The Deterioration of Semantic Memory in Alzheimer's Disease

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Abstract Semantic memory impairment is a common feature of dementia of the Alzheimer type (DAT). Recent research has shown that patients with DAT are more impaired (relative to non-demented controls) in generating exemplars from a particular semantic category (e.g., animals) than words beginning with a particular letter, exhibit an altered temporal dynamic during the production of category exemplars, are impaired on confrontation naming tasks and make predominantly superordinate or semantically related errors, consistently misidentify the same objects across a variety of semantic tasks, and have alterations in multidimensional scaling models of their semantic network that are indicative of a loss of concepts and associations. These results are consistent with the view that Alzheimer's disease results in a breakdown in the organization and structure of semantic knowledge as neurodegeneration spreads to the association cortices that presumably store semantic representations.

Current studies of the cognitive deterioration that occurs in degenerative cortical diseases such as Alzheimer's disease reflect the influence of neuropsychological theories which presume a physiological basis for the representation of knowledge. As Hebb (1949) proposed in his influential theory, the acquisition and retention of knowledge may occur through anatomical changes in the association cortices that come about as the result of persisting activation of a specific group of cells comprising a reverberatory circuit or "cell assembly." The anatomical change, according to Hebb (1949) and others (Eccles, 1953), occurs at the level of the synapse. It follows that a degenerative process that results in synaptic loss would interfere with the representation of knowledge, and indeed, recent studies have demonstrated a strong relationship between cognitive deterioration and synapse loss in the association cortices of patients with Alzheimer's disease (Terry, Masliah, Salmon, Butters, DeTeresa, Hill, Hansen, & Katzman, 1991). Given these results, the relationship between synapse loss (or other neurodegenerative changes) in the association cortices of these patients, and deficits in the more specific cognitive abilities discussed below is the subject of current research.

Alzheimer's disease is a degenerative brain disorder characterized by neocortical atrophy, neuron and synapse loss (Terry, Peck, DeTeresa, Schecter, & Horoupian, 1981; Terry et al., 1991), and the presence of senile plaques and neurofibrillary tangles (Terry & Katzman, 1983) primarily in the hippocampus and entorhinal cortex, and in the association cortices of the frontal, temporal and parietal lobes (Hyman, Van Hoesen, Damasio, & Barnes, 1984; Terry & Katzman, 1983). Although the temporal progression of the neuropathological changes of AD are not fully known, recent studies suggest that the hippocampus and entorhinal cortex are involved in the earliest stage of the disease, and that frontal, temporal and parietal association cortices become increasingly involved as the disease progresses (Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992; Bancher, Braak, Fischer, & Jellinger, 1993; Braak & Braak, 1991; DeLacosta & White, 1993; Hyman et al., 1984; Pearson, Esiri, Hiorns, Wilcock, & Powell, 1985). In addition to these cortical changes, subcortical neuron loss occurs in the nucleus basalis of Meynert and often in the nucleus locus coeruleus, resulting in a decrement in neocortical levels of cholinergic and noradrenergic markers, respectively (Bondareff, Mountjoy, & Roth, 1982; Mann, Yates, & Marcyniuk, 1984; Whitehouse, Price, Struble, Clark, Coyle, & DeLong, 1982).

Alzheimer's disease results in a dementia syndrome typified by global intellectual decline with specific deficits in learning and memory, language, attention, "executive" functions and visuospatial abilities (Corkin, Davis, Growdon, Usdin, & Wurtman, 1982; Moss & Albert, 1988). While an inability to learn and retain new information (i.e., an episodic memory deficit) is usually the earliest and most prominent feature of dementia of the Alzheimer type (DAT; Bondi, Salmon, & Butters, 1994; Welsh, Butters, Hughes, Mohs, & Heyman, 1992), an impaired ability to recollect or retrieve previously acquired knowledge from a long-standing store (i.e., a semantic memory deficit) also occurs as the disease progresses. The episodic memory deficit associated

with DAT has been extensively studied and is invariably attributed to the damage that occurs to the hippocampus and related structures early in the course of the disease (Bondi et al., 1994; Delis, Massman, Butters, Salmon, Kramer, & Cermak, 1991; Hyman et al., 1984). The semantic memory deficit that occurs in DAT, in contrast, has only recently become the focus of intensive investigation and the nature of the deficit and its neurological basis remains controversial (Hart, 1988; Nebes, 1989).

