems exhibiting relatively greater right lateralization. They suggest that this differential lateralization alters information-processing operations qualitatively. They propose that the "receptive attentional controls of arousal" (p. 202) may be right lateralized, while the left hemisphere "is linked specifically to an active, vigilant attentional mode" (p. 201).

Dopaminergic overstimulation results in "highly routinized motor output in animals" (p. 204). In humans, "at extreme levels this may produce pathological stereotypy" (p. 205). Noradrenergic depleted animals may be "more distractible by irrelevant cues" (p. 191). Therefore, disruption to either of these systems may lead to attentional/executive deficits and the production of perseverations, to be described below.

Memory Testing

In a series of experiments, Weingartner, Cohen, Murphy, Martello,

and Gerdt (1981) showed that depressive patients benefited less from semantically processing a list of words to-be-remembered than did controls. Indeed, the depressives were indistinguishable from the controls in remembering acoustically processed words. Additionally, when these subjects were asked to sort a group of related or unrelated words, depressed subjects later recalled significantly fewer of the unrelated words than controls; the groups did not differ in the number of related words which they recalled.

In the third experiment, subjects learned seven different 32 item word lists. One list used random words (zero categories); two lists had two categories with the words either clustered by category or unclustered. Two lists had four categories which were presented either in a clustered or an unclustered manner. The remaining two lists had eight categories with presentation in either a clustered or and unclustered order. Depressed patients did not differ from controls when recalling the lists with obvious clustering. However, depressed subjects differed significantly from controls in the unclustered conditions. The largest differences appeared in the recall of the random list. The authors commented:

> "In each study, we observed that the depressed patients failed to use encoding operations that would be useful in reorganizing input and that would then facilitate later recall. On the other hand, when information was presented in an organized or structured form, then that organization was appreciated and used by the depressed patient and resulted in more complete, essentially normal learning-recall performance" (p. 46).

The authors interpreted these results as being consistent with an impairment in

encoding. Further, they postulated that "some disruption in brain state arousal and activation may account for an encoding processing failure that leads to memory learning failures" (p. 46).

Cohen, Weingartner, Smallberg, Pickar, and Murphy (1982) tested depressive patients with both motor and memory tasks. They found that depressives were impaired on a consonant trigram task at delays of zero to 18 seconds. Additionally, they found that there was a significant negative correlation between mood and both peak and sustained motor performance on a hand dynamometer task. The authors interpreted these findings as "a single deficit in the area of the central motivational state" (p. 596). Thus, the memory impairments associated with depression have often been characterized as deficits of "effortful" versus "automatic" processing (Grafman, Weingartner, Lawlor, Mellow, Thompsen-Putnam, & Sunderland, 1990).

Depressives have also been found to show impairments on nonverbal tests of memory. Caine (1981) found that depressives commonly omitted details from their drawings and were impaired, relative to age matched controls, on a test of immediate visual memory.

Perseverations and Intrusions

Perseveration "is generally used to describe any continuation or recurrence of experience or activity without the appropriate stimulus" (Sandson & Albert, 1984, p. 715). Prior-item intrusive errors are defined as "the inappropriate intrusion of previously presented stimuli into an individual's current performance on a cognitive task" (Troster, Jacobs, Butters, Cullum, & Salmon,1989). Perseverations and intrusions appear to

be the same entity, i.e., an inappropriate response based on current or past activity. A distinction has sometimes been drawn in which a perseveration is considered to be a repetition within the same cognitive mode or list, and an intrusion is considered to be an inclusion of an extra-list item (Delis, Kramer, Kaplan, & Ober, 1987). At least two theoretical models have been proposed to explain perseverative behaviour.

Goldberg and Tucker (1979) proposed a taxonomy of perseveration which delineated four different types of perseveration. These are: perseveration of activities, perseveration of features, perseveration of elements, and hyperkinesia-like motor perseveration. Sandson and Albert (1987) proposed a similar taxonomy of three different types of perseveration. These are: stuck-in-set perseveration, recurrent perseveration and continuous perseveration. Although Goldberg and Tucker developed the taxonomy from an empirical study, and Sandson and Albert developed their classification based on a literature review, the two taxonomies are quite similar.

Perseveration of activities and stuck-in-set perseveration both refer to the continued inappropriate maintenance of a previous set or framework so that semantic categories or types of activity are confused. Examples are: the inability to switch from writing words to performing mathematical computations (Goldberg & Tucker, 1979) or, in continuing to bisect lines when the new task is to connect circled numbers sequentially, (after previously bisecting lines)(Sandson & Albert, 1984).

Hyperkinesia-like perseveration and continuous perseveration both refer to the continued inappropriate repetition of a current behaviour. Examples are: multiple circular drawings when asked to draw a single circle

(Goldberg & Tucker, 1979) or additional loops instead of the requested three loops (Sandson & Albert, 1987). An example of this type of perseveration is reproduced in Figure 1 of Appendix C. In this example, 16, rather than four, dots are produced in each quadrant of the square of Design B.

Recurrent perseveration is defined by Sandson and Albert (1984) as "the unintentional repetition, after cessation, of a previously emitted response to a subsequent stimulus" (p. 727-728). Goldberg and Tucker further subdivide recurrent perseveration into two types: perseveration of features and perseveration of elements. Perseveration of elements is the repetition of an entire previous response. For example, the repetition of a circle when asked to draw a cross after just drawing a circle (Goldberg & Tucker, 1979), or repeating "lay on" as a definition for ship after having defined bed as "lay on" previously, or repeating the number "7" when asked to draw a clock (Sandson & Albert, 1984, p. 731). Perseveration of features involves confusion of the "generic aspects of the shapes" (p. 280). For example, drawing a cross as two intersecting lines but then drawing it as a Greek cross after drawing a circle. An example of recurrent visual perseverations is provided in Figure 2 of Appendix C. In this example, the "X" from Design A is inappropriately repeated in Design B, rather than the correct production of a square figure. Thus, perseverations can be elicited in a variety of ways with both verbal and nonverbal tasks.

