BEHAVIORALLY DEFINED SUBGROUPS

OF PATIENTS WITH ALZHEIMER'S DISEASE

by

DAVID MATTHEW FREED

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ABSTRACT

It has been proposed that rapid forgetting of recently learned visual information is a consequence of medial temporal-lobe pathology. This hypothesis was tested in patients with Alzheimer's disease (AD), who have marked degeneration in medial temporal-lobe structures.

Picture recognition was studied in 20 patients with AD and in 20 control subjects, using a procedure that matched these groups for initial performance. The groups did not differ significantly in overall forgetting, although 10 patients displayed improved recognition performance 72 hours after learning relative to their performance 24 hours after learning. These same patients were impaired relative to other AD patients on a test of attentional focusing, as revealed by posthoc analyses.

A subsequent predictive experiment involving 20 new patients with AD confirmed the initial findings: A subset of patients displayed a rebound in recognition performance 72 hours after learning. This subgroup of AD patients also displayed impairments in attentional focusing. It was postulated that these behavioral deficits were the result of locus coeruleus degeneration, which has been reported at autopsy in some patients with AD.

This hypothesis was tested in a third experiment, which examined the association between deficits in selective attention and reduced levels of MHPG, the major metabolite of norepinephrine, in the cerebrospinal fluid of 22 AD patients. A significant relation between deficits in selective attention and reduced levels of the metabolite was noted when the data were grouped according to gender.

In a fourth experiment, the picture-recognition and attentional focusing tests were used to classify patients according to presumptive locus coeruleus pathology. The two groups of patients thus identified were administered clonidine, a noradrenergic agonist. The two groups responded differentially to clonidine, suggesting that behavioral tests can identify a subgroup of patients with abnormal noradrenergic neurotransmission, possibly reflecting marked degeneration in the locus coeruleus.

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BIOGRAPHICAL NOTE

David Matthew Freed was born March 24, 1958, in Corvallis, Oregon. He graduated from Crescent Valley High School in June 1976. David attended the University of Oregon during the 1976-1977 academic year, and then attended Lane Community College, where he studied automotive technology. David returned to the University of Oregon and graduated with a Bachelor of Science degree in Psychology in June 1982. Upon completion of his studies at the University of Oregon, David was elected to Phi Beta Kappa. David began his graduate studies at the Massachusetts Institute of Technology in 1982, under the guidance of his thesis supervisor, Suzanne Corkin, Ph.D. While at MIT, David was elected to Sigma Xi and appointed a Student Associate of MIT's Clinical Research Center.

INTRODUCTION

It is estimated that 2.5 million Americans have Alzheimer's disease (AD), a neurological disorder characterized by progressive dementia (Blessed, Tomlinson, and Roth, 1968). The essential feature of dementia is a loss of intellectual abilities in a number of realms to the extent that the individual's social or occupational functioning is impaired (D.S.M. III, 1984). Patients with AD display numerous cognitive deficits, including loss of recent memory, disorientation, aphasia, and constructional apraxia (Corkin, 1981). Clinically, a diagnosis of AD is made when other systemic and brain diseases can be excluded as the cause of dementia (McKahn et al., 1984; Khachaturian, 1985).

The memory impairments associated with AD are believed to be due at least in part to a loss of cholinergic neurons originating in the medial septum, diagonal band of Broca, and nucleus basalis of Meynert, which project to the amygdala, hippocampus, cerebral cortex, and olfactory bulb (Whitehouse et al., 1981). It has been suggested that agents that increase the release of acetylcholine (ACh) from cholinergic neurons in the basal forebrain could ameliorate the memory loss (Wurtman et al., 1981). The cholinergic hypothesis, however, has not been validated by clinical trials of choline, lecithin, or physostigmine in patients with AD (Corkin, 1981).

Recent autopsy studies note the existence of a subgroup of patients with severe locus coeruleus (LC) degeneration (Bondareff, Mountjoy, and Roth, 1982; Iversen et al., 1983). Both studies showed that female patients with AD are more likely to display severe LC degeneration than male patients. The purpose of the following experiments was to identify a subgroup of patients with LC pathology using neuropsychological tests.

The experiments addressed four questions: (1) Is there an interaction between recognition memory and selective attention; (2) Are the LC and its major neurotransmitter norepinephrine (NE) involved in selective attention; (3) Can neuropsychological tests identify patients with LC pathology; (4) Are female patients with AD more likely than male patients to display deficits in selective attention, and are these deficits secondary to LC pathology?

The results of these experiments have broader implications for AD research. The identification of subgroups of patients related to neuropathology will improve the physician's ability to treat individual patients. In addition, studies of subgroups of patients are likely to provide insight into the etiology of AD. Other neurological disorders are also associated with LC degeneration (e.g., Parkinson's disease). The results of these experiments provide a framework for studies of selective attention in other types of patients with LC degeneration.

These experiments examine the role that NE plays in recognition memory and selective attention. Because there is a circadian rhythm of NE release in the human (Major, Lerner, and Ziegler, 1984), the experiments reported here have ramifications for studies of human performance. Because brain NE concentrations have been shown to decrease with age (Carlsson, Nyberg, and Winblad, 1984; Robinson et al., 1977), and age-related reductions in LC cell volume have been reported (Mann and Yates, 1979), these experiments also have an impact on studies of normal aging.

SPECIFIC AIMS

The purpose of these experiments was to (1) investigate the psychological basis of the rebound in recognition performance observed in the first experiment by replicating and extending the findings in a second group of patients; (2) test the hypothesis that the LC is involved in the rebound phenomenon by examining the correlation between test performance and levels of metabolites in the cerebrospinal fluid (CSF) of patients with AD; (3) test the hypothesis that noradrenergic neurons are involved in human selective attention by administering the noradrenergic agonist, clonidine, to patients with AD; and (4) assess the adequacy of hypotheses developed from animal research in explaining cognitive deficits related to LC pathology in patients with AD. The following experiments were thus designed to test the hypothesis that neuropsychological tests can identify a subgroup of patients with AD who have LC pathology.

BACKGROUND

Clinical Features of Alzheimer's Disease

AD accounts for approximately 50% of the patients diagnosed as demented and is more prevalent among women than men (McKahn et al., 1984). In the past, the term Alzheimer's disease referred to dementia in patients under the age of 65 (so-called presenile dementia); the term senile dementia was applied to patients over the age of 65 (Katzman, Terry, and Bick, 1978). At present, there is no clear rationale for this distinction, and I will use the term AD to refer to both senile and presenile forms of the disease.

Clinically, a diagnosis of probable AD is made when there is insidious onset and progression of dementia, and no other systemic, brain, or psychiatric disease can be found to account for the disorder (McKahnn et al., 1984). AD is characterized by marked cognitive deficits, including problems in learning and memory, orientation, perception, word-finding, fluency, and praxis. The experiments that comprise this disseration focus on deficits in memory, attention, and word-finding as displayed by patients with AD, and neurochemical correlates of impaired cognition in these realms.

AD advances in an uneven manner, with the initial symptom usually a loss of recent memory, followed by difficulties with language and constructional tasks (Corkin, 1981). Personality changes and behavioral abnormalities are common

features of mild to moderate AD. Other symptoms which are observed in the late stages of AD include poor appetite, unsteady gait, sleep disturbance, and agitation. Most patients' social behavior remains appropriate until the late stages of the disease (Corkin, 1981).

In AD, the snout and grasp reflexes have been correlated with impaired performance on cognitive tests, but not accentuated jaw-jerk, glabellar reflex, paratonia, suck, root, or palmomental reflexes (Tweedy et al., 1982). Generally, these signs correlate more strongly with CT evidence of ventricular dilatation than with cortical atrophy and cannot be considered clinical markers of dementia (Tweedy et al., 1982). It has been noted that the scores on the Digit Symbol subtest of the Wechsler Adult Intelligence Scale (WAIS) and an aphasia battery correctly predicted the stage of dementia 1 year later in a group of mildly demented AD patients over the age of 65 (Berg et al., 1984).

Age at onset has been used to delineate subgroups of patients with AD. Early onset dementia has been associated with more severe aphasia (Seltzer and Sherwin, 1983) and with more severe neurochemical and pathologic features (Bondareff, 1983). Ties between early onset dementia and specific impairments in recognition memory and selective attention will be examined in the experiments that comprise this dissertation. Associations between early onset, aphasia, and familial AD have been emphasized in previous studies (Folstein

and Breitner, 1981; Breitner and Folstein, 1984; Mohs, Silverman, Greenwald, and Davis, 1984).

AD is more prevalent among women than men (McKahn et al., 1984), but it is uncertain whether this finding is an artifact due to the longer life expectancy of women. Recent autopsy reports suggest that women with early-onset AD are more likely to display severe LC degeneration than men (Bondareff et al., 1982; Iversen et al., 1983). The number of cases examined in these studies is relatively small, and the significance of the observation remains unclear. The association between gender and LC degeneration will be examined in the following experiments.

Recent behavioral studies provide further evidence for the existence of subgroups of patients with AD. Chui, Teng, Henderson, and Moy (1985) evaluated clinical subtypes of AD by comparing age at onset, family history, aphasia, and motor disorder in a series of 146 patients. These investigators concluded that early onset was significantly associated with more prevalent and more severe language disorder. Myoclonus and noniatrogenic extrapyramidal disorder were associated with greater severity of dementia, independent of duration of illness. These results provide behavioral evidence of a subgroup of patients with AD, a subgroup characterized by a movement disorder and greater severity of dementia. Mayeux, Stern, and Spanton (1985) confirmed these observations in a series of 121 patients with AD, noting

that patients with extrapyramidal signs or myoclonus had greater intellectual decline and functional impairment in daily activities. Among patients studied longer than 4 years, Mayeux et al. concluded that there were four groups: benign, myoclonic, extrapyramidal, and typical. The authors suggested that "dementia of the Alzheimer type is heterogenous, and that certain clinical manifestations may be useful in predicting outcome."

Chui et al. (1985) also noted that 45% of all probands had a family history of dementia. There was a trend in this study that suggested a relationship between aphasia and family history. Furthermore, there was a near significant trend for patients who could not write a sentence during the course of a mental status examination to have a higher prevalence of familial cases of dementia than those who were not agraphic. These observations support the findings of Breitner and Folstein (1984), who reported that, in older women who were demented for at least 4 years, an inability to write a sentence was associated with a higher family incidence of dementia. These investigators proposed that agraphia or aphasia identifies a subgroup of patients with AD that is transmitted in an autosomal dominant fashion with incomplete and delayed penetrance. It is presumed that the identification of patients with a family history of dementia will delineate a relatively homogenous subgroup of patients with AD prior to autopsy. Unfortunately, it

is difficult to establish a family history of AD retrospectively.

The literature on the clinical features of AD suggests that age at onset, family history, and possibly gender provide a way to categorize patients. Gender and age at onset are the most likely variables to yield a categorization scheme for AD in the near future.

The results of studies by Chui et al. (1985) and Mayeux, Stern, and Spanton (1985) suggest that behavioral measures are also useful in classifying patients with AD. It is assumed that a subgroup of patients displaying specific behavioral deficits are likely to share a pattern of neuropathology as well. Therefore, the identification of distinct subgroups of patients would provide the practicing physician with the means to tailor pharmacological treatments to individual patients.

Neuropathology of Alzheimer's Disease

The neuropathology observed in AD includes senile plaques, neurofibrillary tangles, granulovacuolar degeneration, cerebral atrophy, and subcortical nuclear degeneration (Blackwood and Corsellis, 1976). These topics are addressed in the following paragraphs.

The neuropathologic hallmarks of AD include senile plaques (extracellular clusters of abnormal cell processes and amyloid) and neurofibrillary tangles (intracellular paired helical fragments), which are particularly abundant in temporal-lobe structures, including the hippocampus (Whitehouse et al., 1981; Hyman et al., 1984).

Progressive deterioration of dendrites in cortical and hippocampal pyramidal cells, and granulovacuolar degeneration in the hippocampus are also consistent neuropathological features of AD. Medial temporal-lobe structures, particularly the hippocampus, are known to be involved in disorders of human memory, as epitomized by the famous neurological patient H.M. H.M. underwent a bilateral medial temporal-lobe resection for the relief of intractable epilepsy and has been the subject of many experiments (Milner, Corkin, and Teuber, 1968; Corkin, 1984).

The pathological changes in the brains of AD patients also include diffuse cortical degeneration, especially severe in the temporal and parietal lobes (Blackwood and Corsellis,

1976; Brody, 1978). The posterior cingulate gyrus, amygdala, hypothalamus, hippocampus, and certain midbrain structures are also affected in AD (Arai, Kosaka, and Iizuka, 1985).

In regard to subcortical nuclear degeneration, Whitehouse et al., (1981) reported that patients with AD had significantly fewer cholinergic neurons in the nucleus basalis of Meynert than did age-matched control subjects. Recently, it was suggested that when the cholinergic cell count in the basal forebrain drops below about 100,00 cells, the level of cortical choline acetyl-transferase (CAT) may be so low that clinical dementia appears (McGeer et al., 1984). Other investigators noted significant decreases in the level of CAT, the rate limiting enzyme in the formation of ACh, in the brains of patients with AD (Davies and Maloney, 1976). The decrease in CAT activity in AD is much greater than occurs in elderly subjects who are not demented. Furthermore, the decrease in CAT activity correlates with the regional distribution and number of senile plaques and neurofibrillary tangles in patients with AD.

The basal forebrain is a primary source of cholinergic neurons that project widely to cortical targets (Whitehouse et al., 1981). It was hypothesized that the memory impairments associated with AD were due at least in part to degeneration of neurons in the nucleus basalis of Meynert, diagnonal band of Broca, and medial septal area, structures that project to the amygdala and hippocampus as well as the cerebral

cortex (Whitehouse et al., 1981). It was assumed, therefore, that the memory impairments seen in AD were due to a loss of cholinergic neurons in structures believed to be important for learning and memory. Recent attempts to treat the memory impairments associated with AD using cholinergic agents have been disappointing, however. This lack of support for the cholinergic hypothesis might mean that one or more non-cholinergic neurotransmitters are involved in AD (Corkin, 1981).

Reports of subcortical nuclear degeneration in AD suggest that the LC, raphe nuclei, and substantia nigra are also affected and that neurotransmitters other than ACh may be involved in the pathogenesis of AD; evidence exists of chemoanatomical heterogeneity in the neuropathology of AD (Perry et al., 1981; Bondareff et al., 1982; Mann, Yates, and Hawkes, 1982; Iversen et al., 1983; Arai et al., 1985). Bowen et al. (1983) concluded that biochemical markers of serotonergic synapses are significantly reduced in neocortical brain tissue from patients with AD. For samples from the temporal lobe, the reduction in markers of postsynaptic serotonergic receptors was a feature only of neocortical samples taken from the brains of patients with early onset AD (Bowen et al., 1983). These same authors concluded that CAT activity was significantly reduced in all groups of Alzheimer specimens, irrespective of age. Bowen et al. (1983) suggested that in AD there is loss of neuronal structures

other than those associated with cholinergic perikarya in the basal forebrain. This suggestion is supported by the results of a study by Arai et al. (1985). These investigators noted significant degeneration in midbrain raphe neurons in patients with AD, as well as elevated numbers of neurofibrillary tangles in this region.