In the present paper we will review a number of recent studies from our laboratory that have examined the semantic memory deficit in patients with DAT. These studies were conceived in the context of constructs and models developed in cognitive psychology. In this context, semantic memory refers to our general fund of knowledge which consists of the meanings and representations of words, concepts and overlearned facts that are not dependent upon contextual cues for their retrieval (Tulving, 1983). Models of semantic memory (e.g., Collins & Loftus, 1975) usually assume that semantic knowledge is organized as a complex network of associated concepts, and that within the network, concepts that have many attributes in common are more strongly associated than those that share fewer attributes. These strongly related concepts are thought to form conceptual categories made up of exemplars which share many attributes. The attributes not only provide a means of grouping concepts into categories, but also provide a means of distinguishing among the various exemplars that constitute a given category. Thus, car and truck are both categorized as vehicles because they share attributes such as being mobile, having wheels and providing transportation; however, they can be distinguished from each other by such attributes as size, shape and use.

Although some investigators propose that DAT patients suffer from a general impairment in retrieving or accessing knowledge from a relatively intact semantic store (Nebes & Brady, 1988; Nebes, Brady, & Huff, 1989; Nebes, Martin, & Horn, 1984), others suggest that there is a breakdown in the organization and structure of semantic knowledge, and that knowledge concerning specific concepts and their attributes is actually lost during the course of the disease as a result of the degradation of the neocortical association areas that are presumed to store these representations (Butters, Salmon, & Heindel, 1990; Grober, Buschke, Kawas, & Fuld, 1985; Martin, 1987; Smith, Murdoch, & Chenery, 1989). Loss of semantic knowledge results in concepts becoming less well defined as their distinguishing attributes are eliminated, and in a weakening of the formerly strong associations between related concepts in the semantic network. Our studies, which are reviewed below, tend to support this latter view.

Some of the earliest and most important evidence supporting the view that DAT patients suffer a breakdown in the organization of semantic memory emanates from studies examining their performance on various tests of verbal fluency. Butters and his colleagues (Butters, Granholm, Salmon, Grant, & Wolfe, 1987), for example, compared the performance of DAT patients and patients with Huntington's disease (HD), another dementing neurological disorder that results from degeneration of subcortical brain structures in the striatum (particularly the caudate nucleus), on verbal fluency tasks that differ in the demands they place on semantic memory. In the letter fluency task used in this study, subjects orally generated words beginning with the letters F, A, and S, with one minute allowed per category. In the category fluency task, subjects generated exemplars from the semantic category "animals" for one minute. The letter fluency task does not place great demands on the organization of semantic memory since it can be performed using phonemic cues to search a very extensive set of appropriate exemplars within the lexicon. In contrast, the category fluency task requires the generation of words from a small and highly related set of exemplars within a single abstract semantic category.

Although the DAT and HD patient groups were matched for overall severity of dementia with the Dementia Rating Scale (DRS) (Mattis, 1976), the two groups produced different patterns of performance on the two fluency tasks. Patients with HD demonstrated severe deficits (relative to normal control subjects, NC) on both fluency tasks, whereas the mildly demented Alzheimer's disease patients were impaired *only* on the semantically demanding category fluency task. In a subsequent study that attempted to verify the findings from the study by Butters et al. (1987) with a larger group of subjects, Monsch and colleagues (Monsch, Bondi, Butters, Paulsen, Salmon, Brugger, & Swenson, 1994) administered the letter and category fluency tasks described above (however, in this case three semantic categories were sampled: animals, fruits and vegetables) to 44 patients with DAT and 42 HD patients matched for overall level of dementia. When the performances of the two patient groups were expressed as fluency scores normalized to their respective normal control group scores, HD patients were severely and equally impaired on both letter and category fluency tasks. Patients with DAT were also clearly impaired on both tasks, but demonstrated a much greater impairment on the semantically based category fluency task than on the letter fluency task.

The DAT patients' greater impairment on category than on letter fluency tasks demonstrated in these studies is consistent with the notion that they suffer a loss or breakdown in the organization of semantic memory rather than from a general inability to retrieve or access semantic knowledge. While normal control subjects are able to use the organization within a restricted semantic category to guide their responses on the category fluency task, patients with DAT appear to be deficient in their knowledge of the attributes and/or exemplars that define the relevant semantic category and are thus unable to use this knowledge to

locate specific category exemplars. When semantic organization is less salient or useful in the fluency task, as in the letter fluency task, DAT patients show less impairment relative to control subjects. In contrast to DAT patients, the equally impaired performance of HD patients on letter and category fluency tasks is consistent with an inability to effectively retrieve information from semantic memory rather than with a specific loss of semantic knowledge or organization.

