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The deterioration of semantic networks in patients with Alzheimer's disease: A cross-sectional study

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Abstract—Previous studies showed that the semantic networks of Alzheimer's disease (AD) patients are disrupted in the early stages of the disease. The present study examined the semantic networks of 33 AD patients in different stages of disease severity to compare the quantitative and qualitative changes in their networks as the disease progresses. The properties of the semantic networks (e.g. the dimensionality and strength of the connections) were examined with multidimensional scaling and Pathfinder analyses. The results showed that, as AD patients became more demented, they focused less on abstract attributes in categorizing concepts, and have an alteration in the relative strength of associations between concepts. These findings indicate that the structure of semantic knowledge deteriorates in a systematic manner throughout the course of AD. © 1997 Elsevier Science Ltd. All rights reserved.

Key Words: deterioration; semantic networks; Alzheimer's disease; cross-sectional study.

Introduction

A number of studies indicate that degradation of the organization of semantic knowledge is one of the prominent characteristics of patients with Alzheimer's disease (AD [4, 14, 24]). A series of recent studies, using graphic analyses to model the semantic networks of patients with AD, provides additional compelling evidence that the structure of their semantic knowledge is disrupted [6, 7, 8, 9]. In an initial study in this series [6], the cognitive maps representing the semantic networks of AD patients were generated by a multidimensional scaling (MDS) technique and ADDTREE clustering analysis. These statistical procedures allowed the investigators to use a measure of proximity between concepts (i.e. strength of association or degree of similarity) that was based upon the subjects' responses on an animal fluency task. The results indicated that the cognitive map of AD patients was characterized by uninterpretable clusters. In contrast, the cognitive maps of demented patients with Huntington's Disease (HD) and of normal control (NC) subjects displayed two well-organized clusters; one of wild animals and the other of domestic animals.

In follow-up studies [7–9], the proximity among concepts used in the graphic analysis was measured by a triadic comparison task (the advantages and disadvantages of the triadic comparison and fluency tasks in measuring proximity were discussed in Chan *et al.* [8]). On each trial of this task, three concepts (e.g. animal names) were presented at once, and the subject was told to choose the two, among the three choices, that were most alike. The degree of association or similarity between any two concepts (i.e. their proximity) was determined by the frequency with which they were chosen as being most alike across all trials in which they appeared.

Chan and her colleagues [8] compared the MDS generated cognitive maps of AD and NC subjects, and the findings suggested that AD patients focus upon a concrete perceptual attribute (i.e. size) when categorizing concepts on the triadic comparison task, while NC subjects rely primarily upon an abstract conceptual attribute (i.e. domesticity). This qualitative difference in the primary dimension of the cognitive maps seems to reflect a unique characteristic of AD patients since the cognitive maps of HD and amnesic (AM) patients displayed the same primary dimension (i.e. domesticity) as those of their age-matched NC counterparts [8].

When the semantic networks of AD patients were generated by Pathfinder analysis [8], a scaling procedure designed to model the links among concepts, the results

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suggested that, in addition to being dominated by a concrete dimension of organization, the structure of semantic knowledge of these patients consisted of more associative links, and many more atypical associations (i.e. links that were not common in the semantic networks of NC subjects), than those of elderly NC subjects. In contrast, the semantic networks of HD and AM patients were essentially identical to those of middle-aged NC subjects [8].

The scaling studies mentioned above suggest that the structure of semantic knowledge is altered in AD patients. However, little is known about the effects of disease progression on the integrity of the semantic network. Based upon the hypothesis that semantic knowledge is stored in a distributed fashion in the association cortices [25], the degree of abnormality of AD patients' semantic networks should increase as the disease progresses and pathological changes intensify and spread to an increasing number of these cortical systems. To examine this postulated deterioration, the present study extended the previous analyses [7–9] to AD patients with varying levels of dementia severity. While the previous investigations of Chan and her colleagues focused upon the relatively early stages of the disease, the present study compared the semantic networks of AD patients in the early, middle and advanced stages of disease progression.