A number of investigators have reported significant LC degeneration in the brains of patients with AD (Perry et al., 1981; Bondareff et al., 1982; Iversen et al., 1983; Arai et al., 1985). Bondareff et al. (1982) reported significant LC degeneration in 12 of 20 cases of AD studied at autopsy. The subgroup of AD patients with significant LC degeneration included more women than men and was characterized by a high dementia score and a relatively young age at death. Iversen et al. (1983) studied 6 cases of AD and reported that LC neuron loss varied considerably, with some cases showing significant LC degeneration. Mann et al. (1982) reported that in 8 of 19 AD cases, there was "gross underpigmentation" in the LC.

The subcortical nuclear degeneration observed in the brains of patients suggest that the cholinergic, noradrenergic, and, to a lesser extent, the serotonergic neurotransmitter systems are affected in AD. Due to the disappointing results of attempts to treat the memory impairments associated with AD using choinergic agents, recent reports of severe LC degeneration in a subgroup of patients with AD, and the

results of animal experiments which suggest that NE is involved in learning and memory (see the section on animal behavior), the experiments that comprise this dissertation focus on the noradrenergic system and its role in AD.

Neurochemistry of Alzheimer's Disease

The neurochemical changes that take place in the brains of patients with AD are presumed to be the result of alterations in the expression of functional molecules in specific clusters of neurons, as described in the previous section. Therefore, the following discussion on the neurochemistry of AD will begin with a review of abnormal proteins found in the brains of patients with AD and subsequent sections will be organized according to the neurotransmitters involved.

Abnormal Proteins

Amyloid deposition in the walls of small intracortical blood vessels (congophilic angiopathy) occur less frequently in cortex from patients with AD than do neuritic plaques and neurofibrillary tangles (Blackwood and Corsellis, 1976). The term amyloid refers to tissue deposits of proteinaceous fibrils, which vary widely in their protein compositions. Amyloid deposits have a common molecular conformation, referred to as a beta-pleated sheet configuration. Amyloid fibrils are composed of immunoglobulin light chains or their proteolytic fragments or both. Amyoid is an end-stage product of a variety of disease processes. All amyloid is characterized by a high degree of insolubility in laboratory solvents and resistance to proteolytic digestion (Selkoe, 1982). The nature of amyloidosis observed in the human brain as

neuritic plaque cores and congophilic angiopathy, therefore, is not well understood and awaits purification and chemical analyses (Selkoe, 1982).

Lipofuscin deposition in neurons and glia has been linked to the aging process. Lipofuscin granules are highly heterogenous and include lipids, proteins, cations, and acid-resistant residues (Corsellis and Blackwood, 1976). It is of interest that lipofuscin granules copurify with neurofibrillary tangles and the amyloid core of senile plaques in the detergent-insoluble fraction of cortex from patients with AD (Selkoe, 1982).

Recently, Wolozin, Pruchnicki, Dickson, and Davies (1986) prepared monoclonal antibodies against brain tissue from patients with AD in order to study abnormal proteins that may be present in AD. The investigators isolated an abnormal protein called Alz-50 from the brains of patients with AD. This protein is found in neurons involved in the formation of neuritic plaques and neurofibrillary tangles. Alz-50 immunoreactivity appears to precede the deposition of neurofibrils to form tangles. Thus Alz-50 may recognize a precursor to tangle formation. The function and identity of the proteins recognized by Alz-50 remains to be elucidated, however. The results of this study raise the possibility that a diagnosis of AD can be confirmed through the use of monoclonal antibodies to Alz-50 and that blocking the synthesis of Alz-50 may be useful in the treatment of patients

with AD.

Acetylcholine

Bowen, Smith, White, and Davison (1976) presented the first evidence that a specific neurotransmitter deficit occurred in AD. These authors reported that the activity of choline acetyl-transferase (CAT), the enzyme that acetylates choline to form ACh, was reduced in the brains of patients with AD. Other investigators quickly confirmed these results (Davies and Maloney, 1976), and noted that muscarinic receptor binding was normal in AD (Perry, Perry, Blessed, and Tomlinson, 1976; White et al., 1977). Acetyl cholinesterase (AChE), the enzyme that degrades ACh, is significantly reduced in the brains of patients with AD (Terry and Davies, 1980). The decrease in CAT activity observed in AD correlates with the regional distribution and number of senile plaques and neurofibrillary tangles, as well as mental status (Blessed et al., 1968). These correlations suggested that decreased CAT activity may be important in the clinical manifestation of AD and motivated a number of attempts at therapeutic intervention (Growdon and Corkin, 1980), which to date have been disappointing (Corkin, 1981).

Norepinephrine

Decreased brain levels of NE apparently occur as part of the aging process (McGeer and McGeer, 1976). The metabolism

of NE has been reported to be affected by AD as well (Adolfsson et al., 1978; Nyberg et al. 1984). Reports that certain patients with cholinergic deficits also show reductions in NE have been discounted on the grounds that the clinical diagnoses of AD were not checked against autopsy findings (Corkin, 1981). However, the apparent ineffectiveness of lecithin precursor treatment in AD may mean that one or more non-cholinergic neurotransmitters are involved in AD (Corkin, 1981). Moreover, recent neuropathological evidence demonstrates the existence of a subgroup of patients with severe LC degeneration (Bondareff et al., 1982; Iversen et al., 1983), as discussed in the previous section.

Reports of LC degeneration are supported by the existence of significant decreases of NE and its metabolites in the brains of patients with AD (Arai et al., 1985; Winblad et al., 1980) because the LC is the major source of cortical NE. A noradrenergic deficit in AD has been found by almost all investigators who have studied this possibility (Nyberg, 1984). These studies are complicated by the fact that the superior cervical ganglion, a peripheral nervous system structure, has extensive noradrenergic projections to cerebral arteries. It is difficult, therefore, to claim that reductions in brain NE are due solely to LC degeneration. Regardless, it is likely that the noradrenergic as well as the cholinergic neurotransmitter system is affected in AD.

Dopamine

Evidence for a reduction in levels of dopamine (DA) in the brains of patients with AD is less conclusive than that for involvement of the cholinergic or noradrenergic systems (Nyberg, 1984). Thus, there is evidence supporting (Adolfsson et al., 1979; Carlsson et al., 1980; Mann et al., 1980) and refuting (Yates et al., 1979; Yates et al., 1983) a dopaminergic loss. Data concerning the DA metabolite homovanillic acid (HVA) in both brain and CSF are also conflicting (Nyberg, 1984).

Serotonin

Data concerning the state of the serotonergic system in AD are relatively sparse (Nyberg, 1984). Most studies to date, however, agree that there is a loss of serotonergic activity in the brains of patients with AD. Reduced nucleolar volume in the raphe area (Mann and Yates, 1983) and the presence of tangles in these nuclei (Ishii, 1966) have been observed. Serotonin concentrations in the brains of patients with AD have been reported to be reduced (Adolfsson et al., 1979; Carlsson et al., 1980). Bowen et al. (1983) reported that when AD samples were subdivided according to age, there was a significant reduction in serotonin binding, but not DA binding, that was a feature of autopsy samples from younger patients only. In contrast, presynaptic cholinergic activity was reduced in all groups of AD samples in this study.

Bowen et al.'s (1983) results must be regarded carefully, however, because the exact relationship between neurotransmitter synthesis and receptor binding is unclear as of yet; decreases in neurotransmitter synthesis do not necessarily imply decreases in receptor binding. In fact, reductions in brain levels of NE have been shown to result in increased numbers of noradrenergic receptors (U'Prichard, Greenberg, Sheehan, and Snyder, 1977; Pandey and Davis, 1981; Janowsky et al., 1982), which has been termed up-regulation. This form of regulation may also exist for other neurotransmitter systems.

Somatostatin

Another neurotransmitter that has been investigated in patients with AD is somatostatin. A recent study by Beal, Growdon, Mazurek, McEntee, and Martin (1984) demonstrated reduced CSF concentrations of somatostatin-like immunoreactivity (SLI) in AD. The reduced CSF concentrations of SLI are consistent with known reductions of SLI in the cerebral cortex of patients with AD (Rossor, Emson, Iversen, Mountjoy, and Roth, 1984). The results of Beal et al.'s (1984) study suggest that decrements in CSF SLI concentration lack diagnostic specificity and must be considered in combination with other neurochemical markers.

The studies described above suggest that levels of biogenic amines may be reduced in the brains of patients

with AD. It should be noted, however, that measures of neurotransmitters in the brain can be affected by a variety of factors, including age, sex, and the amount of time elapsed since death. Only reports of reduced brain levels of ACh, NE, and to a lesser extent serotonin, are supported by studies of the neuropathology characteristic of AD, as described in the previous section. Because recent attempts to treat patients with AD using cholinergic agents have been disappointing and reports of raphe neuropathology in AD are relatively sparse, the following experiments center on the behavioral deficits presumed to be related to LC degeneration.

Overview of Locus Coeruleus Neuroanatomy

Given the reports of LC neuropathology in patients with AD, knowledge of the organization of this nucleus is likely to provide clues to its role in cognition.

The cell bodies and efferent connections of the LC have been studied since the 1960s using the Falck-Hillarp fluorescent histochemical method, which allows the visualization of catecholamine-containing neurons (Swanson and Hartman, 1975; Moore and Bloom, 1979). The LC is a source of both dopaminergic and noradrenergic fibers, which cannot be reliably differentiated using the Falck-Hillarp method alone (Foote, Aston-Jones, and Bloom, 1980). The development of immunohistochemical methods in the past decade has provided the means to identify catecholamine-containing neurons through antibodies directed against tyrosine hydroxylase. Immunohistochemical methods can also be used to distinguish NE-containing neurons through antibodies directed against dopamine-beta-hydoxylase, an enzyme specific for these cells.

In the rat, the ascending fibers of the LC that enter the medial forebrain bundle give rise to several distinct groups of fibers (Swanson and Hartman, 1975; Moore and Bloom, 1979). The largest group is made up of fibers that leave the medial forebrain bundle laterally along its course to enter the ansa peduncularis/ventral amygdaloid bundle. Another group enters the mammillothalamic tract to ascend

to anterior thalamic nuclei. At the caudal septum, fibers in the medial forebrain bundle divide into five major groups. One group ascends medially into the diagonal band of Broca to innervate the septum and enter the fornix. A second group enters the stria medullaris caudally and continues to the habenular nuclei. A third group enters the stria terminalis and eventually reaches the amygdaloid complex. A fourth group continues in the medial forebrain bundle and projects to the basal telencephalon. A fifth group of fibers projects around the genu of the corpus callosum and then continues caudally in the cingulum (Moore and Bloom, 1979).

Two other groups of fibers leave the LC. One ascends via the superior cerebellar peduncle to innervate the cerebellum. Another descends in the central tegmental bundle to enter the ventral portion of the lateral column of the spinal cord (Moore and Bloom, 1979).

The septal area of the rat is known to receive a rich projection of axons arising from the LC and nuclei in the caudal brainstem. LC axons distribute in the septal area to the hippocampal rudiment, the nucleus of the diagonal band, the interstitial nucleus of the stria terminalis, the medial septal nucleus, the lateral septal nucleus, and the nucleus septofimbrialis (Moore, part 1, 1978).

Moore (part 2, 1978) used histofluorescence and a tyrosine hydroxylase assay to study the efferent connections of the

LC. Moore noted that the amygdala and entorhinal cortex have a moderate catecholamine content, arising primarily from the LC. Later studies have confirmed that the LC is the major source of NE innervation of the telencephalon (Grzanna and Molliver, 1980; Foote, Bloom, and Aston-Jones, 1980) through the use of the NE-specific dopamine-beta-hydroxylase immunocytochemistry. It has recently been shown that populations of LC neurons contain the peptides neuropeptide Y and galanin, in addition to NE (Holets, Hokfelt, Terenius, and Goldstein, 1984). These investigators concluded that 99% of LC neurons contain tyrosine hydroxylase. Of the population of neurons containing tyrosine hydroxylase, 25% contained neuropeptide Y and 83% contained galanin. Holets et al. (1985) suggested that there are functional divisions in the LC based on the peptide contained within the neurons and their afferent projections.

Shipley, Halloran, and De La Torre (1985) used a horseradish-peroxidase retrograde tracing method in rats and reported that at least 40% of all LC neurons project to the olfactory bulb. Shipley et al. (1985) noted that the LC projection to the olfactory bulb is nearly 10 times greater than to any other part of the cerebral cortex. These data suggest that patients with LC degeneration may display deficits in olfaction.

Other investigators found that the distribution of LC neurons and their fibers in a pygmy primate was similar

to that observed in the rat (Jacobwitz and MacLean, 1978). Jacobwitz and MacLean (1978) used the Falck-Hillarp method and noted that the findings "conform in essential details to what has been described in rodents." Later studies of the primate LC (Schofield and Everitt, 1981a; Schofield and Everitt, 1981b) have been consistent with the previously described reports in rodents.

Morrison, Molliver, Grzanna, and Coyle (1981) studied the trajectory of the coeruleo-cortical projection in the rat using histofluorescence as well as immunohistochemistry. The immunohistochemical procedure made use of an antibody directed against rat dopamine-beta-hydroxylase, which is specific to noradrenergic neurons. Morrison et al. (1981) concluded that "the tangential, intracortical trajectory of the noradrenergic fibers would confer upon the coeruleo-cortical system the capacity to modulate neuronal activity simultaneously through a vast expanse of cortex." The ultra-structure of LC neurons suggest that NE may function to modulate ongoing activity over widely dispersed neuronal populations for relatively long periods of time rather than exerting a direct one-to-one influence on individual postsynaptic cells (Dismukes, 1977).

The LC projects to virtually all components of the amygdaloid complex, although these projections are preferential to the central nucleus of the amygdala (Moore and Bloom, 1979). The hippocampus receives NE projections exclusively

from the LC (Moore and Bloom, 1979). The amygdala and hippocampus are known to be involved in human memory disorders, as epitomized by the patient H.M. For other cortical areas, it is estimated that each cubic millimeter of cerebral cortex contains approximately 96,000 LC NE terminals (Lapierre et al., 1973). Each rat LC neuron is believed to have an axon at least 30 cm in length, with over 100,000 terminals (Moore and Bloom, 1979).

The LC has rich projections to the amygdala, hippocampus, and basal forebrain. These areas are the primary sites of neuropathology in AD (Whitehouse et al., 1981). A monosynaptic pathway from the LC to the hippocampus has been described (Segal and Bloom, 1974). Cytochemical, pharmacological, and iontophoretic data indicate that this pathway utilizes NE to inhibit hippocampal pyramidal cells. In addition, there is a striking correlation between the reinforcing properties of LC stimulation and the inhibitory effects in the hippocampus (Segal and Bloom, 1976). Based on physiological and behavioral data, Segal and Bloom (1976) concluded that the LC and its projections to the hippocampus are involved in selective attention. Detailed electrophysiological studies of the basis of NE-induced depression suggest that NE differentially suppresses background activity induced by afferent input with a resulting enhancement of the evoked excitation (Quartermain, 1983; Segal and Bloom, 1976). NE appears to increase signal-to-noise ratio rather than uniformly

inhibiting activation (Segal and Bloom, 1976). It has been suggested that NE could promote learning and facilitate retrieval by suppressing irrelevant background information, while simultaneously amplifying inputs from significant environmental stimuli (Segal and Bloom, 1976).