The deficiency in DAT patients' knowledge of the attributes and exemplars that define a specific semantic category is more explicitly provided by an examination of the types of responses they produce on category fluency tasks (Martin & Fedio, 1983; Troster, Salmon, McCullough, & Butters, 1989). In a study directed toward this goal, Troster and his colleagues (1989) required DAT, HD and NC subjects to generate items that can be found in a supermarket as quickly as possible for one minute and then classified their responses as either specific category items (e.g., hamburger, asparagus) or more general category labels (e.g., meat, vegetables). These investigators found that moderately demented DAT patients produced fewer exemplars per category sampled than NC subjects and HD patients (who had equivalent word generation deficits), and had a greater propensity to produce general category labels than did either of the other subject groups. These results suggest that DAT patients suffer an initial loss of subordinate knowledge about the most specific attributes of a semantic category, with relative preservation of more general superordinate knowledge. Martin (1987) has proposed that the semantic representations of objects and categories can be viewed as being organized in a hierarchical fashion with the most general (i.e., superordinate) aspects at the top and more specific (i.e., subordinate) features at the bottom. Within this framework, the DAT patients in the study by Troster et al. (1989) demonstrated a progressive "bottom-up" breakdown in the hierarchical organization of semantic knowledge.

Further evidence of a loss of semantic knowledge in patients with DAT was provided by a recent study that examined the temporal dynamics of retrieval from semantic memory during verbal fluency tasks (Rohrer, Wixted, Salmon, & Butters, 1995). This study employed a mathematical model of the exponential decline in retrieval from semantic memory as a function of time. The model assumed that the retrieval cue provided during the fluency task (e.g., farm animals) delimits a mental search set that contains the relevant exemplars (e.g., cow, horse, pig, and so forth). According to well-known, random-search models (McGill, 1963), the exemplars are randomly sampled one at a time, at a constant rate, and each item has the same probability of being sampled. Each sampled exemplar is recognized as either a not-yet-sampled item (and reported) or as a previously sampled item (and not reported). As the number of not-yet-sampled items decreases, the number of items

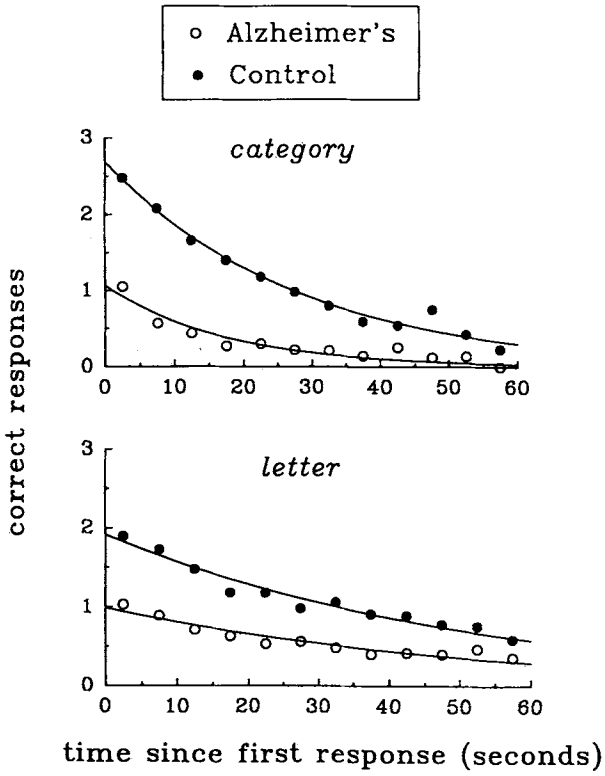

Figure 1. The mean number of items recalled in various category and letter fluency tasks plotted as a function of time since first response. In the category condition, but not in the letter condition, the total mean latency to produce exemplars was faster for patients with Alzheimer's disease than for control subjects, consistent with the view that Alzheimer's disease causes the loss of inter-item associations within semantic memory. (Adapted from Rohrer, Wixted, Salmon, & Butters, 1995.)

retrieved correspondingly declines throughout the recall period producing the exponential function.

Within these parameters, a variable used in the model, mean latency for a retrieved item, is mathematically related to both the breadth of the search and the speed of processing. Mean response latency is the average of the time intervals between production of each response and the onset of the recall period (*not* the time since the previous response). The average time needed to retrieve the items within the search set increases when either the size of the search set increases or the duration of each sampling increases. When applied to the verbal fluency task performance of DAT patients, the measure of mean latency provides a direct test of the two proposed mechanisms of semantic memory deficits in these patients. If the set size for a particular semantic category is reduced in DAT patients due to loss of semantic knowledge, mean latency should *decrease* and be lower than normal. If, on the other hand, the semantic set remains intact but retrieval is slowed, mean latency should *increase* and be higher than normal.