Goldberg and Tucker (1979) considered perseveration to reflect a breakdown of different levels of cognitive processing (executive, motor, or semantic). Sandson and Albert (1987) proposed that perseverations were based on disruption of different anatomic and neurochemical systems. According to their model, recurrent perseverations may be related to

decreased brain levels of acetylcholine and left hemisphere function. Continuous perseverations may be associated with noradrenergic system dysfunction and right hemisphere function. Stuck-in-set perseverations may be related to dopaminergic system and frontal system functioning.

While perseverations can be elicited in a variety of different tasks, the memory impairment exhibited by the AD type and depressive pseudodementia patients is often the presenting feature of the disorders. Since the neurotransmitter systems primarily involved in AD and depressive pseudodementia appear to be different, and these systems are possibly related to the observed memory impairments, the most fruitful search for a behavioral marker for AD may begin by examining memory performance in AD patients for the presence of perseverative errors in contrast to the performance of depressive pseudodementia patients. Although both the AD type and the depressive pseudodementia type groups display memory impairments, there may be a different pattern associated with each group's performance.

Comparisons of Memory Performance

Gainotti, Caltagirone, Masullo, and Miceli (1980) were unable to distinguish depressed from demented patients using global measures of verbal and visual memory. Indeed, according to Cummings and Benson (1983), "memory disturbance cannot be used to distinguish degenerative dementias from the dementia syndrome of depression" (p. 241).

Dannenbaum, Parkinson, and Inman (1988) studied a group of normal controls, depressed, and demented subjects (Alzheimer-type) with a Brown-Peterson paradigm, administered via computer. Letter spans were

significantly different among the three groups with controls performing better than depressives and depressives performing better than demented subjects. When a subgroup of depressed and demented patients were matched for letter span, the AD-type subjects performance was significantly lower than the depressives only on delayed free and serial recall, and not on immediate recall. However, a limitation of this study is that the AD patients were significantly older than the depressive subjects. Also, the depressed subjects were recruited for the study and were not referred for the evaluation of memory impairments.

Whitehead (1973) evaluated depressed and demented patients at a psychiatric hospital. Depressed subjects were also retested when they were thought to be clinically remitted. Subjects did not differ on mean Vocabulary age corrected scaled sores of the WAIS. On a number of verbal learning tasks the demented subjects performed worse than the depressed subjects. The demented patients made more false positive and random errors as well as more omission errors than the depressives. However, the depressives were more prone to omission errors while ill than when in a remitted state. A major limitation with this study, however, is that half the demented subjects were also clinically depressed. This would serve to obscure some differences between the groups.

Poitrenaud and coworkers (1989) tested mildly and moderately impaired demented and depressed subjects. The depressives and mildly demented subjects exhibited similar recall rates of a ten word list over three trials. The number of subjects with three or more omissions did not separate the groups. However, the number of false alarms on recognition testing did separate the groups, with the mildly demented group displaying

more false alarms than the depressed group. A problem with this study is that the depressed subjects were selected by medical exam, but they were not referred for evaluation of memory problems.

Perseverations in Memory Performance

Although the same overall score may be achieved by varying means by different diagnostic groups, the use of a qualitative approach, such as error analysis, may prove useful in differentiating groups. For example, Brandt, Folstein, and Folstein (1988) used an analysis of error patterns to demonstrate distinct cognitive profiles in groups of AD and Huntington's disease patients when they were matched for total score on the Mini-Mental State Exam. AD patients were shown to make more errors on the orientation and recall sections than HD patients, and the HD patients were shown to make more errors than AD patients on the serial sevens task. These distinctions were independent of the severity level of the dementia. Heindel, Salmon, and Butters (1989), in a review of the literature, highlighted studies which used analyses of error patterns to differentiate demented patient groups from each another. Cummings and Benson (1984) state explicitly, "neuropsychologic studies should concentrate on determining the qualitative differences between different dementing disorders" (p. 877).

When AD patients have been asked to make drawings from semantic memory, perseverations have been observed. Brantjes and Bouma (1991) qualitatively examined the drawings of moderately to severely demented AD patients who were asked to draw 12 items from memory in a specified order. The drawings, a table, watch, bird, etcetera, were then examined for

the number of omissions, simplifications, confabulations and perseverations. The drawings were also analyzed for spatial disorientations, stereotypies (the addition of more details than necessary), and type of perseveration. Relative to age matched controls, the AD subjects made more errors of omission, simplification, confabulation and perseveration. Perseverations of activities, perseverations of features, and hyperkinesia-like perseverations were only observed in the drawings of the AD patients. In contrast, the control subjects made more stereotypic errors than did the AD subjects.

