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The types and number of exemplars of categories that are retrieved from semantic memory differentiate elderly normal controls and early stage Alzheimer's disease (AD) patients. Elderly normal controls generated more uncommon exemplars from *closed* semantic categories (fruits and vegetables) than did AD patients 2 1/2 years *prior* to the presumed onset of AD. AD patients, however, were just as productive as elderly normal controls in generating associations to *open* categories (letters). The findings suggest that one of the early cognitive symptoms of AD is changes in availability of uncommon exemplars of semantic networks.
Key Words: Semantic memory, Aging, Alzheimer's disease

Changes in Semantic Memory in Early Stage Alzheimer's Disease Patients[1]

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This study contrasts changes in semantic memory in elderly normal controls and in Alzheimer's disease (AD) patients before the patients expressed symptoms that serve as a basis for the diagnosis of probable AD, and two to three years later when these patients met NINCDS (McKhann et al., 1984) criteria. Volunteers in this study are participants in the Baltimore Longitudinal Study of Aging (BLSA). Every two years, BLSA subjects that are 60 years of age or older are administered tests evaluating the integrity of a wide spectrum of physiological systems as well as their mental status, as assessed by a standardized neuropsychological examination.

Subtle, but reliable, changes in many aspects of cognitive functioning are apparent in the normal elderly and are expressed more dramatically in AD patients, increasingly so as their disease progresses. For example, both normal elderly and AD patients demonstrate changes on many tests of learning and memory. The source of these changes is currently unknown. Furthermore, it remains uncertain whether the cognitive changes expressed in AD are merely an exaggeration of those that are apparent in normal aging or are qualitatively different.

The focus of the BLSA program of research is to both define and differentiate processes involved in normal and pathological aging. In that context, the goal of this study was to contrast semantic memory functions in AD patients (both before and after the presumed onset of AD) and well-matched elderly normal controls. This is important because changes in recent (episodic) memory, while probably the most obvious symptom in AD, are also a common feature of many disorders of the central nervous system and therefore not very useful for discriminating between different disorders. On the other hand, semantic memory functions are spared in many amnestic patients, and in normal aging, but are impaired in middle and late stage AD patients (see Martin, 1987; Martin, 1992; Martin, Brouwers, Cox, & Fedio, 1985, for a review). A related question that was addressed in this study is whether changes in semantic memory early in the course of AD are attributable to impairments in being able to retrieve category exemplars in a controlled manner, or are due to an actual loss of semantic knowledge. To test whether changes in semantic memory would distinguish AD patients from elderly normal controls, we compared their productivity in generating words that are exemplars of closed or limited categories, fruits and vegetables, and their ability to generate words that begin with the letters F, A, or S (word fluency in response to open or very large categories of information). This comparison was made some years before and after the diagnosis of probable AD could be established in these individuals.

Methods

Subjects

Every two to three years the subjects of this study, participant volunteers in the Baltimore Longitudinal Study of Aging (BLSA), are hospitalized and evaluated. At each admission subjects are administered a wide variety of tests that are used to characterize their physiological and psychological status. Subjects 70 years and older are administered a standard

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neurological examination by a research neurologist (CK). That examination follows standardized methods for obtaining a history from the subject and establishing a diagnosis of AD based on NINCDS-ADRDA criteria for probable Alzheimer's disease (McKhann et al., 1984). All participants 60 years or older are given a neuropsychological battery which includes the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) and measures of semantic memory and fluency.

Six BLSA volunteers were diagnosed as probable AD patients (based upon NINCDS-ADRDA criteria). A diagnosis of dementia was made when there was a history and examination demonstrating progressive cognitive impairment of sufficient severity to interfere with social or occupational functioning, with loss of memory and at least one other area of cognition (language, calculations, attention, apraxia and agnosia) in an alert patient. The diagnosis of Alzheimer's disease utilized criteria recommended by the task force established in 1984 by the U.S. Department of Health and Human Services and NINCDS (McKhann et al., 1984). These criteria allow patients to be characterized as definite AD (postmortem verification), probable AD (meets all criteria), or possible AD (meets most criteria but some unusual features).

