

Semantic network abnormality predicts rate of cognitive decline in patients with probable Alzheimer's disease

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Abstract

The present study examined the relationship between rate of cognitive decline in patients with Alzheimer's disease (AD) and the integrity of the network of associations that comprise their semantic knowledge. The integrity of the semantic network of 12 AD patients was determined by comparing their networks to a standard normal control network derived with Pathfinder analysis, a multidimensional graphic analysis technique. A simple linear regression analysis, comparing the degree of semantic network deterioration with rate of cognitive decline as measured by the difference between the Dementia Rating Scale (DRS) scores obtained at the time of the testing of semantic knowledge (Year 1) and one year later (Year 2), was highly significant ($r^2 = .84$; $p < .001$). These results suggest that a sensitive measure of the structural deterioration of semantic knowledge may be useful for predicting the rate of progression of cognitive changes in patients with AD. (*JINS*, 1995, 1, 297-303.)

Keywords: Semantic network, Cognitive decline, Alzheimer's disease

Introduction

The rate of progression of the cognitive changes associated with probable Alzheimer disease (AD) varies greatly among individuals (Ritchie & Touchon, 1992; Lucca et al., 1993). While some patients remain only mildly demented for five or more years after their initial diagnosis, others become severely demented and totally dependent in only a few years (Botwinick et al., 1986; Katzman & Jackson, 1991). The factors that contribute to this variability in the rate of cognitive deterioration remain largely unknown and attempts to predict the rate of cognitive decline in patients with AD have met with limited success (for review, see Galasko et al., 1991). For example, little or no relationship has been found between rate of global cognitive decline and initial severity of dementia (Knesevich et al., 1986; Boller et al., 1991), age at onset of the disease (Huff et al., 1987; Boller et al., 1991), behavioral or psychotic

symptoms (Teri et al., 1990; Lopez et al., 1992) or findings from metabolic and structural imaging studies (Haxby et al., 1990; McGeer et al., 1990).

Although some studies have failed to find a relationship between rate of global cognitive decline and amount of decline during the previous year (Salmon et al., 1990), other studies have shown that following a plateau phase of varying length, the trajectories of individual AD patient's cognitive decline is generally linear and predictable (Haxby et al., 1992). However, because the plateau phase and the slope of the trajectory of decline varies considerably from patient to patient, the ability to predict an individual patient's rate of cognitive decline in this way is only possible after at least several years of repeated evaluation. Furthermore, the factors that may predict the length of the plateau phase or the slope of the trajectory of decline in an individual patient remain unknown.

In contrast to these generally negative findings, some success has been achieved in predicting AD patients' rate of cognitive decline on the basis of the presence and severity of language dysfunction early in the course of the disease. A number of investigators have reported that AD

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patients with early language disturbances progress more rapidly than those without such deficits (Berg et al., 1984; Seltzer & Sherwin, 1984; Faber-Langendoen et al., 1988), and others have demonstrated a significant relationship between performance on tests of verbal abilities and measures of subsequent cognitive decline (Knesevich et al., 1986; Mortimer et al., 1992). For example, Knesevich et al. (1986) found that the performance of mildly demented AD patients on the Boston Naming Test was significantly correlated with a global rating of dementia (i.e., Clinical Dementia Rating scale; Hughes et al., 1982) 30 mo later. Similarly, Mortimer and colleagues (Mortimer et al., 1992) recently demonstrated that the score of AD patients on a composite verbal cognitive factor consisting of naming, fluency, comprehension, and verbal memory indices was negatively correlated with measures of cognitive decline during a subsequent period of up to four yr.

The results of these studies suggest that measures that are particularly sensitive to language dysfunction early in the course of AD may be useful for predicting the subsequent rate of global cognitive deterioration. Since the language disturbance of AD patients has been attributed to a deterioration of the structure and organization of semantic memory (Martin & Fedio, 1983; Martin, 1987; Chertkow & Bub, 1990; Hodges et al., 1991), the most sensitive measure for this purpose may be one that evaluates the integrity of the network of associations comprising semantic knowledge (i.e., the semantic network).

