Order Number 8801740

Memory dysfunction in Alzheimer's disease and its relationship to brain metabolism as measured by positron emission tomography

Miller, Jeffrey Drew, Ph.D.

City University of New York, 1987

U·M·I
300 N. Zeeb Rd.
Ann Arbor, MI 48106

PLEASE NOTE:

In all cases this material has been filmed in the best possible way from the available copy. Problems encountered with this document have been identified here with a check mark ___√___.

1. Glossy photographs or pages ___
2. Colored illustrations, paper or print _____
3. Photographs with dark background ____
4. Illustrations are poor copy _____
5. Pages with black marks, not original copy ___✓___
6. Print shows through as there is text on both sides of page _____
7. Indistinct, broken or small print on several pages ___✓___
8. Print exceeds margin requirements _____
9. Tightly bound copy with print lost in spine _____
10. Computer printout pages with indistinct print _____
11. Page(s) _____ lacking when material received, and not available from school or author.
12. Page(s) _____ seem to be missing in numbering only as text follows.
13. Two pages numbered _____. Text follows.
14. Curling and wrinkled pages _____
15. Dissertation contains pages with print at a slant, filmed as received _____
16. Other _____

_____

_____

MEMORY DYSFUNCTION IN ALZHEIMER'S DISEASE AND ITS RELATIONSHIP TO BRAIN METABOLISM AS MEASURED BY POSITRON EMISSION TOMOGRAPHY

by

JEFFREY D. MILLER

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1987

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

5/13/87
Date

Max Pollack
Chair of Examining Committee

May 14, 1987
Date

Herbert D. Schlossberg
Executive Officer

Dr. Max Pollack

Dr. James Tweedy

Dr. Mony de Leon

Supervisory Committee

The City University of New York

Abstract

MEMORY DYSFUNCTION IN ALZHEIMER'S DISEASE AND ITS RELATIONSHIP TO BRAIN METABOLISM AS MEASURED BY POSITRON EMISSION TOMOGRAPHY

by

Jeffrey Miller

Advisor: Professor Max Pollack

Elderly controls and probable Alzheimer's disease (AD) patients underwent serial positron emission tomography (PET) studies during a baseline condition and while performing a verbal recognition memory task. A differential metabolic response specific to the temporal lobes was found. In all seven AD patients a greater proportion of the total temporal lobe activity favored the right during the memory condition when compared to baseline. Five out of seven controls showed the opposite effect; a task-related lateral asymmetry of activity that favored the left. Baseline regional metabolic rates were less useful than the memory challenge metabolic rates in differentiating patients from controls. These results suggest that the observed memory processing deficit in AD is related to a temporal lobe metabolic abnormality.

Acknowledgements

I would like to thank Dr. Max Pollack for serving as my sponsor and helping me to try and keep things in perspective. I would also like to thank Drs. Jim Tweedy and Mony de Leon for completing the core committee. The critiques of my outside readers, Drs. Peter Van Gelder and Steve Ferris, were very thoughtful and their questions at the defense dug in a little deeper. Thank-you.

But most of all I want to thank my newlywed dissertation widow, Justine, for hanging in there. What a situation to be engulfed in for the first eight months of marriage. Now that it's done, let's get acquainted!

Table of Contents

List of Tables

List of Figures

INTRODUCTION

Generalized Symptoms and Deficits in Alzheimer's Disease

Alzhemimer's disease (AD) remains a clinically and neuropathologically defined disease (American Psychiatric Association, 1980) whose definitive diagnosis can still only be made at autopsy. The associated clinical symptoms generally begin insidiously and follow a pattern of progressive cognitive deterioration that affects recent and remote memory, concentration, language, visuospatial skills, judgement, orientation, personality, and intellect. Eventually, in the most severe cases, the patient is left unable to speak, ambulate, or manage even the simplest of self-care functions (Cummings & Benson, 1983). In an attempt to increase the accuracy of a positive clinical diagnosis (Reisberg & Ferris, 1982; Shuttleworth, 1982) and better understand the course of the disease, efforts have been made to describe the distinguishing clinical stages of decline (Cummings & Benson, 1983). The earliest and most prominent complaint of AD is memory loss (Reisberg & Ferris, 1982). In fact, if memory impairment is not one of the earliest symptoms, the diagnosis is in doubt (Cummings & Benson, 1983).

As the behavioral hallmark of AD, memory deficit has been consistently associated with marked neuropathology in the temporal lobes (Hyman, Van Hoesen, Damasio, & Barnes, 1984) and with a cholinergic system deficiency (Coyle, Price, & De Long, 1983). The general reduction in cerebral blood flow (Ingvar, Risberg, & Schwartz, 1975) and in glucose metabolic rates (Ferris, de Leon, et al., 1980) in AD patients relative to controls during baseline studies appears to be most prominent in the temporal and parietal lobes (Chase, Foster, &

Mansi, 1983; Friedland, Brun, & Budinger, 1985; Simard, Olesen, Paulsen, Lassen, & Skinhoj, 1971). Furthermore, these reductions in cerebral blood flow (CBF) and metabolism have been found to be associated with measures of memory deficit determined at times other than during scanning procedures (de Leon, Ferris, George, Christman, et al., 1983; Hagberg & Ingvar, 1976). Until now, the effects of cognitive activity on regional glucose metabolism during positron emission tomography (PET) tracer uptake in AD patients has not been reported. The current study was the first to investigate the relationship between memory processing in clinically diagnosed AD patients and brain metabolism. The goal was to extend the findings of previous baseline studies and further examine the pathophysiological basis of memory dysfunction in Alzheimer's disease by measuring regional glucose metabolic rates during participation in a memory task. Such a non-invasive observation of whole-brain functioning should aid in the localization of the abnormal metabolic activity that is associated with memory deficit.

Deficits in Recall and Recognition Memory

Memory Deficits in Normal Aging

Normal aging is associated with impairment in both recall and recognition memory (Botwinick, 1984; Craik, 1977; Schonfield, 1965). Early studies using subjects of varying ages found that while recall scores decreased linearly with age, there was not a significant age-related deterioration in recognition memory scores (Craik, 1971; Schonfield & Robertson, 1966). More recent reports, however, have consistently shown that while recognition memory is typically superior

to recall, there is a significant decline in recognition with aging. This impairment of recognition has been demonstrated with various verbal and nonverbal materials (Burke & Light, 1981) using several paradigms (Erber, 1974; Ferris, Crook, Clark, McCarthy, & Rae, 1980; Harkins, Chapman, & Eisdorfer, 1979; Poon & Fozard, 1980; Rankin & Kausler, 1979; White & Cunningham, 1982). In contrast to the relatively selective impairment of recall associated with normal aging, Alzheimer's disease patients suffer marked impairments in recognition as well as recall.

Alzheimer's Disease Memory Impairment

Clinical descriptions of the usual progression of symptoms in Alzheimer patients refer to an early deficit in recalling names, trouble locating objects, and an impaired recall of recent personal history. As the disease progresses, there is an increasingly severe loss of memory for remote as well as recent events (Cummings & Benson, 1983). Psychometric testing of AD patients reveals a severe deficit in both recall (Branconnier, Cole, Spera, & DeVitt, 1982; Harris & Dowson, 1982; McCarthy, Ferris, Clark, & Crook, 1981; Miller, 1975; Miller, 1971) and recognition memory (Branconnier et al., 1982; Hart, Smith, & Swash, 1985; Miller, 1975; Miller & Lewis, 1977; Wilson, Bacon, Fox, Kramer, & Kaszniak, 1983; Wilson, Kaszniak, Bacon, Fox, & Kelly, 1982).

To summarize, normal aging has a primary effect on recall memory and a lesser effect on recognition memory. Alzheimer's disease, however, is associated with both recognition and recall deficits. Thus, while both recall and recognition tests of memory are capable of discriminating between the loss of memory associated with normal aging and Alzheimer disease memory dysfunction, recognition tests have been

considered by some investigators (Branconnier, Cole, Spera, & DeVitt, 1982) to be the preferred diagnostic screening instrument.

To more fully understand memory dysfunction in Alzheimer's disease, the clinical symptoms and psychological constructs of memory impairment (Miller, 1971; Wilson et al., 1983) need to be related to the anatomic and physiologic changes found in both post-mortem and in vivo studies. As will be seen from the following reviews of AD neuropathology and neurochemistry, temporal lobe pathology and neurochemical deficits are among the brain changes seen in AD that are most consistently implicated in the associated memory impairment. Though the degree to which these changes directly contribute to memory dysfunction is unknown, these findings, in conjunction with human lesion studies, strongly suggest that a metabolic abnormality during memory processing should be observed to be preferentially located in the temporal lobes.

Neuropathology of Aging and AD

The neuroanatomical and neuropathological changes associated with normal aging and pathologically defined Alzheimer's disease have been thoroughly reviewed by Brun (1985), Kemper (1984), and Lauter (1985). Their work is the primary source of this summary. It is important to keep in mind that in neither aged nor Alzheimer brains do the described alterations exist in all regions, proceed at the same pace, or produce changes that are specific to one condition and not present in the other. Even though some of the described AD changes overlap considerably with the changes in normal aging, AD is usually viewed as a specific disease and not as accentuated aging (Kemper, 1984).

Brain weight loss and ventricular dilation occur in normal aging, but are more pronounced in AD. Gyral atrophy, also observed in both processes, is particularly marked in the temporoparietal area and frontal lobes of AD patients. Alzheimer brains have significantly fewer cells in the same regions also preferentially affected by aging and demonstrate a similar pattern of involvement; higher-order "association" cortex is more heavily affected than primary sensorimotor cortex. In the frontal and temporal lobes, and hippocampal formation, cell loss can approach 50%. In contrast to other regions, cell losses in the amygdala occur in all subdivisions in addition to those affected by normal aging.

Neurofibrillary tangles (NFT), senile plaques, and granulovacuolar degeneration also occur in specific topographic patterns. Of the three, neurofibrillary tangle abundance is the most reliable neuropathologic indicator of dementia (Cummings & Benson, 1983). During normal aging, neurofibrillary tangles are limited predominantly to specific areas of the hippocampal formation. In AD they are more widely distributed and follow a progression of increasing density from the primary sensorimotor cortex, which is relatively spared, to the multimodal tertiary zone of the temporoparieto-occipital junction. The limbic system, hippocampal formation and amygdala, and posterior cingulate are also heavily affected.

Aging produces a distribution of senile plaques similar to that of the NFT. However, the distribution is wider and there is a predilection for the neocortex. In AD, the density is higher and the distribution of plaques is more extensive than in normal aging, but the relationship to disease is not as clear as with the NFT. Plaque counts

have, however, been found to correlate with dementia scores (Blessed, Tomlinson, & Roth, 1968). Plaque counts appear to be highest in the higher-order "association" areas of the frontal, temporal, parietal, and occipital lobes and lowest in primary sensorimotor cortex. Though the temporal lobe "association" cortex is the most heavily affected region of the neocortex, the amygdala has the highest concentration of plaques of any area studied in the brain (Jamada & Mahraein, 1968).

Granulovacuolar degeneration is rare before age 60. In normal aging there is a predilection for Sommer's sector of the hippocampus, yet even in this region it appears in only about 9 percent of the cells (Tomlinson & Kitchener, 1972; Woodard, 1962). In Alzheimer's disease, there is a dramatic increase in concentration in this region with a spread to other hippocampal areas. Granulovacuolar degeneration is rare in other parts of the brain in either condition.

To summarize, neurofibrillary tangles and senile plaques follow a similar pattern of neocortical involvement in AD affecting "association" areas the most and primary sensorimotor cortices the least. Granulovacuolar degeneration is primarily restricted to the hippocampus. The NFT is the most reliable marker for AD. Its concentration is most dense in the highly interconnected hippocampus-amygdala-limbic-neocortical "association" areas complex, a system reliably involved in memory function.

Lesion Studies of Memory

While memory impairment is the most evident behavioral symptom of AD, plaques and tangles are its neuropathological markers. Though it is unlikely memory is localized in a particular region of the brain,

most investigators who use lesions to model memory dysfunction focus on the same anatomical areas most heavily affected by AD neuropathology: the hippocampus, amygdala and adjacent temporal lobe structures. It should be noted, however, that although there are memory dysfunction parallels between AD patients and patients with amnesia due to lesions, the memory deficits in AD do not exist as isolated symptoms and are accompanied by broader cognitive and personality changes.

Bilateral medial temporal lobe resections in man result in a persistent anterograde and limited retrograde amnesia that affects both recognition and recall memory (Scoville & Milner, 1957). The critical structures involved appear to be the hippocampal formation and amygdala (Scoville & Milner, 1957; Zola-Morgan, Squire, & Mishkin, 1982). Patients who have undergone unilateral temporal lobectomies do not suffer from the severe amnestic symptoms that are common to patients who have had bilateral operations, though they do have significant memory deficits. Left temporal lesions primarily affect memory of verbal material, while right-sided damage affects memory of visual and spatial material. Furthermore, the degree of memory impairment correlates with the amount of left and/or right temporal lobe damage (Kolb & Wishaw, 1985; Mishkin, 1978; Saunders, Murray, & Mishkin, 1984).

Parietal and frontal lobe lesions may also result in memory impairments. Lesions of the parietal lobe correlate primarily with short-term memory deficits and are associated with an asymmetry of function (Kolb & Wishaw, 1985; Shallice & Warrington, 1970; Warrington, Logue & Pratt, 1971). The right parietal lobe appears to be involved in both verbal and patterned visual information processing, while the

left is nonspecific to modality of presentation but devoted primarily to verbal material (Butters, Samuels, Goodglass, & Brody, 1970). Frontal lobe lesions have been associated with a disturbance in remembering the short-term temporal ordering of events and an increased susceptibility to interference (Kolb & Wishaw, 1985; Walsh, 1978). It has been suggested that these observed deficits may be the result of increased distractibility and decreased arousal (Heilman & Valenstein, 1979, Walsh, 1978).

In conclusion, lesion studies indicate that temporal lobe damage results in more extensive memory impairment than does parietal or frontal lobe insult. They also suggest, in conjunction with AD neuropathology reports, that the temporal lobes are the areas most likely to show an abnormal physiological response during memory processing in AD subjects.

Neurochemistry of Memory Impairment

Acetylcholine (ACh) is the neurotransmitter most often implicated in the memory dysfunction associated with AD (Coyle, Price, & DeLong, 1983; Perry & Perry, 1985; Perry et al., 1978). This is due to several findings: (1) ACh muscarinic receptor blocking agents produce a temporary memory impairment similar to that observed in AD, (2) regions of the brain that are critical to memory processing show reductions in AD in the enzyme that catalyzes the synthesis of ACh, and (3) cells that are the primary source of cortical cholinergic innervation are markedly reduced in number in AD brains (Cooper, Bloom, & Roth, 1986).

Drachman and Leavitt (1974) were the first to report that the administration of scopolamine, a muscarinic blocking agent and

cholinergic antagonist, produced a pattern of scores in young normals on the Wechsler Adult Intelligence Scale similar to that normally seen in elderly individuals. Performance scores were lowered, while verbal scores remained largely unaffected. Studies in monkeys have produced similar results. Young monkeys injected with scopolamine consistently demonstrated performance deficits on memory tasks that remarkably resembled deficits seen in normal aged monkeys (Bartus & Johnson, 1976). Drachman (1977) later reported that a transient early dementia-like memory deficit could be induced in normal subjects by scopolamine and reversed by the cholinergic enhancer physostigmine. These initial studies, then, suggested that a scopolamine-induced memory deficit might be used as a model for the memory dysfunction associated with AD.

Three sets of investigators (Davies & Maloney, 1976; Perry, Perry, Blessed, & Tomlinson, 1977; Spillane et al., 1977) independently showed around the same time that the enzyme responsible for ACh synthesis, choline acetyltransferase (CAT), is significantly decreased in the cerebral cortex of AD patients versus age-matched controls by as much as 90 percent. The areas most heavily effected were the frontal and temporal cortex, and the hippocampus. It has been hypothesized that the marked loss of cell bodies in the nucleus basalis of Meynert (Whitehouse, Price, et al., 1981), which provides the primary cholinergic innervation to the neocortex and amygdala (Mesulam & Van Hoessan, 1976) and the medial septal nucleus, which projects to the hippocampus (Nakano & Hirano, 1982), is responsible for the decreased cortical cholinergic innervation (Bartus, Dean, Beer, & Lippa, 1982; Wilcock, Esiri, Bowen, & Smith, 1983). These and other studies (Bowen et al.,

1979; Smith & Swash, 1978) indicate that the preferential and selective disruption of the cholinergic system, particularly in the temporal lobes, is intrinsically associated with AD memory impairment.

Summary of Neuroanatomic and Neurochemical Studies

The neuropathological and neurochemical changes observed in the temporal lobe structures of AD patients are consistently and clearly implicated in the associated memory dysfunction. The hippocampus may be essentially disconnected from its neuronal input and output circuitry (Hyman, Van Hoesen, Damasio, & Barnes, 1984) and, along with the amygdala, deprived of normal cholinergic innervation (Coyle, Price, & DeLong, 1983). Both structures are also heavily affected by the neuropathology of the disease (Anderson & Hubbard, 1985; Ball et al., 1985; Collerton & Fairbairn, 1985; Kemper, 1984). Nevertheless, anatomic and biochemical approaches to studying the brain/behavior relationships in AD have drawbacks. Neuropathology and neurochemistry studies that correlate either histologic or pathologic changes with behavior make inferences from postmortem cases. Thus no direct linkage to impaired behavior can be observed. Though human lesion studies were performed on live patients, the problems associated with inferring the function of a structure from postoperative behavioral changes are well known (Kolb & Wishaw, 1985).

Recently developed noninvasive techniques that take advantage of the direct relationship between neuronal activity and cell metabolism provide regional physiological measures of the intact brain and offer the unique opportunity to examine local cerebral functioning during resting states and during behavioral performance. Measuring cerebral

blood flow with the ^{133}Xe inhalation technique and brain glucose metabolism with positron emission tomography (PET) are two such procedures. The following is a review of previous CBF and PET studies that are relevant to memory function, aging, and AD.

Cerebral Blood Flow

Normal Aging Baseline Studies

Cerebral blood flow (CBF) decreases with age (Melamed, Lavy, Bentin, Cooper, & Rinot, 1980; Meyer & Shaw, 1984; Naritomi, Meyer, Sakai, Yamaguchi, & Shaw, 1979) and demonstrates regional specificity (Shaw et al., 1984). Frontal (Meyer & Shaw, 1984), temporo-sylvian (Warren, Butler, Katholi, & Halsey, 1985), and parieto-occipital (Pantano et al., 1984) areas are preferentially affected, while sensorimotor cortex shows the least prominent diminution (Pantano et al., 1984). Furthermore, there is evidence to suggest the decline is not symmetrical. Left hemisphere flow may decrease faster than right, and anterior regions show more marked decreases than posterior regions (Melamed et al., 1980; Meyer & Shaw, 1984). Cell degeneration and loss, along with associated diminished activity, is the most likely explanation for the perfusion change with age (Pantano et al., 1984; Shaw et al., 1984).