It was anticipated that AD patients' categorization of concepts would rely less and less on abstract attributes, and depend more and more on concrete attributes, with increasing dementia severity. In addition, given the results of the previous study [8] that suggested that the semantic networks of AD patients are more complex than those of NC subjects, the complexity (i.e. number of connections) of the semantic networks of AD patients should increase as their level of dementia advances. It was also anticipated that the number of links common to the semantic networks of AD patients and NC subjects would be negatively related to the patients' level of dementia. That is, the more demented the AD patients, the greater the number of atypical links that would be noted in their semantic networks.

Method

Subjects

Thirty-three patients with the clinical diagnosis of probable AD (16 females and 17 males) and 22 NC subjects (10 females and 12 males) participated in this experiment. The subjects were drawn from a pool of about 150 probable and possible AD patients and 100 NC subjects who were participants in the University of California, San Diego (UCSD) Alzheimer's Disease Research Center (ADRC). Participants in the ADRC are volunteers obtained from referrals from San Diego area health professionals and from newspaper advertisements. The AD patients employed in the present study were selected from the ADRC pool in a quasi-random manner to ensure a wide distribution of dementia severity. All subjects' first language was English.

The diagnosis of AD was made by a senior staff neurologist at the UCSD ADRC, according to the criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) [16]. To reduce the possibility of including subjects with multi-infarct dementia, patients with a score of 5 or greater on the modified Hachinski ischemia scale [13, 21] were excluded from the AD patient group. Normal control subjects were either spouses of patients or volunteers obtained through newspaper advertisements. Individuals with a history of alcoholism, drug abuse, learning disabilities, or serious neurological or psychiatric illness were excluded from the control group.

The 33 AD patients were divided into three sub-groups, each with 11 subjects, according to their level of dementia as measured by Dementia Rating Scale (DRS) scores [15]. The three sub-groups were mildly demented (Mild AD, DRS = 137–120), moderately demented (Mod AD, DRS = 119–101), and severely demented (Sev AD, DRS = 100–62) AD patients. Table 1 shows the mean age, years of education, and DRS scores of the NC and AD groups. The comparisons of years of education [$F(3,51) = 1.61$, n.s.] and age [$F(3,51) = 0.48$, n.s.] showed no significant differences. However, the DRS scores of AD patients were significantly lower than those of NC subjects [$F(3,51) = 31.24$, $P < 0.001$]. A Scheffe multiple t-test revealed that the DRS scores between all subject groups were significantly different at the 5% level. Thirteen AD patients, 10 in the mildly demented group and three in the moderately demented group, also participated in Chan *et al.*'s [7] study.

Stimuli

It should be noted that the stimuli used in the present experiment were the same as those used by Chan *et al.* [7].

Triadic comparison task

Twelve high-frequency animal names (dog, cat, cow, horse, rabbit, pig, tiger, lion, bear, elephant, giraffe and zebra) were chosen according to the norms provided by Battig and Montague [2]. These animal names are also among the 30 most frequent responses of AD patients and NC subjects on an animal fluency task [6]. The animal names were presented three to a page in the form of an equilateral triangle. The pages were combined into a booklet containing 220 pages, representing all possible permutations (i.e. orderings and combinations) with the 12 animal names taken three at a time.

Word–picture matching task

The stimuli consisted of black and white drawings of the 12 animals used in the triadic comparison task. The size of each picture was about 7 cm^2, and the pictures were mounted individually on 9-cm^2 pieces of cardboard. The label (name) of each target animal was also mounted individually on a 2 cm × 9 cm piece of cardboard.

Procedures

All testing was performed on an individual basis in a quiet testing room. The triadic comparison task was administered first. On each of the 220 trials, three animal names were presented simultaneously, and the subject was asked to indicate the two animals that were most alike. The examiner recorded

Table 1. Mean (S.D.) age, years of education, and Dementia Rating Scale scores for normal control (NC) subjects and mildly demented (Mild), moderately demented (Mod) and severely demented (Sev) Alzheimer's disease (AD) patients

Variable	NC ($N=22$)	Mild AD ($N=11$)	Mod AD ($N=11$)	Sev AD ($N=11$)
Age (years)	75 (7.1)	74 (6.4)	75 (8.1)	72 (8.7)
Education (years)	15 (2.5)	16 (3.3)	13 (2.9)	14 (3.6)
Dementia Rating Scale score	141 (2.7)	127 (6.0)	113 (4.7)	89 (9.3)

the subject's response on a record sheet. The entire testing was divided into four sessions (55 trials each) with 5-min rest intervals between sessions.