Rohrer and his colleagues examined the response latencies of DAT and NC subjects during both category and letter

fluency tasks. Although DAT patients were slower to begin responding than NC subjects on both types of verbal fluency task, their mean response latency was significantly lower than that of the NC subjects on the semantic category fluency tasks, but not on the letter fluency tasks. These results are consistent with the view that DAT patients suffer a true loss of semantic knowledge. Interestingly, a subsequent study by these investigators demonstrated that the mean response latency of patients with HD was significantly higher than that of NC subjects on a semantic fluency task (Rohrer, Salmon, Wixted, & Paulsen, in press) consistent with the notion that these patients suffer from a general retrieval deficit.

Over the past decade, numerous studies have shown that DAT patients are much more likely than normal elderly individuals, or patients with other dementing disorders, to perform poorly on object naming tasks (Bayles & Tomoeda, 1983; Bowles, Obler, & Albert, 1987; Hart, 1988; Hodges, Salmon, & Butters, 1991; Huff, Corkin & Growdon, 1986; Martin & Fedio, 1983; Smith et al., 1989). Furthermore, the types of errors they produce on these tasks are indicative of a loss of semantic knowledge and a breakdown in the organization of semantic memory (Bayles & Tomoeda, 1983; Hodges et al., 1991). An example of this phenomenon was provided in a study from our laboratory by Hodges and colleagues (Hodges et al., 1991). They classified the errors produced by DAT and HD patients on a modified version of the Boston Naming Test as non-responses, visually based errors (e.g., calling a pretzel a snake), and semantically based errors. Semantically based errors included producing the name of another item in the category (e.g., broccoli for asparagus), producing the superordinate category rather than the specific exemplar (e.g., animal for rhinoceros), providing an associated feature rather than the name (e.g., found in Egypt for pyramid) and circumlocutory errors. Several additional types of non-semantic and non-perceptual errors were also noted (e.g., repetitions, phonemic errors).

Hodges et al. found that although the DAT and HD patient groups were matched in terms of their overall naming performance to avoid biasing the error analysis, the groups' performances differed qualitatively. Whereas HD patients produced a significantly greater proportion of visually based errors than did patients with DAT, patients with DAT made a significantly greater proportion of semantic-superordinate errors than did HD patients. These results suggest that the naming deficit of patients with HD initially involves a significant disruption of perceptual analysis of the stimulus. In contrast, the DAT patients' naming impairment appears to be due, to a large extent, to a breakdown in semantic processes. More specifically, the propensity of DAT patients to produce semantic-superordinate errors is consistent with the notion that they suffer a bottom-up breakdown in the organization of their semantic knowledge. Even though they have lost knowledge about the specific attributes and exemplars that constitute a given semantic category, they retain general category knowledge. Thus, when shown a rhinoceros and asked to name it, they are likely to respond with the superordinate category name "animal."

Although our studies of the qualitative features of DAT patients' performance on verbal fluency and object naming tasks provides strong evidence that these patients suffer a loss of semantic knowledge rather than a general deficit in retrieving information from an intact semantic memory store, the evidence is primarily indirect. Warrington and Shallice (Shallice, 1988a; 1988b; Warrington & Shallice, 1984) have proposed that to clearly distinguish semantic knowledge loss from an impaired ability to retrieve semantic information, the following criteria should be met. First, a patient should demonstrate consistent failure in accessing a particular item across different tests and test sessions. Second, a patient should derive no benefit from semantic cueing in accessing the item. Third, a patient should demonstrate a loss of detailed knowledge, but relatively preserved superordinate knowledge, about the item.

With the criteria of Warrington and Shallice in mind, Hodges and colleagues (Hodges, Salmon, & Butters, 1992) examined semantic memory in a group of DAT patients using a battery of tests designed to probe for semantic knowledge for a particular item across different modes of access and output. The various tests in the battery all employed the same 48 stimulus items which were exemplars from three categories of living items (i.e., land animals, birds and water creatures) and three categories of non-living items (i.e., household items, vehicles and musical instruments). Knowledge of the items was assessed with fluency tasks, a confrontation naming task, a sorting task designed to test superordinate and subordinate knowledge, a word-to-picture matching task, and a definition task.

The results of this study were consistent with those of a similar study by Chertkow and Bub (1990) and showed that DAT patients were significantly impaired relative to NC subjects on all measures of semantic memory, regardless of method of access. An analysis of item-to-item correspondence in performance across a number of the different tests used in the study indicated that when a particular stimulus item was missed (or correctly identified) in one test, it was likely to be missed (or correctly identified) in other tests that accessed the information in a different way. When comparing naming ability to performance on the other semantic memory tasks, for example, DAT patients were able to name about 78% of the items that they correctly matched on the word-to-picture matching task, but only named about 23% of the items they could not correctly match. Similarly, about 77% of the items correctly sorted could also be named, while only about 58% of incorrectly sorted items were named. The same pattern was also seen with the definition task, with about 59% of correctly defined items

named and only 10% of non-defined items named. The correspondence in items missed by DAT patients across tasks designed to access semantic knowledge through different modes of input and output (and with different levels of cueing) satisfies the first two criteria set forth by Warrington and Shallice for evidence of true semantic memory loss.