AD Baseline Studies

Cerebral blood flow studies in patients with Alzheimer's disease have reported diffuse flow decreases relative to age-matched controls (Lavy, Melamed, Bentin, Cooper, & Rinot, 1978; Obrist, Chivian, Cronqvist & Ingvar, 1970; Risberg, 1980; Simard, Olesen, Paulson, Lassen, & Skinhoj, 1971). In addition to the generalized, bilateral

CBF changes in AD (Yamaguchi, Meyer, Yamamoto, Sakai, & Shaw, 1980), there are also intrahemispheric regional differences. Frontal, temporal, and occipito-parieto-temporal samples show maximal flow diminutions (Ingvar, Risberg, & Schwartz, 1975; Simard et al., 1971), while there is a relative sparing of the sensorimotor cortex (Hachinski et al., 1975). Furthermore, posterior flow values are usually lower than anterior values in AD patients relative to controls (Ingvar, Risberg, & Schwartz, 1975; Risberg, 1980).

Several authors have reported correlations between CBF and dementia severity (Hagberg & Ingvar, 1976; Risberg, 1980; Simard, et al., 1971), though others have not found such associations (Hachinski et al., 1975). At least one author has examined the relationship between memory deficits and resting CBF. Hagberg and Ingvar (1976) studied 49 AD patients under the age of 56 (mean age = 55, SD = 5 years). The total sample was divided into two groups; one with symptoms limited to only memory dysfunctions and a second with global impairments. The group with memory impairment demonstrated a focal temporal flow decrease, while the more severely impaired group had additional parieto-temporo-occipital diminutions. Because the intra-arterial ^{133}Xenon injection technique was used, regional CBF measurements could only be made on one side. In all but two patients the dominant, or left, hemisphere was monitored.

Though resting CBF studies show regional blood flow is associated with behavioral deficits in AD measured at times other than during a CBF monitoring procedure, they do not offer much insight into CBF changes that may take place during active memory processing. More

accurate estimates of flow changes that occur during memory function can be made if memory tasks are performed while CBF is being measured.

Memory Activation Studies in Normals

Cerebral blood flow studies during memory processing have not been reported in AD. Studies in normals do exist, though subjects were usually drawn from hospital populations. An early study that investigated recent memory processing with a paired-associates task reported significant mean hemispheric flow increases of 7% in the left hemisphere relative to baseline. Significant frontal, occipital, and occipito-parietal regional flow increases of 2%, 4%, and 9%, respectively, were also found. Unfortunately, because the intra-carotid injection technique was used, only flows on the left side were measured (Maximilian, Prohovnik, Risberg, Hakansson, 1978). Digit-span-backward (Risberg & Ingvar, 1973) and recognition memory (Wood, Taylor, Penny, & Stump, 1980) paradigms have also produced regional increases of between 4% and 15%. Of the regions that responded during these studies, the temporal lobes most consistently showed significant increases. Again, only one hemisphere was monitored in the digit-span study, so no information could be obtained on possible lateral asymmetries of activation. However, bilateral measurements during the recognition task suggested that accuracy of performance corresponded to a specific left medial temporal lobe activation. In summary, CBF evidence suggests the temporal lobes differentially respond to the functional demands of memory processing and that this activation, at least during verbal recognition tasks, may be specific to the left hemisphere.

Memory Activation Studies in Amnestics

Changes in regional CBF in amnestics during memory task participation has also been investigated. Two case studies by Wood and his colleagues (Wood, Armentrout, Toole, McHenry, & Stump, 1980; Wood, McHenry, Roman-Campos, & Poser, 1980) showed that participation in a recognition memory task produced increased right, rather than left, hemisphere flows. This pattern was opposite to that shown by young normal subjects (Wood, Taylor, Penny, & Stump, 1980). One patient had retrograde amnesia and, upon distraction, could not remember events that occurred even seconds earlier. Neuropsychological testing demonstrated no other focal deficits. The amnesia was believed to be secondary to bilateral medial thalamic infarction (Wood, Armentrout, et al., 1980). The second patient had normal memory for events following her hospitalization, but persistent retrograde amnesia. She had initially presented with confusion and acute memory loss. The cause of the memory impairment was unknown, though EEG and neuropsychological testing suggested residual left medial temporal lobe damage (Wood, McHenry, et al., 1980). In the patient with remitted amnesia, right medial temporal lobe CBF correlated with memory task accuracy, but left temporal flow did not. Interestingly, the subject with the more severe memory deficits performed only at a chance level, yet still showed a right hemispheric activation. Flows in the right angular gyrus area were higher than those in the left. These results suggest that right hemisphere regions continue to function during recognition memory tasks despite left-sided damage. Furthermore, this abnormal asymmetry of activity appears to be independent of memory performance.

Behavioral Activation Studies in AD

There have been two CBF behavioral stimulation studies in AD subjects (Ingvar, Risberg, & Schwartz 1975; Yamaguchi et al. (1980). Both used a variety of tasks during the same session - Raven's matrices, naming, digit-span, counting, or listening to musical tape - yet behavioral activation failed to produce significant flow increases in any of the sampled regions. In some instances, flow actually decreased. Age-matched controls, in contrast, demonstrated significantly augmented mean regional flows of about 10%. It was suggested the abnormal response pattern of AD subjects was due to either cortical neuronal degeneration or a generalized lack of arousal (Ingvar, Risberg, & Schwartz 1975; Yamaguchi et al. (1980).

These behavioral studies suggest that demented subjects do not demonstrate the same task-dependent pattern of CBF increases seen in age-matched normal controls. The AD patients failed to show a cerebrovascular response to the tasks, rather than differential patterns of change in flow relative to the pattern seen in controls. In view of the topographic patterns of neuropathological and neurochemical changes in Alzheimer's disease, task-dependent regional CBF changes in AD subjects, compared to controls, would be expected.

A limitation of the two AD studies reviewed above was that a wide variety of different tasks were used during CBF measurement. Perhaps a better way to analyze brain activity during cognitive processing in AD patients would be to use a single, specific task and to analyze patterns of regional lateral asymmetries rather than mean flow or metabolic rates. Such a method might aid in the identification of more subtle patterns of activity in response to specific behavioral activa-

tion and provide valuable insight into the physiologic nature of the memory dysfunction.

Like the CBF technique, positron emission tomography is also capable of serial same-day studies on the same subject, but can produce cross-sectional tomographic images of high spatial resolution as well. This is in contrast to CBF measurement procedures which are non-tomographic and cannot generate physiologic images of internal, subcortical structures. Another major advantage of PET is that by using labeled glucose analogs to measure the glycolytic rate, a much more direct assessment of cellular function is possible (Phelps, 1981). PET, therefore, has a greater potential to localize specific regional metabolic responses to behavioral tasks with a much higher degree of accuracy than do measures of cerebral blood flow.

Positron Emission Tomography

Overview

Glucose is the only significant source of energy in the brain under normal circumstances (Sokoloff, 1981). By measuring tissue uptake rate of a glucose molecule analogue labeled with a positron-emitting radionuclide, PET provides a three-dimensional map of cerebral functioning (Phelps, Mazziotta, & Huang, 1982; Raichle, 1983). One advantage of PET over CBF is its superior spatial resolution; 8 to 12 mm versus 25 to 40 mm for CBF. This type of resolution, however, comes at the expense of a much lower temporal resolution; 30 minutes or more for PET versus 3 to 4 minutes in CBF (Wood, 1983). Because cerebral tissue is involved in self-sustaining activities and task-related functions simultaneously, in vivo metabolic measures are

nonspecific for the type of activity taking place within a particular brain area at a given time. Therefore, a specific task may produce only very subtle overall changes in glucose metabolic rates (Phelps, 1981). Nevertheless, because the effects of behavioral stimulation and of disease can produce functional anatomical changes and those changes can be revealed in PET metabolic images, valuable insights into brain/behavior relationships can be investigated (Phelps, Mazziotta, & Huang, 1982; Raichle, 1983).

Normal Aging Baseline Studies

The majority of PET baseline studies in normal aging have not demonstrated a significant age effect on regional glucose metabolic rates (rGMR), metabolic lateral asymmetries, or correlations between intellectual changes and metabolic rates (de Leon, et al., 1985; de Leon, Ferris, George, Christman, et al., 1983; de Leon, George, Tomanelli, et al., 1986; Duara et al., 1984; Hawkins, Mazziotta, Phelps, Kuhl, & Reige, 1983; Rapoport, Duara, & Haxby, 1984). An earlier study by Kuhl, Metter, Reige, & Phelps (1982) did, however, report an age-associated nonsignificant trend toward decreased glucose metabolic rates and a decreased frontal-to-parietal ratio with advancing age. de Leon, George, Tomanelli; et al. (1986) also examined the relationship between frontal and parietal metabolic rates as a function of age and found a significant decrease in the frontal-to-parietal ratio, or an increased hypofrontality, in the elderly compared to young normal subjects. These results suggest that despite the lack of generalized metabolic reductions due to aging, there may be alterations in relative metabolic rates between regions.

AD Baseline Studies

In contrast to normal aging, patients with AD suffer both marked structural (de Leon & George, 1983) and metabolic changes. Reported mean glucose metabolic diminutions in AD patients relative to controls range between 20% and 49% (Benson, et al., 1983; Chase, Foster, & Mansi, 1983; Cutler et al., 1985; de Leon, Ferris, George, Christman, et al.,1983; de Leon, Ferris, George, Reisberg, et al., 1983; Friedland, Brun, & Budinger, 1985), with an approximate modal diminution across studies of 22%. Regional studies have produced more variable results. Of six reports that used age-matched controls, one showed the lowest regional glucose metabolic rates to be in the frontal and temporal lobes (Ferris, de Leon, et al., 1980), in two studies the lowest rates were in the thalamic sample (Benson et al., 1983; de Leon, George, et al., 1983) and in three studies the lowest rates were in the parietal lobes (Chase, Foster, & Mansi, 1983; de Leon, Ferris, George, Christman, et al., 1983; Cutler et al., 1985). Primary sensory and motor cortices were generally determined to be the least affected (Benson et al., 1983; Chase, Foster & Mansi, 1983; Cutler et al., 1985). These results, however, should be regarded as tentative. No inter-region statistical analyses were performed by the authors and there were technical differences among studies. For instance, temporal lobe samples were measured in both de Leon studies (de Leon, Ferris, George, Christman, et al., 1983; de Leon, George, et al., 1983), but parietal lobe samples were not. This makes comparisons of inter-regional differences across studies difficult. The problem of identifying regional anatomy on the PET scan can also add to the complexity of comparing results across studies. Only the one study by Ferris et

al. (1980) and the two studies by de Leon (de Leon, Ferris, George, Christman, et al., 1983; de Leon, George, et al., 1983) used subjects' CT scans to map structural outlines onto the metabolic image. Nevertheless, this summary suggests that the temporal and parietal lobes probably suffer the largest metabolic diminutions in AD patients relative to controls.

In contrast to the reviewed AD structural and CBF studies, PET baseline studies have not singled out the temporal lobes as having particularly decreased metabolic rates relative to other regions. Temporal lobe metabolic rates are, however, significantly lower than those of age-matched controls. Though temporal lobe glucose utilization has been found to be significantly correlated with memory deficit in some baseline studies (de Leon, Ferris, George, Christman, et al, 1983; Ferris, de Leon, et al., 1980; Foster et al., 1983), others have not found similar associations (Cutler et al., 1985; Rapoport, Duara, & Haxby, 1984). Even in the studies where there were significant correlations between memory test scores and resting temporal lobe metabolic rates, the correlation coefficients were similar to those associated with other regions.

Though the temporal lobes and related structures are most consistently affected by AD neuropathological changes, metabolically they are not markedly different than other affected regions. Behavioral activation studies and measures of lateral asymmetry, as opposed to resting studies, may enhance regional differences in glucose metabolic rates between normal elderly controls and AD subjects and provide a deeper understanding of the underlying pathophysiologic changes associated with the AD memory deficit.

Metabolic Asymmetries

Asymmetry indexes are advantageous in metabolic studies where the primary interest is inter-regional relationships versus differences in absolute metabolic rates. Because factors such as machine drift and global metabolic rates should act as constants within a given scanning session, results across different days, machines, and experimental conditions are more easily interpreted.

Recent evidence suggests that for resting baseline studies, AD patients demonstrate significantly greater lateral metabolic asymmetries in the frontal, parietal, and temporal lobes than do age-matched controls (Duara et al., 1986; Friedland, Budinger, Koss, & Ober, 1985; Haxby et al., 1986; McGeer et al., 1986). However, there does not appear to be a directional preference for this regional asymmetry of glucose utilization (Benson et al., 1983; Chase, Foster, & Mansi, 1983; Foster et al., 1984; Friedland et al., 1983). It is of interest that the increased metabolic asymmetry is not associated with a significant asymmetry of structural atrophy as measured by CT (Duara, et al., 1986; McGeer, et al., 1986). These results are consistent with the suggestion of de Leon, Ferris, George, Reisberg, et al. (1983) that in Alzheimer's disease the metabolic changes are more salient than the structural changes.

PET Behavioral Studies

Behavioral studies using PET have been much less frequently performed than behavioral activation studies using the ^{133}Xenon inhalation technique to measure CBF. PET studies are more expensive and isotopes with short enough half-lifes to perform serial same-day studies have not been used extensively. When more than one behavioral

condition has been used with PET, subjects were usually tested either on separate days, or different subject groups were used for different conditions. Nevertheless, cognitive activation studies in normals have produced the expected metabolic asymmetries in response to different behavioral paradigms; verbal tasks have resulted in significant regional activations in the left hemisphere, while metabolic rates measured during visuospatial tasks favored the right (Gur, Gur et al., 1983; Mazziotta, Phelps, Carson, & Kuhl, 1982).

Several studies have reported significant correlation coefficients between previously obtained measures of behavioral deficit in AD and regional glucose metabolic rates during a resting state (Cutler et al., 1985; de Leon, Ferris, George, Reisberg, et al., 1983; Ferris, de Leon, et al., 1980; Foster, et al., 1983; Friedland et al., 1983; Koss, Friedland, Ober & Jagust, 1985; Rapoport, Duara, & Haxby, 1984), but none have examined metabolic alterations <u>during</u> cognitive activation. The current study is the first to examine the relationship between memory processing and simultaneous measures of regional glucose utilization in AD patients and normal age-matched controls. By examining the effects of a memory activation condition on regional metabolic rates during the PET tracer uptake period, group differences in regional metabolism will be enhanced and the underlying metabolic abnormalities associated with the AD memory dysfunction will be able to be studied in greater detail than possible with baseline studies alone. It is hoped this study will also demonstrate the feasibility of using PET to examine the regional pathophysiology that is associated with other AD cognitive deficits and that behavioral paradigms, used in

conjunction with PET, might prove to be sensitive diagnostic indicators of disease.

Task Choice

The previously reviewed lesion, neuropathological, neurochemical, and metabolic studies in Alzheimer patients and controls show that the temporal lobes are the regions of the brain most consistently associated with memory processing. It is here, then, that metabolic probes into the memory dysfunction of Alzheimer patients should be focused. Because of the 30 minute tracer uptake period of ^{11}C-2-deoxy-D-glucose and the cognitive impairment of AD patients, task choice is critical. The task must be sufficiently understandable to both groups, keep subjects engaged with minimal experimenter intervention, and allow for some level of appropriate performance.

The principal effect of normal aging on memory is the impairment of recall with a less marked reduction in recognition memory performance. In contrast, AD is characterized by both recall and recognition memory failure. A recognition memory task, then, should provide a larger performance difference between AD and normal groups. In addition to the above theoretical consideration, a recognition task is preferred over a recall task because both normals and demented subjects find these tasks easier to perform (Mohs & Davis, 1982; Schonfield, 1965). For example, the response is cued and consists of a simple yes or no (Brinkman & Gershon, 1983; Hart, Smith, & Swash, 1985; Mohs & Davis, 1982).

A continuous recognition task is particularly advantageous for use with memory studies that last for extended periods of time for several

reasons: (1) it can be used to analyze the pattern of forgetting over brief intervals of time that are measured and manipulated in small controlled units of distraction (Brinkman & Gershon, 1983; Ferris, Crook, et al., 1980; Shepard & Teghtsoonian, 1961), (2) it is amenable to signal detection analysis which allows for independent estimates of memory sensitivity and response bias (Swets, 1973) and (3) it allows for continuous involvement and vigilance in a task that requires no other instructions once the task has begun. Therefore a continuous verbal recognition memory task will be used in this PET study to further examine memory dysfunction in AD.

Rationale and Hypotheses

I. Behavioral assessment - Because recognition memory impairment is greater in AD patients than in age-matched controls, the clinically diagnosed AD patients in the present study should perform significantly more poorly on the behavioral task than age-matched elderly normal controls.

II. Baseline metabolic rates - Neuropathological studies indicate that the parietal and temporal lobes are preferentially affected in AD. Therefore these areas, but not sensorimotor samples, should demonstrate significant diminutions in glucose metabolic rates in AD when compared to age-matched controls. Furthermore, it is expected that the diminutions in glucose metabolic rates in the AD patients relative to controls using ^{11}C will be comparable to the results of past PET studies that used ^{18}F as the tracer isotope. PET studies in AD using ^{11}C have not yet been reported.

III. Memory condition metabolic rates - Participation in a memory task during the isotope uptake period should result in altered metabolic rates in both groups and exaggerate group differences. A lateral asymmetry index of metabolic activity should be a more sensitive indicator of abnormal regional activity during the memory condition than regional metabolic rates alone. CBF reports of cognitive activation in AD patients have been disappointing probably because activation was defined by increased flow rates. Asymmetry measures have the advantage of eliminating confounds due to variation in global metabolic rates and possible machine calibration drift.

A. Motor skills and sensorimotor cortex are relatively spared in AD. Therefore, significant group differences in lateral asymmetries for the sensorimotor cortex sample are not expected during the memory condition.

B. The recognition memory deficit in AD and marked neuropathology of the temporal lobes is expected to be reflected in altered metabolic rates, from baseline to activation, that are restricted to the temporal lobes.

1. Lesion studies indicate that left temporal lobe damage results in verbal memory deficits. CBF measurements during verbal memory processing in normals demonstrate greater left temporal lobe activation than right. Therefore, for the controls it is expected that a greater proportion of glucose metabolic activity will favor the left temporal

lobe during the memory condition compared to baseline.

2. Behavioral, neuropathological, neurochemical, and metabolic studies indicate AD patients suffer from a significant memory deficit that may be related to preferentially impaired, or damaged, temporal lobe structures. The AD group, then, should not show a lateral asymmetry favoring the left temporal lobe.