Immediately following completion of the triadic comparison task, the word–picture matching test was administered. This task required subjects to match the 12 animal names to the 12 animal pictures. First, the drawings of the 12 animals were placed, three rows of four cards each, on the table directly in front of the subject. The placement of the drawings was randomly assigned. The 12 animal names were then handed to the subject one at a time. On each trial, the subject was asked to match the animal name with one of the drawings on the table. After the subject had given a response, the examiner placed the name of the animal under the chosen picture and recorded the response as correct or incorrect. During the task, the subject was allowed to make corrections; however, all corrections were recorded and scored as errors. The total number of correct responses was calculated at the end of the task. This task was administered to ensure that all subjects could recognize the animals used in the triadic comparison task.

Statistical analyses

An MDS analysis and a Pathfinder technique were chosen for analyzing the data. The MDS analysis was used to reveal the dimensions underlying the organization of semantic knowledge. Individual Difference Scaling Analysis (INDSCAL), an MDS method developed by Carroll and Chang [5], was chosen for analyzing the proximity data derived from the triadic comparison task. In this study, the goodness-of-fit of the MDS solution was evaluated by the percentage of variance (R^2) of the proximity data that could be accounted for by INDSCAL. The individual subject difference was measured by the weight index associated with each dimension and the skewness index. The weight index represented the saliency of each dimension for an individual as compared to the other subjects. The higher the weight index, the more important the dimension is for that subject. The skewness index was used as a measurement of consistency. While a subject utilizing primarily one attribute will have a skewness index near one, subjects who use several attributes equally during the triadic comparison task will have a skewness index approaching zero (see [10, 20, 22, 23] for a general discussion of MDS).

Pathfinder analysis [11] shares the goal of MDS in reducing large amounts of proximity data to an interpretable form. However, the Pathfinder analysis is more sensitive in measuring the strength of associations between concepts. A Pathfinder network consists of a set of nodes, with each node representing a concept. The strength of the association between two nodes, represented by an index of internode distance, is determined by the proximity data. That is, a pair of concepts with a low proximity estimate will have a long distance (i.e. high index) between them, while a pair of concepts with a high proximity estimate will have a short internode distance (i.e. low index). Two concepts are directly connected in the generated model if and only if the distance of their direct link is shorter than the sum of all of their indirect links.

The various measures derived from MDS and Pathfinder analyses were used in both correlational and ANOVA analyses to examine their relationship to dementia severity. In addition, a goodness-of-fit measure was used to directly compare the cognitive maps of the individual AD patients to the average NC cognitive map.

Results

Dimensionality

The proximity data of the 22 NC subjects were analyzed by INDSCAL resulting in a three-dimensional cognitive map representing the organization of semantic knowledge in this group of normal elderly individuals (Fig. 1). Visual inspection suggested that the first, second and third dimensions were interpretable as domesticity, size and predation, respectively. The three-dimensional solution was able to account for 86% of the variance in the proximity data with the first, second and third dimensions accounting for 43%, 27% and 16% of the variance, respectively. These results were consistent with those reported by Chan *et al.* [7, 8].

The proximity data of 33 AD patients were analyzed with the same method. The three-dimensional cognitive map of the AD patients accounted for 63% of the variance in the proximity data, a finding which suggested that their proximity data is less consistent than that of the NC subjects. Visual inspection suggested that the first and second dimensions in the AD patient's map were interpretable as size and domesticity, respectively, and the third dimension may be predation (Fig. 1). These results were comparable to those reported by Chan *et al.* [7, 8].