Increased numbers of recurrent perseverative errors, or intrusive errors, have been found in the performance of AD patients on both verbal (Delis, Massman, Butters, & Salmon, 1991; Fuld, 1983) and nonverbal memory tasks (Jacobs, Salmon, Troster & Butters, 1990; Jacobs, Brandt, Salmon, Heindel, Troster & Butters, 1991; Troster, Jacobs, Butters, Cullum, & Salmon, 1989). Fuld (1983) found that Alzheimer patients made a higher number of intrusive errors on a modified Blessed mental status exam and the Fuld-Object Memory Evaluation than normal control subjects. Delis and colleagues (1991) also found that AD patients made more intrusive errors than similarly demented Huntington's disease patients on the California Verbal Learning Test. Additionally, using recall of figural material from the Visual Reproduction subtest of the Wechsler Memory Scale (WMS), Jacobs, Salmon, Troster, and Butters, (1990) and Troster and colleagues (1989) found Alzheimer patients made more prior-item intrusive errors than did Huntington's patients or normal controls. Intrusive errors have also been found in the profiles of only mildly demented AD patients (Jacobs, et al., 1991).

The presence of intrusive errors in AD patients has been negatively

correlated with choline acetyltransferase levels (Fuld, Katzman, Davies, & Terry, 1982). However, plaque counts were also significantly higher in patients with intrusions than in those without (Fuld, 1983). Thus, increased numbers of intrusions in AD patients have been correlated with both decreased choline acetyltransferase levels and increased plaque counts. From these results it is not possible to determine if decreased choline acetyltransferase alone is sufficient to produce intrusions.

AD patients tend to produce high numbers of intrusive errors on both verbal and nonverbal memory tests. Thus, the tendency to produce intrusive errors appears to be a rather ubiquitous finding in Alzheimer patients.

On the other hand, depressive patients appear to make more errors of omission than of commission (Cummings & Benson, 1983). Weingartner and colleagues, (1981) found that depressive patients did not make more intrusive errors than normal control subjects on a variety of verbal memory tasks. Lowenstein et al. (1991) studied a group of probable AD subjects, patients with multiple cerebral infarctions (MCI), depressed inpatients and outpatients, and normal controls using the Fuld Object Memory Evaluation. Intrusive errors were categorized as either shift intrusions, test intrusions, conceptual intrusions, confabulatory intrusions, or unrelated intrusions. The mild AD subjects evidenced more unrelated intrusive errors than the mild MCI patients, the depressed patients, or the normal controls. The groups did not differ in the occurrence of other types of intrusive errors. However, 17 of the 31 depressed patients were not referred for evaluation of memory complaints but were recruited for the study. Both groups of depressed subjects were included together for the purposes of the statistical analyses.

Therefore, more than half of the depressed subjects would not pose a diagnostic problem for the differentiation of dementia versus depression. Nevertheless, these findings together would suggest that a qualitative approach, utilizing error analysis, of memory test performance might be useful in differentiating AD from elderly depressive patients.

In sum, errors of commission reliably have been found to differentiate groups of control subjects and patients with AD and Huntington's disease. On the other hand, depressive patients have not been shown to make these types of errors, rather they have been shown to make errors of omission. These findings suggest that these patients perform poorly on memory tests for different reasons.

Research Questions

The purpose of the present study was to address two general questions. I. Is the presence of intrusive or recurrent perseverative errors in memory test performance specific to Alzheimer type demented patients such that their presence or absence can provide a useful discrimination between these patients and elderly depressive patients? II. Do the different types of perseverative errors found support the distinctions proposed by Sandson and Albert (1987)? The purpose was not to compare the overall level of performance on neuropsychological tests between the groups. To address Question I, we tested the hypothesis that patients with AD-type dementia and elderly depressive patients fail memory tests for different reasons. More specifically, it was hypothesized that the DAT patients would make more intrusive or recurrent perseverations than DEP patients. Additionally, it was hypothesized that DEP patients would make more omissions and continuous perseverations than DAT patients, using the Wechsler Memory Scale. Further, it was hypothesized that the error scores would be reliable enough to predict group membership (above chance levels). An accepted way to test these hypotheses is to use discriminant function analysis (Adams, 1979), which can be useful in "finding the underlying mechanisms of group differences" (p. 260).

To address Question II, we analyzed the types of errors made. It was hypothesized that the types of commission errors made would differ by group, with the DAT patients producing a higher proportion of intrusive errors or recurrent perseverations than the DEP group, and with the DEP patients producing a higher proportion of continuous or hyperkinesia-like perseverations than the DAT group. This hypothesis was tested using a

multivariate analysis of variance on the proportion scores.

Methods

Subjects

Subjects were selected from a sample of patients seen for a neuropsychological evaluation at a rehabilitation hospital. All patients had been referred by a neurologist for the evaluation. The files were housed at the University of Victoria Neuropsychology Center. The sample was drawn from the files available for patients evaluated from 1983 to the present. Archival data were used to increase the potential sample size. All patients previously gave consent for their test data to be used for teaching or research purposes, provided that the patient remained anonymous and identifying information was not used.

After completion of the neuropsychological evaluation and any additional diagnostic tests, subjects were classified into one of two categories by the referring neurologist or the neuropsychologist. Subjects in Category One were classified as brain damaged (Category 1), those in Category Five were classified as psychotic/neurotic (Category 5). All files of patients over the age of 55 years from Categories 1 and 5 who were referred for evaluation of either dementia or memory complaints were examined. Subjects were excluded if they had focal neurological signs on recent neurological examination or if there was a significant history of head trauma, neoplastic or vascular disease, or alcohol or drug abuse. Patients with a previous or current psychiatric history were also excluded from the DAT group. Alzheimer-type patients were considered possibly "demented" by the neuropsychologist and/or the referring physician and met NINCDS-ADRDA diagnostic criteria for possible AD (McKhann et al., 1984). All remaining AD patients who were assessed with the Wechsler Memory Scale

(WMS, Wechsler, 1945) were included in the study.