IV. Memory task performance and metabolic asymmetries - Reductions in AD metabolic rates have been found to be associated with memory deficit measures obtained either before or after PET scanning. Previous studies, then, have not directly assessed the relationship between memory task performance and metabolism. A discrimination index of memory task performance during the uptake period should correlate with temporal lobe lateral asymmetry differences for the memory condition compared to baseline. Normal memory function is expected to increase the metabolic demand of the left temporal lobe. As memory processing becomes less efficient and performance scores drop, indices of metabolic activity should favor the left temporal lobe to a lesser degree.

METHODS

Subjects

All potential subjects received extensive medical, neurologic, psychiatric, neuropsychologic, neuroradiologic, and clinical laboratory examinations to rule out clinically significant medical and neurologic conditions and to establish by exclusion the clinical diagnosis of AD for patients with dementia. Subjects with histories or physical evidence of stroke, psychiatric illness, head trauma, alcohol or drug abuse were also excluded. Furthermore, no individuals requiring medication other than diuretics were accepted nor were individuals accepted whose examinations revealed significant and unstable cardiovascular disease, diabetes (not controlled by diet alone), thyroid or other metabolic dysfunctions. All subjects were right handed.

The 7-point global deterioration scale (GDS) (Reisberg, Ferris, de Leon, & Crook, 1982) was used to characterize overall cognitive impairment. Subjects with a GDS score of 1 had no subjective or objective memory complaints. Subjects with a GDS score of 2 may have had subjective memory complaints, but did not have objective evidence of cognitive impairment on clinical interview. Both groups of subjects were classified as controls (mean age = 67 years, SD = 7.6 years; range = 54 to 76 years; N = 7). Subjects whose GDS score was between 3 and 6 were classified as mild to moderately severe AD (mean age = 68 years, SD = 5.6 years; range = 59 to 74 years; N = 7). The majority of normal subjects were spouses, relatives, or friends of the patients. All subjects were paid $100 to participate in the study and all subjects

(as well as the primary caretakers of the AD patients) signed written informed consent forms.

The 14 selected subjects also received the Guild Memory Test (Gilbert, Levee, & Catalano, 1968). A combined average score was calculated to give equal weight to each subtest. Subtests included paragraphs immediate and delayed, paired associates immediate and delayed, designs, and digits-forward and backward. The mean combined Guild score for the controls was 2.29 (*SD* = .43). The mean Guild score for the clinically diagnosed Alzheimer patients was .49 (*SD* = .21). The range of scores for the two subject groups did not overlap. When compared to Guild scores derived from a larger population of AD subjects (*N* = 69) and age-matched controls (*N* = 58) drawn from the Geriatric Study and Treatment Program of Millhauser Labs at New York University Medical Center, the Guild scores of all 7 subjects classified as controls fell within 1.5 *z*-scores of the larger age-matched control comparison group mean (*M* = 2.06, *SD* = .45). Similarly, none of the Guild scores of the 7 selected AD patients were more than 1.5 *z*-scores from the AD comparison group mean (*M* = .81, *SD* = .47). The correlation between the Guild score and GDS was -.85 for the 14 subjects of the current study and -.87 for the larger (*N* = 128) sample (Miller & de Leon, 1986). The subjects selected for study, then, were typical of a larger AD and age-matched control population.

Apparatus

Within 6 months of the PET study, clinical computed tomography (CT) studies were performed on either a General Electric 8800 or 9800 scanner using standard kilovoltage and milliamperage settings and a

scanning time of 9.6 seconds. One scanning protocol was used for all subjects. No contrast agents were used. Ten CT images 10 mm thick were taken beginning 20 mm above, and parallel to, the canthomeatal plane. One slice through the basal ganglia and one through the centrum semiovale level were selected as matches for the translation of the structural anatomy of the CT onto the comparably aligned PET image.

Serial positron emission tomography studies were performed at Brookhaven National Laboratories using the PET VI scanner (TerPogossian, Flicke, Hood, Yamamoto, & Mullani, 1982) and ^{11}C-2-deoxy-D--glucose (^{11}C-2DG) (t 1/2 [^{11}C] = 20.4 min) as the physiologic tracer for glucose metabolism (MacGregor, Fowler, Shiue, Lade, & Wan, 1981). The PET VI scanner has a full-width-half-maximum spatial resolution of 1.3 cm by 1.3 cm on the x, y plane and 1.4 cm on the z axis at low resolution (D. Christman, personal communication, May 23, 1986). Glucose metabolic rates (µm/100g/min) were calculated using the Brooks and Gershon (1982) version of the Sokoloff model equation (Sokoloff et al., 1977). Rate constants and the measured lumped constant for ^{11}C-2DG as determined by Reivich et al. (1982) were used. The use of the PET technique to study glucose metabolic rates has been described in detail elsewhere (Hoffman, Huang, Plummer, & Phelps, 1982; Phelps, 1981; Raichle, 1985).

Twelve subjects were run first during the baseline condition and again while performing the verbal memory task with an intervening time period of 2 hours. Two of the 14 subjects, both AD subjects, participated in the memory study first followed by the baseline condition. An intravenous bolus of 6-8 mCi of ^{11}C-2DG was given 35 minutes before scanning and 2 minutes after initiation of the memory task. Blood

activity time curves were derived using arterialized venous blood. Two sets of 7 scans each were taken for each condition; one at 35 minutes and one at 45 minutes after isotope injection. To summarize, 2 minutes after the memory task was initiated, the isotope was injected. The task continued for approximately another 26 minutes. Scan 1 was started 35 minutes after the injection and continued for 9 minutes. Scan 2 started 45 minutes after injection and continued for 12 minutes.

Both sets of horizontal scans were taken parallel to the canthomeatal line and were 14 mm thick for a total of 14 interleaving PET scans associated with each condition. The first scan set began 10 mm above the canthomeatal plane. The second set was taken 7 mm superior to the first set while retaining the same head position.

Procedure

During the baseline study subjects rested quietly under dim lighting with their eyes open and ears unplugged. The memory condition consisted of a continuous verbal memory recognition task that involved the presentation of grocery items (eg. apple, sugar, chicken, tomato), one word at a time every five seconds, on a computer screen. Each word was displayed 4 seconds and was followed by a 1 second interval before the next word was presented. During the continuous word sequence, approximately half the items were displayed a second time following either a 0, .5, 1, 2, 4, or 8 minute delay. All six delay intervals were approximately equally sampled. A total of 336 words were displayed during the 28 minute task. Because it took 8 minutes to reach a steady-state condition where each delay interval could be equally sampled, responses to the 240 items displayed during the last 20

minutes of the task were recorded. Of these 240 items, there were 127 possible correct hits, or yes responses, and 113 possible correct no responses. Each subject was instructed to press one of two buttons with either the right index finger or right middle finger to indicate if the item had (a "yes" response) or had not (a "no" response) appeared on the screen previously. A short practice trial was given prior to injection. An IBM PC computer was programmed in BASIC to present the sequence of words and to record the number of correct yes responses for each delay interval, the total number of erroneous yes responses (false alarms), total correct no responses, and erroneous no responses (misses) for each delay interval. The task lasted approximately 28 minutes.

Response accuracy during the memory task was estimated by calculating a discrimination index (DI) that corrects for false alarms according to the formula: DI = Proportion of hits - Proportion of false alarms (Snodgrass, 1986). This discrimination index has been shown in a preliminary study (J. G. Snodgrass, personal communication, June 4, 1986) to be an estimate of memory sensitivity that is independent of bias in a population of clinically diagnosed Alzheimer's patients. Because AD patients may actively participate in the task but score poorly in terms of accuracy, a second index was calculated based solely on the subject's response rate (RR), regardless of whether the response was correct or not, according to: RR = Total number of responses / Total number of items presented.

Brain Region Analysis

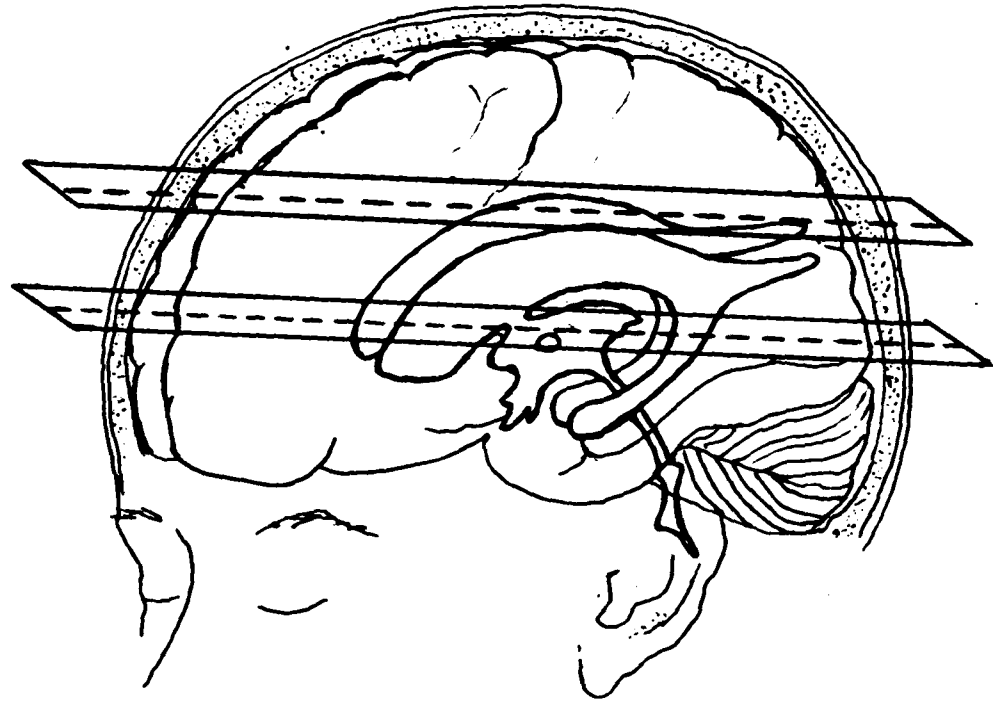
Two PET slices, one that best represented the basal ganglia (BG) level and one that was judged to best represent the centrum semiovale (CS) level, were selected for analysis from both the baseline and memory conditions for a total of 4 slices per subject (see Figure 1). CT scans from each subject were chosen that matched the selected PET sections. A Data General Eclipse computer linked to a Grinnell color graphics system was used to translate the outline of the CT image anatomy onto the PET image and interactively sample brain region metabolic rates (μm/100g/min) using the CT anatomy. The PET and matching CT image were displayed side by side on the graphics display console and comparably aligned using a semiautomated program that used the outline of the CT skull outertable and the PET gallium attenuation transmission scan skull outertable to make the appropriate adjustments. Following the initial alignment, finer adjustments were made as necessary using familiar anatomical landmarks such as changes in the shape of the skull, ventricle outlines, and midline features of subcortical grey and white matter. This procedure and additional programs allowed the accurate outlining of anatomic regions of interest (ROIs) on the CT image. Subsequently this outline was automatically and interactively translated, size-corrected, onto the PET scan. Descriptive statistics were then obtained for each ROI on the PET image.

Bilateral frontal, temporal, and thalamic ROIs were taken from the PET basal ganglia section. The wedged-shaped frontal samples included most of the frontal lobe anterior to the frontal horns of the lateral ventricles. Temporal ROIs were crescent-shaped, included a small

Figure 1. Schematic of the approximate level of the basal ganglia and centrum semiovale horizontal PET metabolic images.

CENTRUM SEMIOVALE LEVEL

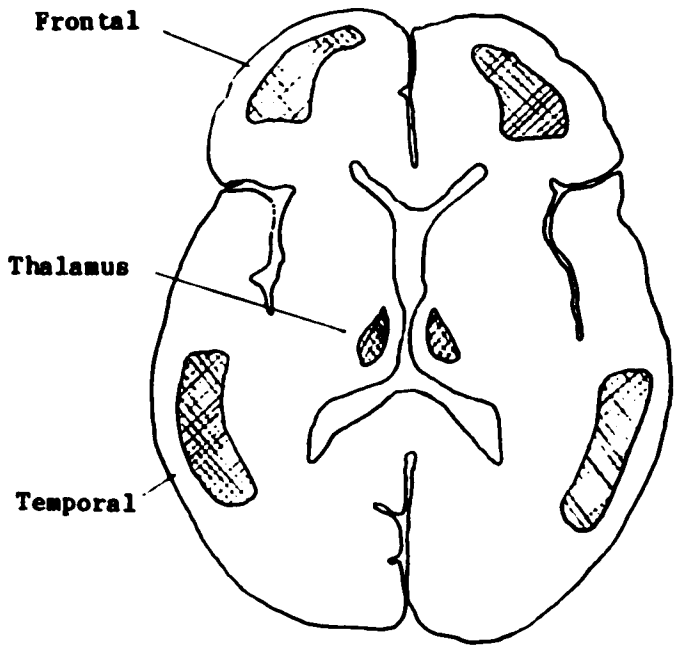
BASAL GANGLIA LEVEL



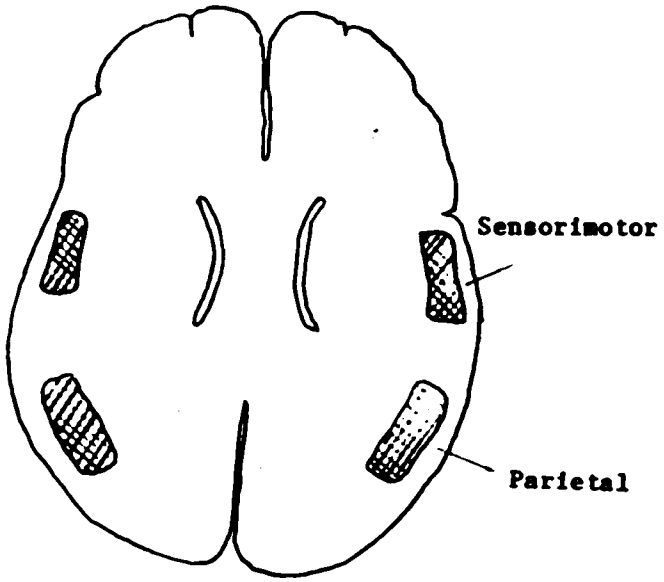
portion of the superior temporal gyrus, and continued posteriorly to include the inferior temporal gyrus. Medially this ROI excluded the atrium of the lateral ventricles. Right and left sensorimotor cortex and posterior parietal lobe samples were taken from the CS section. The sensorimotor sample extended approximately 1.5 cm anterior and 1.5 cm posterior to the central sulcus and was approximately 1.2 cm wide. The parietal lobe sample was approximately 2.0 cm long by 1.2 cm wide and was taken in the area of the angular gyrus. Right and left hemispheric ROIs, both corrected for ventricle, were obtained from the BG slice to be consistent with earlier studies. Figure 2 shows a schematic drawing of ROI placement for both levels.

In addition to sampled metabolic rates, lateral asymmetries (LA) were examined according to the formula: LA = ([(R - L) / (R + L)] X 100) where R stands for the glucose metabolic rate for the right side and L stands for the homologous left side rate. This index indicated whether a larger proportion of the total activity for a region occurred on the right or left side during either the baseline or memory condition. A positive value meant a larger proportion of activity was present on the right; a negative value meant a larger proportion of the total activity for two homologous regions occurred on the left. To determine if there was a difference in the distribution of metabolic activity across right and left homologous regions during the memory condition compared to baseline, a lateral asymmetry difference (LAD) was calculated for each subject according to the following formula: LAD = (LA for memory) - (LA for baseline). A positive LAD index indicated a larger proportion of activity occurred on the right side during the memory condition than during the baseline condition, and a

Figure 2. Placement of basal ganglia and centrum semiovale level regions of interest. (Hemispheric samples taken from basal ganglia slice.)



BASAL GANGLIA LEVEL



CENTRUM SEMIOVALE LEVEL

negative LAD index indicated a larger proportion of metabolic activity was present on the left during the memory condition compared to the resting condition.

Statistical Analysis

I. Behavioral data - The effect of disease on the discrimination index (DI) for the six delay intervals was tested using a mixed repeated-measures analysis of variance (ANOVA) with one between-subjects group factor and one within-subjects delay interval factor. A one-way ANOVA was used to examine group differences in response rate.

II. Metabolic data - analyses of the metabolic rates for the two conditions and two groups:

   A. To test if baseline glucose metabolic rates for the 6 regional samples were significantly decreased in the demented subjects relative to controls, a one-way multivariate analysis of variance (MANOVA) and post-hoc univariate one-way F-tests were used. A MANOVA approach was required because the metabolic rates of one region are not independent of the metabolic rates of other regions. Regional percent diminutions were also calculated as an estimate of the extent to which each region was affected by AD.

   B. To determine if the presence or absence of disease affected regional metabolic rates during the 2 conditions differently, a mixed repeated-measures MANOVA for the composite set of 6 regional samples was performed. Follow-up univariate mixed

repeated-measures ANOVAs were used to test which of the individual regions contributed to the significance.

C. A mixed repeated-measures MANOVA was also used to determine if the baseline and memory conditions differentially affected the control and AD group lateral asymmetries for the set of 6 homologous ROIs. Again, univariate repeated-measures factorial ANOVAs were used for post-hoc testing.

D. The effect of the presence or absence of Alzheimer's disease on the redistribution of metabolic activity during the memory condition relative to baseline for the set of 6 LA differences (LAD) was tested using a one-way MANOVA and post-hoc one-way ANOVAs.

E. 2 X 2 Fisher's Exact tests (group by lateral asymmetry) were used to examine the distribution of left and right LAs for subjects in the 2 groups. Separate tests were run for both the baseline and memory conditions on all 6 samples. Subjects with a LA greater than 0 were classified as showing a lateral asymmetry of metabolic activity that favored the right, while those with a LA index of less than 0 were classified as showing a lateral asymmetry of metabolic activity that favored the left. Separate 2 by 2 Fisher's tests (group by LAD) were also used to examine the distribution of subjects for the two groups according to glucose metabolism lateral asymmetry differences (LAD) for the two conditions. Again, subjects with a positive LAD index were classified as showing a LAD that favored the right homologous region during the memory condition relative to

baseline, while a negative LAD meant a left LAD classification.

III. Behavioral and metabolic correlations - The relationships between the behavioral measures - the discrimination index (DI), the response rate (RR), and global deterioration scale (GDS) - and LAD of metabolic activity were determined with Pearson correlations.