The relatively high degree of inconsistency in the cognitive maps of AD patients may indicate that their individual semantic networks are heterogeneous. It was hypothesized that the level of dementia would be a significant factor in determining heterogeneity. To examine this issue, the proximity data of 11 mildly demented, 11 moderately demented and 11 severely demented AD patients were analyzed separately by INDSCAL analysis. The cognitive maps of Mild AD, Mod AD and Sev AD accounted for 87%, 72% and 40% of the variance of their proximity data, respectively. These findings support

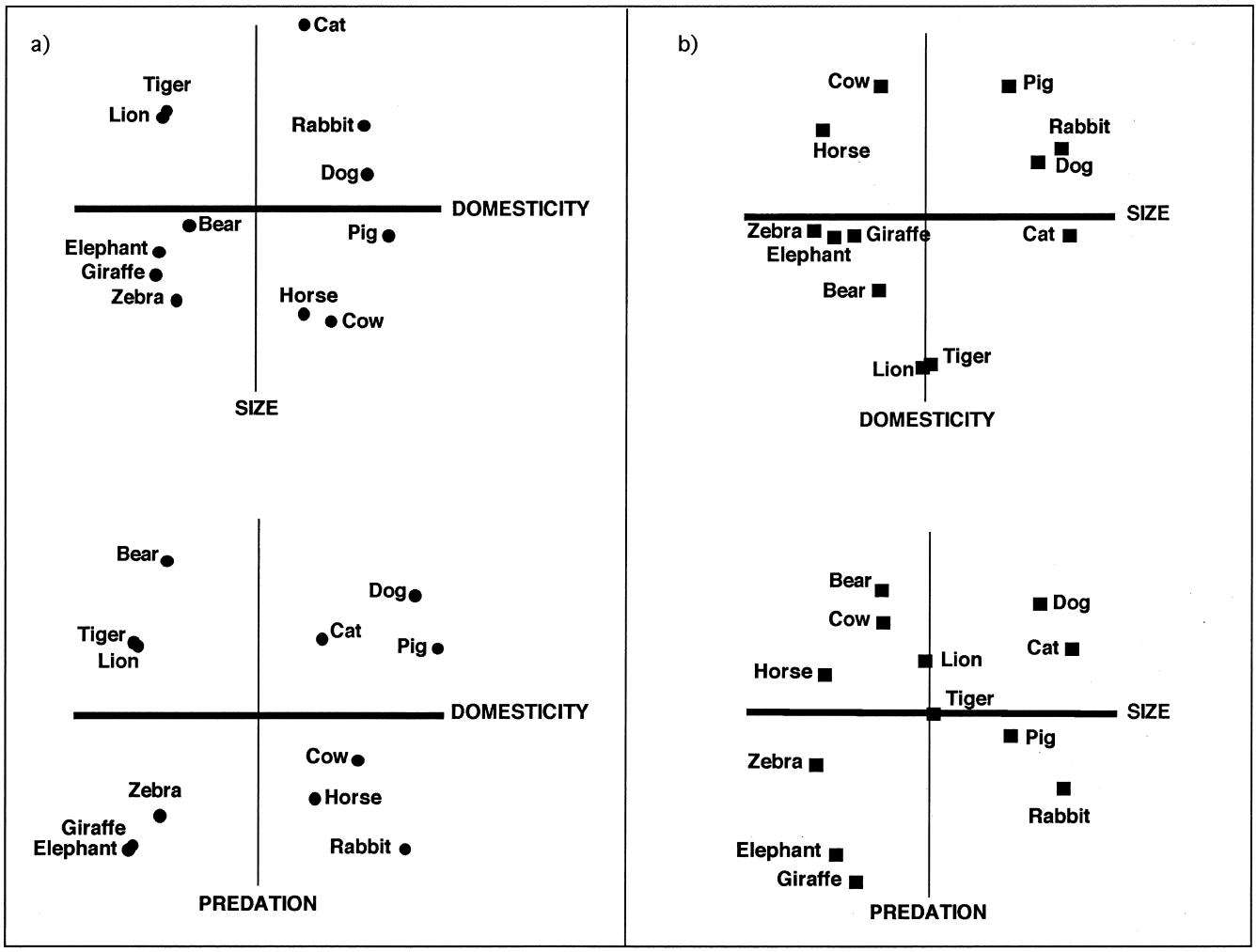

Fig. 1. The cognitive maps of (a) 22 normal control subjects and (b) 33 Alzheimer's disease patients generated by the INDSCAL multidimensional scaling analysis. The most salient dimension that the subjects used in categorizing concepts is represented in bold type.

the hypothesis that the level of dementia is a significant factor in determining the heterogeneity in the cognitive maps.