Dementia syndrome of depression patients were also referred by a neurologist for evaluation of memory problems or possible dementia. Subjects were excluded from the depressed group according to the same criteria as the AD type group with the exception of a positive psychiatric history. The depressed subjects were included if they were considered "depressed" by the neuropsychologist, based on their presenting symptoms and some test results from tests such as: the Minnesota Multiphasic Personality Inventory (MMPI), the Geriatric Depression Scale, the Zung Depression Scale, or the Beck Depression Inventory. It was not always possible to determine if the patient would meet diagnostic criteria for major depression, based on DSM-III-R criteria. Five of the DEP subjects were previously treated with electroconvulsive shock therapy (ECT). Four DEP subjects were being treated with antidepressants at the time of testing. One subject was considered to have a bipolar diagnosis, however, the subject was depressed at the time of testing. Any ambiguous cases for either group were referred to a board certified neuropsychologist (Dr. Otfried Spreen) who made the final decision to include or exclude the patient from the sample.

Procedures

The Wechsler Memory Scale (Wechsler, 1945) test scoring forms and drawings were photocopied with the patient's name omitted from the copy. Only the file number remained on the copy for identification purposes. Other data was obtained from the patient file data base available at the University of Victoria.

All tests were administered according to standard instructions (Spreen & Strauss, 1991), by a trained psychometrician or advanced clinical neuropsychology students. The same psychometrician supervised the student administration. The Vocabulary subtest of the Wechsler Adult Intelligence Scale - Revised (WAIS-R, Wechsler, 1981) was examined and scores used as an estimate of premorbid functioning. Although other measures such as educational level or rankings of current or previous occupation could be used to estimate premorbid functioning, the Vocabulary subtest was chosen as this data was more reliably available from the data base. Two subtests from the Wechsler Memory Scale (WMS, Wechsler, 1945) were also examined for both groups: the Logical Memory (LM) subtest and the Visual Reproduction (VR) subtest. The original Wechsler Memory Scale was used as previous research has shown that more intrusive errors are elicited with its use than with the revised version (Troster et al., 1989).

The LM subtest consists of two brief narrative stories which are read aloud to the subject. After completion of the stories, the subject is asked to repeat as much of the story as he/she can remember. Recall is recorded verbatim by the examiner. The VR stimuli consist of three cards with one design on each of the first two cards and two designs on the third card. The subject is presented with each card for 10 seconds. The card is withdrawn from view and the subject asked to reproduce the designs from memory. Generally, the subject was given a separate 8.5 X 11 inch sheet of paper for each drawing.

Omissions for LM were scored according to the gist scoring criteria of Spreen and Strauss (1991). These criteria are more lenient than the original

criteria in that credit is awarded for remembering the gist of the story as well as the exact details. The criteria have been shown to have acceptable reliability. For VR, omissions were scored according to the appended criteria (Appendix A). These scoring criteria were developed to eliminate the original scoring for reliance on the orientation of details as well as presence or absence of those details.

The presence of intrusive errors for both subtests were scored according to the guidelines of the classification scheme of Sandson and Albert (1984). Specifically, a continuous perseveration was scored if extra dots or borders were drawn in Design B, for example. A stuck in set perseveration was scored if prior task responses were included in the current task responses, for example, the inclusion of digits from the Mental Control subtest into recall of the LM stories. A recurrent perseveration was scored if elements of a preceding story or design were included in subsequent recall of either the next story or design. The number of recurrent perseverations or intrusive errors for the VR were scored generally following the procedure described by Troster et al. (1989). Briefly, "the inclusion of any characteristic unique to a previously presented stimulus in the reproduction of a subsequent figure was scored as an intrusion error" (p. 625). Two raters, blind to diagnosis, scored the data according to the above criteria. Inter-rater reliability was calculated for all the scores.

The quantitative data from the group of demented subjects was then contrasted with that of the depressive pseudodementia subjects on the number of Perseverations and omissions. A two group discriminant function analysis (DFA) was used with diagnosis, DAT or DEP, as the criterion variable. The total number of visual and verbal Perseveration errors and the

total number of visual and verbal omission errors were used as predictor variables.

Intrusions and perseverations were also analyzed according to the "type" of perseveration following the classification system of Sandson and Albert (1987). A proportion score for each subject was then derived for each type of perseveration by total numbe of perseverations, i.e., the number of recurrent perseverations was divided by the total number of perseverations, and the number of continuous perseverations was divided by the total number of perseverations. Proportion scores were then used in a multivariate analysis of variance to examine group differences.

Results

Data were obtained from 88 subjects, 49 with possible Alzheimer's disease and 39 with the dementia syndrome of depression. The subjects from the presumed Alzheimer's group ranged in age from 56 years to 82 years; the subjects from the presumed dementia syndrome of depression group ranged in age from 55 to 79 years. Demographic variables were compared using t-tests (See Table 1 in Appendix B). The groups did not differ by sex ($t = .12$, $df = 1,86$, $p < .9$) or Vocabulary scaled scores ($t = 1.69$, $df = 1,73$, $p < .09$). There were 13 subjects who did not have Vocabulary scores, 12 of these subjects were from the Alzheimer type group. These 12 subjects did not differ from the remainder of the Alzheimer group in terms of mean age ($t = .91$, $df = 1,47$, $p < .37$), sex ($t = .25$, $df = 1,47$, $p < .8$) or Wechsler Memory Quotient scores ($t = 1.55$, $df = 1,47$, $p < .13$) and were therefore included with the remainder of the Alzheimer type group. However, the total presumed Alzheimer group was slightly older (mean = 68.6 years) than the depressed group (mean = 63.7 years, $t = 3.48$, $df = 1,86$, $p < .001$), discussed below.