RESULTS

Behavioral Assessment

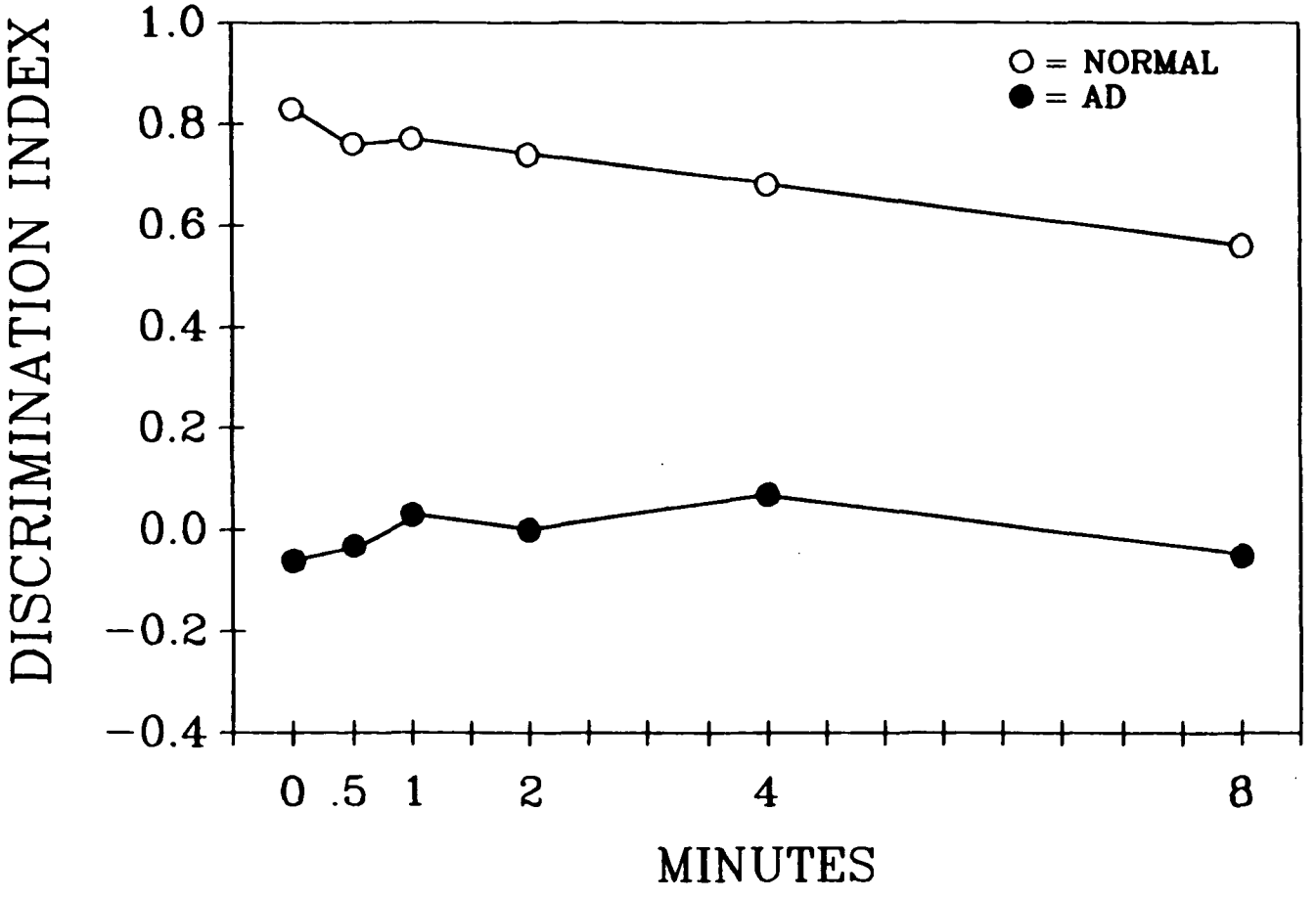
Recognition memory in the Alzheimer subjects was significantly impaired. The mean discrimination indexes (DI) for the elderly normal and AD subject groups at the 6 time-delay intervals during the memory condition are plotted in Figure 3. A computer technical problem prohibited the recording of one moderately impaired AD subject's (GDS = 5) behavioral responses, therefore neither a DI or response rate (RR) could be calculated. The mean DI for the 7 controls (M = .73, SD = .12; range = .55 to .88) was significantly higher than the DI of the 6 AD subjects (M = -.01, SD = .02; range = -.04 to 0), $F(1, 11)$ = 205.9, p = < .001. Controls also demonstrated a decrement in the mean DI over the 6 time interval delays; AD subjects did not. This interaction between the presence or absence of disease and delay interval was significant, $F(5, 55)$ = 5.45, p < .001. The AD subjects, with a mean DI of approximately 0, demonstrated a floor effect.

All subjects responded during the memory task, though the response rate for controls (M = 99.3, SD = 1.5; range = 96 to 100; N = 7) was significantly higher than the response rate for the AD group (M = 72.2, SD = 16.5; range = 53 to 97; N = 6), $F(1, 11)$ = 19.0, p = .001. The AD subjects, then, responded to most trials but were unable to recognize repeated items above a chance level.

Metabolic Rate Assessment

Baseline metabolic rates were analyzed primarily as a resting condition against which to compare the memory condition. They were

Figure 3. Discrimination of old items from new items for elderly normal subjects (N = 7) and AD patients (N = 6) as a function of the delay, in minutes, between the first and second presentation of each repeated word. (Discrimination Index = Proportion of correctly recognized items - Proportion of false alarms.)


DISCRIMINATION INDEX
1.0
0.8
0.6
0.4
0.2
0.0
−0.2
−0.4
○ = NORMAL
● = AD
0 .5 1 2 4 8
MINUTES

also examined to determine if: (1) the Alzheimer subjects of the present study were comparable metabolically to those of previous PET studies, (2) if the use of ^{11}C-2-DG produces results similar those found with ^{18}F-2-deoxy-2-fluoro-D-glucose and, (3) if the regions of the brain most severely affected by the neuropathology of AD will be the regions which show the largest diminutions in metabolic rates compared to normal values. Group differences in regional metabolic rates during the memory study compared to baseline should provide insight into which regions are differentially affected by the task and disease.

Table 1 lists the mean glucose metabolic rates (μm/100g/min) of the 6 averaged right and left homologous brain areas sampled for the normal and demented subject groups during the baseline and memory conditions. Also included are percent diminutions for the AD group relative to controls.

Baseline Condition Group Comparisons

The results for the baseline condition indicated that the demented subjects, as a group, had significantly lower glucose metabolic rates than controls for the set of 6 averaged samples when tested using a one-way MANOVA, $F(6, 7) = 4.05$, $p < .05$. Post-hoc univariate F-tests showed that the individual regions affected significantly ($p < .05$) were the averaged right and left hemispheres, and the averaged frontal, averaged parietal, and averaged temporal lobes. The thalamic and, as predicted, sensorimotor cortex group differences were not significant, though activity tended to be lower in the AD group. The areas of the brain most affected by the neuropathological changes associated with Alzheimer's disease, the temporal and parietal lobes, demonstrated the

TABLE 1

Regional Glucose Metabolic Rates in Normal Elderly and AD Subjects During Baseline and Memory Conditions

		Baseline		Memory	
Region	Group	rGMR	% Decrease	rGMR	% Decrease
Whole Slice	N	35.5	-18.6 *	35.1	-22.2 **
	AD	28.9		27.3	
Frontal	N	34.4	-21.8 *	35.3	-28.6 **
	AD	26.9		25.2	
Thalamus	N	34.7	-6.6	35.0	-11.4
	AD	32.4		31.0	
Temporal	N	35.4	-27.1 **	34.6	-28.6 ***
	AD	25.8		24.7	
Sensori-motor	N	37.1	-16.7	38.1	-20.5 *
	AD	30.9		30.3	
Parietal	N	37.5	-27.2 **	37.6	-33.0 ***
	AD	27.3		25.2	

Note. The whole slice corrected for ventricle, frontal, thalamus, and temporal regions were sampled at the level of the basal ganglia. Sensorimotor and parietal lobe samples were taken at the centrum semiovale level. Percent decrease refers to rGMR of AD subjects relative to elderly controls.

rGMR = Regional glucose metabolic rates (μ/100g/min).

* $p < .05$, 2-tailed F-tests
** $p < .01$, 2-tailed F-tests
*** $p < .001$, 2-tailed F-tests

most marked decreases in metabolic rates (approximately 27%). Thalamic metabolic rates for the 2 groups at baseline were the least divergent.

Memory Condition Group Comparisons

The pattern of diminutions for AD subjects compared to controls was similar for the memory condition. Though the overall between-group differences in mean metabolic rates were not significant for the 6-region composite when tested using a one-way MANOVA ($F(6, 7) = 3.45$, $p = .065$), the metabolic rates of the demented subject group were significantly lower than controls ($p < .02$) for all regions but the thalamus when tested with univariate F-tests (Table 1). The lack of a significant MANOVA F value, however, increases the probability of the overall Type 1 error.

Memory Condition Compared to Baseline

An inspection of Table 1 also indicates a differential effect of the two conditions on regional metabolic rates for the two groups. In 4 out of 6 regions the mean metabolic rate increased during the memory condition for the controls and all 6 regional metabolic rates decreased during the memory condition to values below baseline for the AD group. However, this apparent group difference in the effect of the memory activation was not significant. When tested using a 2 by 2 mixed repeated-measures MANOVA (groups by condition), the multivariate interaction for the set of 6 regions' metabolic rates was not significant, $F(6, 7) = .42$, $p = .84$. Though a significant MANOVA condition effect was found ($F(6, 7) = 4.12$, $p = .04$), none of the regional post-hoc mixed repeated-measures F-tests were significant. The MANOVA group effect was not significant, $p > .05$. The baseline and memory condi-

tions, then, did not affect the mean regional metabolic rates of the control and patient groups differently.

Temporal Lobe Metabolic Rates

Though the group by condition interaction analysis on regional metabolic rates reported in the previous section, "Memory Condition Compared to Baseline", did not produce statistically significant results, the specific interest in the temporal lobe prompted a further analysis. An inspection of the range of right and left temporal lobe metabolic rates for the 2 groups did suggest the groups were affected differently by the task. Table 2 shows the percentage of patients and controls whose glucose metabolic rates did not overlap for both behavioral conditions and for the right and left temporal lobes. Table 2 also includes the number of false positives (controls whose metabolic rates fell within the range of the patients) and false negatives (patients whose metabolic rates fell within the range for controls). There was a complete group separation only for the left temporal lobe during the memory condition. For the right temporal lobe under the memory condition and both the right and left temporal lobes during the baseline condition, only about 50% of the cases were nonoverlapping. Though the distribution of non-overlapping cases for the right and left temporal lobes for the 2 conditions did not differ significantly ($X^2(1) = 1.49$, $p > .05$), these preliminary results suggest an improved diagnostic utility of the memory condition.

Regional Lateral Asymmetries

The most important finding of the study was that clinically diagnosed AD subjects, when compared to controls, exhibited abnormal

TABLE 2

Percentage of Subjects in the Control and Alzheimer Groups Whose Metabolic Rates in the Right and Left Temporal Lobes do not Overlap with Values Obtained for the Other Group.

		Non-overlapping Cases	False Positives[a]	False Negatives[b]
Baseline	Left	50%	4	3
	Right	57%	5	1
Memory	Left	100%	0	0
	Right	50%	5	2

Note. Control Group (N = 7)
Alzheimer Group (N = 7)

[a]Number of controls whose metabolic rate falls within the range of the patients.

[b]Number of patients whose metabolic rate falls within the range of the controls.

lateral asymmetries in metabolic activity during the memory condition relative to baseline. Table 3 lists the mean regional metabolic lateral asymmetries (LA) for the control and AD groups during the baseline and memory conditions. The differences in metabolic lateral asymmetry indexes for the memory condition compared to baseline (LAD), are also included. Mean group LADs for each region are graphically depicted in Figure 4. It is notable that group separation is largest for the temporal lobes.

Baseline Group Comparisons

One-way MANOVAS were used to test if there were group differences in the magnitude of regional lateral asymmetries and directional preference for glucose metabolism. The group difference for the set of regional lateral asymmetry absolute values at baseline was not significant, $F(6, 7) = 1.47$, $p > .05$. This means the magnitude of asymmetries, regardless of side preference, for the composite set of values was not different between groups. Multiple univariate one-way F-tests, however, suggested a group difference in the degree of asymmetry for the frontal lobes, $F(1, 12) = 6.18$, $p < .03$. A second MANOVA for directional preference of glucose metabolism also indicated the lack of a statistically significant group difference, $F(6, 7) = 1.51$, $p > .05$. These results suggest that while there was a tendency for AD patients to show a greater degree of asymmetrical glucose metabolism in the frontal lobes, one side was not consistently favored over the other.

Memory Condition Relative to Baseline

A mixed repeated-measures MANOVA was used to determine if the baseline and memory conditions differentially affected the control and AD group LAs for the set of 6 homologous ROIs. A significant group by condition

TABLE 3

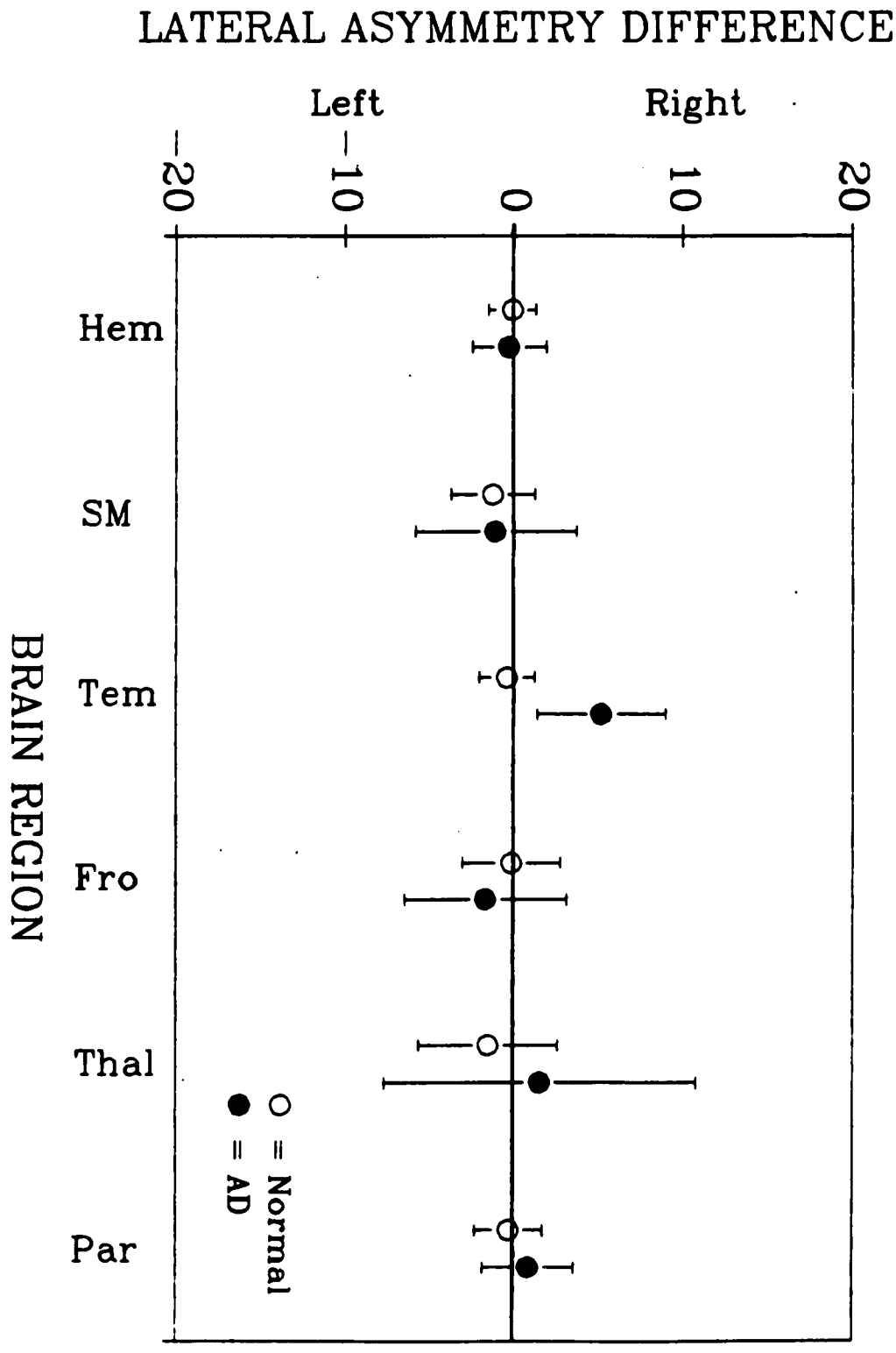
Regional Lateral Asymmetries and Changes in Asymmetries for Normal and Demented Subjects During Baseline and Memory Conditions

		Baseline	Memory	
Region	Group	LA	LA	LAD
Hemi-spheres	N	-0.33	-0.44	-0.10
	AD	+0.45	+0.17	-0.27
Frontal	N	-0.86	-1.01	-0.15
	AD	+2.12	+0.46	-1.66
Thalamus	N	-0.47	-1.98	-1.52
	AD	-0.32	+1.23	+1.55
Temporal	N	+1.24	+0.87	-0.37
	AD	-2.82	+2.37	+5.19
Sensori-motor	N	+1.25	0.00	-1.25
	AD	-0.24	-1.31	-1.06
Parietal	N	-0.23	-0.54	-0.31
	AD	-0.67	+0.21	+0.88

Note. LA = lateral asymmetry index. Lateral asymmetry was calculated from the right (R) and left (L) homologous region metabolic rates (μ/100g/min) according to: [(R - L) / (R + L)] X 100.

LAD = lateral asymmetry difference index. The difference in lateral asymmetries during the memory condition compared to baseline was calculated according to: (LA for memory - LA for baseline).

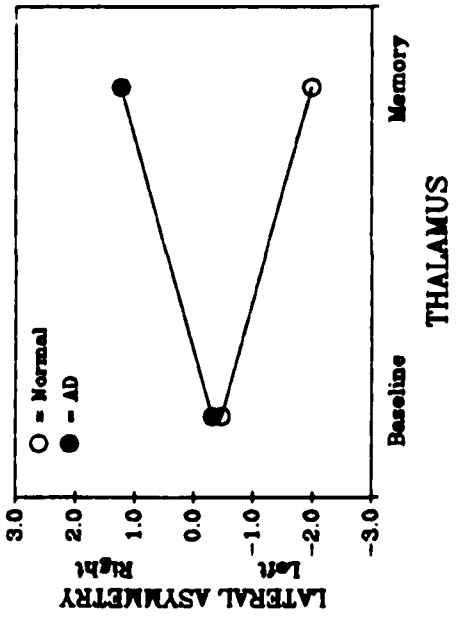
Figure 4. Mean lateral asymmetry differences (LAD) for elderly normal subjects (N = 7) and AD subjects (N = 7) by region. Hem = Hemisphere; SM = Sensorimotor; Tem = Temporal; Fro = Frontal; Thal = Thalamus; Par = Parietal. Bars represent mean value, +/- 1 standard deviation.