Other investigators have proposed that selective attention is the result of a neural mechanism that serves a screening function similar to the one identified by Segal and Bloom in their electrophysiological data (Rabbitt, 1965; Mason and Iversen, 1978a; Mesulam and Geschwind, 1978; Quartermain, 1983; Foote, Bloom, and Aston-Jones, 1983; Mair and McEntee, 1983; Posner, Walker, Friedrich, and Rafal, 1984). A number of these studies implicate NE in the neural processes that filter out irrelevant stimuli (Mason and Iversen, 1978a; Quartermain, 1983; Foote, Bloom, and Aston-Jones, 1983; Mair and McEntee, 1983). These studies support the prediction that patients with AD who have LC degeneration display deficits in selective attention.

Animal Behavior and the Locus Coeruleus

A number of procedures have been used to study the role of LC noradrenergic neurons in behavior. Because the LC is the major source of cortical NE, pharmacological techniques are particularly relevant. This approach uses drugs that fall into one of several categories: synthesis blockers (e.g. diethyl dithiocarbamate [DEDTC] and bis[4-methyl-1-hompiperazinylthiocarbonyl] isulphide [FLA-63]), neurotoxins (e.g. 6-hydroxydopamine [6-OHDA]), receptor blockers (e.g. propranolol), reuptake blockers (e.g. desipramine), MAO inhibitors (e.g. iproniazid), and receptor agonists (e.g. clonidine).

Synthesis blockers have been used in a large number of studies. The results indicate that this manipulation may impair, enhance, or have no effect on retention depending upon the training regime and retention intervals employed (Quartermain, 1983). The first study that demonstrated that depletion of NE can impair memory was a study by Krantz and Seiden (1968). These investigators found that DEDTC administered 24 hours after learning disrupted retention when rats were tested 6 hours following drug treatment but not at longer times. Spontaneous recovery following amnesia induced by the use of synthesis blockers has been reported in several other studies. For example, Botwinick, Quartermain, Freedman, and Hallock (1977) found that amnesia for a multiple-trial discrimination task induced by FLA-63 was present 24 hours after training, but full recovery was observed at 48 hours. A similar

recovery from amnesia was reported after the administration of DEDTC (Freedman, Backman, and Quartermain, 1979). Quinton and Bloom (1977) demonstrated that administration of d-amphetamine 30 minutes before testing induces recovery of memory in DEDTC-treated mice who had failed to show spontaneous recovery. A study by Izquierdo, Beamish, and Anisman (1979) investigated the amnestic effects of FLA-63 on four different avoidance tasks in mice. Results showed that pre- but not post-training resulted in amnesia in three of the four tasks. The drug did not disrupt retention of a task requiring immobility to avoid shock. This experiment confirmed several findings reported by Botwinick et al., (1977). Taken together these results suggest that NE is involved in spontaneous recovery of memory and that improved performance is not due to transient FLA-63 or DEDTC toxicity.

Rainbow, Adler, and Flexner (1976) compared the amnestic effects of 6-OHDA treatment to those induced by the protein synthesis inhibitor cycloheximide. Retention was tested 6 hours and 24 hours posttraining. The results of this study indicated that whereas cycloheximide-induced amnesia disrupted retention at both retention intervals, 6-OHDA-treated mice were amnestic only at the 24-hour test. Flexner and Rainbow (1978) reported that mice with 6-OHDA lesions of the dorsal bundle displayed amnesia for a multiple trial discrimination task 24 hours after learning but not 72 hours after learning, also implicating NE in the phenomenon of spontaneous recovery. It should be noted that the dorsal bundle is the major efferent pathway of the

LC.

Crow and Wendlandt (1976) examined the effects of depletion of hippocampal and forebrain NE by injecting 6-OHDA bilaterally into the LC. Rats were subsequently trained on a passive avoidance task and retention tested immediately and 72 hours posttraining. Acquisition and immediate retention were normal, but significant retention deficits were observed at the 72-hour retention interval.

Increased resistance to extinction appears to be the most obvious sequela of depletion of NE (Mason and Iversen, 1979). Lorden, Rickert, Dawson, and Pelleymounter (1976) reported that rats with 6-OHDA lesions of the dorsal bundle failed to suppress previously learned behavior after reinforcement was discontinued. These results are consistent with the hypothesis that NE plays a role in selective attention. It has been suggested that NE could promote learning and facilitate retreival by suppressing irrelevant background information while amplifying inputs from significant environmental stimuli (Segal and Bloom, 1976). Animals with reductions in brain NE would thus be expected to display increased resistance to extinction as a result of impaired attention to the new task demands. Mason and Iversen (1979) reported that rats with dorsal bundle lesions were more distractable than normal animals, providing further support of this hypothesis. Similar observations have been made concerning rats with hippocampal lesions (Mason and Iversen, 1979), raising the possibility that the hippocampus mediates some of the behavioral effects of NE. This conclusion is supported by the numerous behavioral deficits

common to rats with dorsal bundle lesions and hippocampal lesions. Both result in reduced spatial alternation, improved reversal learning in spatial tasks, impaired light/dark discrimination and reversal learning, increased resistance to extinction, failure to display blocking in the non-reversal shift paradigm, reduced latent inhibition, decreased habituation, and "neophobias" to novel environments (Mason and Iversen, 1975; Mason and Iversen, 1979; Mason and Iversen, 1978 a,b,c; Lorden et al., 1976; Mason and Fibiger, 1978; Mason and Fibiger, 1979).

A number of investigators have noted that rats with 6-OHDA lesions of the dorsal bundle displayed deficits in selective attention (Mason and Iversen, 1978; Lorden et al., 1976). These same animals had significantly decreased levels of forebrain NE. Segal and Bloom (1976), on the basis of electrophysiological evidence, proposed a role for NE in selective attention. Mason and Iversen (1978) suggested that the LC is involved in "filtering out irrelevant stimuli," based on behavioral data. Other investigators have concluded that rats with dorsal bundle lesions are unable to ignore redundant stimulus information (Lorden et al., 1976), consistent with the hypothesized role of NE in selective attention. These findings lead to the prediction that in the human subject, LC degeneration secondary to AD will result in deficits similar to those observed in experimental animals.

Recently, Arnsten and Goldman-Rakic (1983) demonstrated that the alpha-2 noradrenergic agonist clonidine can ameliorate the cognitive deficts exhibited by aged nonhuman primates on

a delayed-response task. These investigators noted that there is an age-related decline in brain levels of NE in man and animals. The results of this study demonstrate that the noradrenergic system contributes to cognitive function. Furthermore, the demands of the delayed-response task require the subject to ignore one or more identical food wells, and thus the task requires the means to filter out irrelevant stimuli.

Other aspects of attention will be reviewed in the following section, particulary as they relate to the human. It will be shown that selective attention is the domain most likely to be impaired in patients with LC pathology, consistent with the results of studies using experimental animals.

The Role of NE in Human Cognition

The discovery of LC neuropathology in patients with AD, as well as the failure of ACh precursor treatment, argue that the role of NE in human cognition must be investigated. Several lines of evidence from the animal literature suggest that the noradrenergic system is involved in memory (Quartermain, 1983) and selective attention (Segal and Bloom, 1976; Lorden et al., 1976; Mason and Fibiger, 1978 a,b), as reviewed in the preceding section. The present discussion is confined to the clinical literature, including the cognitive impairments associated with aging and Korsakoff's syndrome (KS).

Attention is not a unitary factor and has been subdivided into three realms: vigilance, arousal, and selective attention (Posner, Nissen, and Ogden, 1978). Davies and Griew (1965) reviewed the literature on the effects of aging on vigilance. These investigators concluded that there is not a consistent effect due to age in studies of vigilance. Davies and Griew (1965) also concluded that vigilance and arousal interact. Rosvold, Mirsky, Sarason, Bransome, and Beck (1956) reported that patients with senile dementia were impaired on a vigilance task which they called the Continuous Performance Test. It should be noted that the deficits observed in this group of patients could be attributed to impairments in selective attention, rather than vigilance, due to the nature of the task, which required subjects to respond to a target sequence

of letters and to ignore irrelevant sequences of letters. This report illustrates the difficulty involved in separating aspects of attention. It has been argued that the effect of arousal on test performance is due to motivational factors, which are subject to individual differences and are difficult to assess reliably (Davies and Griew, 1965). Selective attention has been defined as the ability to ignore redundant or irrelevant stimuli (Segal and Bloom, 1976; Lorden et al., 1976; Mason and Iversen, 1978a), and it is this realm of attention which is most likely to be impaired in patients with LC degeneration, as noted in the previous section.

Mair and McEntee (1983) believe that KS has two major advantages as a human model of central NE impairment. First, KS is associated with a consistent pattern of pathology that is restricted to medial regions of the brainstem and diencephalon (Victor and Adams, 1953). The LC lies on the floor of the fourth ventricle, an area of the brainstem affected by KS (Victor and Adams, 1953). Second, KS is associated with a "homogenous and circumscribed pattern of cognitive impairment" (Mair and McEntee, 1983, p. 9), consistent with the impairments in selective attention displayed by animals with 6-OHDA lesions of the dorsal bundle (Lorden et al., 1976; Mason and Fibiger, 1978). McEntee, Mair, and Langlais (1982) reported that patients with KS had significantly reduced levels of MHPG in lumbar CSF, further evidence that KS is associated with central NE impairment.

The reductions in CSF MHPG observed in patients with KS had a small effect on overall intelligence (McEntee, Mair, and Langlais, 1982), as measured by the Wechsler Adult Intelligence Scale (WAIS). Patients with KS were impaired, however, on two subtests of the WAIS, Digit-Symbol substitution and Object Assembly. In addition, patients were significantly impaired on Wechsler Memory Scale (WMS) subtests that measure recall of a brief story, visual reproduction, and associative learning.

When patients with KS were given the noradrenergic alpha-2 agonist, clonidine, a significant improvement was noted in the WMS subtests that measure visual reproduction and story recall (Mair, McEntee, and Zatorro, 1982). For 21 patients with KS, a positive correlation was observed between levels of MHPG in CSF and performance of the memory passages, associative learning, and visual reproduction (Mair, McEntee, and Zatorro, 1982). There is no explanation, however, as to why clonidine, a drug that decreases NE release in normal subjects due to agonistic effects exerted on alpha-2, presynaptic autoreceptors, should improve memory performance in patients with KS, who have reduced levels of NE. It is possible that changes in receptor sensitivity and number may mediate the therapeutic effects of clonidine in patients with KS.

Talland (1965) studied the cognitive impairments observed in patients with KS. He found that although KS patients were capable of resisting distraction in a simple task, they displayed diminished orientation responses and were strikingly impaired in their ability to shift the focus of attention in a digit-span task. Talland also noted that the performance of KS patients on a motor task decayed more quickly than did that of normal subjects when required to divide attention. Talland remarked that the capacity to shift the focus of attention involves the ability to attend to a relevant set of stimulus cues and subsequently to refocus attention. Talland's (1965) study suggests that patients with KS display deficits in selective attention that are similar to those displayed by animals with 6-OHDA lesions of the dorsal bundle (Segal and Bloom, 1976; Lorden et al., 1976; Mason and Fibiger, 1978 a,b,c).

Mair and McEntee (1983) measured the orientation responses of KS patients to an auditory stimulus and found that they had smaller initial galvanic skin responses and habituated less rapidly than did brain-damaged control subjects, consistent with Talland's (1965) findings. When the patients with KS were given clonidine, they showed improved memory performance and orientation, with galvanic skin responses approaching normal amplitude and normal rate of habituation. These results are consistent with the hypothesis that attention is dependent upon the level of central NE activity. The

implication of deficits in selective attention in KS thus provides a mechanism that may account for other deficits associated with this syndrome (Mair and McEntee, 1983).

Given the findings in patients with KS, it is likely that AD patients with reduced levels of MHPG secondary to LC degeneration will display deficits in selective attention. A role for NE neurons in selective attention is consistent with observations drawn from studies of experimental animals (Segal and Bloom, 1976; Lorden et al., 1976; Mason and Fibiger, 1978 a,b,c).

Previous Studies of Forgetting in Amnesic Patients

In humans, global amnesia can result from damage to a variety of brain structures and can be consequent to a number of neurological conditions. The etiologies considered in the present discussion involve either diencephalic or medial temporal-lobe structures bilaterally. Specifically, lesions in the dorsomedial nucleus of the thalamus and the mamillary bodies are the neuropathological hallmarks of the amnesia seen in Korsakoff's syndrome (Victor and Adams, 1953; Victor, Adams, and Collins, 1971; Mair, Warrington, and Weiskrantz, 1979); lesions of medial temporal-lobe structures are also implicated in global memory disorders, as epitomized by the famous neurological patient H.M. This patient underwent a bilateral medial temporal-lobe resection in 1953 and has had a profound anterograde amnesia since that time (Scoville and Milner, 1957; Milner, Corkin, and Teuber, 1968; Corkin, 1984).

L'Hermitte and Signoret (1972) hypothesized that amnesias can take different forms related to the site of neuropathology. Huppert and Piercy (1979) reported that H.M. displayed rapid forgetting in relation to control subjects, whereas patients with diencephalic pathology due to Korsakoff's syndrome did not. Huppert and Piercy (1979) argued that there was a functional basis for distinguishing amnesias associated with lesions in medial temporal-lobe structures from amnesias

associated with lesions in the medial thalamus and mamillary bodies. The evidence for this distinction came from studies with a picture-recognition technique in which amnesic patients were provided additional study time in order to make their initial yes-no recognition performance comparable to that of control subjects (Huppert and Piercy, 1978). Forgetting was then assessed 24 hours and 1 week later.

Huppert and Piercy's (1979) study is flawed, however. H.M.'s initial performance was below that of control subjects, despite Huppert and Piercy's attempt to equate H.M.'s initial performance to that of control subjects. Huppert and Piercy's conclusion that medial temporal-lobe pathology is associated with rapid forgetting is therefore open to question.

Also problematic is the interpretation of Squire's (1981) experiments with the same paradigm, which he cited as supporting Huppert and Piercy's view. Squire found that patients tested 2 hours after electroconvulsive therapy (ECT) displayed rapid forgetting for sentences relative to their performance on another form of the sentence test administered 4 months later, and relative to the performance of a patient (N.A.) with well-localized damage to the dorsomedial nucleus of the left thalamus. This latter patient showed a rate of forgetting similar to that of control subjects. These findings provide only weak support for Huppert and Piercy's view that medial temporal-lobe pathology is associated with rapid forgetting because the brain areas implicated

in the memory disorder seen after ECT have not been identified. Squire's presumption that bilateral involvement of the medial temporal lobes causes the memory disorder after ECT was based upon indirect evidence (Inglis, 1970) and on Huppert and Piercy's questionable results with H.M.