Evidence that DAT patients exhibit a loss of detailed knowledge, but relatively preserved superordinate knowledge, about items was also provided in the Hodges et al. (1992) study, and is best illustrated in the results of the semantic sorting task. In this task, subjects first sorted the 48 stimuli into the global categories of living versus man-made, then sorted living items and man-made items into three superordinate categories each (e.g., land animal vs. sea creature vs. bird), and finally sorted the stimuli on the basis of subordinate attributes (e.g., locality, size and fierceness). At the global level, knowledge about whether an item was living or man-made was preserved in DAT patients. At the superordinate level (e.g., land animal vs. sea creature vs. bird), DAT patients were impaired overall relative to NC subjects, but the impairment was relatively mild and evident in only certain categories. At the subordinate level, DAT patients were severely impaired when they had to sort items on the basis of their specific attributes. This pattern of relatively preserved superordinate knowledge with a loss of subordinate information satisfies Warrington and Shallice's third and final criterion for a true loss of semantic knowledge and is consistent with the "bottom-up" breakdown in semantic memory described earlier.

To further explore the deterioration of semantic memory in patients with DAT, we have recently conducted a series of studies using multidimensional scaling techniques (Romney, Shepard, & Nerlove, 1972; Shepard, Romney, & Nerlove, 1972) to model the organization of their semantic knowledge. Multidimensional scaling provides a method for generating a spatial representation of the degree of association between concepts in semantic memory. The spatial representation, or cognitive map, generated in this manner clusters concepts along one or more dimensions according to their proximity, or degree of relatedness, in the patient's semantic network. The distance between concepts in the cognitive map reflects the strength of their association. Our studies have sought to determine how the organization of semantic knowledge in mildly demented DAT patients differs from that of normal individuals and patients with other dementing disorders (e.g., HD), and how the organization of their semantic knowledge changes over time as cortical deterioration and dementia severity increases.

The first study in this series compared the organization of semantic knowledge for the category "animals" in DAT, HD and normal control subjects (Chan, Butters, Paulsen, Salmon, Swenson, & Maloney, 1993a). Proximity scores that could be subjected to multidimensional scaling and cluster analyses were estimated for each subject from the pattern of

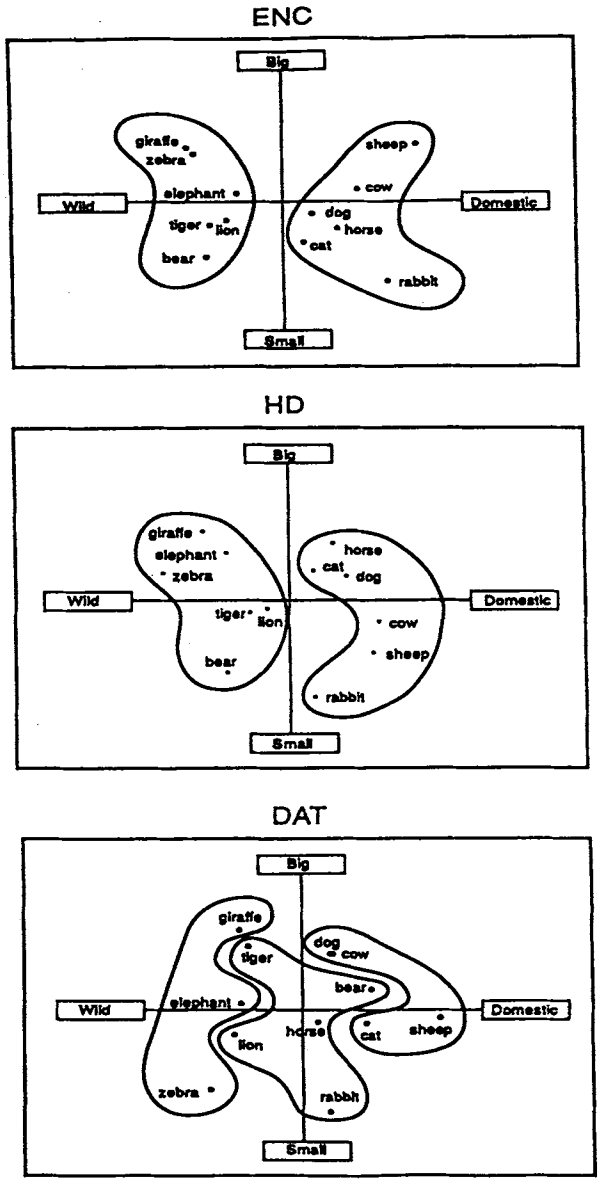

Figure 2. The cognitive maps of elderly normal control (ENC) subjects, patients with Huntington's disease (HD), and patients with dementia of the Alzheimer type (DAT) obtained from multidimensional scaling and clustering analyses performed on data from a verbal fluency task. The position of each animal name is determined by multidimensional scaling; animals in the same cluster are encircled together. (Adapted from Chan, Butters, Paulsen, Salmon, Swenson, & Maloney, 1993.)