Of the 6 patients diagnosed with Alzheimer's disease, 4 patients met criteria for probable Alzheimer's disease with a classic course as defined by the NINCDS criteria (patients 1, 4, 5, and 6). Three of these patients (4, 5, and 6) have progressed to the point that they have recently required nursing home care. Two patients met criteria for possible Alzheimer's disease. Patient 2 appeared clinically typical for Alzheimer's disease but workup revealed a marginally low B12 level of 105. The patient had no anemia or other neurologic findings consistent with the diagnosis of subacute combined systems disease (B12 deficiency). Treatment was initiated with B12 injections but, despite this, the patient continued to have deterioration consistent with Alzheimer's disease. Patient 3 also received a diagnosis of possible Alzheimer's disease. This patient appeared to be a typical Alzheimer's patient but a routine workup revealed an abnormal electroencephalogram (EEG) which showed frequent epileptiform spike and slow wave transients in the left temporal region. The patient had never had a clinical seizure or any history suggestive of a seizure disorder. Treatment with dilantin did not result in improvement. The patient continued to deteriorate in a manner consistent with Alzheimer's disease.

We selected 6 normal controls that matched these patients with respect to their age, number of years of education, gender and number of years of participation in the BLSA project. We compared the semantic memory and fluency performance of these elderly normal controls with those of the AD patients at two points in time. Time 2 was when 6 of these BLSA subjects were diagnosed as probable or possible AD, while the controls appeared to not suffer from any disease that could involve the central nervous system. These same subjects were also compared at Time 1, 2.3 years earlier (±.89 years), when AD patients appeared to be unimpaired and clinically indistinguishable from normal controls.

The mean age of all subjects at Time 1 was 76.0 years with a standard deviation of ±3.26 years. The mean age of subjects at Time 2 was 78.75 ± 3.05. For AD patients, the mean MMSE score at Time 1 was 25.33 (±3.67) and 20.60 (±6.80) at Time 2. The MMSE levels for normal control subjects were 28.0 (±2.10) at Time 1 and 28.17 (±1.60) at Time 2, scores that are significantly higher than those obtained in early stage AD patients.

Procedures

Subjects were tested on a task that is commonly used to assess verbal fluency and the ability to access and make use of semantic knowledge. Subjects were asked to generate as many words as possible, within 60 seconds, that belong to two closed or limited categories, fruits and vegetables. The order in which subjects were asked to generate exemplars to the categories fruits and vegetables was randomized across subjects. They were also asked to generate as many words as possible, within 60 seconds, to open or large categories, words that start with the letters F, A, and S. The latter test is one that is often used to assess controlled verbal fluency. Again, letter stimuli were presented in a random order. Each word generated in response to the category fruits or vegetables was classified as either a common or high frequency exemplar (H), one of medium strength or moderately frequent occurrence (M), or an uncommon, low frequency response (L). Category norms which provide data for classifying exemplars in terms of their frequency of occurrence in tests of free association (Battig & Montague, 1969) were used to classify these responses. A high frequency category exemplar was defined as a word that occurs as a response in 20 to 250 out of 442 subjects who produce a single word association to these category names. Typical common category exemplars include words like apple and orange in response to fruit and carrot and potato in response to vegetables. A medium strength association (M) is one that is generated by from 2 to 10 of 442 college students who responded to these category names with a single word response. Fruits such as blackberry and honeydew, and vegetables such as mushroom and sweet potato, are medium strength responses. An uncommon, low frequency category exemplar was used to designate words that were appropriate category exemplars but were generated by no more than one of the 442 subjects that were tested in compiling the category norms of Battig and Montague. For example, words categorized as uncommon responses included kiwi and starfruit as a fruit, and snowpeas as a vegetable.