A recent study (Freed, Corkin, and Cohen, manuscript submitted) calls into question Huppert and Piercy's (1979) conclusion that medial temporal-lobe pathology is associated with rapid forgetting. This study employed a picture-recognition task, incorporating a two-alternative forced-choice format (also called delayed-match-to-sample or DMS) in addition to the yes-no format that Huppert and Piercy used. When the mean of several test administrations was examined, H.M. displayed a normal rate of forgetting over a 1-week delay interval using both yes-no and DMS procedures. Further, we have subsequently shown that H.M.'s DMS and delayed-non-match-to-sample (DNMS) recognition 6 months after learning was similar to that of control subjects (Freed and Corkin, 1985), although H.M.'s yes-no recognition at this delay interval was at a chance level. The DMS and DNMS data are at variance with Huppert and Piercy's claim that bilateral lesions in medial temporal-lobe structures cause accelerated forgetting. Taken together, these results argue that the amnesia due to a radical resection of the medial temporal-lobes cannot be explained by abnormally rapid forgetting, provided that initial learning has been equated.

H.M.'s memory disorder resulted from surgical excision of medial temporal-lobe structures (Scoville and Milner, 1957; Milner, Corkin, and Teuber, 1968; Corkin, 1984). The memory disorder associated with AD is believed to be due at least in part to pathology in the same areas (Whitehouse et al., 1981; Hyman, Van Hoesen, Damasio, and Barnes, 1984). Therefore, the role of medial temporal-lobe structures in forgetting should be investigated further in patients with AD.

EXPERIMENT 1

Rate of Forgetting in Alzheimer's Disease

It is conceivable that the unrecognized existence of subgroups of patients related to neurotransmitter abnormality has precluded the identification of drugs useful in the treatment of AD (Corkin, 1981). The characterization of neurotransmitter-related subgroups of patients with AD would therefore allow tailoring of treatments to specific patient groups. The premorbid identification of subgroups of patients with AD would also have profound implications for studies concerned with etiology because different patterns of neuropathology are likely to be related to different causes.

Attempts to distinguish behavioral subgroups have focused on initial symptom. It has been noted that the largest subgroup includes those patients with a memory disorder as the initial symptom (Corkin, 1981). L'Hermitte and Signoret (1972) hypothesized that amnesias can take different forms related to the site of neuropathology. Huppert and Piercy (1979) used a picture-recognition paradigm to study rate of forgetting in patient H.M. and in patients with KS, as discussed in the preceding section. The following experiment explored the possible existence of subgroups of patients with AD, focusing on memory performance, while testing Huppert and Piercy's (1979) hypothesis that medial temporal-lobe

pathology is associated with rapid forgetting.

Method

Subjects

The subjects were 10 men and 10 women with AD and 8 healthy men and 12 healthy women, matched to the patients on the basis of age and educational background (Table 1). The patients had a clinical diagnosis of AD made in accordance with recent NINCDS and NIA diagnostic guidelines (McKahn et al., 1984; Khachaturian, 1985). The 20 patients had a mean Blessed Dementia Scale Score (BDS) of 15.6 (range: 5 - 30). Patients with a BDS score below 10 were considered mildly demented, those patients with a score of 10 to 19 moderately demented, and those patients with a score over 19 severely demented. Healthy elderly subjects scored from 0 - 3 on the BDS and were not demented according to DSM-III, NINCDS, and NIA criteria. All patients with AD had evidence of memory impairment on neuropsychological testing.

Test Materials

A picture-recognition procedure was chosen for this investigation because the technique is ecologically valid, is pleasurable for the subjects, and allows the matching of initial recognition performance across patients who vary in the severity of their memory disorder.

Table 1

Characteristics of Control Subjects and Patients in Experiment 1

Group	Male	Female	Mean Age (years)	Mean Ed (years)
Healthy Elderly Subjects	8	12	63.4	13.1
Patients with Alzheimer's Disease	10	10	65.6	13.5

Four different forms of the picture-recognition test were constructed from a total of 720 color slides of complex photographs reproduced from foreign language magazines. The material for each form of the test was organized into 2 sets of 90 slides: 1 set was designated to serve as targets and the other set as distractors. Each set of 90 slides was matched on the basis of content, containing an equal number of slides from each of 6 categories related to the subject of the slide: animals, buildings, interiors, people, nature, and single objects. The target set and the distractor set were then organized separately into three sets of 30 slides, which were used to construct the three retention tests for each form of the picture-recognition test. Each set of 30 contained an equal number of slides from each of the six categories related to the subject of the slide. In assembling the pairs of slides used in recognition testing, one of the 30 target slides was randomly paired with one of the 30 distractor slides and assigned a position in the retention test. This procedure was repeated in constructing the three retention tests for each form. In this manner, the three retention tests were balanced with respect to content. The presentation set was assembled using duplicate slides of the full set of targets, which were randomly assigned to 1 of the 90 positions in the learning phase.

Procedure

Subjects were tested individually. In the learning phase, control subjects viewed each target slide for 1 second. The exposure time for patients with AD ranged from 4 to 16 seconds. The greater the severity of dementia, as measured by the BDS, the longer the exposure time required to bring the patient to the same level of initial learning as control subjects. The interstimulus interval for all subjects was approximately 750 msec. All targets were shown in the learning phase, and again in 1 of 3 tests in the retention phase, where each target was paired with a distractor. Recognition performance was assessed using a DMS procedure, which has been shown to be easier, as well as more reliable, for amnesic subjects (Freed, Corkin, and Cohen, manuscript submitted). In this procedure, the subject is shown a target and a distractor and is asked "Which is the old picture?" All subjects were tested 10 minutes, 24 hours, and 72 hours after the end of the learning phase.

Results

Data on three versions of the test given to the 20 control subects were examined. One of the three versions of the test was carefully scrutinized for differences in the degree of difficulty between subtests. A Latin Square

ANOVA with 3 subjects in each cell was performed on these data. This analysis indicated that there were no systematic differences between subtests in this version ($F(2,18) = 3.02$, $p > .05$). For the other three versions, a comparison of the mean score on each subtest in each of three orders failed to reveal any systematic differences between subtests. It is thus reasonable to conclude that there were no significant differences between subtests in terms of degree of difficulty.

Figure 1 presents the mean percent correct for 20 patients with AD and 20 control subjects at the three delay intervals. A repeated measures ANOVA performed on the data indicated that the two groups did not differ with respect to overall forgetting ($F(1,38) = 2.55$, $p > .05$). A main effect for time was noted whereby scores for both groups were lower at the longer delay intervals ($F(2,76) = 58.96$, $p < .01$). The group x time interaction was significant ($F(2,76) = 14.9$, $p < .01$), reflecting a large difference between the performance of the two groups 24 hours after learning, when the patients performed worse than the control subjects ($t(19) = 2.8$, $p < .01$). At 72 hours, however, there was no difference. This result is due to the fact that 10 of the 20 patients with AD displayed a rebound in recognition performance 72 hours after learning, whereas 10 did not (Figure 2). None of the control subjects displayed a rebound in recognition performance (Figure 2).

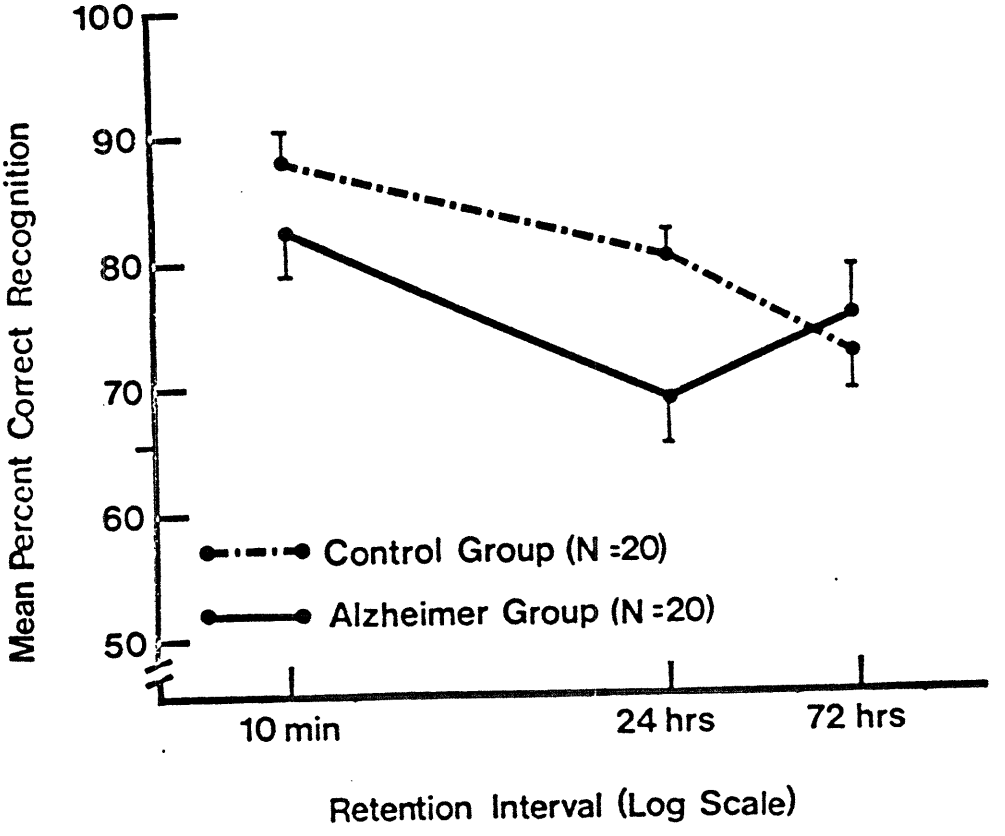

Figure 1. DMS recognition of 20 patients with AD and 20 control subjects, as assessed in Experiment 1. The vertical bars through the data points represent a range of plus or minus one standard error of the mean.

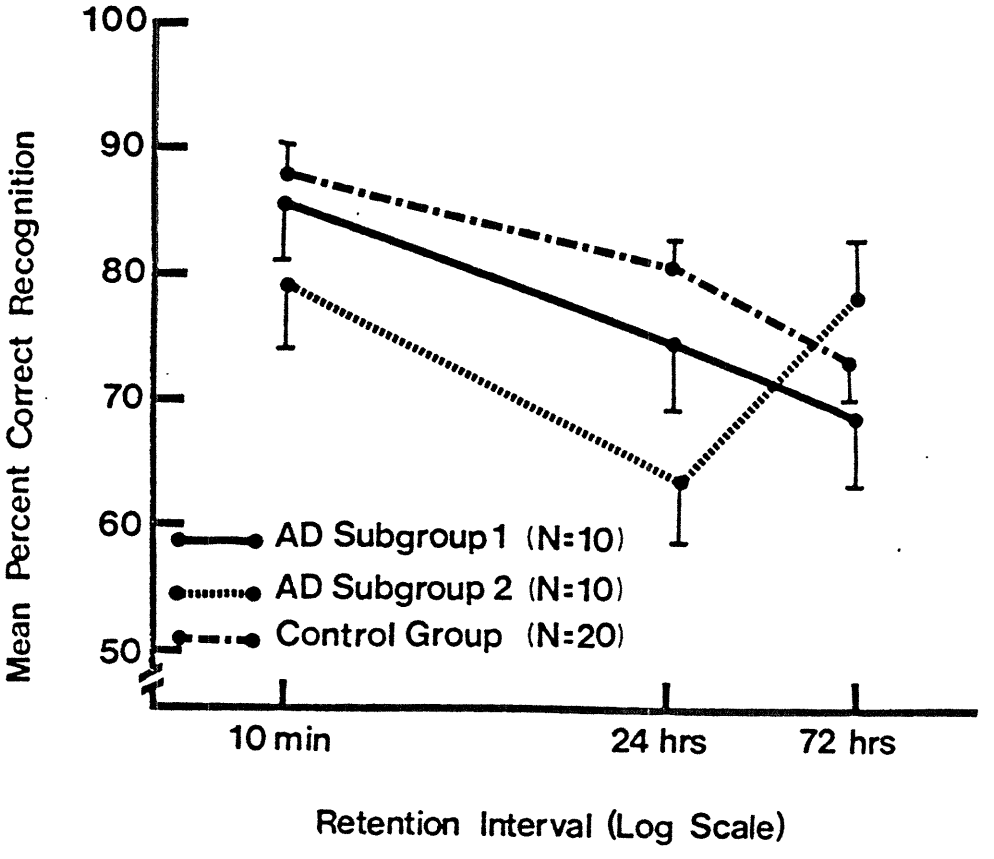

Figure 2. DMS recognition of two subgroups of patients with AD, as assessed in Experiment 1. The data for the control subjects are included for comparison. The vertical bars through the data points represent a range of plus or minus one standard error of the mean.

The present study identified a subgroup of patients with AD who displayed impaired recognition 24 hours after learning, followed by a rebound in recognition performance 72 hours after learning. Posthoc analyses of the data revealed a significant correlation between the magnitude of the rebound in recognition and performance on a selective attention task (Pearson's r = .38, p < .10). The attentional focusing test was modeled after a paradigm developed by Posner, Nissen, and Ogden (1978). In addition, post hoc analyses revealed a relationship between anomalous performance on the picture-recognition task and anomalous performance on this test of selective attention. A Chi-Square analysis revealed a significant correlation (Chi-Square = 11.55, p < .005) between anomalous performance on these two tasks (Tables 2 and 3).

All 10 patients who displayed a rebound in DMS recognition performance did so at the 72-hour retention interval, and their performance profile resembles the letter V when graphically presented (Figure 2). Of the 10 patients who displayed a rebound in DMS recognition performance, 6 were females and 4 were males. The other possible pattern of rebound performance, that which resembles an inverted V when graphed, was not observed in this experiment.

BDS scores for the two groups of patients (those that displayed a rebound in recognition performance and those that did not) were also examined. There were no significant

Table 2

Chi Square Data for Patients (Experiment 1)

	Attentional Focusing Test		
	Expectancy Effect	No Expectancy Effect	N=
AD Subgroup 1 (Nonrebound)	8	0	8
AD Subgroup 2 (Rebound)	3	7	10
N=	11	7	18

Table 3

Chi Square Data for Control Subjects (Experiment 1)

	Attentional Focusing Test		
	Expectancy Effect	No Expectancy Effect	N=
No Rebound in DMS performance	10	0	10
Rebound in DMS performance	0	0	0
N=	10	0	10

differences between the two groups with regard to severity of dementia (t (19) = 0.07, p > .50). Furthermore, the groups did not differ with respect to age, age at onset, or duration of disease (Table 4).

Discussion

Over a 72-hour delay interval, patients with AD displayed normal forgetting of pictorial stimuli. These results are in accord with the findings of Kopelman (1985), who reported that patients with AD displayed normal rates of forgetting after a one-week delay. The findings of an earlier study of forgetting in H.M., as well as the findings of the current study, indicate that abnormally fast forgetting over extended delay intervals is not a consequence of medial temporal-lobe pathology. Taken together, these results suggest that there are no human disorders characterized by rapid forgetting of visual information when assesed with DMS recognition procedures.