responses they produced on a category fluency task in which they generated names of animals for one minute. It was assumed that through spreading activation within the semantic network (Collins & Loftus, 1975; Meyer & Schvaneveldt, 1975), animals that are highly associated would tend to be produced closer together within a subject's sequential responses on the fluency task than animals that are not highly associated. Thus, the number of items that intervene between two target words, corrected for the total number of words produced, provides an estimate of the

semantic proximity of the target words. Twelve target animal names were selected to be used in the analyses because they were among the 25 most frequent responses of DAT, HD and NC subjects during the fluency task, and they could be clearly categorized within domestic-wild, carnivore-herbivore, and small-large dimensions.

While the cognitive maps generated by the multidimensional scaling procedure for all three subject groups were best represented by two dimensions, domesticity and size, the classification of individual exemplars within the map of the DAT patients differed considerably from that of the NC subjects. For example, in the cognitive map of DAT patients, but not NC subjects, *bear* appeared in the space representing domestic animals, *zebra* appeared in the space representing small animals, and *dog* was categorized as more representative of a large animal than elephant. Differences in the results of the cluster analyses also were evident with two global clusters representing wild and domestic animals produced for the NC subjects, and three essentially uninterpretable clusters derived for the DAT patients.

In contrast to those of the DAT patients, the HD patients' cognitive maps and clusters of animal names were virtually identical to those of the NC subjects, even though these subjects produced as few exemplars in the fluency task as the DAT subjects. As mentioned earlier, the poor fluency performance of HD patients is presumed to be due to a general retrieval deficit rather than to a breakdown in the organization of semantic memory. The normal cognitive maps of these subjects is consistent with this notion and provides some evidence that the abnormal cognitive maps of the DAT patients are not likely to be an artifact of poor fluency performance per se, but are likely to be indicative of a true breakdown in the structure of semantic memory.

A second study in this series (Chan, Butters, Salmon, & McGuire, 1993b) examined the organization of semantic knowledge for the category "animals" in DAT patients using a more systematic procedure to estimate the relative strength of semantic associations. The strength of association between concepts, or their proximity, was estimated using a triadic comparison task in which subjects chose, from among three concepts (i.e., among three animals), the two that are most alike. Every possible combination of three animal names, from a total sample of twelve animals, was presented. This procedure produced a proximity score reflecting strength of association for each pair of animals in relation to all of the other animal names; that is, how frequently those two animals were chosen as most alike. This systematic determination of relative associative strength not only allows a cognitive map to be generated with multidimensional scaling, but also allows the saliency of a particular dimension for categorizing concepts to be determined, and permits an examination of individual differences in the semantic networks of subjects.

When the proximity data produced on the triadic comparison task were subjected to the multidimensional scaling procedure, a three-dimensional solution provided the best spatial representation of the semantic network of both DAT and NC subjects. The three dimensions appeared to correspond to domesticity (i.e., wild vs. domestic), predation (herbivore vs. carnivore) and size (large vs. small). In addition to the cognitive map, this analysis provided the strength of the various dimensions for categorizing concepts (dimension weights), and the subjects' degree of reliance on one or more of the dimensions (skewness index). These measures, and an examination of the cognitive map itself, demonstrated several significant alterations in the semantic network of the DAT patients.

First, DAT patients focused primarily on concrete conceptual information (*size*) in categorizing animals, whereas control subjects stressed abstract conceptual knowledge (*domesticity*). Second, a number of animals that were highly associated and clustered together for control subjects were not strongly associated for patients with DAT. For example, DAT patients tended to cluster cat with small wild carnivores, whereas, control subjects clustered cat with small domestic carnivores. Third, patients with DAT were less consistent than NC subjects in utilizing the various attributes of the animals (*predation*, *domesticity* and *size*) in categorization as indicated by a significantly lower skewness index for the patients than for the controls.