The Thorndike and Lorge word count of the English language (Thorndike & Lorge, 1952) provided the normative data for classifying the word responses that subjects generated that started with letters F, A, and S. A high frequency or common response occurs more than 50 times per million in written language that was used to compile this word frequency count of the language. High frequency responses included words like front, above, and small. Words with frequencies between 1 and 49 per million, such as fabulous, anxious, and sandwich were designated as medium frequency responses. Uncommon, low frequency responses were designated as words that did not appear in the Thorndike Lorge word count but were in fact real words given in response to the letter stimuli, and included words like flapjacks, abacus, scam.

The category boundaries that were used to define the frequency of occurrence of subjects' responses, as members of superordinate categories, or in terms of usage in the English language, were somewhat arbitrary and emphasized the low frequency responses. The same criteria used for categorizing these responses have been used in several completed studies of drug and mood effects on access to semantic memory and therefore allow us to compare the findings from this study to several other types of treatment effects. In one of the studies we used the same method of analysis that was used in this study to evaluate the effect of cholinergic antagonists on memory (Molchin et al., 1992). In a second study these stimuli and methods were used to examine the dose-dependent effects of benzodiazepines on explicit and implicit episodic and semantic memory functions (Weingartner et al., in press). In a third paper the same measures of semantic memory were used to demonstrate affect state-dependent retrieval of information in semantic memory (Szostak, Lister, & Weingartner, in press). While the Thorndike-Lorge norms are rather old, they remain useful in evaluating the frequency of occurrence of words in the language (i.e., Ober et al., 1986). To evaluate the utility of these norms in evaluating the frequency of occurrence of words in the language, we correlated and compared the number of high frequency responses that were generated by 15 subjects under placebo, and following the administration of three different doses of the benzodiazepine triazolam using the older Thorndike-Lorge norms and newer word frequency norms (Francis & Kucera, 1982). The average of the correlations obtained from an analysis of these data obtained from these four treatment conditions (where the responses were scored separately using these two different sets of norms) was $r = .96$; $p < .01$. Despite this high correlation, the extent to which word frequency norms or category norms are appropriate to a given population of subjects can still vary, not just on the basis of when the norms were developed, but on the basis of many other factors such as the educational, social-cultural background of the subjects studied.

Results

Statistical Analysis

The results were analyzed as follows. A 2-factor repeated measures analysis of variance (ANOVA) was used to evaluate possible differences in the total number of generated exemplars that are members of open and closed categories of information by AD patients and normal controls at Time 1 and at Time 2. These same data were then analyzed using a 3-factor ANOVA which allowed us to evaluate differences between the two groups of subjects on the basis of the number of high, medium, and low frequency exemplars that were generated by these subjects at Time 1 and at Time 2. The responses to the open categories, letters, were analyzed using identical 2- and 3-factor ANOVAs and pair-wise *t*-tests with Bonferroni corrections to test for differences between means (Miller, 1966). These same data were also analyzed using a non-parametric statistical method, the Mann-Whitney U-Test. The Mann-Whitney U-Test does not assume normality of the underlying distributions required in ANOVA, and in cases of non-normality can be more powerful than the parametric ANOVAs. The Mini-Mental scores of patients and controls, at Time 1 and Time 2, were also analyzed using a 2-factor repeated measures ANOVA. Finally, it should be noted that one of the subjects that was identified as an AD patient at Time 2 had a Mini-Mental score that was lower than all of the other subjects at Time 1. For this reason a second set of repeated measures ANOVAs was also performed, dropping this subject from the analysis. The rationale for doing this was to test whether any group or interactive effects with groups that emerged from an analysis of all of the data would still be apparent even when this most impaired subject at Time 1 was dropped from the analysis. This was another way of testing for the relative robustness of any group effects.