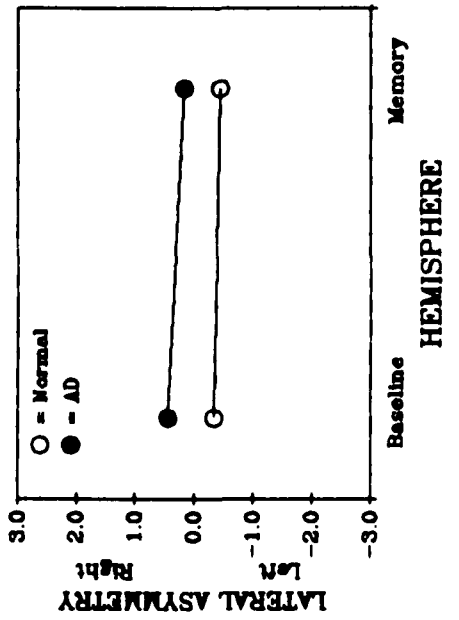

LATERAL ASYMMETRY DIFFERENCE
Left
Right
-20
-10
0
10
20
Hem
SM
Tem
Fro
Thal
Par
BRAIN REGION
○ = Normal
● = AD

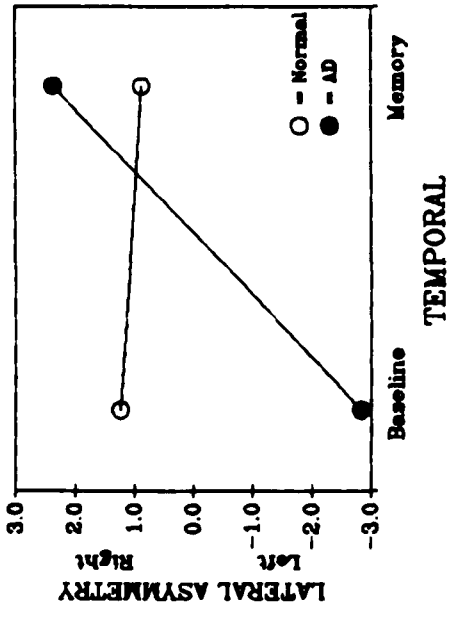
interaction was found ($F(6, 7) = 5.62$, $p = .02$) and, as expected, only the temporal lobe demonstrated a significant interaction effect when all samples were tested individually using post-hoc univariate mixed repeated-measures F-tests, $F(1, 12) = 12.46$, $p = .004$. As seen in Figure 5, the controls, on the average, favored the right temporal lobe during both conditions, but were less disposed toward the right during the memory condition (mean LA = 1.24, SD = 2.9, for baseline and mean LA = .87, SD = 3.4, for memory). For the AD group, the mean LA favored the left temporal lobe during the baseline condition (mean LA = -2.82, SD = 7.8) and the right during the memory condition (mean LA = 2.37, SD = 8.5). Figure 5 also displays the nonsignificant, but directionally comparable, condition by group interaction for the thalamus. The hemispheric LAs (Figure 5) showed a parallel nonsignificant trend to the left from baseline to memory which indicated the temporal lobe effect cannot be accounted for by a generalized hemispheric activation. Similarly, the sensorimotor samples demonstrated the expected, though nonsignificant, trend toward a left lateral asymmetry during the memory condition relative to baseline (Figure 5). The multivariate group effect on the LA for the set of regional samples was not significant, $F(6, 7) = .76$, $p > .05$, although a significant condition effect was found, $F(6, 7) = 3.87$, $p = 05$. Again, follow-up univariate F-tests indicated that only the temporal lobe reached significance, $F(1, 12) = 9.35$, $p = .01$.

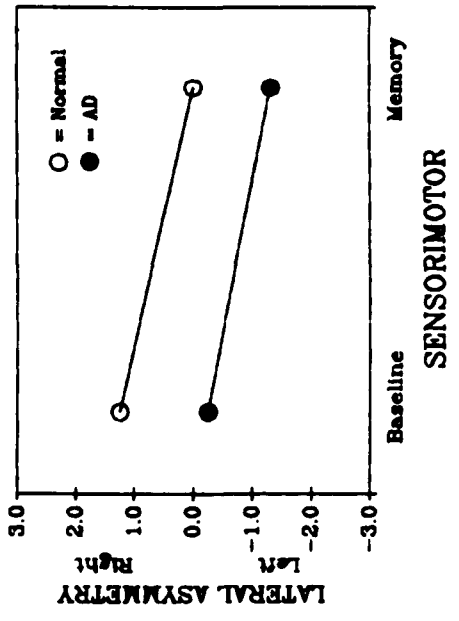
A one-way MANOVA was used to test if the mean LAD for the memory condition compared to baseline was different for the AD subjects compared to controls for the 6-ROI composite (see Figure 4). A significant group difference was found ($F(6, 7) = 5.62$, $p = .02$) and,

Figure 5. Regional lateral asymmetries of glucose metabolism (μm/100g/min) as a function of condition for elderly normals (N = 7) and AD patients (N = 7).


THALAMUS
LATERAL ASYMMETRY
Left
Right
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
Baseline
Memory
O = Normal
● = AD


HEMISPHERE
LATERAL ASYMMETRY
Left
Right
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
Baseline
Memory
O = Normal
● = AD


TEMPORAL
LATERAL ASYMMETRY
Left
Right
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
Baseline
Memory
O = Normal
● = AD


SENSORIMOTOR
LATERAL ASYMMETRY
Left
Right
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
Baseline
Memory
O = Normal
● = AD

again, only the temporal lobe LAD for the AD group (M = 5.19, SD = 3.8) differed from controls (M = -.37, SD = 1.61) upon follow-up univariate F-tests, $F(1, 12) = 12.46$, $p = .004$. These results indicate that for the AD subjects, on the average, a greater proportion of the total temporal lobe activity favored the right during the memory condition compared to the baseline condition. Controls, however, showed the expected redistribution of activity to the left. A greater proportion of the total temporal lobe activity occurred on the left side during the memory condition relative to baseline.

The relative frequency of normal and AD subjects that showed either a left (L) or right (R) lateral asymmetry (LA) for any of the 6 individual regions during either the baseline or memory condition did not differ when tested using serial 2 by 2 Fisher's Exact tests, $p > .05$. In other words, the group by left or right LA interaction was tested separately for each region during each condition, for a total series of 12 crosstables, and the distribution of L and R lateral asymmetries did not differ between the 2 groups.

As hypothesized, the relative frequency of normal and AD subjects that demonstrated a different metabolic asymmetry across the homologous R and L temporal lobe samples during the memory condition relative to baseline was significantly different, Fisher's Exact, $p < .025$. A negative LAD index meant a subject was classified as demonstrating a left LAD; a positive value meant a right LAD. All 7 AD subjects demonstrated a LAD that favored the right during the memory condition compared to baseline and 5 out of 7 controls showed a LAD that favored the left. It is possible, however, this outcome may have been due to chance since 7 different Fisher's tests were performed. The hemi-

spheric, frontal, parietal, sensorimotor, and thalamic metabolic responses did not show any evidence of this redistribution of activity during the memory challenge relative to baseline. That is, there were no significant group differences in lateral asymmetry differences for the two conditions.

As described in the Methods section, two AD subjects participated in the memory task before the baseline condition. The other 12 subjects participated in the baseline condition first. LAD indexes were examined to determine if the order of conditions had a differential effect on the two subjects who received the memory condition first. The LAD indexes for both subjects were within 1.5 standard deviations of the mean hemispheric and temporal LAD indexes for the AD group. Rankings of the two subjects' LAD indexes for the hemispheric, sensorimotor, temporal, and frontal samples were also examined. No consistent pattern was found. In other words, neither of the two subjects had consistently high or low LAD index when compared to the other AD subjects.

Behavioral/Metabolic Asymmetry Correlations

The magnitude of the LAD for the temporal lobe correlated significantly with accuracy of item recognition as estimated by DI (r = -.79, p = .002, N = 13; see Figure 6), with response rate (r = -.71, p = .01, N = 13; see Figure 7), and the GDS rating of global cognitive impairment (r = .66, p = .02, N = 14; see Figure 8). The high correlation between the DI and LAD should be interpreted with caution, however. As Figure 6 shows, it is primarily due to the closely clustered points of

the two groups at opposite ends of the graph. No other significant correlations between LAD and DI, RR, or GDS were found.

Figure 6. Temporal lobe lateral asymmetry difference (LAD) as a function of discrimination index (DI) for elderly normal subjects (N = 7) and AD subjects (N = 6).

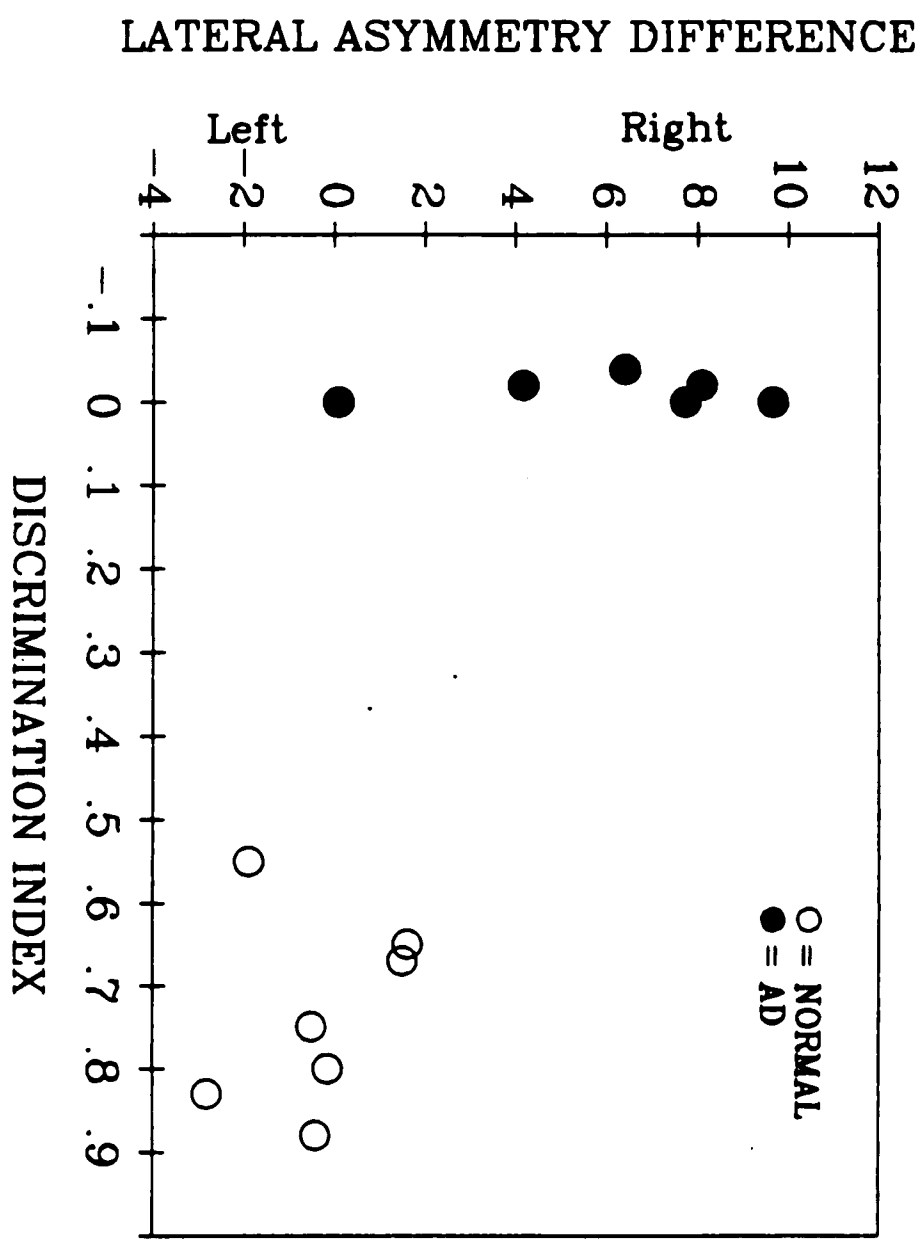

LATERAL ASYMMETRY DIFFERENCE
Left
Right
−4
−2
0
2
4
6
8
10
12
DISCRIMINATION INDEX
−.1
0
.1
.2
.3
.4
.5
.6
.7
.8
.9
○ = NORMAL
● = AD

Figure 7. Temporal lobe lateral asymmetry difference (LAD) as a function of response rate (RR) for elderly normal subjects (N = 7) and AD subjects (N = 6).

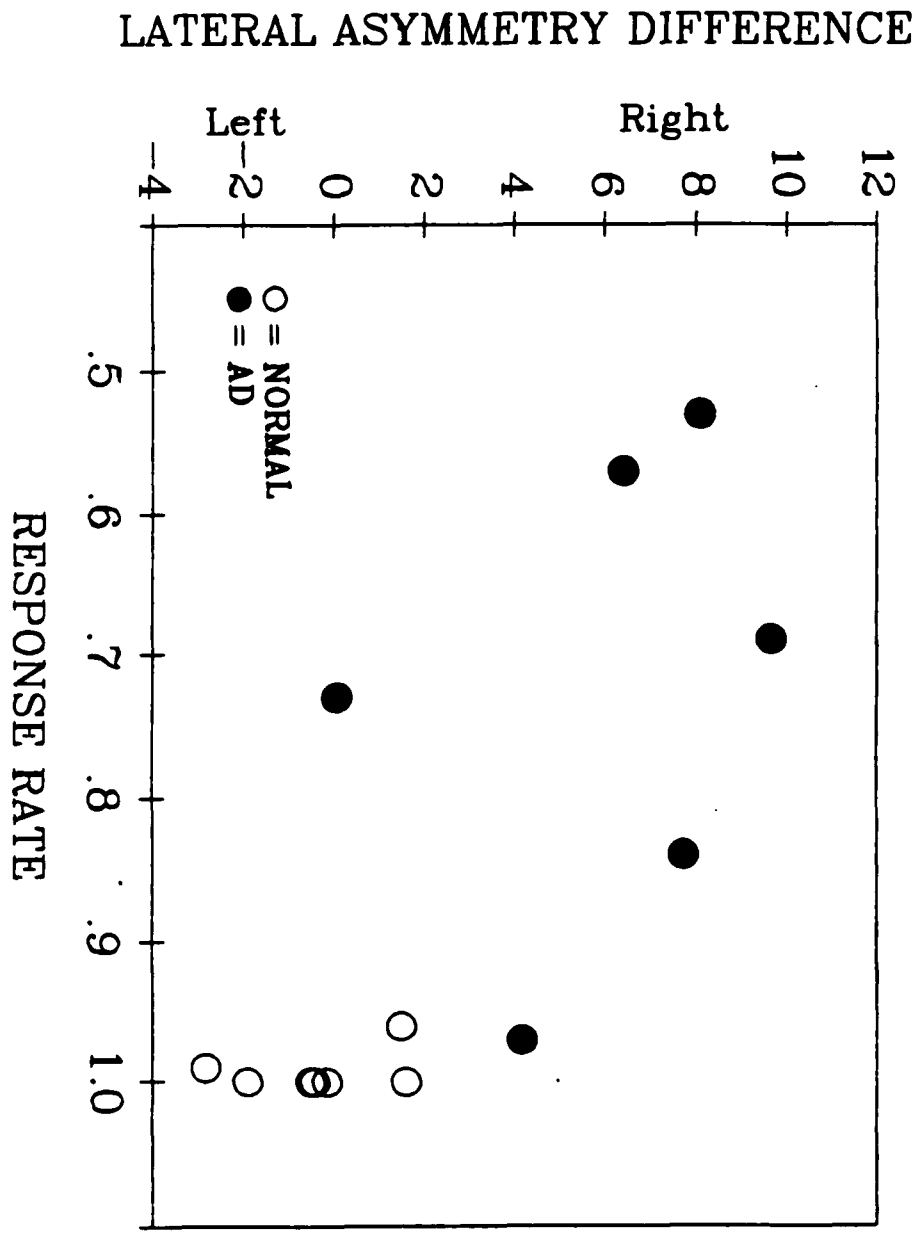
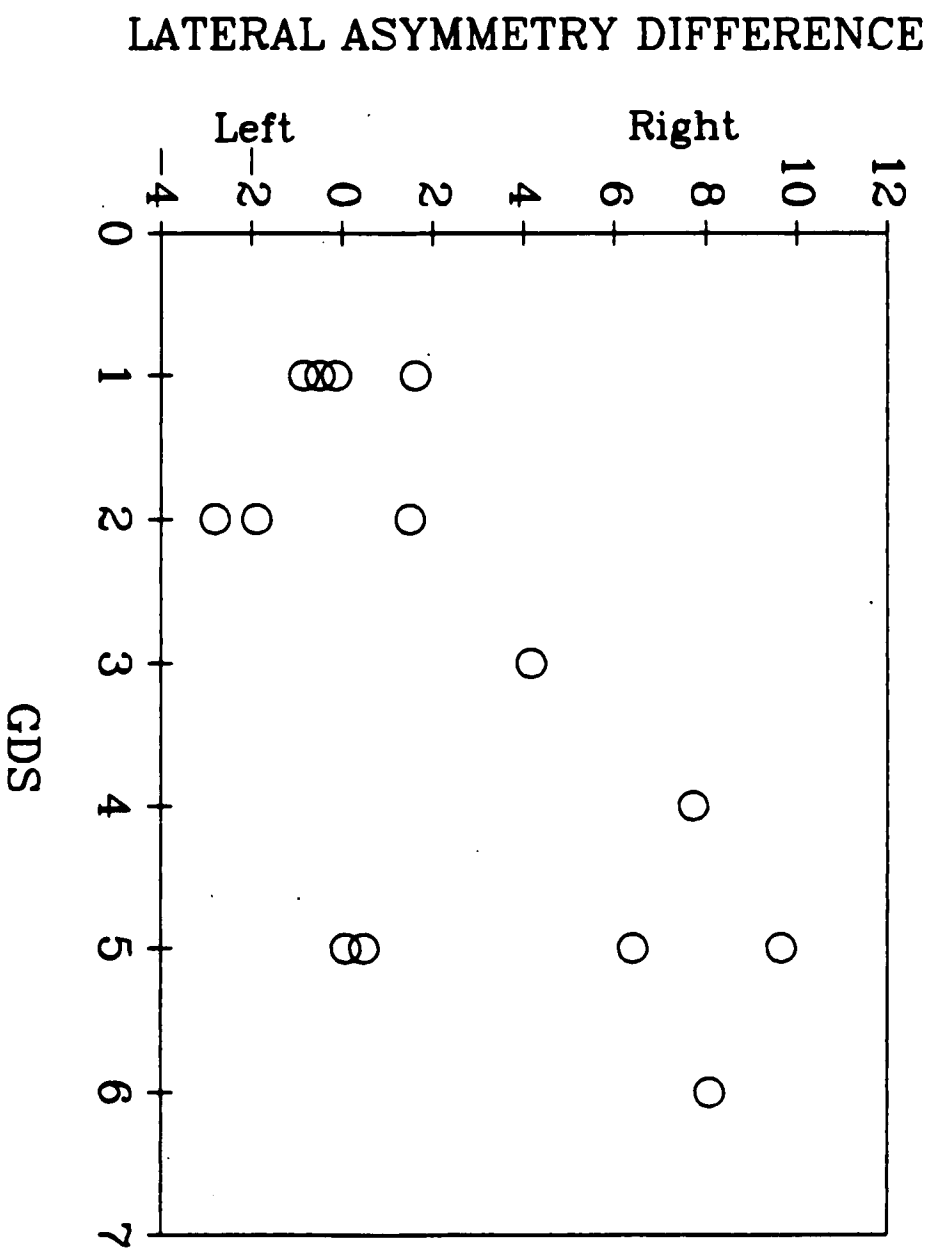

LATERAL ASYMMETRY DIFFERENCE
Left
Right
-4
-2
0
2
4
6
8
10
12
○ = NORMAL
● = AD
.5
.6
.7
.8
.9
1.0
RESPONSE RATE

Figure 8. Temporal lobe lateral asymmetry difference (LAD) as a function of global cognitive impairment (GDS) for elderly normal subjects (N = 7) and AD subjects (N = 7).