In contrast to the patients with DAT, the cognitive maps generated for HD patients using these same triadic comparison and multidimensional scaling techniques were almost identical to those of their age-matched control subjects (Chan, Butters, Salmon, Johnson, Paulsen, & Swenson, 1995a). Although the semantic networks of these two subject groups were best represented by only two dimensions, domesticity was the most salient dimension for categorizing animals in both cases, and the groups did not differ in the importance they applied to the various dimensions or in their reliance on a particular dimension for categorization.

Taken together, the results from these three initial multidimensional scaling studies are consistent with the notion that patients with DAT suffer a breakdown in the structure and organization of semantic memory. The cognitive map representing the semantic network of DAT patients is characterized by abnormal clusters of concepts, and the deterioration in the associations between formally highly related concepts forces these patients to rely heavily on a concrete perceptual dimension (i.e., size) in categorizing animals rather than on the more semantically demanding abstract conceptual dimension (i.e., domesticity) used by NC subjects. Furthermore, the performance of HD patients in these studies shows that it is unlikely that the alterations in the DAT patients' semantic networks are due to a deficit in retrieving information from semantic memory. Although evidence indicates that HD patients have a general retrieval

deficit and perform as poorly as DAT patients on verbal fluency tasks, the cognitive maps of these patients are normal in all qualitative and quantitative aspects.

Recent evidence suggests that the abnormalities observed in the cognitive maps of patients with DAT become increasingly more pronounced as the disease progresses. In a cross-sectional study, Chan, Butters, and Salmon (1997) examined the relationship between severity of dementia and the degree of deterioration of DAT patients' semantic networks. Cognitive maps for the category "animals" were derived separately for mildly, moderately, and severely demented DAT patients using the triadic comparison and multidimensional scaling techniques previously employed by Chan et al. (1993b). While the cognitive maps of mild and moderate DAT patients, like those of NC subjects, were characterized by a primary dimension of domesticity, size was the primary dimension of the cognitive map of the severely demented patients. A regression analysis revealed that the weight indices of the domesticity dimension were significantly correlated with the DAT patients' scores on the Dementia Rating Scale (DRS), indicating that as the disease progresses these patients focus less and less on this abstract dimension when classifying animals. The DRS scores of the DAT patients were also significantly correlated with the degree of integrity of their cognitive maps as measured by the percentage of variance in each patient's proximity data that could be accounted for by a standard map generated for a group of normal control subjects.

The triadic comparison data from this study were also analyzed with the Pathfinder analysis technique (Dearholt & Schvaneveldt, 1990) in order to determine if the complexity of the DAT patients' semantic network changed with progressing dementia. The Pathfinder analysis is a scaling procedure designed to systematically construct a model of the semantic network that consists of nodes representing concepts and links representing the connections between concepts. It has been proposed that individuals who possess sufficient knowledge in a particular domain to evaluate the degree of association between concepts will develop a clear and concise network composed only of relevant connections. Individuals who never developed this degree of knowledge, or who have lost knowledge they once possessed, tend to organize concepts in a relatively chaotic way with many unnecessary adjunct connections. The Pathfinder analysis revealed that moderately and severely demented patients with DAT had more connections in their semantic network than NC subjects, and that the number of connections was significantly negatively correlated with DRS scores. Furthermore, the number of connections that were common in the semantic networks of DAT patients and NC subjects decreased across levels of dementia severity. Thus, both quantitative and qualitative features of the semantic network of DAT patients deteriorate as the disease progresses.

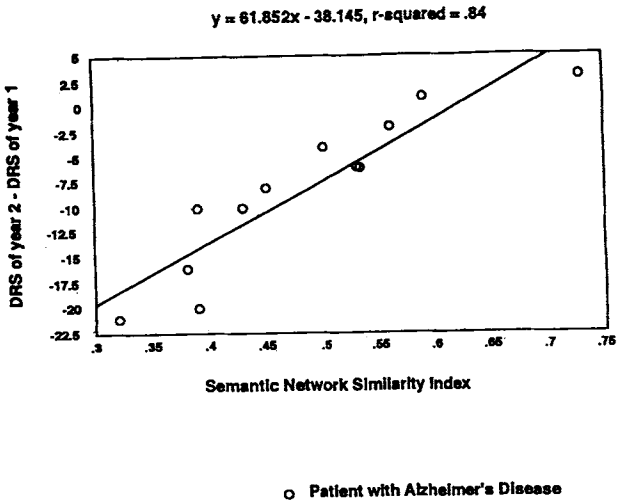

Figure 3. The semantic network similarity index of 12 AD patients plotted as a function of rate of cognitive decline as measured by the difference between the Dementia Rating Scale (DRS) scores obtained near the time of semantic knowledge testing (year 1) and approximately one year later (year 2). (Adapted from Chan, Salmon, Butters, & Johnson, 1995b.)