Squire (1981) tested patients on a similar task immediately after ECT and found that these patients displayed rapid forgetting relative to control subjects 32 hours after learning. Squire's conclusion that these results support Huppert and Piercy's hypothesis may have been premature, however. The deficit observed by Squire 32 hours after learning may be comparable to the decrement in performance observed at the

Table 4

Characteristics of Patients in Experiment 1

	Male	Female	Mean Age (years)	Mean Ed (years)	BDS	Duration (years)	Onset (age)
AD Subgroup 1 (Nonrebound)	6	4	63.8	13.1	17.2	2.7	61.1
AD Subgroup 2 (Rebound)	4	6	66.6	14.1	16.8	4.3	62.3

24-hour retention interval in the present study. Further experiments with ECT patients, using 72-hour and 1-week retention intervals, are needed to resolve this question.

In this experiment, there was a significant association between a rebound in DMS recognition and anomalous performance on a test of attentional focusing. These data suggest the existence of a subgroup of patients with AD who have deficits in the realms of memory and selective attention, as predicted. The phenomenon observed in Experiment 1, a rebound in DMS recognition performance, was unexpected. Little information exists regarding this phenomenon in humans, other than references to the "reminiscence effect" (Stevens, 1951), a term used to describe an improvement in recognition performance observed in normal subjects (particularly "slow learners") over extended delays. Accounts of similar phenomena are found in the experimental animal literature; they provide insight into possible anatomic and biochemical substrates. Most of these accounts focus on the LC and changes in NE neurotransmission. Given the existence of LC pathology in AD, the previous work in animals concerning the behavioral role of the LC, and the results of this experiment, it was hypothesized that neuropsychological tests could identify a subgroup of patients with deficits in the domain of selective attention, secondary to LC pathology.

EXPERIMENT 2

Selective Attention in Alzheimer's Disease

Next, a predictive study was undertaken to study the relationship between anomalous performance on the picture-recognition task and the selective attention task. The following predictions were made: (1) as a whole, the patients will display a normal rate of forgetting, (2) there will be two patterns of DMS performance displayed by distinct subgroups of patients, and (3) a rebound in DMS recognition will be associated with abnormal performance on the test of attentional focusing. It was further hypothesized that neuropsychological tests can identify a subgroup of patients with AD who have marked deficits in the domain of selective attention, secondary to LC pathology.

The picture-recognition task was modified to include both DNMS and DMS forced-choice recognition procedures. This modification permitted the study of the interaction of recognition memory and selective attention in patients with AD by examining the relationship between DMS and DNMS recognition performance.

Method

Subjects

Subjects were 7 men and 13 women with AD, and 4 healthy men and 10 healthy women matched to the patients for age and educational background (Table 5). The 20 patients were not participants in Experiment 1; they did have a clinical diagnosis of AD, established by the same criteria as in Experiment 1, and they were referred from the same source. The 20 patients in Experiment 2 had a mean BDS score of 15 (range: 8 - 27). Thus, the patients in Experiment 2 were, as a group, similar to the previous group of patients (Experiment 1) in terms of severity of dementia. Our control subjects were not demented according to DSM-III, NINCDS, and NIA criteria.

Test Materials

Four unique versions of the picture-recognition task were constructed in the same manner as described in Experiment 1. In Experiment 2, each version consisted of 240 slides, instead of 180, as in Experiment 1. This manipulation allowed for the use of two different recognition procedures in assessing recognition memory. A comparison of the performance of 4 control subjects on the 90 and 120 slide versions indicated that the length of the test had no significant effect on rate of forgetting.

Table 5

Characteristics of Control Subjects and Patients in Experiment 2

Group	Male	Female	Mean Age (years)	Mean Ed (years)
Healthy Elderly Subjects	4	10	60.2	13.2
Patients with Alzheimer's Disease	7	13	63.9	13.8

Procedure

Recognition testing procedures were the same as in Experiment 1, except for the addition of the DNMS recognition procedure. In DMS testing, the subject was asked "Which picture is old?" In DNMS testing, the subject was asked "Which picture is new?"

Due to the significant posthoc correlation in Experiment 1 between anomalous picture-recognition performance and anomalous performance on a test of attentional focusing, the test of attentional focusing was incorporated into Experiment 2. Each of 90 test trials began with the presentation of the message "Get ready" on a video screen controlled by an Apple II Plus microcomputer. After 5 seconds, the message was replaced by a visual warning signal at the center of the screen. The warning cue was accompanied by an auditory signal. On one-third of the trials, the cue was an arrow pointing right; on one-third, it was an arrow pointing left; and on one-third, it was a doubleheaded arrow pointing both left and right (neutral trials). Either 2 or 3 seconds after the warning cue, an X appeared 3.7 degrees to the right or the left of the arrow. The subject's task was to press a single response key as fast as possible after the appearance of the target. Subjects were instructed that when the warning cue was a single arrow, the X would probably appear in the direction of the arrow, and when the warning signal was a double-headed arrow, the two locations

were equally likely. The single arrow cues were valid 80% of the time (expected trials); on the remaining 20% of the single arrow trials, the X appeared on the side opposite the direction indicated by the arrow (unexpected trials).

Normal subjects benefit from the appearance of valid single arrow cues, as shown in mean reaction times for the different types of trials. The performance of normal subjects was typified by the occurrence of a positive value for the mean difference between unexpected and expected trials (in other words, the mean of 2U-2E + 3U-3E). Anomalous performance was typified by the occurrence of a negative value for the mean difference between unexpected and expected trials.

Results

Figure 3 presents picture-recognition performance as assessed using the DMS procedure in 20 patients with AD and 14 control subjects. A repeated measures ANOVA indicated that the two groups did not differ with respect to overall forgetting ($F(1,32) = 0.04$, $p > .05$). A main effect for time was noted in that scores for both groups were lower at the longer delay intervals ($F(2,64) = 25.03$, $p < .001$). There was a significant group x time interaction ($F(2,64) = 3.34$, $p < .05$) due to the fact that 10 of the 20 patients with AD displayed a rebound in DMS recognition performance (Figure 4). This finding replicated the results of Experiment

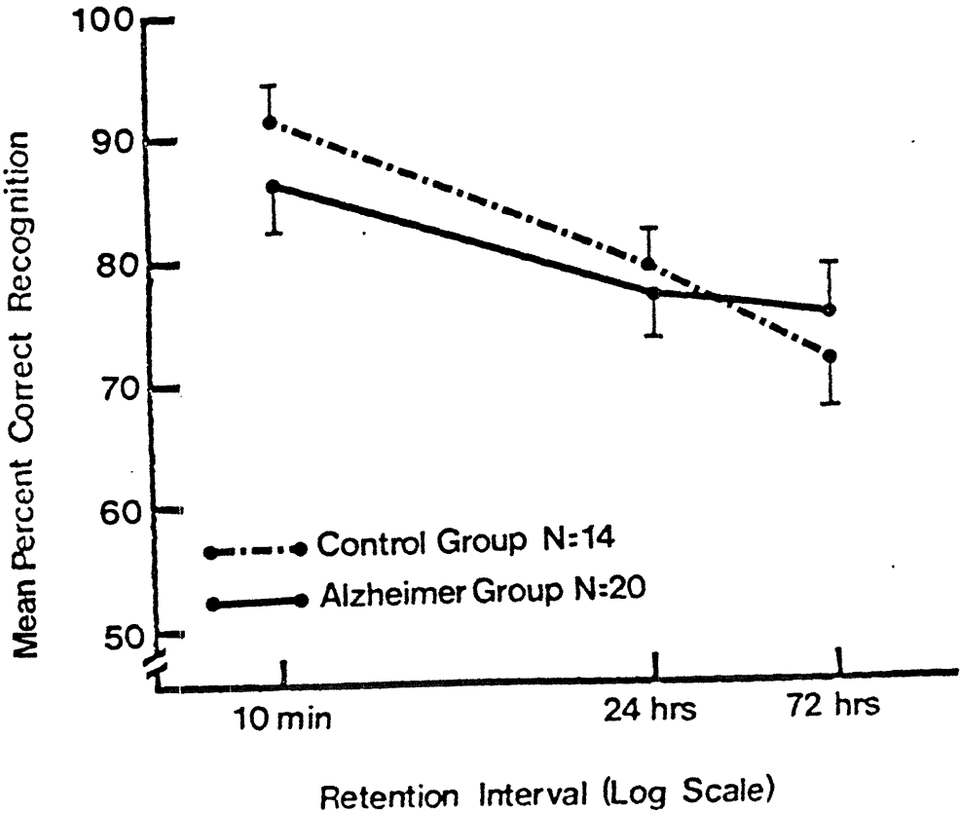

Figure 3. DMS recognition of 20 patients with AD and 14 control subjects, as assessed in Experiment 2. The vertical bars through the data points represent a range of plus or minus one standard error of the mean.

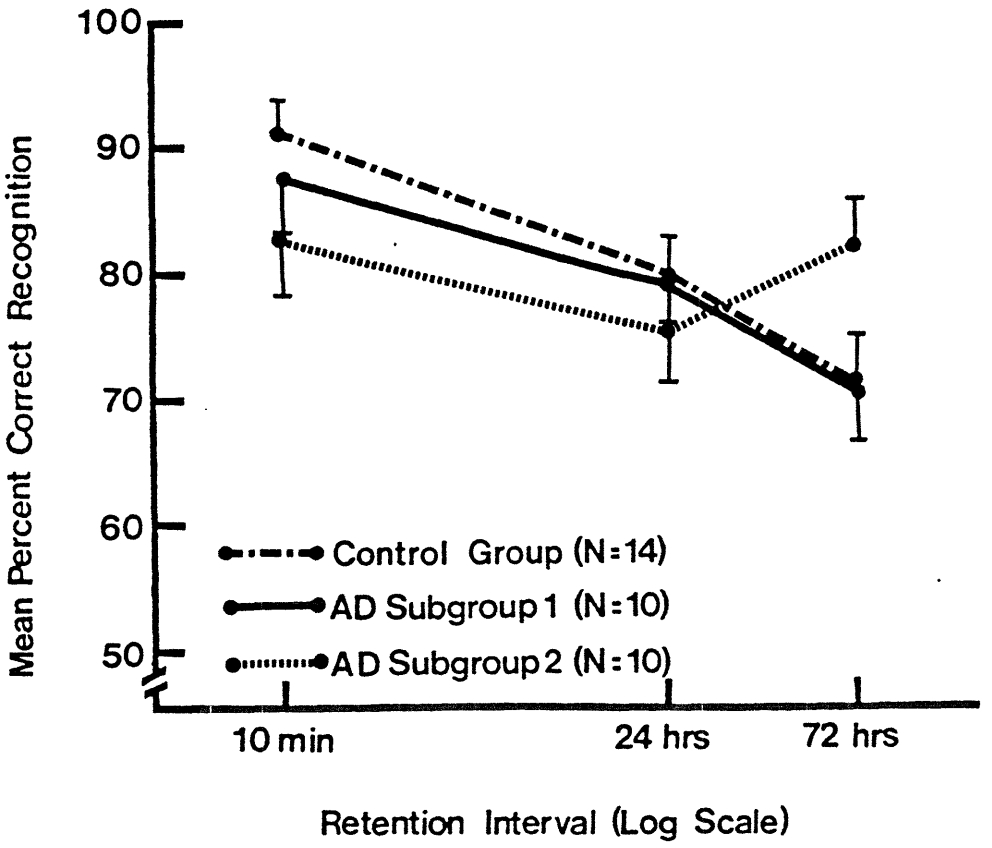

Figure 4. DMS recognition of two subgroups of patients with AD, as assessed in Experiment 2. The data for the control subjects are included for comparison. The vertical bars through the data points represent a range of plus or minus one standard error of the mean.

1 (Figure 2).

Figure 5 presents the mean percent correct recognition as assessed using the DNMS procedure in the same two groups. A repeated measures ANOVA indicated that they did not differ with respect to overall forgetting ($F(1,32) = 0.55$, $p > .05$) in the DNMS procedure. A main effect for time was noted in the lower scores for both groups at the longer delay intervals ($F(2,64) = 24.97$, $p < .001$). A near significant group x time interaction was noted ($F(2,64) = 2.53$, $p < .10$). Overall, the patients with AD displayed normal forgetting when tested with either DMS or DNMS recognition procedures.

The more revealing findings relate to the existence of subgroups of patients with AD. The DMS results of Experiment 2 replicated and extended the observations made in Experiment 1 in that half of the patients displayed anomalous performance, as assessed by DMS recognition procedures. In addition, the significant association between anomalous recognition performance and anomalous performance on a test of attentional focusing noted in Experiment 1 was replicated in Experiment 2 (Tables 6 and 7). A Chi-Square analysis of the data from Experiment 2 revealed a significant correlation (Chi-square = 13.3, $p < .005$) between anomalous performance on these two tasks. The proposed classification scheme for patients is thus supported by the DMS and attentional focusing data.

This categorization is further legitimized by the DNMS data. For the patients who displayed a rebound in DMS recog-

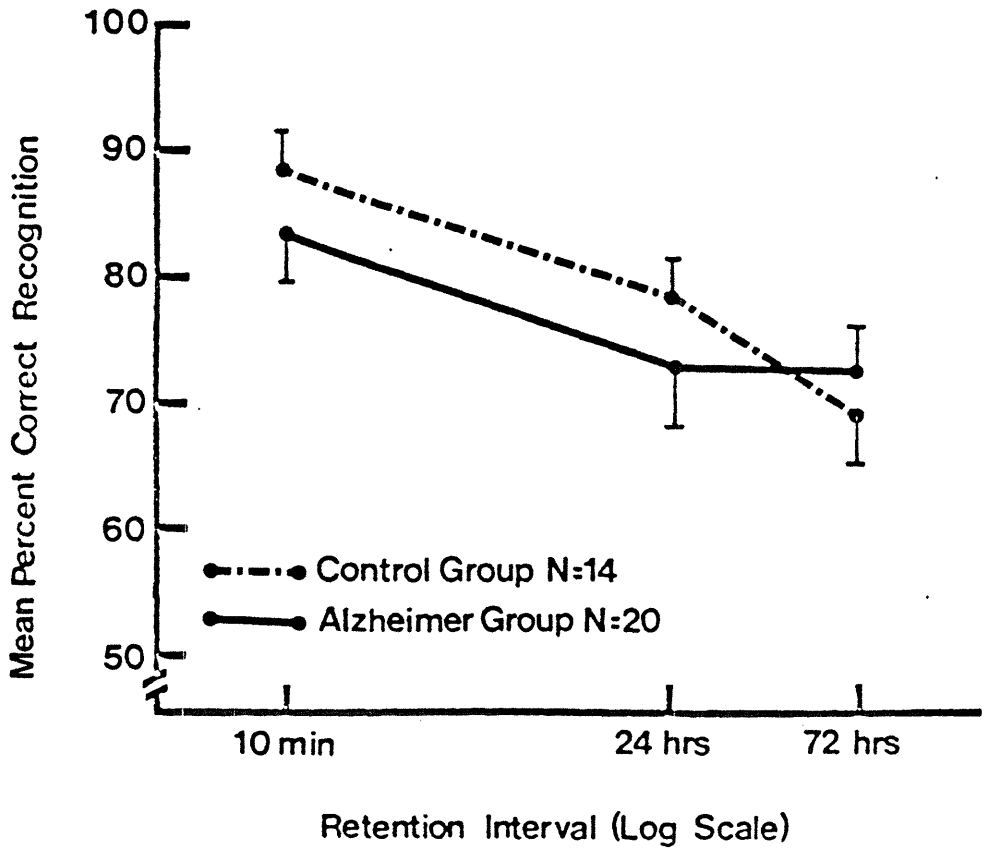

Figure 5. DNMS recognition of 20 patients with AD and 14 control subjects, as assessed in Experiment 2. The vertical bars through the data points represent a range of plus or minus one standard error of the mean.