As shown in Fig. 2, while the cognitive maps of Mild AD and Mod AD were interpretable with domesticity as the primary dimension, the cognitive map of Sev AD was interpretable with size as the primary dimension. This result suggested that the level of dementia in AD patients may affect their choice of attribute in categorizing concepts. It should be noted that the cognitive maps of Mild AD and Mod AD seem grossly intact. This result is consistent with the findings of Bonilla and Johnson [3], but this may be due to the fact that averaged similarity data are likely well fitted by an MDS analysis even if the data of the individual subjects are not [1]. Therefore, in order to evaluate more systematically the relationship between the relative saliency of each of the dimensions and the level of dementia, the weight indices of the three dimensions and the skewness indices for each AD patient were correlated with the level of dementia as measured by the DRS. A regression analysis with the weight indices of the first dimension (i.e. domesticity) as the dependent variable and the level of dementia as the independent variable yielded a significant negative correlation ($R^2 = 0.45$, $P < 0.001$). This result suggested that, as the disease progressed, AD patients focused less and less on the abstract dimension (i.e. domesticity).

The same analysis was performed to evaluate the relationship between dementia severity and the saliency of the second and third dimensions, and the skewness indices. These regression analyses showed that neither the second ($R^2 = 0.11$, n.s.) nor the third ($R^2 = 0.12$, n.s.) dimensions, nor the skewness indices ($R^2 = 0.25$, n.s.), correlated strongly with the level of dementia; however, the saliencies of all three dimensions were negatively correlated with the level of dementia. This finding suggests that, as the disease progresses, AD patients possess less and less knowledge about the attributes of the concepts.

To further evaluate the hypothesis that the level of dementia may be a significant factor affecting the integrity of the cognitive maps of AD patients, INDSCAL analysis was used to compare the cognitive map of each AD patient to the average cognitive map of the group of NC subjects. The percentage of variance (R^2) in each AD