A 2-factor ANOVA of the MMSE scores demonstrated a statistically reliable group × time interaction ($F(1,10) = 10.91$; $p < .01$). Post hoc tests of these findings showed that the two groups of subjects did not differ at Time 1 but were reliably different at Time 2, $p < .01$. There was no overall effect of groups ($F(1,10) = 4.79$; $.10 > p > .05$). These MMSE scores are summarized in Table 1.

AD patients generated fewer responses than elderly controls in response to the closed categories of fruits and vegetables, an overall group effect ($F(1,10) = 12.13$; $p < .01$). AD patients generated fewer closed category exemplars than elderly normal controls at Time 1 ($F(1,10) = 9.11$; $p > .1$) as well as at Time 2 ($F(1,10) = 12.07$; $p < .01$). The analysis of the categorical responses, using a 3-factor ANOVA, demonstrated a statistically significant triple interaction: groups, time of testing, and type of response (H, M, or L), ($F(2,10) = 5.34$; $p < .05$). Post hoc simple effects demonstrated the following pattern differences between AD and normal control subjects. At Time 1, AD patients generated fewer closed category moderate ($t(1,10) = 3.0$; $p < .05$) and uncommon exemplars ($t(1,10) = 3.0$; $p < .05$) than normal controls. However, the two groups were not different in terms of the number of generated common names of fruits and vegetables. At Time 2, AD patients generated fewer common ($t(1,10) = 2.47$; $p < .05$), moderate ($t(1,10) = 2.54$; $p < .05$), and uncommon responses ($t(1,10) = 2.57$; $p < .05$) than elderly normal controls. These findings are displayed in Figure 1.

The 2-factor ANOVA of the number of open category exemplars generated by AD and elderly normal controls demonstrated an overall group effect ($F(1,10) = 8.09$; $p < .05$) and a significant groups × time effect ($F(1,10) = 16.76$; $p < .01$). The two groups of subjects were not different at Time 1 ($F(1,10) = 2.40$; $p < .01$). However, at Time 2, AD patients generated fewer responses starting with the letters F, A, and S than did elderly normal controls ($F(1,10) = 14.97$; $p < .01$). A 3-factor ANOVA demonstrated that at Time 1, the AD patients were not different from controls in the number of generated common, moderate, or uncommon category responses. However, at Time 2, the AD patients generated fewer moderate ($t(1,10) = 5.63$; $p < .01$) and uncommon words ($t(1,10) = 3.85$; $p < .01$) but not common responses ($t(1,10) = 1.37$; $p > 05$) when compared to controls. These findings are displayed in Figure 2.

Table 1. Mini-Mental Scores of Elderly Controls and Subjects Who at a Later Point in Time Are Identified as Probable Alzheimer's Disease Patients but Before and After the Presumed Onset of the Disease

	Time of Testing	
Alzheimer's disease patients	Time 1	Time 2
Subjects (identified by number)		
Patient 1	28	27
Patient 2	27	23
Patient 3	27	22
Patient 4	27	22
Patient 5	26	24
Patient 6	17	9
Mean Mini-Mental score	25.17	21.17
Standard deviation	4.07	6.24
Elderly normal controls		
Normal control 1	26	28
Normal control 2	30	29
Normal control 3	30	28
Normal control 4	25	26
Normal control 5	29	30
Normal control 6	28	27
Mean Mini-Mental score	28.00	28.00
Standard deviation	2.10	1.41

These ANOVAs were repeated with one of the AD patients omitted, subject 6, who had a relatively low MMSE score at Time 1. The conclusions from this analysis of results were the same as those that were based on an analysis of the data based on all subjects studied. In addition, we performed a non-parametric analysis of these data (using a Mann-Whitney U-Test). These tests, which make no assumptions about the underlying normality of the distribution of scores, replicated the pattern of statistically significant results that are obtained in the parametric tests.