Table 6

Chi Square Data for Patients (Experiment 2)

	Attentional Focusing Test		
	Expectancy Effect	No Expectancy Effect	N=
AD Subgroup 1 (Nonrebound)	6	2	8
AD Subgroup 2 (Rebound)	0	10	10
N=	6	12	18

Table 7

Chi Square Data for Control Subjects (Experiment 2)

	Attentional Focusing Test		
	Expectancy Effect	No Expectancy Effect	N=
No Rebound in DMS performance	8	0	8
Rebound in DMS performance	0	0	0
N=	8	0	8

nition, there was a strong negative correlation between the magnitude of the rebound in DMS recognition and the magnitude of the rebound in DNMS recognition (Pearson's $r = -.34$, $p > .10$). For the patients who did not display a rebound in DMS recognition, there was a weak positive correlation between the magnitude of the rebound in DMS recognition and the magnitude of the rebound in DNMS recognition (Pearson's $r = -.06$, $p > .50$). Thus, for the patients who displayed a rebound in DMS recognition, there is a strong negative correlation between the magnitude of that rebound and the magnitude of a decrement in DNMS recognition.

BDS scores were examined for the two groups of patients. There was no significant difference in terms of severity of dementia for the two groups ($t(19) = .24$, $p > .50$) (Table 8). In addition, 6 of the 10 patients who displayed a rebound in DMS recognition also displayed a rebound in DNMS recognition, where a rebound in recognition is defined as any increase in performance over time.

An ANOVA performed on the data from patients with AD indicated that the order in which the DMS and DNMS procedures were administered had no significant effect upon test performance ($F(1,18) = 0.54$, $p > .20$). In this analysis, the effect due to time was significant ($F(2,36) = 7.47$, $p < .001$). The interaction between order of administration and time approached significance ($F(2,36) = 2.69$, $p < .10$), due to the existence of a subgroup of 10 patients who displayed

Table 8

Characteristics of Patients in Experiment 2

	Male	Female	Mean Age (years)	Mean Ed (years)	BDS	Duration (years)	Onset (age)
AD Subgroup 1 (Nonrebound)	4	6	63.0	13.8	14.7	2.8	58.0
AD Subgroup 2 (Rebound)	3	7	66.2	13.4	12.9	2.8	63.4

a rebound in DMS recognition (Figure 4).

Discussion

The results of Experiments 1 and 2 indicated that patients with AD displayed normal forgetting of pictorial stimuli over a 72-hour delay interval provided that they are given additional study time in order to equate their initial recognition performance to that of control subjects. One criticism of these experiments concerns the use of additional study time for the patients relative to control subjects. The learning experience of the two groups differs and conclusions regarding overall forgetting are therefore tenuous, according to this argument. It should be noted, however, that these investigations were concerned with forgetting in patients with AD, not with problems in acquisition. There are no ideal means to equate the initial performance of two groups of subjects that differ in terms of speed of acquisition. For example, if both patients and control subjects were given 10 seconds study time, the recognition of the control subjects 72 hours after learning would be near ceiling performance, preventing comparisons of forgetting in the two groups. If both groups were given 1 second of study time, the recognition of the patients with AD 72 hours after learning would be near chance performance, again preventing comparisons of forgetting. In addition, if the patients with AD were given 1 second study time it is likely that the existence of the

subgroup of patients that displayed a rebound in DMS recognition would have gone undetected.

The major finding of Experiment 2 was the identification of a subgroup of patients with AD using behavioral testing. Prehoc analysis of test data (based upon the findings of Experiment 1) revealed a relationship between anomalous performance on the picture-recognition task and anomalous performance on an attentional focusing paradigm. The results of Experiment 2 support the existence of a behavioral subgroup of patients with AD who have deficits in visual selective attention. For the patients who displayed a rebound in DMS recognition, there was a strong negative correlation between the magnitude of the rebound in DMS performance and the magnitude of the rebound in DNMS performance. These data suggest that shifting response biases underlie the rebound in DMS recognition.

The cognitive changes observed in the subgroup of patients displaying anomalous performance are consistent with a body of literature concerned with behavioral deficits in animals due to lesions of the ascending noradrenergic system (Segal and Bloom, 1976; Lorden, et al., 1980; Botwinick et al., 1977; Mason and Iversen, 1978; Rainbow and Flexner, 1978). Based upon the data, it is reasonable to hypothesize that the changes in visual selective attention observed in a subgroup of patients with AD are associated with LC pathology in the human.

EXPERIMENT 3

CSF Monoamine Metabolites and Selective Attention

Experiment 3 evaluated the hypothesis that deficits in selective attention are associated with reductions in brain NE. In order to investigate the hypothesis that impairments in selective attention are behavioral evidence of LC pathology, a physiological measure of LC function was required. Four alternatives exist to test the hypothesis in living patients: examine brain biopsy material, examine CSF levels of the metabolite of NE, administer pharmacologic agents that are known to affect NE, or use positron-emission tomography (PET) to image NE receptors. PET imaging of receptors is a recent development (Farde, Hall, Ehrin, and Sedvall, 1986) and noradrenergic receptors have not yet been studied. CSF studies were performed because this approach was judged to be the safest and easiest procedure. The results of clinical trials of clonidine will be reported in Experiment 4.

Recent reports of neuropathology in AD have suggested that female patients displayed more severe LC degeneration than did male patients (Bondareff et al., 1982; Iversen et al., 1983). Of the AD patients who displayed a rebound in DMS recognition in Experiments 1 and 2, there were nearly twice as many females as males (13 vs 7). The possibility

that male and female patients with AD differ with regard to levels of monoamine metabolites in CSF was therefore examined.

Reports on sex differences in the brains of controls subjects are sparse (Carlsson, Nyberg, and Winblad, 1984). Bowers (1972) noted that brain levels of 5-HIAA and HVA do not vary with gender. Adolfsson et al. (1979) found no sex differences in DA and HVA levels from 16 human brain regions. Spokes (1979) did not detect any sex differences in DA or NE concentrations in corpus striatum, substantia nigra, red nucleus, or motor cortex. More recently, Carlsson, Nyberg, and Winbald (1984) reported significantly lower amounts of 5-HIAA in thalamus and higher levels of serotonin in medulla oblongota of female subjects relative to male subjects, but no other differences in a wide variety of brain structures.

With regard to CSF studies in normal subjects, Ballenger, Post, and Goodwin (1984), in a large and carefully controlled study, noted that the only variable for which there was a significant difference in group means between male and female control subjects was GABA levels in subjects under the age of 40. These authors found no significant sex differences in CSF levels of 5-HIAA, HVA, and MHPG. Recently, Mayeux, Stern, Cote, and Williams (1984) measured CSF metabolites in a group of 15 nondepressed, hospitalized patients with either neuromuscular disorders or stroke for use as control

subjects in a study of Parkinson's disease. The mean age of this group was 65.5 years, and there was no significant difference between the age of male and female control subjects in this study ($t(12) = .91$, $p > .1$). There was no significant difference between male and female control subjects with regard to CSF levels of MHPG ($t(12) = 1.49$, $.10 > p > .05$), although there was a nonsignificant trend for male subjects to have higher MHPG levels. Taken together with the results of autopsy studies, these findings provide no reason to hypothesize sex-differences in CSF levels of 5-HIAA, HVA, or MHPG in healthy elderly subjects. Therefore, if significant sex-differences are noted in the CSF of patients with AD, it must be presumed that these differences are a manifestation of the disease process. Such an observation may provide clues about etiology.

Method

Subjects

Subjects were 13 women and 9 men with AD for whom both neuropsychological and CSF data were available. These 22 patients were participants in Experiments 1 and 2 and were similar to the remaining participants for whom CSF data were unavailable (Table 9). The 22 patients had a clinical diagnosis of AD and were referred from the same source as patients in Experiments 1 and 2. In addition, CSF data

Table 9

Characteristics of Patients in Experiment 3

	Male	Female	Mean Age (years)	Mean Ed (years)	BDS	Duration (years)	Onset (age)
Participants in Experiment 3	9	13	64.8	13.4	15.9	3.5	61.2
Remaining Participants in Experiments 1 and 2	8	10	65.1	13.8	15.2	2.7	59.2

from a larger group of 57 patients with AD (31 women and 26 men) were examined for sex-differences.

Test materials

Samples of CSF were routinely drawn from patients with AD seen at MIT's Clinical Research Center. The patient remained recumbent overnight and a sample was drawn from the lumbar sac. All subjects agreed to this procedure beforehand and signed a consent form in the presence of witnesses, in accordance with the procedures outlined by MIT's Committee on the Use of Humans as Experimental Subjects. For CSF data to be included in the present study, the patient had to be medication free and the assay had to be performed within 30 days of neuropsychological testing. In most cases, the lumbar puncture was performed during the week in which the neuropsychological testing occurred.

Procedure

HVA and free MHPG were measured by an LC-304B high pressure liquid chromatography (HPLC) system coupled with electrochemical detection (Bioanalytical Systems). The detector consisted of a dual glassy-carbon electrode oriented in a parallel-adjacent arrangement (potentials +800/650 mV vs. Ag-AgCl reference electrode, sensitivity 2 or 5 na/V). Separation was achieved on a 250 x 4.6 mm Biophase ODS 5 um column (Bioanalytical Systems) preceded by a guard column,

using a 0.05 M sodium acetate buffer with pH 5.0 (Baker Analyzed Reagents). Distilled-deionized water was used, and the buffer was filtered (Millipore HA: 0.45 um) and degassed before use. Stock solutions of HVA, 5-HIAA, and free MHPG were prepared in 0.1 N perchloric acid. Standard curves ranging from 0-10 ng of HVA, 5-HIAA, and MHPG were injected intermittently between CSF samples. CSF samples were deproteinized, centrifuged, and injected directly onto the HPLC column. The current ratio, expressed as the peak height at the low potential electrode divided by that at the higher potential electrode, and the retention time were used to identify compounds. Linear regression on data from the higher potential electrode was used to calculate amounts of HVA, 5-HIAA, and MHPG.

Results

Data from the larger group of 57 patients with AD were grouped according to gender; t-tests were performed, comparing male and female patients with respect to levels of catecholamine metabolites including MHPG, 5-hydroxy, indoleacetic acid (5-HIAA, major metabolite of serotonin), and HVA (homovanillic acid, major metabolite of dopamine). It was noted that male and female patients differed with regard to levels of MHPG ($t(26) = 2.05$, $p = .02$), with males having significantly higher levels of MHPG (8.76 vs 7.12, respectively) (Figure

6). Male and female patients did not differ with regard to levels of 5-HIAA ($t(27) = 1.32$, $p = .123$) or HVA ($t(27) = 1.43$, $p = .083$). Accordingly, the MHPG data for Experiment 3 were grouped according to gender.

Table 10 presents the data for the 22 patients who were participants in Experiment 3, with the data grouped according to anomalous performance on the picture-recognition test and gender. A Chi-Square analysis revealed a near significant association (Chi-Square = 2.745, $.10 > p > .05$) between anomalous performance on the picture-recognition test and reduced levels of MHPG (Table 11). Anomalous picture-recognition performance was defined by the occurrence of an increase in DMS recognition performance, regardless of the retention interval. In Experiments 1 and 2, 16 of the 20 patients who displayed a rebound in DMS performance did so at the 72-hour retention interval. For this and the following Chi-Square analysis, MHPG levels were reduced to a bivariate distribution. An individual patient's MHPG level was defined as normal if the value was equal to or greater than the mean MHPG value for AD patients of the same sex, as justified by analyses that revealed a significant difference between MHPG levels in male and female patients. Similarly, MHPG levels were defined as reduced only if that individual's values were below the mean MHPG value for patients of the same sex.

A related Chi-Square anlaysis (Table 12) revealed a

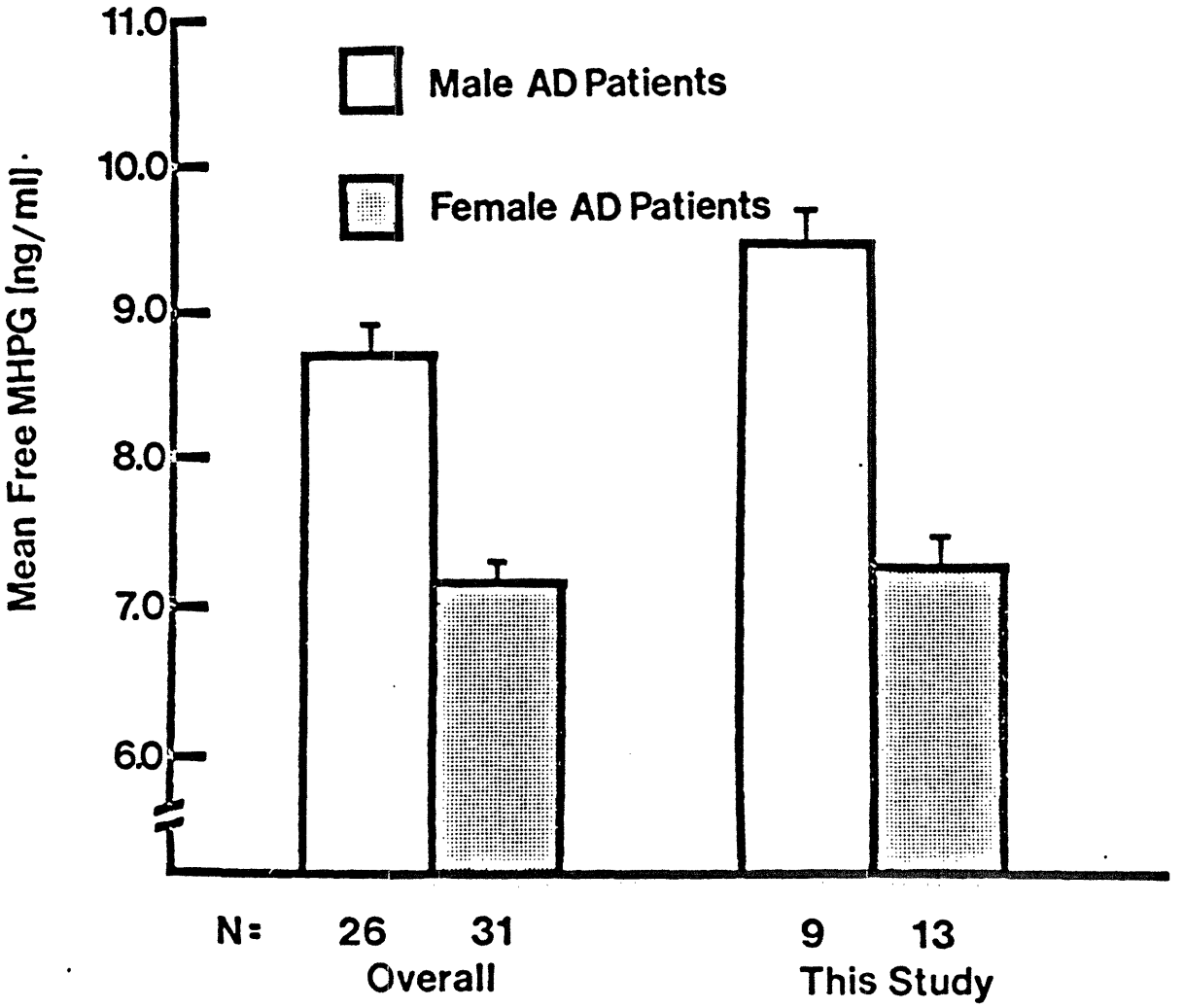

Figure 6. Mean free MHPG in CSF for the full group of 57 patients with AD, as well as the group of 22 patients who participated in Experiment 3. The vertical bars through the data points represent a range of plus or minus one standard error of the mean.