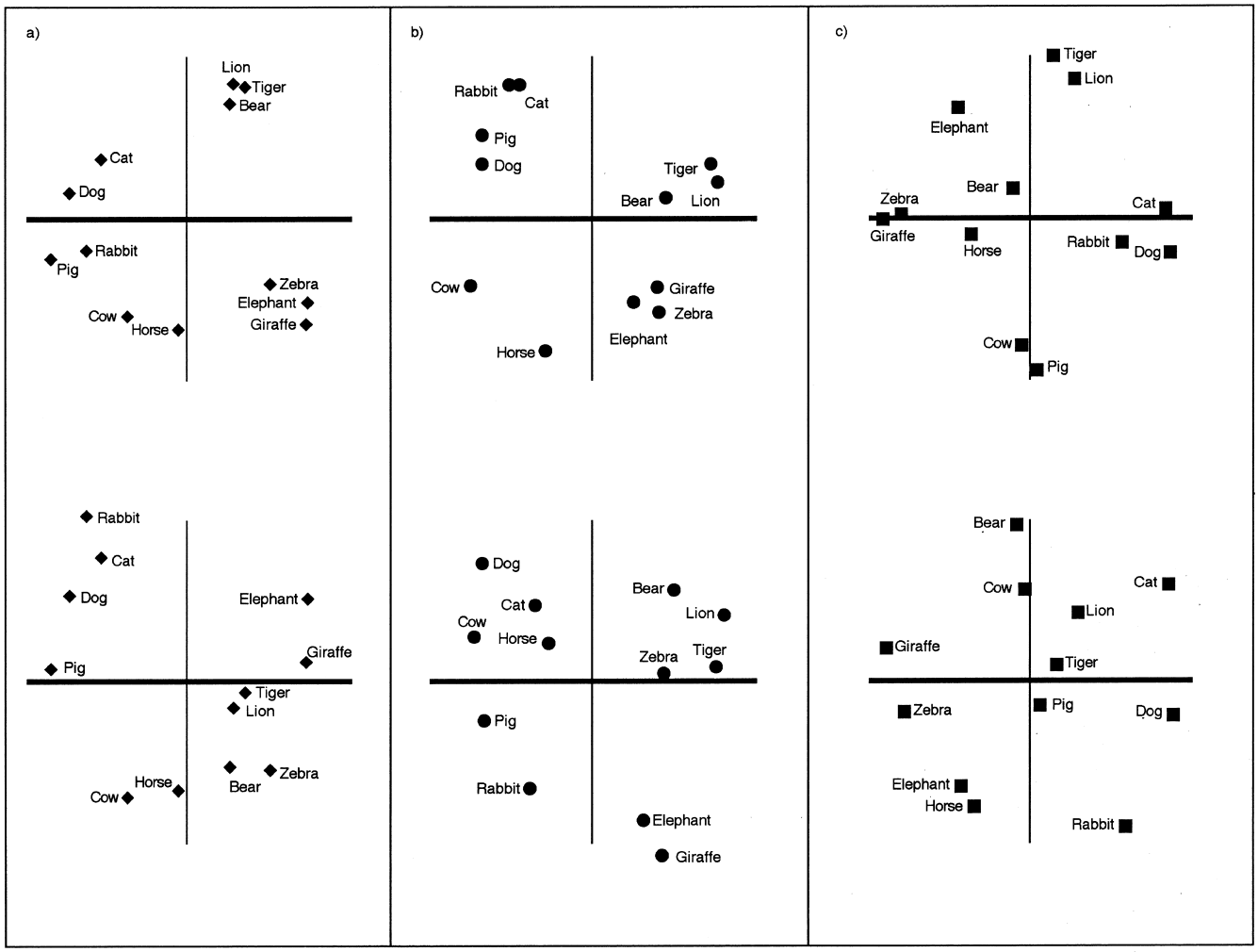

Fig. 2. The cognitive maps of (a) 11 mildly demented, (b) 11 moderately demented and (c) 11 severely demented Alzheimer's disease patients generated by the INDSCAL multidimensional scaling analysis. The most salient dimension that the subjects used in categorizing concepts is represented in bold type.

patient's proximity data that could be accounted for by the NC subjects' cognitive map was calculated as a measure of the degree of integrity of the AD patient's cognitive map. The more similar the AD patient's cognitive map to that of the NC subjects, the higher the R^2.

The R^2 values for the AD patients' cognitive maps were then correlated with their level of dementia as indicated by their DRS scores. A significant correlation ($R^2 = 0.62$, $P < 0.01$; see Fig. 3), obtained from a simple regression analysis, suggested that the level of dementia is negatively correlated with the degree of integrity of the cognitive maps. In other words, the more demented the AD patients, the less similar their cognitive maps were to those of the NC subjects.

Number of links

The second characteristic of the semantic network that was examined was its complexity (i.e. number of links). It has been proposed that the complexity of an individual's network is related to the amount of knowledge that he or she possesses [22]. Individuals with less knowledge in a dominant dimension will be less able to differentiate necessary connections from adjunct links, and, therefore,

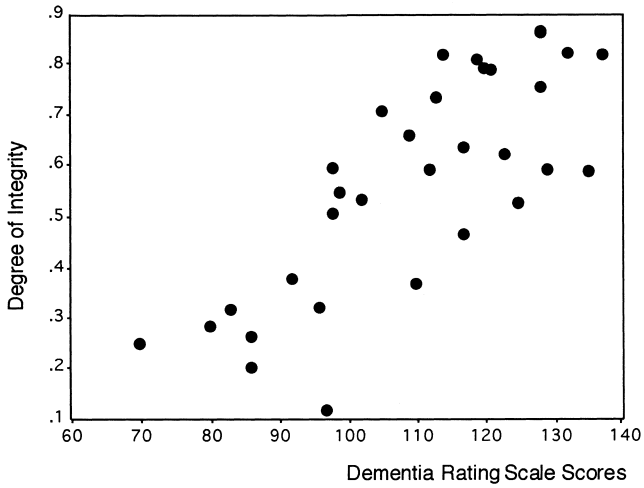

Fig. 3. The degree of integrity of each Alzheimer's disease patient's cognitive map as a function of the level of dementia.