Discussion

The findings from this study suggest that changes in semantic memory are apparent in AD patients before they manifest other clinically relevant symptoms that are used to establish the diagnosis of AD. These changes in semantic memory are reflected in an inability to generate exemplars of categories of closed categories of information and, later, with the

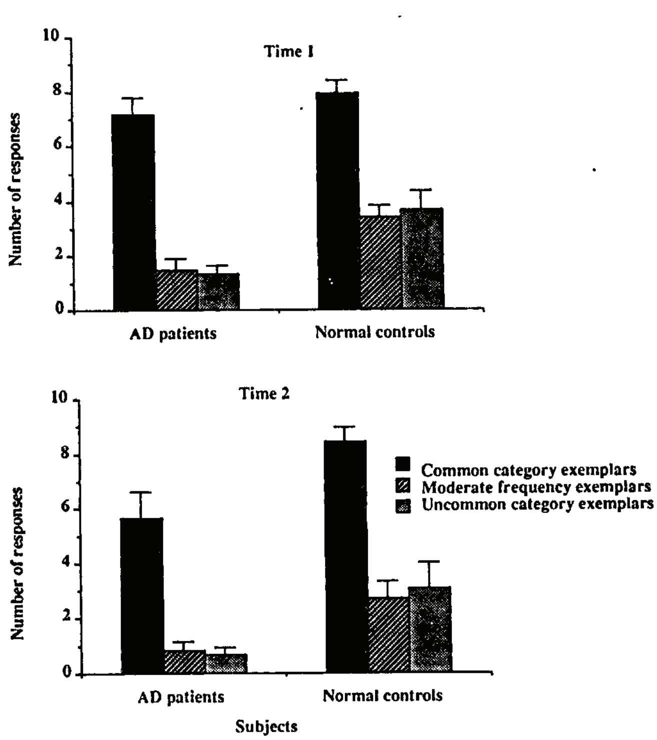

Figure 1. Number of exemplars belonging to closed categories of information (fruits and vegetables) in Alzheimer's disease (AD) patients and normal controls (before and after the onset of AD). The findings displayed in the figure are the mean number of responses for each group for each category.

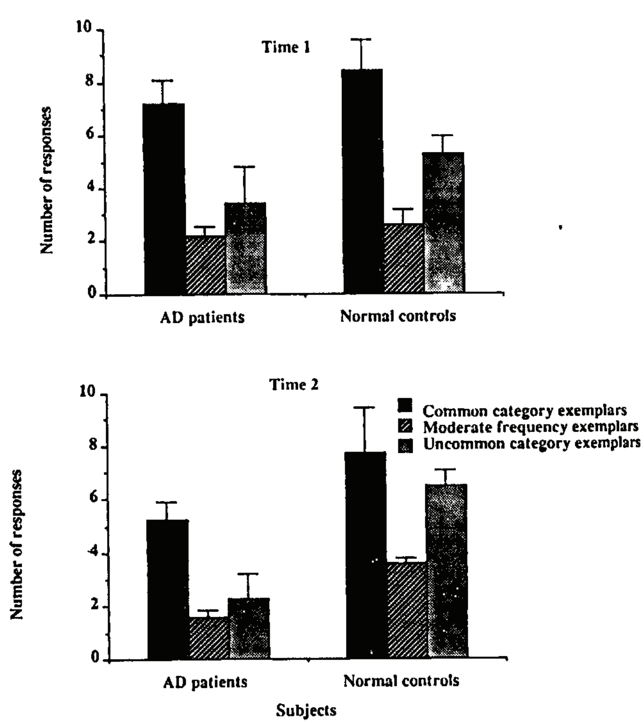

Figure 2. Number of exemplars belonging to open categories (letters) of information in Alzheimer's disease (AD) patients and normal controls (before and after the onset of AD). The findings displayed in the figure are the mean number of responses for each group for each category.

progression of the disease, are also reflected in more general and profound impairments in semantic memory as expressed in the inability to generate exemplars to open categories of knowledge. These changes in semantic memory that are apparent early in the course of AD may be more apparent in the generation of uncommon category exemplars rather than more common categorical responses. The selectivity of these early AD semantic memory changes requires further study, with larger numbers of subjects tested and alternative methods for categorizing responses in terms of frequency of occurrence and strength of relationship to category labels.