Two raters, blind to diagnosis, independently scored 50 of the 88 protocols. Pearson product moment correlations were then calculated for each dependent measure to determine inter-rater reliability. All correlations were highly significant (all p's $< .001$), indicating the scoring criteria were reliable (See Table 2 in Appendix B).

The lowest correlation (.70) was obtained for the VRA Perseveration measure. Raters were in complete agreement on 49 of the 50 protocols, however, there was very little variability in this measure as most subjects produced no Perseverations. Therefore, this correlation was also considered

acceptable.

Since the groups differed in mean age, with older patients in the DAT group, separate analyses of variance were calculated to analyze the effect of age on the dependent variables. There was no significant effect of age on any of the dependent variables (see Table 3 in Appendix B). However, the number of subjects in each cell was likely to be small, therefore, further age analyses were conducted.

To examine further the effect of age on the dependent variables, the age distribution for each group was examined. Three subjects in the DEP group were noted to be over the age of 70 years (i.e. 74, 75 and 79 years of age). Therefore, an attempt was made to produce two patient groups of equivalent age by selecting a subset of patients, 70 years of age or younger, from each diagnostic group from the total sample. This resulted in two smaller subsets of patients being selected from each group; these subgroups did not differ in mean age. Similarly, these age equivalent subgroups did not differ in mean proportion of females or mean Vocabulary scaled scores (See Table 4 in Appendix B).

Within each diagnostic group the means of the younger and older subgroups were compared by individual t-tests. The mean scores did not differ significantly within each diagnostic group (p's $>.1$, See Table 5 in Appendix B), suggesting age did not significantly affect the following results. Further, the data were examined for the presence of unusual cases. All the older DAT patients scores fell within the range of dependent variable scores of the younger DAT group with two exceptions. One of these patients (aged 73 years) produced a higher number of both verbal and visual recurrent errors than did the patients in the age equivalent group. Another

older patient (aged 75 years) produced verbal stuck-in-set perseverations while no other patient produced these types of perseverative errors. As these patients were not the oldest patients for either group, their scores were not considered to be merely a function of age.

Although these findings suggest that the obtained results were independent of age, two separate discriminant function analyses were performed. The first used data from the entire sample, and the second used data from the age equivalent sample.

With data from the entire sample, a two-group Discriminant Function Analysis (DFA) was performed, using diagnosis as the criterion variable, and the total omission and perseveration scores for the verbal and visual memory tasks as the predictor variables (i.e., LM Total Recall, LM Total Perseverations, VR Total Omissions, and VR Total Perseverations). The analysis was significant (canonical correlation = .68, DF = 4, $p < .0000$); 75 of the 88 patients were correctly classified. Only six DAT subjects and seven DEP subjects were misclassified, resulting in an overall correct classification rate of approximately 85 percent correct (See Table 7 in Appendix B). This DFA classified more patients correctly than did a DFA using the total Memory Quotient (MQ) score (overall 79% correct classification).

To verify that the preceding results were not a function of the older mean age of the DAT subjects, a second DFA was performed with data from the age equivalent sample, using the same criterion and predictor variables. This resulted in an overall correct classification rate of approximately 79 percent correct. Once again, six DAT patients were misclassified, while eight DEP patients were misclassified. This resulted in

14 misclassified patients in total. Twelve of the 13 previously misclassified patients were included in this analysis, and all 12 were again misclassified (See Table 8 in Appendix B). This DFA classified more patients correctly than did a DFA using the MQ score (overall 73 percent correct classification).

To determine which single variable was the most discriminating, the data from the entire sample were entered into a stepwise discriminant function analysis, using the same criterion and predictor variables. The first variable entered into the analysis was Logical Memory Total Recall. Logical Memory Total Perseverations was entered on Step 2, followed by Visual Reproduction Total Recall, and lastly, Visual Reproduction Total Perseverations.

To test the hypothesis that the DAT group produced a higher percentage of recurrent to total perseverations than the DEP group, while the DEP group made a higher proportion of continuous to total perseverations than the DAT group; proportion scores for each patient were calculated for each type of error by total number of errors (See Table 9 in Appendix B). A multivariate analysis of variance on the proportion scores was then conducted. According to Wilk's criteria, there was a significant group effect ($F = 4.6$, $p < .01$). Univariate F tests were also significant for a higher proportion of continuous perseverations in the DEP group ($F(1,61) = 9.21$, $p < .004$) and a higher proportion of recurrent perseverations in the DAT group ($F(1,61) = 8.60$, $p < .005$).

The proportion scores from the age equivalent sample were also examined, however, a multivariate analysis of variance could not be performed due to linear redundancy in the data. Univariate analyses of

variance were performed; the DAT group again produced a significantly higher proportion of recurrent perseverative errors than did the DEP group ($F(1,43) = 2.42$, $p < .02$). The DEP group produced a higher proportion of continuous perseverations than did the DAT group ($F(1,43) = 2.42$, $p < .02$). The mean proportion scores are presented in Table 10 in Appendix B.

To examine the relationships among the dependent variables, correlations were calculated. These are presented in Table 11 in Appendix B.