Table 10

Data Relating to CSF MHPG (Experiment 3)

	Mean CSF MHPG Levels		
	Females	Males	Group
AD Subgroup 1 (Nonrebound)	9.55	10.5	10.025
AD Subgroup 2 (Rebound)	6.26	8.45	7.355
N=	13	9	22

Table 11

Chi Square Data Relating to CSF MHPG (Experiment 3)

	CSF MHPG Levels		
	Above Mean For Same Gender	Below Mean For Same Gender	N=
AD Subgroup 1 (Nonrebound)	7	2	9
AD Subgroup 2 (Rebound)	5	7	12
N=	12	9	21

Table 12

Chi Square Data Relating to CSF MHPG and Performance on the Test of Attentional Focusing (Experiment 3)

		CSF MHPG levels		
		Above Mean For Same Gender	Below Mean For Same Gender	N=
Attentional Focusing	Expectancy Effect	8	2	10
	No Expectancy Effect	3	6	9
N=		11	8	19

significant correlation between anomalous performance on the test of attentional focusing and reduced levels of MHPG (Chi-Square = 4.242, $p < .05$). Anomalous performance on the test of attentional focusing was defined by the occurrence of a negative value for the mean difference between unexpected and expected trials (in other words, the mean of 2U-2E + 3U-3E). In addition, a significant correlation between CSF MHPG levels and performance on a test of attentional focusing was noted when the data were ranked (Spearman's $r = .57$, $p < .01$).

Discussion

The major findings of Experiment 3 concerned the significant correlation between anomalous performance on the attentional focusing test and reduced levels of MHPG. A near significant correlation between deviant performance on the picture-recognition test and reduced levels of MHPG was also noted. When the data from both Experiments 1 and 2 were combined, a significant association between anomalous performance on the attentional focusing test and the picture-recognition test was noted (Tables 13 and 14). These experimental results support the hypothesis that reductions in brain NE result in impairments in selective attention. The impairments in selective attention displayed by the identified subgroup of patients were associated with reduced levels of MHPG

Table 13

Chi Square Data for Patients Regarding the Association Between Anomalous Performance on Two Tests (Experiments 1 and 2)

	Attentional Focusing		
	Expectancy Effect	No Expectancy Effect	N=
AD Subgroup 1 (Nonrebound)	14	2	16
AD Subgroup 2 (Rebound)	3	17	20
N=	17	19	36

Table 14

Chi Square Data for Control Subjects Regarding the Association Between Anomalous Performance on Two Tests (Experiments 1 and 2)

	Attentional Focusing		
	Expectancy Effect	No Expectancy Effect	N=
No Rebound in DMS performance	18	0	18
Rebound in DMS performance	0	0	0
N=	18	0	18

in CSF. Reduced MHPG levels were defined as those below that of the mean value of same sex patients.

A comparison of neurotransmitter markers for male and female patients revealed a significant sex difference for MHPG, but not 5-HIAA or HVA found in the CSF of patients with AD. An analysis of CSF from 57 patients with AD revealed that male patients had significantly higher levels of MHPG than did female patients. Given that recent reports indicate that LC degeneration is more common in female patients with AD than male patients, the occurrence of a gender-related difference in levels of MHPG is consistent with what is known about the neuropathology of AD.

A study of CSF biogenic amine metabolites was undertaken by Young and Ervin (1984). These authors concluded that there are many similarities between vervet monkeys and humans with regard to monoamine CSF metabolites. Young and Ervin (1984) noted that mean levels of 5-HIAA, HVA, and MHPG were, respectively, 33%, 29%, and 17% higher in female vervet monkeys relative to males, and that the same is also true of humans. Although to date, studies of CSF taken from healthy elderly subjects have not revealed significant sex differences in levels of brain monoamines, Young and Ervin's (1984) results suggest that this possibility should be re-examined.

It is conceivable that gender-related differences in LC cell density, morphology, or biochemistry predispose

females to the type of AD neuropathology characterized by LC degeneration. If this notion is true, then studies of gender-related differences in catecholamine-containing neurons will be important in the search for clues to the etiology of AD. While clinical neurology and neuropathological studies of human brain material provide no support for this supposition as of yet, investigations using experimental animals provide some interesting data. It is known that the highest density of opiate receptors in the rat brain is found in the LC (Messing et al.,1980). Messing et al. (1980) reported regionally specific changes in both numbers and apparent affinities of opiate receptors during aging, along with significant sex differences. In aged female rats, there were decreases in receptor densities in the midbrain and thalamus. In aged male rats, opiate binding sites in the frontal poles had a higher affinity than in younger animals, but there was no decrease in receptor density in the midbrain LC. While indirect, these results suggest that sex differences in the LC may occur during aging.

EXPERIMENT 4

Clinical Trials Using Clonidine

The previous experiments demonstrated that the picture-recognition test and the test of attentional focusing identify a subgroup of patients with deficits in selective attention. These deficits are associated with reduced CSF levels of MHPG, the major metabolite of NE. Assuming that MHPG levels in CSF accurately reflect the metabolism of NE within intact LC neurons, these results suggest that neuropsychological tests are able to identify a subgroup of patients with AD who have LC degeneration.

The hypothesis that LC noradrenergic neurons play a role in selective attention in the human was further tested using psychopharmacological procedures. In Experiment 4, 7 patients with AD were administered the noradrenergic agonist, clonidine, in ascending doses. Clonidine is an antihypertensive medication that reduces blood pressure by stimulating presynaptic alpha-2 autoreceptors in the vasomotor center of the brain. Clonidine is a potent autoreceptor-stimulating drug but at higher doses it may also stimulate postsynaptic adrenergic receptors (Cooper, Bloom, and Roth, 1982).

A number of studies suggest that there can be an abundance of postsynaptic adrenergic receptors (both alpha-1 and beta) in brain regions deprived of NE (U'Prichard, Greenberg,

Sheehan, and Snyder, 1977; Bylund and Snyder, 1976; Alexander, Davis, and Lefkowitz, 1975), providing evidence of up-regulation. Down-regulation of postsynaptic beta-adrenergic receptors is also known to occur. For example, desipramine, a potent inhibitor of NE uptake that has only a minimal effect on dopamine uptake (Cooper, Bloom, and Roth, 1982), has been shown to reduce the sensitivity and density of beta-adrenergic receptors in the brain (Pandey and Davis, 1981). It is clear that the responsiveness of the beta-adrenergic receptor complex is inversely related to the degree of prior adrenergic stimulation (Freilich and Weiss, 1983). These results suggest that due to receptor up-regulation, low doses of clonidine may interact with postsynaptic adrenergic receptors in AD patients with reductions in brain NE secondary to LC degeneration. Clonidine would be expected, therefore, to exert a therapeutic effect on cognition.

It was hypothesized that the subgroup of patients presumed to have LC degeneration would show improvements in selective attention during clonidine administration while other patients would not. This hypothesis was based upon the work of McEntee and Mair (1980), which was discussed in a previous section. In addition, it was hypothesized that the picture-recognition and attentional focusing tests would be useful in measuring aspects of selective attention that are NE dependent. Psychopharmacology thus provided the means to test the theory that behavior is a sensitive indicator of LC function, as

well as to investigate a rational treatment strategy for a subgroup of patients with AD.

Method

Subjects

The subjects were 7 women with AD (Table 15). The patients had a clinical diagnosis of AD based upon strict diagnostic criteria, which were in accordance with recent NINCDS and NIA diagnostic guidelines (McKahn et al, 1984; Khachaturian, 1985). The 7 patients, with one exception, did not participate in any of the previous experiments. The 7 patients had a mean BDS score of 17.1 (range 9.0 - 26.0). The 7 AD patients who participated in this experiment thus had evidence of memory impairment on neuropsychological testing and were, as a group, similar to the participants of Experiments 1 and 2 in terms of severity of dementia (Table 15). Patients with a BDS score below 10 were considered mildly demented, those patients with a score of 10 to 19 moderately demented, and those patients with a score over 19 severely demented.

Table 15

Characteristics of Patients in Experiment 4

Patient Group	Male	Female	Mean Age (years)	Mean Ed (years)	Mean BDS
Experiment 1	10	10	63.4	13.1	15.6
Experiment 2	7	13	63.9	13.8	15.0
Experiment 4	0	7	61.4	14.7	17.1

Drugs

The patients were administered clonidine in ascending doses from .025 mg to .2 mg (Table 16) until side effects (dry mouth, drowsiness, lowered blood pressure, or agitation) were apparent. Medication was discontinued at that time. In Table 16, WO denotes washout.

Test Materials

Two additional versions of the picture-recognition test were constructed in the same manner as described in Experiment 2, for use in this experiment. In addition, materials were assembled for the administration of a series of neuropsychological tests including the the Continuous Performance Test (Rosvold et al., 1956), Stroop Color Naming Test (Stroop, 1935), Rabbitt Card-Sorting Test (Rabbitt, 1963), Category Fluency Test (Fuld, Katzman, Davies, and Terry, 1982), and Boston Naming Test (Kaplan, Goodglass, and Weintraub, 1978). The Rabbitt Card-Sorting Test and a new variant of the test of attentional focusing using peripheral cues were not given to two subjects who entered the study before these tests were ready.

Recognition testing procedures for the picture-recognition test were the same as in Experiment 2. The test of attentional focusing was also administered in the same manner as in Experiment 2.

Table 16

Dosages and Drug Schedule for Patients in Experiment 4

DOB	DOT	Test conditions/dosages						
8/17/11	5/85	Base	Plac	.10	.20	WO		
6/2/31	6/85	Base	Plac	.05	.10	WO		
1/26/28	7/85	Base	Plac	.05	.10	.15	.20	WO
8/16/26	9/85	Base	Plac	.025	.05	.10	.15	.20	WO
6/25/18	9/85	Base	Plac	.025	.05	WO	WO	
11/20/22	10/85	Base	Plac	.025	.05	.10	.15	.20	WO
1/12/28	11/85	Base	Plac	.025	.05	.05	.10	WO	

Results

Performance on the picture-recognition test and the test of attentional focusing was used to classify the patients in terms of anomalous performance on the these tests, as discussed earlier. Table 17 presents the age and BDS scores for the two groups of patients classified in this manner. Data from 1 patient were excluded from further analysis because this patient was unable to complete one of the two tests at baseline.

Table 18 presents the behavioral data for the 2 groups of patients under two conditions, baseline and best dose of clonidine. The best dose was determined through analysis of behavioral test scores rather than by a human rater, allowing more objective evaluation of drug effects. Best dose was defined as the dose of clonidine that resulted in test performance that was superior to performance on other doses of the drug. The best dose for an individual, therefore, was defined by the highest number of "personal bests" relative to performance on the other doses. Note that the group of patients presumed to have LC degeneration displayed improved performance on the picture-recognition and attentional focusing tests during the administration of the best dose of clonidine, while the performance of the other group of patients deteriorated (Table 18). In this table, N denotes "No rebound observed" and R denotes

Table 17

Characteristics of Two Groups of Patients in Experiment 4

Patient Group	Mean Age (years)	Mean Ed (years)	Mean BDS	Duration (years)	Onset (Age)
AD Subgroup 1 (Nonrebound)	61.0	15.3	15.5	2.0	56.0
AD Subgroup 2 (Rebound)	61.6	15.0	15.7	4.5	59.0

Table 18

Performance of 6 Patients in Experiment 4

Test	Subgroup 1 Nonrebound Group (N=3)	Subgroup 2 Rebound Group (N=3)
Picture-recognition		
Baseline	N, N, N	R, R, R
Clonidine	N, R, N	R, N, R
Attentional focusing		
Baseline	+83.7	-101
Clonidine	+14.3	+167
Stroop Color Naming Test		
Baseline	12.6	6.0
Clonidine	15.0	9.7
Category fluency		
Baseline	31.3	15.3
Clonidine	37.0	17.3
Boston Naming		
Baseline	28.3	25.6
Clonidine	28.0	27.0

"Rebound observed" in DMS recognition. One of the patients who displayed a rebound in DMS recognition at baseline did not display a rebound in DMS recognition while taking clonidine. Because the rebound phenomenon is reliable and replicable in individual patients, this result suggests that pharmacologic manipulation of the noradrenergic system may be a useful treatment for the subgroup of AD patients with presumed LC degeneration.

Table 19 presents data from the picture-recognition test for the two groups of patients at baseline and best dose of clonidine. Note that the patients who displayed a rebound in DMS recognition at baseline benefited more from the administration of clonidine than did the other group of patients (Chi-Square = 2.71, $p < .10$).

Discussion

The results of Experiment 4 support the hypothesis that behavioral tests are a sensitive indicator of LC degeneration. In this experiment, the differential response to clonidine of two groups of patients categorized on the basis of behavioral testing provided further support of the hypothesis that deficits in selective attention are associated with reductions in brain NE. The subgroup of patients presumed to have LC degeneration displayed improved performance on

Table 19

Decline in Performance on the Picture-Recognition Test Between the 10-Minute and 24-Hour Retention Intervals in Experiment 4

	Baseline	Best Dose
	10min - 24hrs	10min - 24hrs
AD Subgroup 1 (Nonrebound) N=3	16.7	5.0
AD Subgroup 2 (Rebound) N=3	26.7	3.3

the picture-recognition test and test of attentional focusing while taking clonidine. The performance of the other subgroup of patients on these two test deteriorated during clonidine administration.

In addition, the results of Experiment 4 suggested that NE plays a role in word-finding difficulties in patients with AD. Of the 6 female patients whose performance was classified according to procedures described earlier, 2 had significant word-finding problems, as reported by family members. Both of the patients with word-finding difficulty were members of the subgroup of patients who displayed anomalous performance on the picture-recognition and attentional focusing tests. The language performance of these 2 patients improved on clonidine, as revealed by observations made by testing staff (Marie Wininger and David Freed, personal observations) and spontaneous reports by family members. These results suggest that word-finding difficulty in patients with AD may be associated with reduced levels of brain NE. Unfortunately, the standard neuropsychological tests used to study language function were not sensitive to these changes in performance (Table 18). It is possible that the repeated use of the same test stimuli in multiple conditions (i.e. different dosages) may have allowed patients with language difficulties to learn the correct responses to test items on the Boston Naming, Naming to Definition, and Word-list Learning tests.