their semantic networks tend to consist of more unnecessary connections. Such semantic networks are often viewed as highly complex [22]. It was, therefore, predicted that the number of links in an AD patient's semantic network should increase as the disease progresses. To examine this issue, a Pathfinder analysis was used to calculate the number of links in the semantic network of each AD patient. The number of links in AD patients' networks were then correlated with their level of dementia as measured by the DRS. As predicted, the level of dementia was significantly correlated with the number of links in the network ($R^2 = 0.71$, $P < 0.001$; Fig. 4).

To compare further the complexity of semantic networks of NC and AD patients in different stages of the disease, a one-way ANOVA was performed to compare the number of links of NC subjects with the three groups of AD patients. The result was significant [$F(3,51) = 46.2$, $P < 0.001$]. The mean numbers of links of NC, Mild AD, Mod AD and Sev AD subjects were 25 (S.D. = 5.1), 26 (S.D. = 5.9), 34 (S.D. = 7.8) and 49 (S.D. = 5.3), respectively. A Scheffe multiple *t*-test was used for *post-hoc* comparisons among the groups. Except for the comparison between the NC subjects and the Mild AD patients, the number of links between all the groups was significantly different at the 5% level.

Common links

Besides examining the quantitative features of the connections in the network, the qualitative characteristics (i.e. which concepts are connected) of the links were also evaluated. The algorithm developed by Goldsmith and Davenport [12] was used for these comparisons. First, the data of all NC subjects were analyzed by a Pathfinder analysis which generated a semantic network representing the average performance of the group. Each AD patient's network was then compared to the network of the NC subjects. A similarity index, ranging from 0 to 1, was calculated for the semantic network of each AD patient. This index represents how many common links are shared by the semantic network of an AD patient with that of the NC subjects. The similarity indices of all 33 AD patients were then correlated with their DRS scores. The results revealed a significant correlation ($R^2 = 0.42$, $P < 0.001$) in which the level of dementia accounted for 36% of the variance in the similarity indices (Fig. 5).

Discussion

The purpose of the present study was to examine the relationship between the level of dementia and the deterioration of the organization of semantic knowledge in AD patients. It was hypothesized that the structure of the semantic knowledge in AD patients would become increasingly abnormal as the disease progressed. Indeed, the significant negative relationship that was observed between the level of dementia and the level of comparability of AD patients' cognitive maps to those of NC subjects (evaluated by a measure of goodness of fit) suggests that the integrity of the cognitive maps decreases as the level of dementia increases. In addition, the examination of the relationship between the results of the MDS analysis and the severity of dementia revealed that the deterioration of the AD patients' cognitive maps was accompanied by their relying less and less on the abstract attribute (i.e. domesticity) for categorizing concepts as their disease progressed. Instead, they focused more than the NC subjects on concrete perceptual information.

The results obtained from the Pathfinder analysis indicated that the deterioration of the semantic networks of AD patients is not due solely to changes in the saliency of dimensions used to categorize concepts, but also involves both qualitative and quantitative changes in the associ-

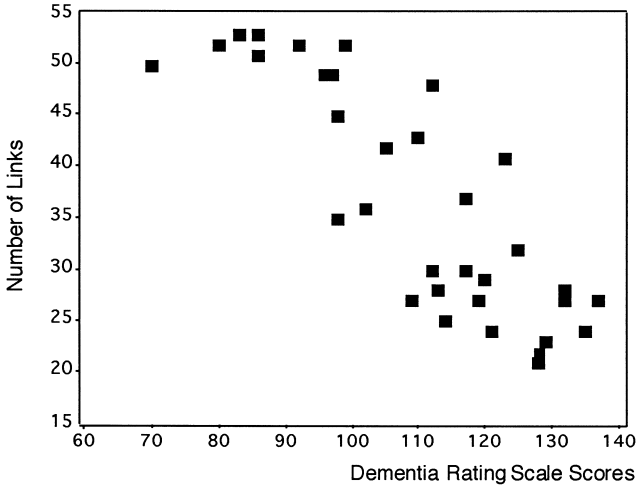

Fig. 4. The number of links in each Alzheimer's disease patient's semantic network as a function of the level of dementia.