Discussion

In this sample, the original groups differed in mean age, with the DAT group significantly older than the DEP group. No significant age effects were found for the dependent variables using an analysis of variance. However, to justify using the total sample, the groups were subdivided to produce two age equivalent subgroups by selecting patients younger than 70 years of age or younger. Analyses were conducted to examine the means of the dependent variables for the younger and older subgroups within each diagnostic group. No significant differences were found, indicating that the older DAT group did not differ from the younger DAT group, and the three older DEP subjects did not differ from the younger DEP subjects. These findings suggest that the differences between the diagnostic groups were not merely a function of the older age of the DAT group.

In summary, the older subjects were not significantly different than their younger counterparts, but separate analyses were conducted, nevertheless, to verify the obtained results were not a function of the older age of the DAT group. Vocabulary scaled scores did not differ between groups, suggesting equivalent premorbid ability. This suggests that the results obtained were not due to prior differences in ability between the two groups.

The qualitative scoring system was more effective in classifying the patients by groups than the MQ alone (85 percent correct versus 79 percent correct). The qualitative system had a high true-positive classification rate; 43 of 49 (88 percent) of the DAT patients were correctly classified. Seven of 39, or 18 percent of the DEP patients were incorrectly classified (false

positives). When data from the age equivalent sample was used in a similar DFA, all the originally misclassified DAT patients were again misclassified. Similarly, all the DEP patients who were originally misclassified were again misclassified. Although the second DFA was less powerful, due to the smaller sample size of the age equivalent group, approximately the same total number of patients were misclassified. Additionally, all the originally misclassified patients included in the analysis were again misclassified. This consistency suggests the results are indeed independent of age. Thus, the current findings support the use of specific scoring of perseverative errors to classify subjects as the inclusion of error scores improved classification over recall measures alone.

Also, as predicted, the DAT group made a higher proportion of recurrent perseverations than did the DEP group for both analyses. This supports previous research findings of an increased propensity towards producing recurrent perseverative errors in DAT patients. Of the six DAT patients who were misclassified, four of these patients made no perseverative errors whatsoever. The other two misclassified DAT patients made only continuous perseverative errors without making any recurrent perseverations. All DAT subjects who made even one recurrent perseveration were correctly classified.

Also as predicted, the DEP group made a higher proportion of continuous perseverations than the DAT group. In general, the DEP group made continuous perseverations almost exclusively, with few patients producing recurrent perseverative errors. Three of the five DEP patients who were previously treated with ECT were misclassified; two of these subjects made recurrent perseverations. Two of the other misclassified

patients were being treated with antidepressants; one of these patients was also treated with Stelazine and Digoxin. This patient made a recurrent perseveration. One misclassified patient was considered to have a bipolar diagnosis, although the patient was depressed at the time of testing. These three patients were somewhat atypical of the total DEP group.

The presence of a recurrent perseveration was strongly associated with the diagnosis of DAT in this sample. Approximately half of the DAT sample made at least one recurrent perseveration. This is consistent with Fuld's (1983) finding that 60 percent of her DAT sample made an intrusive error during memory testing. While this suggests that intrusive errors are a positive sign for DAT, the absence of a recurrent perseveration on memory testing does not preclude a diagnosis of DAT. Fuld (1983) found that an additional 28 percent of her sample made recurrent perseverations when other test performances were examined. This suggests that a majority of DAT patients may make recurrent perseverative errors if given the opportunity with enough testing. However, the presence or absence of a recurrent perseveration cannot in itself be considered diagnostic. Rather, it may serve as a useful adjunct when considered in conjunction with other indicators, such as rapid decay of memory for learned material.

In this sample, the DAT subjects also made a high number of continuous perseverations. This was an unexpected finding, which has not been reported previously in the literature. A high number of continuous perseverations in the DAT sample would not be predicted by Sandson and Albert's (1984) model. While it is possible that the DAT group also has noradrenergic dysfunction (Kopelman, 1986), it is unlikely that the dysfunction is as significant as that in the DEP group, as no patients in the

DAT group were also considered depressed. Thus, noradrenergic dysfunction in the DAT group does not appear to explain the higher number of continuous perseverations observed relative to the DEP group. Previous investigators (Brantjes & Bouma, 1991) have suggested that different error types may be related to compensatory mechanisms, with either relevant or irrelevant attempts at compensation. If recurrent perseverations are considered an irrelevant compensatory attempt and continuous perseverations considered a relevant compensatory attempt, then the results would suggest that the DAT group was making more attempts to compensate for their memory difficulties than the DEP group. As decreased effort has been postulated in depressed patients, this explanation seems plausible. However, other evidence argues against this explanation. An active attempt to compensate for a memory impairment implies some awareness of the memory deficit. A diminished awareness of cognitive impairments has been found in DAT subjects (McGlynn & Kaszniak, 1991; Reed, Jagust, & Coulter, 1993). On the other hand, DEP subjects are reported to overestimate their cognitive impairments (Wells, 1979). Therefore, an active compensatory attempt seems more plausible in DEP subjects than DAT subjects, despite the reported lack of effort of depressed subjects.

A normal, age-matched control group was not used in this study. As noradrenaline has been observed to be reduced in the normal aging brain, it is possible that elderly normal controls could also produce continuous perseverations. If we speculate that normal elderly controls could also produce these perseverations, then the diminished number of continuous perseverations in the DEP group could indicate a lack of effort.

Another possible explanation is that continuous perseverations are also related to attentional deficits. Posner, Walker, and Friedrich (1984) reported that patients with parietal lesions have difficulty shifting attention within a visual field and that this is due to a failure to disengage attention from the current focus. DAT patients are known to have biparietal dysfunction (Chui, 1989). We may speculate that this may result in the production of continuous perseverations at a higher rate than in the DEP subjects.