It should be noted that we would assume that the onset of AD is gradual, and not abrupt, and that the symptoms and expression of AD change over time. Furthermore, the cognitive changes that do appear in AD both when the disease first is detectable and in the progression of the disease can be rather variable. For example, in some patients the progression of cognitive symptoms is more apparent on visual spatial tasks with relative sparing of linguistically based functions. It may also be the case that some of the subtle differences in the expression of cognitive deficits such as the progressive erosion of semantic functions can also be attributable to the premorbid status of patients, including their educational achievement. This factor may be one of the reasons why Ober et al. (1986) obtained somewhat different results from those described here with respect to the selective effects of AD on low frequency exemplars. Clearly a much larger sample of normal controls as well as early AD patients must be studied before the findings that are presented here become useful in identifying early stage AD patients.

Impairments in many mental functions, in addition to changes in recent memory, are readily apparent with the progression of Alzheimer's disease. For example, unlike memory-impaired amnestic patients, AD patients demonstrate impairments in the availability and accessibility of information that is part of a knowledge base in long-term memory (Albert & Milberg, 1989; Hart, Smith, & Swash, 1988; Huff, Corkin, & Growden, 1986; Martin, 1987; Martin et al., 1985; Weingartner, Grafman, Boutelle, Kaye, & Martin, 1983), and this is expressed in aphasia-like symptoms as well as apraxias and agnosias. It is, however, unclear at what stage in AD it is possible to identify impairments in knowledge memory in general and semantic memory functions in particular and whether some of these changes may be responsible for the more obvious changes in recent memory functions in AD. Some of the findings recently obtained from ongoing studies in our laboratory also highlight some of the distinctive roles of impaired semantic memory functions in amnesia and dementia. It should be noted, however, that it is also possible that some of the impairments in both episodic and semantic memory functions may be secondary to disruptions in other information processing functions that are used in carrying out operations that are important in remembering recent events or previously acquired knowledge (Nebes, 1992).

Using the semantic memory assessment methods described here we have recently begun to compare the explicit semantic memory functions of 6 more impaired AD patients with Wechsler Memory Scale (WMS) scores of 68.5 ± 18 and with elderly normal controls whose WMS is well within normal range (124.9 ± 15). We have tested the same subjects five times, over the course of several days, using the same stimuli. We found the same reliable pattern of differences in the production of category exemplars but in an exaggerated form, as those seen in the early-stage AD patients described in this study. That is, AD patients were highly discriminable from normal controls in terms of the total number of category exemplars that they could generate in 60 seconds ($F(1,12) = 37.5$; $p < .00001$) and this effect is most pronounced for low and medium strength categories. Furthermore, the ability of AD patients to access semantic knowledge from closed categories of information does not change even after they have had a chance to practice this procedure several times.