LATERAL ASYMMETRY DIFFERENCE
Left
Right
-4
-2
0
2
4
6
8
10
12
GDS
0
1
2
3
4
5
6
7

DISCUSSION

Behavioral Performance

The results of the present study are consistent with previous reports that a recognition task will differentiate elderly controls from Alzheimer patients (Branconnier et al., 1982, Miller & Lewis, 1977). The performance of Alzheimer patients on the recognition memory task was significantly poorer than normal elderly controls. Though Alzheimer subjects did, on the average, respond to a majority of items, they responded to significantly fewer trials than did controls and were unable to discriminate old items from new above a chance level.

The floor effect for the AD patients explains the seemingly contradictory forgetting curves seen in Figure 3. These curves suggest that while controls recognized fewer items with increasing delay intervals, AD patients did not forget. The reduction in discrimination accuracy as a function of delay interval in elderly normals using a verbal continuous recognition paradigm is consistent with previous studies (Harker & Reige, 1985; Poon & Fozard, 1980). The lack of a negative slope in the forgetting curve of AD patients occurred because they were unable to recognize even those items that were immediately redisplayed on the monitor.

This inability of AD subjects to recognize repeated items above a chance level suggests that the task may have been too hard for them and raises the question of whether or not they were, in fact, participating in the memory task. Other results of the study suggest that the demented patients were performing under the constraints of the memory task: (1) they responded to the majority of trials, (2) the abnormal

metabolic brain response was restricted specifically to the temporal lobes, and (3) all 7 AD subjects demonstrated a differential metabolic response to the memory task relative to baseline that favored the right temporal lobe, while 5 out of 7 controls, as expected, favored the left.

Poor performance also does not necessarily preclude mental effort. An individual might understand a task and try to perform accurately, yet fail to execute the task efficiently. Wood, Armentrout, et al. (1980), in a CBF case study, instructed a subject with retrograde and anterograde amnesia to try his best to recognize words in a second word list that he had seen previously displayed in a first list. Though the subject gave 16 out of 40 "yes" responses, his performance accuracy was at a chance level. The authors stated that the patient understood the task and did appear to be trying to recognize the words. Interestingly, he too showed a specific right posterior brain activation during the memory task which was opposite to an observed left-sided response in normals (Wood, Taylor, Penny, & Stump, 1980). The AD patients in the present study also may have been trying to perform the task accurately, but were unsuccessful because it was too difficult.

Regional Metabolic Rates for Baseline and Memory

Baseline Condition

The significant decrement in basal ganglia whole slice, frontal, temporal, and parietal regional glucose metabolic rates, using ^{11}C-2DG, in the AD group compared to age-matched controls is consistent with earlier studies using both PET with ^{18}F-2-deoxy-2-fluoro-D-glucose (de Leon, Ferris, George, Christman, et al., 1983; de Leon, George, Ferris,

et al., 1983; Chase, Foster, & Mansi, 1983; Cutler, et al., 1985; Friedland, Brun, & Budinger, 1985) and CBF (Simard et al., 1971; Yamaguchi et al, 1980). However, the nonsignificant thalamic decreases in the present study were much less than in our previous studies; -7% versus 20% (de Leon, George, Ferris, Christman, et al., 1983). This discrepancy is probably due to the improved spatial resolution of the PET VI scanner, compared to PET III, and the improved method of mapping structural CT anatomy onto PET scans. Though CT anatomy was also used to outline metabolic anatomy in PET III images, the process has been refined for use with PET VI images. With PET VI, more sharply defined ROI placement is possible and artifact from partial voluming is minimized (Mazziotta, Phelps, Plummer, & Kuhl, 1981). Although sensorimotor samples were not taken in our previous studies, other PET (Benson et al., 1983, Cutler et al., 1985) and CBF (Hachinski et al, 1975) reports have also indicated a relative sparing of the primary sensorimotor cortex.

These results support the hypothesis that the higher-order "association" areas most heavily affected by the neuropathological and neurochemical changes in AD also show the largest metabolic diminutions: the temporal and parietal lobe samples were 27% lower than those of age-matched controls. As expected, AD sensorimotor and thalamic metabolic rates were not significantly decreased relative to controls, though they did tend to be lower. Sensorimotor samples were 17% less than controls; thalamic samples, 7%. One interpretation of this hypometabolism in AD is that it reflects hypofunction. Partial degeneration, deafferention, or a loss of intrinsic cortical neurons (Foster et al., 1984) all may contribute.

These results suggest that while AD is a global disease, it does not affect all brain regions uniformly. This nonuniformity is consistent with the clinical features of the disease. Memory, language, visuospatial skills, and orientation are markedly impaired, while sensorimotor deficits are relatively preserved until the later stages.

The similar diminution in the frontal, temporal, and parietal regional metabolic rates found in this and previous reports (Benson et al., 1983; de Leon, Ferris, George, Christman, et al., 1983; de Leon, George, Ferris, et al., 1983) is in disagreement with the more marked decreases found in the parieto-temporal area relative to frontal lobe samples reported by other investigators (Chase, Foster, & Mansi, 1983; Duara, et al., 1986; Foster et al., 1984; Friedland et al., 1983). This discrepancy may be due to differences in patient severity of cognitive deficits. It is possible, for example, that our AD subjects were relatively more demented than patients used by Friedland et al. (1983). That study included six mildly impaired and four moderately impaired patients, while our group consisted of two mildly impaired and five moderately to severely impaired patients. Other between-study differences include dissimilar procedures for identifying metabolic anatomy. Some groups have used standardized atlases or the PET scan alone to define regional activity. Such procedures, in the absence of specific anatomic information from individual patients, would lead to inconsistent ROI samples.

As mentioned before, interpretation of study results across groups has been further complicated by different ways of reporting results. For example, ratio data been reported by some groups (Friedland, Brun, & Budinger, 1985), whereas mean metabolic rates have been reported by

others (Chase, Foster, & Mansi, 1983; de Leon, Ferris, George, Christman, et al., 1983). It should be pointed out that in studies that report metabolic rates, the pattern of diminutions described is a qualitative one. Tests of significance comparing regions are usually not reported. Also, some studies report a relative sparing of the frontal lobe compared to the temporal and parietal regions. The use of "relative" can be misleading. For example, in two such studies the frontal diminutions were substantial; 21% (Chase, Foster, & Mansi, 1983) and 24% (Foster et al., 1984). These metabolic decreases for the frontal lobe are similar to that found in the present study (22%). Nevertheless, neuropathological, neurochemical, CBF, and PET studies demonstrate that the temporoparietal areas are relatively more affected by AD than the frontal area and suggest that these changes are probably responsible for many of the cognitive impairments associated with the observed dementia.

Memory Condition: Normal Subjects

It was expected that the memory condition would result in significantly increased metabolic rates for the normal group relative to baseline, especially for the temporal lobe. Cerebral blood flow tasks that have measured brain activity in response to verbal memory processing in normals have reported left hemisphere regional CBF increases that range from 4% during episodic memory tasks (Wood, Taylor, Penny, & Stump, 1980), to 7% during the learning and recall of paired associates (Maximilian, Prohovnik, Risberg, & Hakansson, 1978), to as high as 15% in a digit-span-backward task (Risberg & Ingvar, 1973). It is unclear why the paradigm used in the present study did not produce significant increases in temporal lobe mean metabolic rate. Though Wood, Taylor et

al. (1980) reported small flow increases of 4% during recognition memory processing, the largest regional increases in the present study were less than 2%.

One possible reason for this discrepancy may be the definition and use of "baseline" or "resting" conditions. Cerebral blood flow studies, in contrast to the present study, frequently compare the behavioral activation condition with a markedly reduced sensory stimulation baseline. Subjects often lay quietly with their eyes closed (Ingvar, Risberg, & Schwartz, 1975) and ears plugged (Meyer, Fumihiko, Naritomi, & Grant, 1978) in a dark room (Yamaguchi et al., 1980). We chose to have the resting environment as similar as possible to the testing environment. Subjects sat quietly, but their eyes were open and their ears were unplugged in a lit room. Therefore, our baseline condition provided more sensory stimulation than did the CBF studies and may have resulted in a higher baseline activity level against which the memory condition metabolic rates were compared.

It has been suggested that simple cognitive tasks do not require a great deal of mental effort and therefore do not produce significant brain responses (Maximilian et al., 1978). It is possible, then, that the lack of significant increases in temporal lobe metabolic rates in the normals was because the task was too easy. However, the average discrimination index (proportion of hits - proportion of false alarms) for normals in the present study was 0.73. This does not appear to reflect a ceiling effect.

Another possible factor may be the poorer temporal resolution of PET relative to CBF. PET metabolic rates represent an average of what takes place during the 30 minute uptake period. CBF studies are

generally shorter; the behavioral task may only need to take place for 3 to 4 minutes (Wood, 1983). As Birkett (1977) and Levy (1983) have suggested, brain function is dynamic. The functional competency of a given region, or hemisphere, is not fixed but varies during task execution as a function of several factors such as focusing of attention, momentary distraction, or psychological set at a given moment. As a result, the "average" metabolic response specific to memory processing over a period of 30 minutes may be small compared to that generated by the overhead of dynamic taskswitching and basic background activity needed to maintain function. In a sense, there is a tradeoff; the coarser temporal resolution of PET compared to CBF in exchange for the 3-dimensional tomographic image and much increased spatial resolution of PET which is not possible with CBF.

Memory Condition: AD Patients

The lack of significantly increased metabolic rates in the AD patients during memory processing compared to baseline was not unexpected. These patients have marked neuropathological and neurochemical changes in temporal lobe structures which have been implicated in memory processing; the hippocampal formation and amygdala as well as neocortex. Also, of the few CBF studies that presented several types of cognitive tasks to AD subjects and controls, AD patients did not demonstrate the marked cerebrovascular responses seen in the normals. Neither problem solving (Ingvar, Risberg, & Schwartz, 1975), or counting, listening to music, or speech (Yamaguchi et al., 1980) resulted in increased regional gray matter flow. It has been suggested that the lack of activation during problem solving in AD patients may be explained by cortical neuronal degeneration in the higher-order

"association" areas which are specifically involved in the cognitive task (Ingvar, Risberg, & Schwartz, 1975), a lower level of general activity (Ingvar, Risberg, & Schwartz, 1975; Risberg & Ingvar, 1973; Yamaguchi et al., 1980), or by the patients not understanding the task (Ingvar, Risberg, & Schwartz, 1975). For example, the patients may not have realized that the test involved problem solving. So while the task may induce greater activation in primary and secondary sensorimotor areas which are less affected by the disease, little activation occurs in the "association" areas expected to be activated during problem solving (Risberg & Ingvar, 1973). This explanation, however, does not take into account that the demented subjects of Ingvar, Risberg, and Schwartz (1975) also failed to demonstrate significantly augmented grey matter flows in the sensorimotor cortex.

The cognitive activation procedures of the Ingvar, Risberg, and Schwartz (1975) and Yamaguchi et al. (1980) studies makes a comparison of their results and those of the current study quite tentative. The CBF studies did not use memory tasks, did not give the control and demented groups identical tasks, and did not present the behavioral tasks in a controlled manner. Also, neither CBF study analyzed lateral asymmetries during the behavioral activation condition relative to baseline.

Memory Condition: Group Comparisons

It was of interest that during the memory condition the brain regions of the AD patients and controls tended to respond metabolically to the functional demands of the task in opposite directions. For the controls, four of the six regions, on the average, tended to demonstrate an increase in metabolic rates during the memory task, while all

six regions for the AD group decreased. Though the difference between conditions was minimal and nonsignificant, a similar paradoxical effect has been reported using CBF measurements (Ingvar, Risberg, & Schwartz, 1975). During testing with Raven's matrices, 7 of 11 AD patients demonstrated decreased flows in pre- and postcentral regions, particularly in the parietal lobe. This effect did not occur in psychometrically normal controls. Ingvar and his colleagues described the phenomenon as "intellectual steal". The hypothesis is that a region with low flows during resting is an ischemic region that cannot respond to the functional demands that occur during behavioral activation. Surrounding areas vasodialate and the flow in the affected region decreases further. The results of Yamaguchi et al. (1980), however, are not consistent with this hypothesis. In their behavioral activation study with demented subjects, no significant increases in regional CBF accompanied the regional CBF reductions that occurred during activation. Similarly, the demented subjects in the present study did not show any regional metabolic increases during the task relative to baseline. Though the hypothesis proposed by Ingvar, Risberg, and Schwartz is intriguing, further research is needed to test the theory.

Summary

Although the baseline and memory conditions did not show the expected differential effect on group mean metabolic rates, a comparison of ranges for the AD and control metabolic rates did imply that the temporal lobes do not function normally in AD patients during attempted memory processing. The distributions of metabolic rates for the left temporal lobe alone, during the memory condition, did not overlap for the groups (see Table 2). An examination of individual

metabolic values showed that the left temporal lobe of the patients was always lower than that of the controls. These results suggest that the left temporal lobe of the AD patients may be selectively impaired and might have a reduced ability to respond to the functional demands of memory processing. They also suggest, as have CBF studies in psychiatric populations (Gur, Skolnick, et al., 1983; Gur et al., 1984), that cognitive activation studies may provide a more sensitive diagnostic probe for Alzheimer's disease than do resting baseline studies.

Metabolic Lateral Asymmetries

Overview

Although the baseline and memory conditions did not differentially affect the metabolic rates of the two groups, there were significant lateral asymmetry group differences. Asymmetry ratios are advantageous because confounding between-study factors such as machine drift, different calibrations across machines, and global metabolic rates should act as constants and not affect regional comparisons derived from a particular scanning session. It follows that a greater sensitivity to detecting metabolic differences due to cognitive or sensorimotor processing can be achieved by using ratios. The rate of metabolism necessary to keep a particular region at a physiologic baseline level would also be a constant. The difference in activity above this level of functioning may be assumed to be due to task processing. Therefore, if subtle metabolic asymmetries exist due to behavioral activation, ratios will be more likely to detect those differences than will metabolic rate comparisons. If, however, metabolic rates increase bilaterally by the same amount, lateral asymmetry indexes would not

detect an activation effect. In the current study, the lateral asymmetry index did prove to be a more sensitive measure of changes in regional activity that occurred during the memory condition compared to baseline. The results showed a non-significant group by condition interaction for mean metabolic rates, but a significant group by condition interaction using mean lateral asymmetries.

Group Differences at Baseline

Though significant group differences in mean regional lateral asymmetries at baseline were not found, differences in the absolute value of lateral asymmetries for the two groups were detected in the frontal lobe. This indicates that there are differences between AD patients and controls in the magnitude of metabolic asymmetries, but no predominant direction of asymmetry. These results are consistent with previous PET studies that have analyzed metabolic lateral asymmetries in AD patients and age-matched controls, although temporal and parietal lobe asymmetries have also been reported (Benson et al., 1983; Chase, Foster, & Mansi, 1983; de Leon, Miller, & Klinger, 1986; Duara et al., 1986; Foster et al., 1984; Friedland, Budinger, et al., 1985; Friedland et al., 1983; Haxby et al., 1986; McGeer et al., 1986).

Though emerging evidence suggests that AD patients have a greater degree of lateral metabolic asymmetry than do controls, the reason for this is unclear. Most neuropathological and neurochemical studies do not report lateralized differences in cell counts or morphological changes, or in transmitters and their associated enzymes. Unfortunately, samples are taken from either the right or left side or both sides, and, in many cases, the methods section does not mention from which hemisphere the sections were taken. One recent abstract suggests

that in AD there are post-mortem right-left variations in morphologic and cholinergic markers, but does not specify the nature of the asymmetries (Moosey, Hanin, Martinez, & Rao, 1985). CT studies also either fail to report hemispheric differences or have reported specifically that regional atrophy is symmetrical (Duara et al., 1986; McGeer et al., 1986). However, the increased variability of metabolic asymmetries and lack of a right-left preference is consistent with the variety of clinical symptoms and may be another clue to the heterogeneity of Alzheimer's disease (de Leon, et al., 1986; Mayeux, Stern, & Spanton, 1985).

Task-Dependent Asymmetries

The impaired verbal recognition memory of the AD patients appears to be directly linked to an abnormal asymmetry of glucose utilization in the temporal lobe. More specifically, the memory task and the baseline condition differentially affected the mean temporal lobe lateral asymmetries of the clinically diagnosed AD subjects and control groups. In all seven AD patients a greater proportion of metabolic activity favored the right temporal lobe during the memory condition compared to baseline. The opposite effect occurred in the controls; in five out of seven subjects, more activity was focused on the left during the memory condition relative to baseline. Though neuropathological and neurochemical studies predict that AD memory impairment is primarily related to bilateral temporal lobe disease, these results are unique because they suggest a preferential left temporal lobe impairment. Apparently, there is no current structural or neurochemical evidence to indicate that Alzheimer's disease has a predilection for the left temporal lobe.

This abnormal metabolic response of the demented patients during the memory task was specific to the temporal lobes, not the result of a generalized right-hemispheric response. Like the elderly normal subjects, AD patients demonstrated a change in metabolic lateral asymmetries during the memory condition relative to baseline that tended toward the left hemisphere. The favoring of the right temporal lobe in AD subjects also cannot be attributed to the sensorimotor stimulation that occurred from pressing the response buttons with the fingers of the right hand. Right hand movements have been shown to cause a preferential activation of the contralateral primary sensorimotor cortex (Olesen, 1971). Consistent with this finding, both groups in the present study showed higher metabolic rates in the left, compared to right, sensorimotor cortex during the memory task relative to baseline. It appears, then, that the cognitive, and not the sensorimotor, component of the memory task specifically induced the task-dependent change in temporal lobe metabolic lateral asymmetries.

The relationships between the indexes of on-line task performance (discrimination index and response rate) and magnitude of change in temporal lobe lateral asymmetries further supports the specificity of the temporal lobe metabolic findings to the cognitive components of the behavioral task. There were no significant correlations for other brain regions between change in lateral asymmetries during the memory condition compared to baseline and behavioral performance measures. While it is clear that the abnormal metabolic response of the AD subjects during the memory task is related to both their "on-line" performance and to their more general clinical memory impairment, it is

not clear why a greater proportion of the temporal lobe activity should favor the right side during the memory task compared to baseline.