Chan and colleagues (Chan, Salmon, Butters, & Johnson, 1995b) also recently demonstrated that the degree of deterioration of the semantic network revealed by these multivariate measures can predict the subsequent rate of global cognitive decline in patients with DAT. The semantic network of individual DAT patients was generated by Pathfinder analysis of data from the triadic comparison task and compared to a standard network derived from the averaged data of age- and education-matched NC subjects. This comparison provided a Similarity Index which represents the degree of disruption of the organization of semantic memory for each DAT patient. The Similarity Index was highly correlated ($r^2 = .84$) with subsequent global cognitive decline as measured by changes over one year in the subjects' scores on the DRS.

The success of a measure of the abnormality of semantic networks in predicting the rate of cognitive decline in DAT patients may lie in the relationship between the disruption of semantic memory and cortical deterioration. As mentioned previously, theoretical frameworks view semantic memory as a systematically organized network of interrelated concepts and representations which are presumably stored in a distributed fashion in the association cortices. As the association cortices gradually deteriorate in patients with DAT, the structure and organization of semantic memory is disrupted, and language dysfunction becomes evident. Early evidence of semantic memory dysfunction may therefore serve as a marker for the integrity of the association cortices and indicate their susceptibility to further deterioration.

The studies of semantic memory in patients with DAT reviewed in this chapter provide strong evidence that there is a true loss of semantic knowledge in these patients, and

suggest that this loss occurs in a "bottom-up" fashion with specific knowledge lost before more general superordinate knowledge. The normal organization of semantic memory is disrupted by this loss of semantic knowledge and the semantic network appears to deteriorate as the disease progresses. Although the neuroanatomical basis of the deterioration of semantic memory in patients with DAT is currently unknown, it is likely that it results from synapse loss, neuron loss, and other neurodegenerative changes in the association cortices that presumably store semantic representations. The relationship between these neurodegenerative changes and semantic memory loss in patients with DAT is the focus of current research.

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Sommaire

La maladie d'Alzheimer est une maladie dégénérative du cerveau caractérisée par l'atrophie du néocortex, la perte neuronale, et celle des synapses dans la formation de l'hippocampe et dans les associations corticales du lobe frontal, temporal et pariétal. La maladie découle du syndrome de démence généralisée typique par les déficits d'apprentissage et de mémorisation, de langage, d'attention, d'accomplissement des fonctions de «commande», et par des pertes visuo-spatiales. Alors qu'une incapacité d'apprentissage de mémorisation de nouvelles informations (p. ex., une déficience de la mémoire épisodique) est habituellement la caractéristique la plus précoce et la plus éminente de la maladie d'Alzheimer, une dégradation de la capacité de se souvenir ou de retrouver des acquis antérieurs, de vieille date (p. ex., une déficience de la mémoire sémantique) peut aussi survenir au fur et à mesure que la maladie continue de progresser. Les deux hypothèses principales concernant la nature de la déficience de la mémoire sémantique dans un cas de maladie d'Alzheimer sont: (1) une dégradation générale pour retrouver ou pour accéder à des connaissances d'une mémoire sémantique relativement intacte, et (2) une dégradation dans l'organisation et la structure d'une connaissance sémantique tout comme la connaissance relative à des concepts spécifiques et à leurs attributs qui sont actuellement perdus pendant le cours de la maladie. La recherche de notre laboratoire soutient le dernier point de vue en démontrant que les patients atteints de la maladie d'Alzheimer (1) sont plus compromis par rapport à des personnes non atteintes de démence en regard des tâches de facilité d'élocution qui exigent la génération d'enregistrements d'un certain type particulier de catégorie de sémantique (p. ex., les animaux) que des mots commençant par une lettre précise, (2) exposent une dynamique temporelle pendant la production de catégories d'exemplaires de référence qui est altérée d'une façon qui est le signe d'une perte de connaissances sémantiques, (3) sont compromis lors de la confrontation de la dénomination de tâches et font de façon prédominante des erreurs reliées sémantiquement prépondérantes, (4) commettent de façon constante des erreurs d'identification à propos des mêmes objets au sujet d'une variété de tâches sémantiques tout comme la confrontation de dénomination, relier des images à des noms, faire le tri par attributs, et la génération des définitions et (5) commettent des modifications aux modèles de mesure multidimensionnels de leur réseau sémantique qui sont cohérents avec la perte d'exemplaires de référence, d'attributs d'information, des concepts et des associations. Bien que la base neuro-anatomique de la détérioration de la mémoire sémantique des patients atteints de la maladie d'Alzheimer nous soit actuellement inconnue, elle découlerait, selon toute vraisemblance, d'une neurodégénération des cortex d'association qui emmagasinent fort probablement les représentations sémantiques.