Thus, the current study provided some support for Sandson and Albert's (1984) proposed theory of perseverations. The DAT group did produce more recurrent perseverations than the DEP group, and the proportion of recurrent perseverations to total perseverations was higher in the DAT group. This supports the contention of cholinergic dysfunction associated with recurrent perseverations. Sandson and Albert (1987) further clarified their original model and proposed that recurrent perseverations were related to disorders of language. In this study, we found that DAT patients produced recurrent perseverations with both verbal and visual stimuli, suggesting that for DAT subjects, these errors are not specific to the language modality. However, inspection of the data revealed an unexpected finding. Verbal recurrent perseverative errors were made exclusively by the DAT group; the DEP group made none whatsoever. Although it is tempting to speculate that the exclusive production of verbal recurrent perseverations in the DAT group may be related to the relatively greater left lateralization of the cholinergic neurotransmitter system as proposed by Tucker and Williamson (1984), the verbal and visual memory tests differ not only in modality, but they also differ in mode of presentation

and number of items. Therefore, further examination of perseverative error types in performance of other memory tasks would be warranted.

The DEP group produced a higher proportion of continuous to total perseverations than did the DAT group. However, the DAT group produced a higher absolute total number of continuous perseverations than did the DEP group. We may speculate that this finding is related to disorders of attention in the DAT group, possibly due to parietal lobe dysfunction, rather than simply noradrenergic dysfunction.

This study relied on the use of archival data, while this is beneficial in examining the performance of a large number patients, it also poses a number of limitations. First, normal elderly were not included in the study, precluding a direct examination of the effect of age on the possible production of perseverative errors. Second, the original classification of the patients was not made based on performance on a fixed battery or according to standard clinical criteria for depression. Third, a consistent measure of the severity of the dementia or depression was not used. Fourth, additional memory measures were not included.

Future studies could be improved in a number of ways. The addition of a normal, age-matched control group would allow the examination of the relationship of the production of perseverative errors with age directly. The inclusion of patients meeting criteria for a depressive disorder, rather than patients with a cluster of depressive symptoms, would also improve the original classification of the groups. The use of a scale which provides measures of severity of depression would also be useful to indicate the relationship of severity with the production of perseverative errors. Selecting patients with "probable" rather than "possible" dementia of the

Alzheimer type might also increase the diagnostic accuracy of the original groups. Additionally, the inclusion of a measure of dementia severity, such as a mental status exam or a dementia rating scale would provide a means of equating groups for overall severity level. Traditionally, list-learning tasks have been used to elicit recurrent perseverations; the inclusion of such a task might be beneficial in increasing the number of patients who produce recurrent perseverations. This might result in an improved classification rate.

To examine the possibility of different subgroups of DAT subjects, long-term follow-up studies would be necessary. Approximately half of the DAT subjects produced at least one recurrent perseveration. It would be interesting to examine the group at a later date when the dementia had presumably become more severe to observe the rate of production of recurrent perseverations. If the same subjects continued to produce recurrent perseverations while the other subjects did not, this would suggest distinct subgroups of DAT patients. A subgroup of patients producing recurrent perseverations may have implications for the rate of progression of the disease or possibly for treatment approaches. Perhaps programs could be designed to minimize recurrent perseverations and thereby increase memory ability. Alternatively, perhaps pharmaceutical agents aimed at improving the functioning of the cholinergic system might be beneficial in those patients who produce recurrent perseverations rather than in those who do not.

Longitudinal study of the DEP group could also be interesting to examine the possibility that those subjects who made recurrent perseverations have a different course of illness than other depressives.

Previous research has suggested that some late-life depressives do eventually develop a progressive dementia (Reding, et. al., 1985). The production of recurrent perseverations would then have important prognostic implications.

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Appendix A

Table 1. Scoring Criteria for Omissions on the Visual Reproduction Subtest of the Wechsler Memory Scale (1945)

Card A	Two lines, crossed	1 point
	Four square flags	1 point
Card B	One large square	1 point
	Two diameters	1 point
	Four small squares	1 point
	Two diameters in each small square	1 point
	Sixteen dots (total)	1 point
Card C	Three open rectangles	1 point
	Two loops	1 point
	One large rectangle	1 point
	One small rectangle	1 point
	Four lines	1 point
	Total	12 points

Appendix B

Table 1: Means and (Standard Deviations) for Age, Sex Distribution (Sex), and Vocabulary Scaled Scores and Memory Quotients (MQ)

		Variables			
Group	n	Age	Sex	Vocabulary	MQ
DAT	49	68.6(7.1) [1]	.45(.5)	9.3(2.9)[2]	81.3(11.6)[4]
DEP	39	63.7(5.8) [1]	.44(.5)	10.3(3.1)[3]	106.8(18.2)[4]

Note[1]. $p < .001$, Note[2]. n=37, Note[3]. n=38, Note[4]. $p<.000$, Note[5]. Females were coded as 0.