Speculations on the Metabolic Response to Memory Task Participation

As hypothesized, memory task participation and the resting baseline condition affected the distribution of temporal lobe metabolic activity in elderly normal subjects and AD patients differently. Controls favored the left; AD patients the right. Furthermore, task performance and overall cognitive impairment correlated significantly with the magnitude of asymmetry change for the two conditions. The poorer the performance or greater the cognitive deterioration, the more metabolic rates favored the right temporal lobe. This abnormal response may have been due to several factors: (1) noncompliance due to left temporal lobe neuropathology, (2) inefficient memory processing due to a decreased general arousal, or (3) the right temporal lobe assuming an active role in the memory task despite an unresponsive left temporal lobe.

Noncompliance and Left Side Damage

The poor recognition memory performance and simultaneous failure of the left temporal lobe to show evidence of activation in the AD subjects may have been due to preferential left temporal lobe neuropathology. Neuropathological (Ball et al., 1985; Hyman, Van Hoesen, Damasio, & Barnes, 1984) and neurochemical (Coyle, Price, & DeLong, 1983) studies indicate that the temporal lobes are markedly impaired in AD. Lesion studies show that left temporal lobe structures, primarily the hippocampal formation and amygdala, are intimately involved in verbal memory processing (Kolb & Wishaw, 1985). Finally, CBF studies

suggest that compromised brain regions do not react normally to mental activation (Ingvar, Risberg, & Schwartz, 1975). Thus it is possible that the poor memory performance of the AD subjects may have been due to an inability of the left temporal lobe to respond appropriately, or at all, to the functional demands of the memory task. A likely conclusion to follow is that AD patients were simply responding in some fashion to a series of geometric shapes appearing on the display console and that the right temporal lobe was responding to nonverbal visuospatial stimulation.

If the change in lateral asymmetries toward the right in the AD group was due to simply to the visuospatial stimulation qualities of the letters, without a concordant lexical component, cerebral blood flow studies suggest that the parietal-occipital junction would be the region to show the expected activation (Risberg, Halsey, Wills, & Wilson, 1975). Though the right parietal lobe of the demented subjects was marginally favored in this study during the memory condition compared to baseline, the alteration was minimal and nonsignificant. Furthermore, normal subjects received the same visual stimulation, yet tended to favor the left parietal lobe.

Two CBF case studies in amnestic patients (Wood, Armentrout, et al., 1980; Wood, McHenry, et al., 1980) provide additional evidence against the possibility that the abnormal metabolic response in the AD patients was simply due to not understanding the task demands. Both subjects participated in a verbal recognition memory task, both had left-sided damage either in the temporal lobes or thalamus, and both demonstrated an increase in right hemisphere flows. One patient had remitted retrograde amnesia and performed well on the task, yet right,

not left, medial temporal lobe activity correlated with task accuracy (Wood, McHenry, et al., 1980). The other amnestic subject understood the task and indicated he was trying to remember the words, but like the demented subjects of the present study, recognized new items only at a chance level. He too showed higher activity levels in the right hemisphere (Wood, Armentrout, et al., 1980). These results indicate that left-side brain damage can result in a preferential right hemisphere response to recognition memory task participation. They also suggest that this abnormal activation is independent of how accurately the subject performed.

Decreased Arousal in AD

Lower levels of cerebral activity and the lack, or diminution, of a general arousal response have been used to explain the failure of hemispheric CBF increases in AD patients during behavioral activation paradigms (Ingvar, Risberg, & Schwartz, 1975; Yamaguchi et al., 1980). An abnormal general arousal response has also been used by Talland (1965) to explain the amnestic component of Korsakoff's syndrome. According to Talland, memory impairment in Karsakoff's may be caused by incomplete, rather than nonexistent, memory processing. The hypothesis is that recognition marks the closing of search cycle; ie. the finding of a match or close fit. This match can occur immediately or, as is usually the case, may be sustained over repeated attempts. Because of an abnormal general arousal and a premature closing of function, or search, the amnestic is unable to sustain the searching operations in the same way as normal individuals. It is of interest that this failure to complete goal-oriented responses, or to sustain excitatory

activity in the brain, has been tied to impaired hippocampal function (Adel, cited in Talland, 1965).

The impaired memory performance of the AD subjects, carrying Talland's hypothesis further, may be due not to a lack of memory processing, but to inefficient memory processing. Generalized lower cerebral metabolic rates in AD may be associated with a diminished arousal. Temporal lobe neuropathology probably compromises verbal recognition memory. Together, these two impairments could severely limit memory processing in AD patients.

Right Temporal Lobe Activation

The possible compromised function of the left temporal lobe does not exclude the possibility that the right lobe remains active in AD patients during memory processing. The baseline and memory conditions did affect the lateral asymmetries of the two groups significantly differently and the effect was particularly marked for the AD group. It may be that the distinctive neuroanatomical organization of the right and left hemispheres is a contributing factor to the abnormal right-sided metabolic response observed in the AD patients.

Goldberg and Costa (1981) have argued that the right hemisphere is primarily organized for inter-regional integration, while left hemisphere organization suggests a predominant focus on intra-regional integration. According to the authors, this difference in organization may result in fundamental distinctions in cognitive processing:

> ... the right hemisphere has a greater ability to perform inter-modal integration and to process novel stimuli; the left hemisphere is more capable of unimodal and motor processing as well as the storage of compact codes. In the process of acquisition of a

> new descriptive system, the right hemisphere plays a critical role in initial stages of acquisition, whereas the left hemisphere is superior at utilizing well-routinized codes. This leads to a right-to-left shift of hemisphere superiority as a function of increased competence with respect to a particular type of processing (Goldberg & Costa, 1981, p.144).

The cognitive consequences of this hypothesis also predict that during the early stages of acquisition, the right hemisphere should demonstrate a preferential superiority in performance, while the performance of the left hemisphere should gain superiority as the skills needed for task execution are acquired and routinized.

For the normal subjects in the present study, this hypothesis suggests a possible sequence of events that could have taken place during the memory task. First, the concept of the recognition task may have been very familiar to them in which case the left hemisphere would have taken the predominate role from the beginning. Or, secondly, as the task became quickly mastered, a shift in activity from the right to left hemisphere would have occurred. In either case, the left hemisphere would play the dominate role throughout most of the task and this is what the results suggest.

More interestingly, the Goldberg and Costa hypothesis also suggests a plausible explanation for the marked AD change in lateral asymmetries toward the right. Because of left temporal lobe damage and associated recognition memory impairment, perhaps the demented individuals continuously responded to the item presentations as if they were novel. If so, the AD patients would have remained in the early stages of acquisition throughout the task. As a result, they would have been

unable to routinize the task and its execution. The normal right-to-left shift in hemispheric performance and metabolic activity would not have occurred and the right hemisphere would have predominated throughout the task.

To fully investigate the merits of this hypothesis, however, the change in hemispheric activity would need to be analyzed over the changes in psychometric performance. One would also expect that if the right hemisphere is organized for inter-regional integration, other areas of the right hemisphere in AD subjects would have shown a task-dependent, right-sided superiority. This was not the case. The results were highly specific to the temporal lobe. Even within these limitations, however, the Goldberg and Costa hypothesis remains an intriguing speculation.

Conclusions

Previous PET studies have reported relationships between cognitive impairment in AD and glucose metabolic rates (de Leon, Ferris, George, et al., 1983; Ferris, de Leon, et al., 1980; Foster et al., 1984; McGeer, et al., 1986; Rapoport, Duara, et al., 1984), but have correlated their measures with neuropsychological scores obtained at times other than during the PET procedure. The abnormal task-dependent change in temporal lobe asymmetry to the right is the first direct evidence of a relationship between memory performance in AD patients and simultaneous alterations in temporal lobe activity. More specifically, the results of the current study suggest that the poor AD performance may have been due to preferential left temporal lobe damage and that the right hemisphere may have responded to functional demands

of the task that it is more adept at performing. Furthermore, the differential metabolic alterations also demonstrate the feasibility of using PET to examine the regional pathophysiology that is associated with other AD cognitive deficits and that behavioral paradigms, used in conjunction with PET, might prove to be sensitive diagnostic indicators of disease.

Future Research

This initial memory processing study demonstrates the feasibility of correlating memory task participation and performance with simultaneous measures of glucose metabolic rates in normal elderly and AD subjects. It also, however, points out the need to develop tasks with wider ranges of difficulty that would permit a more accurate and meaningful psychometric performance in both demented subjects and controls. An experimental design that incorporates a memory task paradigm with two or three levels of difficulty matched across three subject groups - young, elderly normals, and AD patients - would allow a comparison of groups that are matched in performance, or differ in performance, but are performing similar tasks. Such a design would aid in determining if: (1) metabolic rates differ for the three groups under conditions of equated cognitive activation, (2) if different levels of cognitive activation have different effects on regional metabolic rates and (3) if different levels of behavioral activation have differential conjoint effects on regional metabolic rates of the three groups. This design may also aid in the identification of a potential metabolic response as pathological. Such an experiment is needed to add to our understanding of the underlying pathophysiology of

the memory impairment associated with Alzheimer's disease and normal aging.

REFERENCES

American Psychiatric Association. (1980). Diagnostic and statistical manual of mental disorders (3rd ed.). Washington, DC: Author.

Anderson, J. H., Hubbard, B. M. (1985). Definition of Alzheimer's disease. Lancet, 1, 408.

Ball, M. J., Fishman, M., Hachinski, V., Blume, W., Fox, A., Kral, V. A., Kirshen, A. J., & Fox, H. (1985). A new definition of Alzheimer's disease: A hippocampal dementia. Lancet, 1, 14.

Bartus, R. T., Dean, R. L., Beer, B., & Lippa, A. S. (1982). The cholinergic hypothesis of geriatric memory dysfunction. Science, 217, 408-417.

Bartus, R. T. & Johnson, H. R. (1976). Short term memory in the rhesus monkey: Disruption from the anticholinergic scopolamine. Pharmacology, Biochemistry and Behavior, 5, 39-40.

Benson, F. D., Kuhl, D. C., Hawkins, R. A., Phelps, M. E., Cummings, J. L., & Tsai, S. Y. (1983). The fluorodeoxyglucose ^{18}F scan in Alzheimer's disease and Multi-infarct dementia. Archives of Neurology, 40, 711-714.

Birkett, P. (1977). Measures of laterality and theories of hemispheric process. Neuropsychologia, 15, 693-696.

Blessed, G., Tomlinson, B. E., & Roth, M. (1968). The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. British Journal of Psychiatry, 114, 797-811.

Botwinick, J. (1984). Aging and behavior (3rd ed.). New York: Springer Publishing Company, Inc.

Bowen, D. M., Spillane, J. A., Curzon, G., Meier-Ruge, W., White, P., Goodhardt, M. J., Iwangoff, P., & Davison, A. N. (1979). Accelerated ageing or selective neuronal loss as an important cause of dementia? Lancet, 1, 11-14.

Branconnier, R. J., Cole, J. O., Spera, K. F., & DeVitt, D. R. (1982). Recall and recognition as diagnostic indices of malignant memory loss in senile dementia: A Bayesian analysis. Experimental Aging Research, 8, 189-193.

Brinkman, S. D., & Gershon, S. (1983). Measurement of cholinergic drug effects on memory in Alzheimer's disease. Neurobiology of Aging, 4, 139-145.

Brooks, R. A. (1982). Alternate formula for glucose utilization using labeled deoxyglucose. Journal of Nuclear Medicine, 23, 538-539.

Brun, A. (1985). The structural development of Alzheimer's Disease. Danish Medical Bulletin, 32(Suppl. 1), 25-27.

Burke, D. M., & Light, L. L. (1981). Memory and aging: The role of retrieval processes. Psychological Bulletin, 90, 513-545.

Butters, N., Samuels, I., Goodglass, H., & Brody, B. (1970). Short-term visual and auditory memory disorders after parietal and frontal lobe damage. Cortex, 6, 440-459.

Chase, T. N., Foster, N. L., & Mansi, L. (1983). Alzheimer's disease and the parietal lobe. Lancet, 2, 225.

Collerton, D., & Fairbairn, A. (1985). Alzheimer's disease and the hippocampus. Lancet, 1, 278-279.

Cooper, J. R., Bloom, F. E., & Roth, R. H. (1986). The biochemical basis of neuropharmacology (5th ed.). New York: Oxford University Press.

Coyle, J. T., Price, D. L., & DeLong, M. R. (1983). Alzheimer's disease: A disorder of cortical cholinergic innervation. Science, 219, 1184-1190.

Craik, F. I. M. (1971). Age differences in recognition memory. Quarterly Journal of Psychology, 23, 316-323.

Craik, F. I. M. (1977). Age differences in human memory. In Birren, J. E., & Schaie, K. W. (Eds.). Handbook of the psychology of aging (pp. 384-420). New York: Van Nostrand Reinhold Company.

Cummings, J. L., & Benson, D. F. (1983). Dementia: A clinical approach. Boston: Butterworth Publishers.

Cutler, N. R., Haxby, J. V., Duara, R., Grady, C. L., Kay, A. D., Kessler, R. M., Sundaram, M., & Rapoport, S. I. (1985). Clinical history, brain metabolism, and neuropsychological function in Alzheimer's disease. Annals of Neurology, 18, 298-309.

Davies, P. & Maloney, A. J. F. (1976). Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet, 2, 1403.

de Leon, M. J., Ferris, S. H., George, A. E., Christman, D. R., Fowler, J. S., Gentes, C., Reisberg, B., Gee, B., Emmerich, M., Yonekura, Y., Brodie, J., Kricheff, I. I., & Wolf, A. P. (1983). Positron emission tomographic studies of aging and Alzheimer disease. American Journal of Neuroradiology, 4, 568-571.

de Leon, M. J., Ferris, S. H., George, A. E., Reisberg, B., Christman, D. R., Kricheff, I. I., & Wolf, A. P. (1983). Computed tomography and positron emission transaxial tomography evaluations of normal aging and Alzheimer's disease. Journal of Cerebral Blood Flow and Metabolism, 3, 391-394.

de Leon, M. J., & George, A. E. (1983). Computed tomography in aging and senile dementia of the Alzheimer type. In R. Maycus & W. G. Rosen (eds.), The dementias (pp. 103-122). New York: Raven Press.

de Leon, M. J., George, A. E., Ferris, S. H., Christman, D., Gentes, C. I., Miller, J. D., Fowler, J., Reisberg, B., & Wolf, A. P. (1985). CT, PET, and NMR brain imaging in aging and Alzheimer's disease. In C. G. Gottfries (Ed.), Normal aging. Alzheimer's disease and senile dementia (pp. 199-202). Bruxelles: Editions de l'Universite de Bruxelles.

de Leon, M. J., Ferris, S. H., George, A. E., Miller, J. D., Klinger, A. J., Franssen, E., Kluger, A., Sachs, H., La Regina, M. E., Cohen, J., & Wolf, A. P. (1986). Leukoencephalopathy in normal aging and Alzheimer's disease: Studies of CT brain lucencies with 11-CDG and PET. Manuscript submitted for publication.

de Leon, M. J., George, A. E., Ferris, S. H., Rosenbloom, S.,Christman, D. R., Gentes, C. I., Reisberg, B., Kricheff, I. I., & Wolf, A. P. (1983). Regional correlation of PET and CT in senile dementia of the Alzheimer type. American Journal of Neuroradiology, 4, 553-556.

de Leon, M. J., George, A. E., Tomanelli, J., Christman, D., Kluger, A., Miller, J., Ferris, S. H., Fowler, J., Brodie, J., Klinger, A., & Wolf, A. P. (1986). Positron emission tomography studies of normal aging: A replication of PET III and 18-FDG using PET VI and 11-C-2DG. Unpublished manuscript.

de Leon, M. J., Miller, J., & Klinger, A. (1986). [Lateral asymmetries in normal aging and Alzheimer's disease]. Unpublished raw data.

Drachman, D. (1977). Memory and cognitive function in man: Does the cholinergic system have a specific role? Neurology, 27, 783-790.

Drachman, D. A. & Leavitt, J. L. (1974). Human memory and the cholinergic system. A relationship to aging? Archives of Neurology, 30, 113-121.

Duara, H., Grady, C., Haxby, J., Ingvar, D., Sokoloff, L., & Rapoport, S. I. (1984). Human brain glucose utilization and cognitive function in relation to age. Annals of Neurology, 16, 702-713.

Duara, R., Grady, C., Haxby, J., Sundaram, M., Cutler, N. R., Heston, L., Moore, A., Schlageter, N., Larson, S., & Rapoport, S. I. (1986). Positron emission tomography in Alzhemier's disease. Neurology, 36, 879-887.

Erber, J. T. (1974). Age differences in recognition memory. Journal of Gerontology, 29, 177-181.

Ferris, S. H., Crook, T., Clark, E., McCarthy, M., & Rae, D. (1980). Facial recognition memory deficits in normal aging and senile dementia. Journal of Gerontology, 35, 707-714.

Ferris, S. H., de Leon, M. J., Wolf, A. E., Farkas, T., Christman, D. R., Reisberg, B., Fowler, J. S., MacGregor, R., Goldman, A., George, A. E., & Rampal, S. (1980). Positron emission tomography in the study of aging and senile dementia. Neurobiology of Aging, 1, 127-131.

Foster, N. L., Chase, T. N., Fedio, P., Patronas, N. J., Brooks, R. A., & Di Chiro, G. (1983). Alzheimer's disease: Focal cortical changes shown by positron emission tomography. Neurology, 33, 961-965.

Foster, N. L., Chase, T. N., Mansi, L., Brooks, R., Fedio, P., Patronas, N. J., & Di Chiro, G. (1984). Cortical abnormalities in Alzheimer's disease. Annals of Neurology, 16, 649-654.

Friedland, R. P., Budinger, T. F., Koss, E., & Ober, B. A. (1985). Alzheimer's disease: Anterior-posterior and lateral hemisphere alterations in cortical glucose utilization. Neuroscience Letters, 53, 235-240.

Friedland, R. P., Brun, A., & Budinger, T. F. (1985). Pathological and positron emission tomographic correlations in Alzheimer's disease. Lancet, 1, 228-229.

Friedland, R. P., Budinger, T. F., Ganz, E., Yano, Y., Mathis, C. A., Koss, B., Ober, B. A., Huesman, R. H., & Derenzo, S. E. (1983). Regional cerebral metabolic alterations in dementia of the Alzheimer type: Positron emission tomography with ^{18}F Fluorodeoxyglucose. Journal of Computer Assisted Tomography. 7(4), 590-598.

Gilbert, J. G., Levee, R. F., & Catalano, F. L. (1968). A preliminary report on a new memory scale. Perceptual and Motor Skills, 27, 277-278.