In contrast, amnestic conditions are not associated with impaired semantic memory. For example, in another recently completed study we observed that benzodiazepines, such as triazolam administered at doses of .250, .375 and .500 mg, induced dose-dependent change in recent memory without impairing access to knowledge memory. Triazolam, administered orally in doses of .5 mg to 15 young healthy normal volunteers, induced a 78% decrease in free recall without altering either the number of responses nor the qualitative features of the responses they generated to letters as well as closed categories of information. They generated the same number and pattern of low, medium, and high probability responses to letters $F(4,32) = .28$; $p > .05$) and to closed categories of information, including the fruit ($F(4,32) = .32$; $p > .05$) (Weingartner, Adams, Eckardt, George, Joyce, & Lister, in press). This same pattern of data has also been seen in another study using anagram solutions as a means of assessing changes in semantic memory functions in response to triazolam treatment in normal volunteers (Weingartner, Hommer, Lister, Thompson, & Wolkowitz, 1992). In this study benzodiazepine induced a robust, dose-dependent impairment in explicit memory without disrupting free recall of, but did not alter the ability to solve, anagrams. These studies demonstrate that benzodiazepines model the type of memory function that is apparent in amnesia but not the features of the memory impairment seen in AD, where changes in semantic memory functions are associated with the recent memory changes seen in these patients (Lister & Weingartner, 1987). In contrast, elderly normal controls treated with a cholinergic antagonist, such as scopolamine, demonstrate cognitive changes that simulate a dementia of an Alzheimer's type rather than an amnestic-like disorder. Following treatment with scopolamine, recent memory impairments are associated with impairments in accessing semantic memory as evidenced by decreased ability to generate exemplars of closed categories of information. These findings are described in Weingartner (1985); Sunderland, Tariot, Weingartner, Murphy, Newhouse, & Cohen (1986); and Molchin et al. (1992).

There are a number of models of how semantic network models are organized (Chang, 1986). In general, these models have been used to ascribe the failure in semantic memory in AD as resulting from impairments in memory for information about either a specific item within a category of information, e.g., broccoli as a type of vegetable, or a feature of some element that is part of a larger structure, such as knowing that broccoli grows like cauliflower, has a similar type of leaf, and is in the same family. The loss of an entire category of knowledge is not likely to be apparent in these patients. For example, when AD patients make naming errors their responses are generally related to the to-be-named object (Bayles, 1983; Huff, Corkin, & Growden, 1986; Martin, 1983). Early- and middle-stage AD patients demonstrate intact semantic memory when these functions are tested implicitly, e.g., using semantic priming tasks, they nevertheless also express impairments in explicit semantic memory processes (Weingartner et al., 1983; Martin, 1983; Kertesz, 1986). The interpretation of this pattern of implicit, in contrast to explicit, impairments in semantic memory, particularly in relationship to the other memory functions, remains to be defined (Grober, Buschke, Kawas, & Fuld, 1985; Huff et al., 1986; Nebes, 1989). Instead, the erosion of knowledge memory appears to be "bottom up," with the elements and associations that are the least tightly bound to other elements within some structure being the ones that are "lost" first.

In conclusion, the findings from this study suggest that changes in semantic memory are apparent in AD patients very early in the course of their disease, and, as such, may be useful as an early diagnostic sign of AD which is more specific than changes in recent memory. These changes in semantic memory may be apparent before other symptoms are expressed that are necessary for establishing the diagnosis of probable AD and become more obvious as the disease progresses. Likewise, these changes in semantic memory are not apparent in many other conditions in which impaired memory is a cardinal symptom, such as in amnestic disorders. These changes in semantic memory appear to be systematic and orderly. That is, AD patients appear to first be unable to generate infrequent low probability items that belong to categories of knowledge and only later "lose" the more common and obvious elements that make up networks of knowledge. Furthermore, these changes in semantic memory are not attributable to an ability to generate appropriate word responses in a controlled manner as in tests of verbal fluency, since AD patients are just as productive on a fluency task that tests their ability to generate words starting with some letter. At the same time, they appear to be unable to generate exemplars of closed categories of information (Butters, Granholm, Salmon, Grant, & Wolfe, 1987). These changes in semantic memory appear to be attributable to a loss of stored information rather than a failure to retrieve available information (Hodges, Salmon, & Butters, 1992). The fact that semantic memory functions are often spared in many other neuropsychiatric disorders is also important if this specific change in cognitive functioning should prove useful in the early diagnosis of AD. These early cognitive symptoms of AD patients would appear to be associated with changes in the neocortex (association cortex) which may precede or parallel the neuropathology associated with the hippocampus and other structures associated with the medial temporal lobes. Damage that is limited to these structures typically is associated with deficits in explicit recent memory but not impairments in knowledge memory.

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