Table 2: Inter-Rater Reliability Correlations for Dependent Variables and Totals

Variable	Correlation
LM-A Recall	.97
LM-A Perseverations	.86
LM-B Recall	.96
LM-B Perseverations	.97
VR-A Omissions	.81
VR-A Perseverations	.70
VR-B Omissions	.89
VR-B Perseverations	.88
VR-C Omissions	.95
VR-C Perseverations	.84
LM Total Recall	.98
LM Total Perseverations	.96
VR Total Omissions	.95
VR Total Perseverations	.82

Note: All correlations significant at $p<.001$

Table 3: F tests and Significance Levels for Age Effects

Variable	F value	Significance
LM-A Recall	.68	.86
LM-A Perseverations	.62	.91
LM-B Recall	.78	.75
LM-B Perseverations	1.41	.14
VR-A Omissions	.82	.70
VR-A Perseverations	1.24	.24
VR-B Omissions	1.09	.37
VR-B Perseverations	.91	.60
VR-C Omissions	1.43	.13
VR-C Perseverations	1.49	.10

Legend: LM-Logical Memory, VR-Visual Reproduction.

Table 4: Means and (Standard Deviations) for Age, Sex Distribution (Sex) and Vocabulary Scaled Scores of Age Equivalent Groups

		Variables		
Group	n	Age	Sex	Vocabulary
DAT	29	63.9(4.6)	.45(.5)	9.55 (1.79)
DEP	36	62.7(4.5)	.44(.5)	10.36 (1.76)

Note: Females were coded as 0, * $p > .05$

Table 5: Mean Logical Memory (LM) and Visual Reproduction (VR) Scores by Group

			Variable			
Group		n	LM-TR	LM-TP	VR-TO	VR-TP
DAT						
	young	29	5.8(4.6)	.3(.7)	6.6(3.6)	1.9(1.5)
	old	20	5.4(4.2)	.5(1.0)	7.2(1.7)	1.8(1.2)
DEP						
	young	36	14.4(7.0)	0.0(0.0)	3.4(2.5)	.9(1.2)
	old	3	14.7(3.2)	0.0(0.0)	5.0(2.0)	.7(1.2)

Note[1]. TR -Total Recall, TP -Total Perseverations, TO -Total Omissions.

Note[2]. Within each diagnostic category no significant differences were found between the young and old subgroups.

Table 6: Discriminant Function Analysis Classification Table for Total Sample

		Predicted Group Membership	
Actual Group	n	DAT	DEP
DAT	49	43 (87.8%)	6 (12.2%)
DEP	39	7 (17.9%)	32 (82.1%)

Note: Overall 85.23 percent correct classification

Table 7: Discriminant Function Analysis Classification Table for Age Equivalent Groups

		Predicted Group Membership	
Actual Group	n	DAT	DEP
DAT	29	23 (79.3%)	6 (20.7%)
DEP	36	8 (22.2%)	28 (77.8%)

Note: Overall 78.5 percent correct classification

Table 8: Mean Proportion Scores for Groups

	Variable	
Group	Pcon	Prec
DAT	.68	.31
DEP	.92	.08

Note: Pcon = Proportion Continuous/Total;

Prec = Proportion Recurrent/Total

Table 9: Mean Proportion Scores for Age Equivalent Groups

	Variable	
Group	Pcon	Prec
DAT n=24	.74	.26
DEP n=21	.91	.09

Note: Pcon = Proportion Continuous/Total;

Prec = Proportion Recurrent/Total.

Table 10: Intercorrelation Matrix of Dependent Variables

Variables	LM-A Recall	LM-B Recall	LM-A Persev.	LM-B Persev.	VR-A Omiss.	VR-B Omiss.	VR-C Omiss.	VR-A Persev.	VR-B Persev.	VR-C Persev.
LM-A Recall	1.00	.75**	.01	.14	.35*	.51**	.57*	.18	.25*	.20
LM-B Recall		1.00	.05	.22	.42**	.53**	.61**	.14	.23	.19
LM-A Persev.			1.00	.28*	.00	.00	.11	.06	.03	.23
LM-B Persev.				1.00	.00	.09	.06	.02	.12	.39**
VR-A Omiss.					1.00	.49**	.42**	.34**	.07	.02
VR-B Omiss.						1.00	.58**	.27*	.08	.09
VR-C Omiss.							1.00	.13	.20	.14
VR-A Persev.								1.00	.08	.10
VR-B Persev.									1.00	.26*
VR-C Persev.										1.00

Legend: LM-Logical Memory, VR-Visual Reproduction.
Note[1]. N=88 Note[2]. 1-tailed: *p<.01, **p<.001.
Note[3]. " . " is printed if a coefficient cannot be computed.

Appendix C

Figure 1: Example of Continuous Perseveration

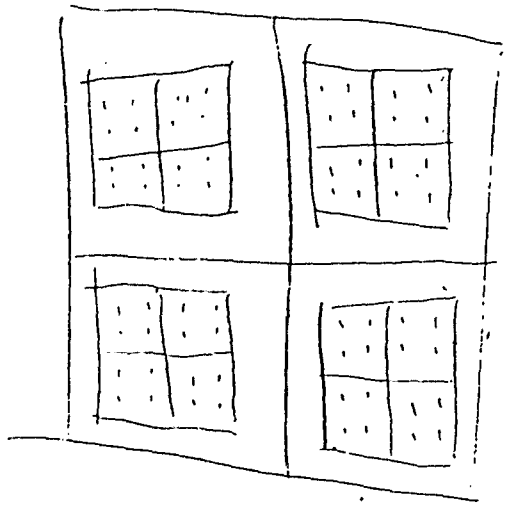
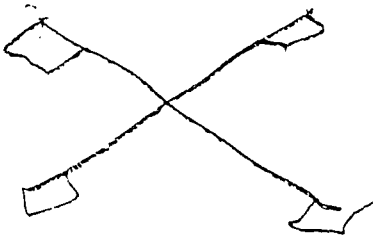


Figure 2: Example of Recurrent Perseveration

VI-A



VI-B