Godfries, C. G. (1985). Neurotransmitters in the brains of patients with dementia disorders. Danish Medical Bulletin, 32(Suppl. 1), 44-48.

Goldberg, E. & Costa, L. D. (1981). Hemispheric differences in the acquisition and use of descriptive systems. Brain and Language, 14, 144-173.

Gur, R. E., Skolnick, B. E., Gur, R. C., Caroff, S., Rieger, W., Obrist, W. D., Younkin, D. & Reivich, M. (1983). Brain function in psychiatric disorders. I. Regional cerebral blood flow in medicated schizophrenics. Archives of General Psychiatry, 40, 1250-1254.

Gur, R. E., Skolnick, B. E., Gur, R. C., Caroff, S., Rieger, W., Obrist, W. D., Younkin, D., & Reivich, M. (1984). Brain function in psychiatric disorders. II. Regional cerebral blood flow in medicated unipolar depressives. Archives of General Psychiatry, 41, 695-699.

Gur, R. C., Gur, R. E., Rosen, A. D., Warach, S., Alavi, A., Greenberg, J., & Reivich, M. (1983). A cognitive-motor network demonstrated by positron emission tomography. Neuropsychologia, 21(6), 601-606.

Hachinski, V. C., Iliff, L. D., Phil, M., Zilhka, E., Du Boulay, G. H., McAllister, V. L., Marshall, J., Russell, R. W. R., & Symon, L. (1975). Cerebral blood flow in dementia. Archives of Neurology, 32, 632-637.

Hagberg, B., & Ingvar, D. H. (1976). Cognitive reduction in presenile dementia related to regional abnormalities of the cerebral blood flow. British Journal of Psychiatry, 128, 209-222.

Harker, J. O., & Reige, W. H. (1985). Aging and delay effects on recognition of words and designs. Journal of Gerontology, 40, 601-604.

Harkins, S. W., Chapman, C. R., & Eisdorfer, C. (1979). Memory loss and response bias in senescence. Journal of Gerontology, 34, 66-72.

Harris, S. J., & Dowson, J. H. (1982). Recall of a 10-word list in the assessment of dementia in the elderly. British Journal of Psychiatry, 141, 524-527.

Hart, S. A., Smith, C. M., & Swash, M. (1985). Recognition memory in Alzheimer's disease. Neurobiology of Aging, 6, 287-292.

Hawkins, R. A., Mazziotta, J. C., Phelps, M. E., Huang, S., Kuhl, D. E., Carson, R. E., Metter, E. J., & Reige. (1983). Cerebral glucose metabolism as a function of age in man: Influence of the rate constants in the fluorodeoxyglucose method. Journal of Cerebral Blood Flow and Metabolism, 3, 250-253.

Haxby, J., Grady, C. L., Duara, R., Schlageter, N., Berg, G., & Rapoport, S. I. (1986). Neocortical metabolic abnormalities precede nonmemory cognitive defects in early Alzheimer's disease-type dementia. Archives of Neurology, 43, 882-885.

Heilman, K. M., & Valenstein, E. (1979). Clinical neuropsychology, New York: Oxford Press.

Hoffman, E. J., Huang, S., Plummer, D. & Phelps, M. E. (1982). Quantitation in positron emission computed tomography: 6. Effect of nonuniform resolution. Journal of Computer Assisted Tomography, 6(5), 987-999.

Hyman, B. T., Van Hoesen, G. W., Damasio, A. R., & Barnes, C. L. (1984). Alzheimer's disease: Cell-specific pathology isolates the hippocampal formation. Science, 225, 1168-1170.

Ingvar, D. H., Risberg, J., & Schwartz, M. S. (1975). Evidence of subnormal function of association cortex in presenile dementia. Neurology, 25, 964-974.

Jamada, M., & Mehraein, P. (1968). Verteilungsmuster der senilen veranderungen im gehern. Die beteiligung des limbischen systems bei hirnatrophischen prozessen des.senium und bei Morbus Alzheimer. Archives of Psychiatry and Neurology, 211, 308-324.

Kemper, T., (1984). Neuroanatomical and neuropathological changes in normal aging and in dementia. In M. L. Albert (Ed.). Clinical neurology of aging (chap. 2). New York: Oxford University Press.

Kolb, B., & Wishaw, I. Q. (1985). Fundamentals of human neuropsychology (2nd ed.). New York: W. H. Freeman and Company.

Koss, E., Friedland, R., Ober, B., & Jagust, W. (1985). Differences in lateral hemisphere asymmetries of glucose utilization between early- and late-onset Alzheimer-type dementia. American Journal of Psychiatry, 142, 638-640.

Kuhl, D. E., Metter, E. J., Riege, W. H., & Phelps, M. E. (1982). Effects of human aging on patterns of local cerebral glucose utilization determined by the ^{18}F fluorodeoxyglucose method. Journal of Cerebral Blood Flow and Metabolism, 2, 163-171.

Lauter, H. (1985). What do we know about Alzheimer's disease today? Danish Medical Bulletin, 32(Suppl. 1), 1-21.

Lavy, S., Melamed, E., Bentin, S., Cooper, G., & Rinot, Y. (1978). Bihemispheric decreases of regional cerebral blood flow in dementia: Correlation with age-matched normal controls. Annals of Neurology, 4, 445-450.

Levy, J. (1983). Is cerebral asymmetry of function a dynamic process? Implications for specifying degree of lateral differentiation. Neuropsychologia, 21, 3-11.

MacGregor, R. R., Fowler, J. S., Wolf, A. P., Shiue, C. Y., Lade, R. E., Wan, C. N. (1981). A synthesis of ^{11}C-2-deoxy-D-glucose for regional metabolic studies: concise communication. Journal of Nuclear Medicine, 22, 800-803.

Maximilian, V. A., Prohovnik, I., Risberg, J., & Hakansson, K. (1978). Regional cerebral blood flow changes in left cerebral hemisphere during word pair learning and recall. Brain and Language, 6, 22-31.

Mayeux, R., Stern, Y., & Spanton, S. (1985). Heterogeneity in dementia of the Alzheimer's type: Evidence of subgroups. Neurology, 35, 453-461.

Mazziotta, J. C., Phelps, M. E., Carson, R. E., & Kuhl, D. E. (1982). Tomographic mapping of human metabolism: Auditory stimulation. Neurology, 32, 921-937.

Mazziotta, J. C., Phelps, M. E., Plummer, D., & Kuhl, D. E. (1981). Quantitation in positron emission computed tomography: 5. Physical-anatomical effects. Journal of Computer Assisted Tomography, 5(5), 734-743.

McCarthy, M., Ferris, S. H., Clark, E., & Crook, T. (1981). Acquisition and retention of categorized material in normal aging and senile dementia. Experimental Aging Research, 7(2), 127-135.

McGeer, P.L., Kamo, H., Harrop, R., Li, D. K. B., Tuokko, H., McGeer, E. G., Adam, M. J., Ammann, W., Beattie, B. L., Calne, D. B., Martin, W. R. W, Pate, B. D., Rogers, J. G., Sayre, C. I., & Stoessl, A. J. (1986). Positron emission tomography in patients with clinically diagnosed Alzheimer's disease. Canadian Medical Association, 134, 597-607.

Melamed, E., Lavy, S., Bentin, S., Cooper, G., & Rinot, Y. (1980). Reduction in regional cerebral blood flow during normal aging in man. Stroke, 11, 31-35.

Mesulam, M. M., & Van Hoesan, G. W. (1976). Acetylcholinesterase-rich projections from the basal forebrain of the rhesus monkey to neocortex. Brain Research, 109, 152-157.

Meyer, J. S., Sakai, F., Naritomi, H., & Grant, P. (1978). Normal and abnormal patterns of cerebrovascular reserve tested by ^{133}Xe inhalation. Archives of Neurology, 35, 350-359.

Meyer, J. S., & Shaw, T. G. (1984). Cerebral blood flow in aging. In M. L. Albert (Ed.). Clinical neurology of aging (chap. 9). New York: Oxford University Press.

Miller, E. (1971). On the nature of memory disorders in presenile dementia, Neuropsychology, 9, 75-81.

Miller, E. (1975). Impaired recall and the memory disturbance in presenile dementia. British Journal of Social and Clinical Psychology, 14, 73-79.

Miller, E., & Lewis, P. (1977). Recognition memory in elderly patients with depression and dementia: A signal detection analysis. Journal of Abnormal Psychology, 86, 84-86.

Miller, J. D., & de Leon. (1986). [Guild scores in a large sample of normal elderly and Alzheimer subjects]. Unpublished raw data.

Mishkin, M. (1978). Memory in monkeys severely impaired by combined but not by separate removal of amygdala and hippocampus. Nature, 273, 297-298.

Mohs, R., & Davis, K. (1982). A signal detectability analysis of the effect of physostigmine on memory in patients with Alzheimer's disease. Neurobiology of Aging, 3, 105-110.

Moosey, J., Hanin, I., Martinez, A. J., & Rao, G. (1985). Lateral variations in morphological and cholinergic markers in Alzheimer's disease and other dementias. Presented at the American Association of Neuropathology, 61st Annual Meeting, June 13-16, Boston.

Nakano, I. & Hirano, A. (1982). Loss of large neurons of the medial septal nucleus in anatomy cases of Alzheimer's disease. Journal of Neuropathology and Experimental Neurology, 41, 341.

Naritomi, H., Meyer, J. S., Sakai, F., Yamaguchi, F., & Shaw, T. (1979). Effects of advancing age on regional cerebral blood flow. Archives of Neurology, 36, 410-416.

Obrist, W. D., Chivian, E., Cronqvist, S., & Ingvar, D. H. (1970). Regional cerebral blood flow in senile and presenile dementia. Neurology, 20, 315-322.

Olesen, J. (1971). Contralateral focal increase of cerebral blood flow in man during arm work. Brain, 94, 635-646.

Pantano, P., Baron, J., Lebrun-Grandie, P., Duquesnay, N., Bousser, M., & Comar, D. (1984). Regional cerebral blood flow and oxygen consumption in human aging. Stroke, 15, 635-641.

Perry, E. K. & Perry, R. H. (1985). A review of neuropathological and neurochemical correlates of Alzheimer's disease. Danish Medical Bulletin, 32(Suppl. 1), 27-34.

Perry, E. K., Perry, R. H., Blessed, G., & Tomlinson, B. E. (1977). Necrospy evidence of central cholinergic deficits in senile dementia. Lancet, 1, 189.

Perry, E. K., Tomlinson, B. E., Blessed, G., Bergmann, K., Gibson, P. H., & Perry, R. H. (1978). Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. British Medical Journal, 2, 1457-1459.

Phelps, E. P. (1981). Positron computed tomography studies of cerebral glucose metabolism in man: Theory and application in nuclear medicine. Seminars in Nuclear Medicine, 11(1), 32-49.

Phelps, M. E., Mazziotta, J. C., & Huang, S. (1982). Study of cerebral function with positron computed tomography. Journal of Cerebral Blood Flow and Metabolism, 2, 113-162.

Poon, L. W., & Fozard, J. L. (1980). Age and word frequency effects in continuous recognition memory. Journal of Gerontology, 35, 77-86.

Raichle, M. E. (1983). Positron emission tomography. Annual Review of Neuroscience, 6, 249-267.

Rankin, J. L., & Kausler, D. H. (1979). Adult age differences in false recognitions. Journal of Gerontology, 34, 58-65.

Rapoport, S., Duara, R., & Haxby, J. (1984). Positron emission tomography in normal aging and Alzheimer's disease. Psychopharmacology Bulletin, 20(3), 466-471.

Reisberg, B., & Ferris, S. H. (1982). Diagnosis and assessment of the older patient. Hospital and Community Psychiatry, 33, 104-110.

Reisberg, B., Ferris, S. H., de Leon, M. J., & Crook, T. (1982). The global deterioration scale for assessment of primary degenerative dementia. American Journal of Psychiatry, 139, 1136-1139.

Reivich M. , & Greenberg. (1985). Glucose metabolic rate kinetic model parameter determination in humans: The lumped constants and rate constants for ^{18}F-Fluorodeoxyglucose and ^{11}C-deoxyglucose. Journal of Cerebral Blood Flow and Metabolism, 5, 179-192.

Risberg, J. (1980). Regional cerebral blood flow measurements by ^{133}Xe-inhalation: Methodology and applications in neuropsychology and psychiatry. Brain and Language, 9, 9-34.

Risberg, J., Halsey, J. H., Wills, E. L., & Wilson, E. M. (1975). Hemispheric specialization in normal man studied by bilateral measurements of the regional cerebral blood flow. Brain, 98, 511-524.

Risberg, J., & Ingvar, D. H. (1973). Patterns of activation in the grey matter of the dominant hemisphere during memorizing and reasoning. Brain, 96, 737-756.

Saunders, R. C., Murray, E. A., & Mishkin, M. (1984). Further evidence that amygdala and hippocampus contribute equally to recognition memory. Neuropsychologia, 22, 785-796.

Schonfield, D. (1965). Memory changes with age. Nature, 208, 918.

Schonfield, D. & Robertson, B. (1966). Memory storage and aging. Canadian Journal of Psychology, 20, 228-236.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. Journal of Neurology, Neurosurgery, and Psychiatry, 20, 11-21.

Shallice, T. & Warrington, E. K. (1970). Independent functioning of verbal memory stores: A neuropsychological study. Quarterly Journal of Experimental Psychology, 22, 261-273.

Shaw, T. B., Mortel, K. F., Meyer, J. S., Rogers, R. L., Hardenberg, J., & Cutaia, M. M. (1984). Cerebral blood flow changes in benign aging and cerebrovascular disease. Neurology, 34, 855-862.

Shepard, R. N., & Teghtsoonian, M. (1961). Retention of information under conditions approaching a steady state. Journal of Experimental Psychology, 62, 302-309.

Shuttleworth, E. C. (1982). Memory function and the clinical differentation of dementing disorders. Journal of the Geriatric Society, 30, 363-366.

Simard, D., Olesen, J., Paulson, O. B., Lassen, N. A., & Skinhoj, E. (1971). Regional cerebral blood flow and its regulation in dementia. Brain, 94, 273-288.

Smith, C. M., & Swash, M. (1978). Possible biochemical basis of memory disorder and Alzheimer disease. Annals of Neurology, 3, 471-473.

Snodgrass, J. G. (1986). [The pragmatics of measuring recognition memory performance]. Unpublished equations for discrimination indices.

Sokoloff, L. (1981). Circulation and energy metabolism of the brain. In G. J. Siegal, R. W. Albers, B. W. Agranoff, & R. Katzman (Eds.), Basic neurochemistry (3rd ed.) (chap. 24). Boston: Little, Brown and Company.

Sokoloff, L., Reivich, M., Kennedy, C., DeRosiers, M. H., Pattak, C. S., Pettigrew, K. C., Sakurada, O., & Shinohara, M. (1977). The (^{11}C) deoxyglucose method for the measurement of local cerebral glucose utilization: Theory , procedure, and normal values in the conscious and anesthetized albino rat. Journal of Neurochemistry, 28, 897-916.

Spillane, J. A., White, P., Goodhardt, M. J., Flack, R. H. A., Bowen, D. M., & Davison, A. N. (1977). Selective vulnerability of neurones in organic dementia. Nature, 266, 558-559.

Swets, J. A. (1973). The relative operating characteristic in psychology. Science, 182, 990-1000.

Talland, G. A. (1965) Deranged memory. New York: Academic Press.

TerPogossian, M., Flicke, D. C., Hood, J. T., Yamamoto, M., & Mullani, N. A. (1982). PETT VI: A positron emission tomograph utilizing cesium fluoride scintillation detectors. Journal of Computer Assisted Tomography, 6, 125-133.

Tomlinson, B. E., & Kitchener, D. (1972). Granulovacuolar degeneration of hippocampal pyramidal cells. Journal of Pathology, 106, 165-185.

Walsh, K. W. (1978). Neuropsychology: A clinical approach. New York:Churchill Livingston.

Warren, L. R., Butler, R. W., Katholi, C. R., & Halsey, J. H. (1985). Age differences in cerebral blood flow during rest and during mental activation measurements with and without monetary incentive. Journal of Gerontology, 40, 53-59.

Warrington, E. K., Logue, V., Pratt, R. T. C. (1971). The anatomical localization of selective impairment of auditory short-term memory. Neuropsychologia, 9, 377-397.

White, N., & Cunningham, W. R. (1982). What is the evidence for retrieval problems in the elderly? Experimental Aging Research, 8, 169-171.

Whitehouse, P. J., Price, D. L., Clark, A. W., Coyle, J. T., & De Long, M. R. (1981). Alzheimer's disease: Evidence for selective loss of cholinergic neurons in the nucleus basalis. Annals of Neurology, 10, 122-126.

Wilcock, G. K., Esiri, M. M., Bowen, D. M., & Smith, C. C. T. (1983). The Nucleus Basalis in Alzheimer's disease: Cell counts and cortical biochemistry. Neuropathology and Applied Neurobiology, 9, 175-179.

Wilson, R. S., Bacon, L. D., Fox, J. H., Kaszniak, A. W. (1983). Primary memory and secondary memory in dementia of the Alzheimer type. Journal of Clinical Neuropsychology, 5, 337-344.

Wilson, R. S., Bacon, L. D., Fox, J. H., Kramer, R. L., & Kaszniak, A. W. (1983). Word frequency effect and recognition memory in dementia of the Alzheimer type. Journal of Clinical Neuropsychology, 5, 97-104.

Wilson, R. S., Kaszniak, A. W., Bacon, L. D., Fox, J. H., Kelly, M. P. (1982). Facial recognition in dementia. Cortex, 18, 329-336.

Wood, F. (1983). Laterality of cerebral function: Its investigation by measurement of localized brain activity. In J. B. Hellige (Ed.), Cerebral Hemisphere Asymmetry (chap. 10). New York: Praeger Publishers.

Wood, F., Armentrout, R., Toole, J. F., McHenry, L., & Stump, D. (1980). Regional cerebral blood flow response during rest and memory activation in a patient with global amnesia. Brain and Language, 9, 129-136.

Wood, F., McHenry, L., Roman-Campos, G., & Poser, C. M. (1980). Regional cerebral blood flow response in a patient with remitted global amnesia. Brain and Language, 9, 123-128.

Wood, F., Taylor, B., Penny, R., & Stump, D. (1980). Regional cerebral blood flow response to recognition memory versus semantic classification tasks. Brain and Language, 9, 113-122.

Woodard, J. S. (1962). Clinicopathologic significance of granulo-vacuolar degeneration in Alzheimer's disease. Journal of Neuropathology and Experimental Neurology, 21, 85-91.

Yamaguchi, F., Meyer, J. S., Yamamoto, M., Sakai, F., Shaw, T. (1980). Noninvasive regional cerebral blood flow measurements in dementia. Archives of Neurology, 37, 410-418.

Zola-Morgan, S., Squire, L. R., Mishkin, M. (1982). The neuroanatomy of amnesia: Amygdala-hippocampus versus temporal stem. Science, 218, 1137-1139.