The suggestion that NE plays a role in language function

is consistent with two lines of evidence. Recent neuropathological studies suggest that female patients with early-onset AD are more likely than male patients to display significant LC degeneration (Bondareff et al., 1982; Iversen et al., 1983; Bondareff, 1983). Clinical studies suggest that early-onset AD is associated with an earlier and more severe language disorder (Breitner and Folstein, 1984; Folstein and Breitner, 1981; Mayeux, Stern, and Spanton, 1985; Chui et al., 1985). These studies suggest that females with early-onset AD may have a high incidence of LC degeneration, which is associated with an earlier and more severe language impairment. The results of the previous experiments support the theory that LC degeneration is associated with impairments in selective attention and picture-recognition. The results of the present experiment suggest that word-finding difficulty may also be a sensitive behavioral index of LC function. With regard to this suggestion, it should be noted that all 6 of the patients who were administered clonidine displayed modest improvements in their scores on language tests (Appendices 3-8). This observation is consistent with reports from the human literature of an age-related decline in brain NE levels (Adolfsson, 1978) and with reports from the animal literature suggesting that age-related declines in cognitive performance can be alleviated by the administration of clonidine (Arnsten and Goldman-Rakic, 1985).

GENERAL DISCUSSION

It was hypothesized that neuropsychological tests can distinguish a subgroup of patients with AD who have LC pathology. Anomalous performance on the picture-recognition task and the attentional focusing test were significantly correlated in Experiments 1 and 2, suggesting that a deficit in visual selective attention underlies anomalous performance in both tasks. It was suggested that the impairments in selective attention observed in a subgroup of patients with AD were the result of a bias to novel locations or stimuli. This type of bias would produce the pattern of results observed in both the picture-recogntion and attentional focusing tasks.

The hypothesis that reductions in brain NE secondary to LC degeneration result in anomalous performance was tested in Experiment 3. When the MHPG data were grouped according to gender, as justified by experimental findings, a significant correlation between anomalous performance and reduced levels of MHPG was noted. In Experiments 1 and 2, it was noted that there were nearly twice as many female patients who displayed a rebound in DMS recognition performance as male patients (Table 20), consistent with the finding that female

Table 20

Characteristics of Two Groups of Patients in Experiments 1 and 2

	Male	Female	Mean Age (years)	Mean Ed (years)	BDS	Duration (years)	Onset (age)
AD Subgroup 1 (Nonrebound)	10	10	63.4	13.5	16.0	2.8	59.6
AD Subgroup 2 (Rebound)	7	13	66.4	13.8	14.9	3.6	62.9

patients with AD had significantly lower levels of MHPG than did male patients. These results are consistent with neuropathological studies, which have noted that female patients are more likely to display severe LC degeneration than male patients (Bondareff et al., 1982; Iversen et al., 1983).

A number of findings suggest sex differences in patients with AD: (1) neuropathological reports indicate that female patients with AD are more likely to possess severe LC degeneration (Bondareff et al., 1982; Iversen et al., 1983; Arai et al., 1984); (2) nearly twice as many female patients displayed a rebound in DMS recognition and anomalous performance on a test of attentional focusing relative to male patients with AD (Experiments 1 and 2); and, (3) female patients with AD had significantly lower levels of MHPG in CSF than did male patients (Experiment 3). Given the existence of sex-differences in patients with AD, it becomes important to examine possible explanations for these differences.

Toward that end, a questionnaire was mailed to female patients who participated in these experiments in order to investigate possible associations with reproductive physiology. This questionnaire focused on age at menarche, regularity of menstrual cycles, pregnancies, birth control, changes in taste and smell, and interest in sex. Questionnaires were mailed to the 23 female patients who participated in the present study; 10 completed questionnaires were returned.

Although the number of respondents was relatively small, a number of interesting observations were made. The subgroup of female patients who displayed a rebound in DMS recognition had an earlier onset of menarche (13.3 vs 15.8 years of age, respectively) and had more regular menstrual cycles. Although the two groups of female patients had nearly identical group means for the question dealing with interest in sex, the group of female patients who displayed a rebound in DMS recognition were reported to be either always interested (3 repondents) or never interested in sex (3 respondents). The other group of female patients were uniformly rated as occasionally interested (4 respondents). Furthermore, for the female patients who displayed a rebound in DMS recognition, all 3 respondents who reported no interest in sex also reported changes in taste and smell. Given the extensive projections of the LC to the olfactory bulb (Shipley, Halloran, and De La Torre, 1985), these preliminary findings are of interest. Further studies of reproductive physiology in female patients may provide a clue to the etiology of AD.

In Experiment 3, anomalous performance on either the picture-recognition test or on the attentional focusing test was associated with reduced levels of MHPG in patients with AD. In Experiment 4, patients who displayed a rebound in DMS performance responded differently to the administration of the noradrenergic agonist, clonidine, than did patients who did not display a rebound. If it is assumed that LC

degeneration was associated with reduced levels of brain NE, and that reductions in brain NE result in up-regulation of postsynaptic noradrenergic receptors, then clonidine administration would be expected to affect test performance differentially in the two groups of patients. The results of Experiment 4 thus provide pharmacological support of the hypothesis that neuropsychological tests can identify distinct groups of patients with AD. The hypothesis that NE plays a role in human selective attention is also supported by the present series of experiments.

The two subgroups of patients were similar in regard to severity of dementia (Table 20). Because the amount of additional study time for AD patients in the learning phase was determined by BDS scores, there were also no significant differences between the subgroups in regard to study time ($t(19) = .89$, $p > .3$). Thus, neither severity of dementia or amount of study time can account for the differences in performance between the two subgroups of patients.

The hypotheses that developed from these experiments have important implications for future investigations. The fact that behavioral tests can identify subgroups of patients provides investigators with a tool to study the longitudinal course of AD in different behavioral subgroups as well as the means to "type" patients in order to tailor pharmacologic treatment. The delineation of subgroups of patients is likely to provide clues to the etiology of AD.

In addition, the results of these experiments suggest that studies of sex-differences in patients with AD may yield clues to the etiology of AD.

The hypothesis that reductions in brain NE secondary to LC degeneration result in deficits in selective attention can be further tested in the following ways: (1) study patients with Parkinson's disease, in which LC degeneration is also known to occur; or, (2) carefully document neuropsychological deficits in the living patient and attempt to correlate these deficits with neuropathology at autopsy. These experiments will help to define the role of the LC and NE in human cognition and begin to bridge the gap between clinical findings and studies using experimental animals.

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Appendix 1

Data for Patients From Experiment 1

id	sex	date	picture-recognition 10min	24hrs	72hrs	focusing 2UE	3UE	CSF metabolites MHPG	5HIAA	HVA
T.M.	F	2/83	90.0	85.0	65.0	-12	65	8.3	23.6	36.4
G.S.	M	6/83	76.6	60.0	53.3	233	106	13.1	16.0	31.4
R.A.	M	6/83	93.3	76.6	73.3	64	80	6.9	10.0	8.5
A.P.	M	4/83	100.0	80.0	95.0	0	-160	5.7	7.6	11.5
E.H.	F	3/83	95.0	70.0	80.0	-152	-102	4.1	7.2	17.3
L.T.	F	6/83	96.6	76.6	63.3	29	21	---	---	---
B.S.	F	6/83	70.0	56.6	60.0	CD	CD	5.3	5.6	12.0
S.B.	F	8/83	80.0	60.0	73.3	-58	-131	7.7	20.3	29.6
R.V.	F	8/83	80.0	53.3	83.3	-45	-54	9.9	13.7	8.9
P.G.	M	9/83	66.6	66.6	60.0	77	143	8.6	7.1	7.9
B.K.	M	9/83	100.0	90.0	86.6	431	370	---	---	---
J.F.	M	9/83	96.6	93.3	90.0	8	0	11.5	7.2	22.2
R.C.	M	8/83	66.6	60.0	73.3	168	-151	11.7	6.4	6.2
A.C.	F	3/84	80.0	55.0	90.0	-169	-138	6.2	1.6	---
E.G.	F	1/84	90.0	76.6	70.0	---	---	12.6	11.0	16.2
A.F.	F	4/84	100.0	80.0	85.0	-28	-25	5.6	19.9	34.7
L.L.	M	11/83	66.6	63.3	66.6	52	144	8.1	11.9	23.9
M.K.	F	3/83	70.0	60.0	55.0	574	391	---	16.9	31.5
A.B.	M	2/84	66.6	50.0	50.0	---	---	6.3	14.1	28.3
L.S.	M	3/84	90.0	90.0	95.0	262	262	10.3	13.3	21.9

Appendix 2

Data for Patients From Experiment 2

id	sex	date	picture-recognition 10min	24hrs	72hrs	focusing 2UE	3UE	CSF metabolites MHPG	5HIAA	HVA
M.C.	F	3/84	100.0 100.0	95.0 100.0	95.0 90.0	31	45	9.4	26.8	51.4
A.S.	F	6/84	75.0 85.0	75.0 55.0	55.0 65.0	87	2	7.9	13.2	31.5
J.A.	F	7/84	100.0 100.0	100.0 80.0	90.0 85.0	11	7	---	---	---
L.M.	M	8/84	100.0 100.0	95.0 97.5	95.0 95.0	57	77	---	---	---
M.W.	F	10/84	80.0 80.0	60.0 60.0	60.0 80.0	23	-34	---	---	---
C.G.	M	10/84	90.0 60.0	85.0 55.0	65.0 55.0	-40	126	---	---	---
K.G.	M	1/85	75.0 70.0	65.0 50.0	50.0 50.0	---	---	---	---	---
J.L.	M	9/85	90.0 85.0	75.0 60.0	65.0 75.0	---	---	---	---	---
J.B.	F	7/85	90.0 80.0	70.0 60.0	50.0 65.0	111	-462	---	---	---
M.K.	F	9/85	85.0 70.0	70.0 70.0	--- ---	-17	77	---	---	---
A.F.	F	4/84	100.0 95.0	80.0 60.0	85.0 65.0	-28	-25	---	---	---
P.H.	F	5/84	100.0 85.0	80.0 95.0	95.0 70.0	11	-14	8.3	6.4	10.0
D.S.	F	5/84	100.0 100.0	85.0 95.0	100.0 95.0	71	-77	5.1	23.2	35.2
H.C.	F	5/84	65.0 90.0	85.0 55.0	65.0 85.0	-101	-115	---	---	---

K.W.	M	7/84	100.0 100.0	95.0 100.0	100.0 85.0	3	-15	---	---	---
M.C	F	9/84	90.0 60.0	55.0 65.0	75.0 60.0	-119	30	---	---	---
E.M.	M	11/84	85.0 90.0	70.0 80.0	80.0 60.0	8	-27	---	---	---
B.L.	F	1/85	70.0 70.0	50.0 80.0	80.0 55.0	-35	-64	---	---	---
R.K.	M	6/85	60.0 75.0	75.0 70.0	75.0 75.0	-74	-29	---	---	---
M.S.	F	3/84	60.0 70.0	80.0 70.0	70.0 50.0	CD	CD	4.1	8.2	11.3

Appendix 3

Test Data for Subject R.V. in Experiment 4

Best dose = .1mg (6/8 tests)
Rebound

Test	Baseline	Best Dose	Washout
Rabbitt sorting	----	----	----
SRT (peripheral)	----	----	----
SRT (central)	-50 msec	-5	-80
CPT	456 msec	421	481
Stroop color naming			
Reading	56	94	71
Naming	50	44	48
Mixed	13	21	20
Picture-recognition			
10 min DMS	85	75	70
10 min DNMS	85	55	70
24 hrs DMS	55	75	65
24 hrs DNMS	75	70	55
Naming to definition	19	21	20
Boston Naming	39	39	40
Word-list learning	25	50	48
Category fluency	28	34	36

Appendix 4

Test Data for Subject L.E. in Experiment 4

Best dose = .1mg (4/8 tests)
Rebound

Test	Baseline	Best Dose	Washout
Rabbitt sorting	----	----	----
SRT (peripheral)	----	----	----
SRT (central)	-77msec	CD	-15
CPT	651msec	CD	558
Stroop color naming			
Reading	50	45	53
Naming	8	4	6
Mixed	0	1	0
Picture-recognition			
10 min DMS	75	60	45
10 min DNMS	55	55	40
24 hrs DMS	45	50	70
24 hrs DNMS	50	70	60
Naming to definition	8	12	11
Boston Naming	21	26	26
Word-list learning	10	10	21
Category fluency	4	6	10

Appendix 5

Test Data for Subject J.B. in Experiment 4

Best dose = .1mg (4/9 tests)
Rebound

Test	Baseline	Best Dose	Washout
Rabbitt sorting	11,288msec	4647	----
SRT (peripheral)	238msec	249	-140
SRT (central)	-175msec	-221	264
CPT	723msec	CD	CD
Stroop color naming			
Reading	63	51	56
Naming	23	20	16
Mixed	5	7	3
Picture-recognition			
10 min DMS	90	65	55
10 min DNMS	80	70	60
24 hrs DMS	70	65	75
24 hrs DNMS	60	40	65
Naming to definition	10	10	10
Boston Naming	17	16	15
Word-list learning	34	35	39
Category fluency	14	12	11

Appendix 6

Test Data for Subject J.A. in Experiment 4

Best dose = .1mg (3/10 tests)
Normal

Test	Baseline	Best Dose	Washout
Rabbitt sorting	2449msec	1253	1189
SRT (peripheral)	-86msec	7	37
SRT (central)	16msec	8	14
CPT (simple)	534msec	581	516
Stroop color naming			
Reading	55	58	49
Naming	33	36	31
Mixed	1	3	4
Picture-recognition			
10 min DMS	100	90	--
10 min DNMS	85	70	--
24 hrs DMS	100	85	--
24 hrs DNMS	80	70	--
Naming to definition	12	15	15
Boston Naming	27	27	28
Word-list learning	48	54	64
Category fluency	16	16	13

Appendix 7

Test Data for Subject M.K. in Experiment 4

Best dose = .05mg (3/6 tests)
Normal

Test	Baseline	Best Dose	Washout
Rabbitt sorting	1163msec	----	795
SRT (peripheral)	30msec	----	5
SRT (central)	210msec	72	67
CPT (simple)	383msec	468	430
Stroop color naming			
Reading	90	100	103
Naming	51	60	60
Mixed	24	35	22
Picture-recognition			
10 min DMS	85	50	--
10 min DNMS	70	80	--
24 hrs DMS	70	--	--
24 hrs DNMS	70	--	--
Naming to definition	20	22	23
Boston Naming	35	--	39
Word-list learning	60	--	--
Category fluency	39	47	40

Appendix 8

Test Data for Subject L.N. in Experiment 4

Best dose = .05mg (5/10 tests)
Normal

Test	Baseline	Best Dose	Washout
Rabbitt sorting	1106msec	825	833
SRT (peripheral)	-12msec	-87	-75
SRT (central)	15msec	-37	123
CPT (simple)	534msec	560	600
Stroop color naming			
Reading	70	45	54
Naming	22	30	31
Mixed	13	25	19
Picture-recognition			
10 min DMS	100	100	--
10 min DNMS	100	100	--
24 hrs DMS	65	95	--
24 hrs DNMS	80	85	--
Naming to definition	21	22	22
Boston Naming	23	29	27
Word-list learning	78	73	78
Category fluency	39	48	47