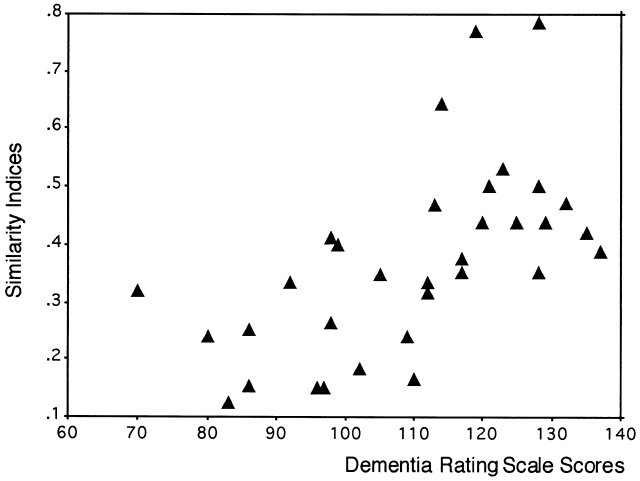

Fig. 5. The similarity index of each Alzheimer's disease patient's semantic network as a function of the level of dementia.

ations between concepts. Qualitatively, the number of associative links that the AD patients' semantic network shared in common with that of the NC subjects decreased as the severity of their dementia increased. This finding suggests that AD patients may perceive the relationships between concepts differently than the NC subjects, and that this difference may continuously increase during the course of the disease.

Quantitatively, all three groups of AD patients demonstrated more associative links than the NC subjects and the number of links increased with the severity of dementia. Although this result may seem somewhat counter-intuitive, it is consistent with the notion that the simplicity or complexity of an individual's cognitive map is determined by the amount of knowledge that he or she possesses about the concepts within a given domain. Individuals who possess detailed knowledge about the associations between concepts in a domain will develop a clear and concise network that consists of a minimum number of necessary connections, whereas those who have not acquired enough knowledge [22], or have lost the knowledge that they once possessed [7], tend to organize concepts in a relatively more chaotic way with many adjunct connections. Given that AD patients' semantic knowledge deteriorates as the disease progresses, it is not surprising that their networks became more and more chaotic.

Although not directly addressed in the present study, at least two results from our previous studies [7, 8] indicate that the observed alteration of the AD patients' cognitive maps is most likely due to a deterioration of their semantic network rather than to non-specific factors such as a general retrieval deficit [17–19] or a decline in their ability to make judgements on the triadic comparison task. First, the cognitive maps of AD patients generated from two administrations of the triadic comparison task separated by 5–7 days were virtually identical. If their cognitive map is a reflection of retrieval or judgement problems rather than the underlying semantic network, this degree of consistency would not be expected [8]. Second, patients with Huntington's disease, a dementing disorder characterized by deficits in retrieval and 'executive' abilities [4], have normal cognitive maps generated from triadic comparison task data [7].

In summary, the present results, in conjunction with our previous findings, suggest that the semantic networks of AD patients are altered over the course of the disease. As AD progresses, changes occur in the number and quality of associative links, and in the saliency of the dimensions used to classify concepts. Although the semantic networks of AD patients manifested extensive alteration, the structure of their networks, even for the patients in the late stages of the disease, remain grossly intact. That is, their networks continue to consist of associative links, still have interpretable dimensions, and share some common links with normal individuals. These results, therefore, suggest that examining the change in the structure of semantic knowledge, rather than the existence of the knowledge, may be more sensitive for revealing the underlying nature of the semantic memory deficit in AD patients.

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