Graphic analyses, such as multidimensional scaling and Pathfinder analysis techniques, have been used to examine the semantic networks of mildly demented AD patients and normal control (NC) subjects (Chan et al., 1993a; Chan et al., 1993b; Chan et al., in press). These analyses revealed a disruption in the organization of semantic knowledge in AD patients that is characterized by a shift in the primary dimension used to classify concepts, an abnormal clustering of concepts, and a change in the strength of association between concepts in the semantic network. Because these multivariate techniques are more sensitive than univariate analyses in revealing the underlying structure of the semantic network, they may be ideal for examining the relationship between semantic memory dysfunction and future cognitive decline.

The present study examined the ability of a multivariate measure of the integrity of the semantic network to predict the subsequent rate of global cognitive decline in AD patients. The semantic network of individual AD patients was generated by a graphic analysis technique (i.e., Pathfinder analysis) and compared to a standard network derived from the averaged data of age- and education-matched normal control subjects. This comparison provided a Similarity Index, which represents the degree of disruption of the organization of semantic memory for each AD patient. The Similarity Index was then used to predict the patients' subsequent global cognitive decline as measured by changes over 1 yr in their scores on a stan-

dardized mental status examination, the DRS (Mattis, 1976).

Method

Subjects

Twelve patients (6 females, 6 males) with the clinical diagnosis of probable AD and 12 NC subjects (6 females, 6 males) participated in this study. The diagnosis of probable AD was made by a senior staff neurologist at the University of California, San Diego (UCSD) Alzheimer's Disease Research Center (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) (McKhann et al., 1984). 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 (Hachinski et al., 1975; Rosen et al., 1980) were excluded from the AD patient group. The NC subjects were either spouses of patients or volunteers obtained through newspaper advertisements. Subjects with a history of alcoholism, drug abuse, learning disabilities, or serious neurological or psychiatric illness were excluded.

As shown in Table 1, the probable AD patients and NC subjects did not differ significantly in age [$t(22) = 1.10$; $p > .05$] or education [$t(22) = .94$; $p > .05$]. As expected, the mean DRS score of the AD patients in yr 1 was significantly lower than that of the NC subjects [$t(22) = 8.20$; $p < .001$].

It should be noted that the 12 AD subjects and their triadic comparison task data were also used in two previously reported studies (Chan et al., 1993b; Chan et al., in press). These other studies focused on the quantification and comparisons of AD and other demented patients' semantic networks using multidimensional scaling and Pathfinder techniques. However, in the present study, the semantic networks of AD and NC subjects were compared to ascertain the degree of abnormality, and the resulting index of network abnormality was used to predict the rate of subsequent global cognitive decline.

Table 1. Age, years of education, and DRS scores [M (SD)] of NC subjects and AD patients

	NC (N = 12)	AD (N = 12)
Age (yr)	76 (5.2)	74 (4.3)
Education (yr)	14 (2.1)	15 (3.8)
DRS	142 (1.7)	121 (8.4)

DRS = Dementia Rating Scale; NC = normal control; AD = Alzheimer's disease.

Stimuli—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 (1969). These animal names are also among the 30 most frequent responses of AD patients and NC subjects on the animal fluency task (Chan et al., 1993a). The stimuli were presented, in a fixed random order, three at a time in the form of an equilateral triangle on a computer screen. There were, in total, 220 trials representing all possible permutations (i.e., orderings and combinations) with the 12 animal names taken three at a time.

Procedures

All testing was performed on an individual basis in a quiet testing room. The triadic comparison task was presented on a Macintosh IIci computer with a 14-in. monitor. On each of the 220 trials, three animal names were presented on the computer screen, and the subject was asked to indicate the two animals that were most alike. The examiner recorded the subject's response by touching on the interface the icons corresponding to the selected words. Once the subject's response had been recorded, another triad was presented on the screen. The entire testing was divided into four blocks (55 trials each) with 5-min rest intervals between blocks.

Several months ($M = 4.7$ mo) prior to testing with the triadic comparison task, the DRS (Mattis, 1976), a 30-item version of the Boston Naming Test (BNT; Goodglass & Kaplan, 1972), and two verbal fluency tasks employing letter and semantic categories were administered to each AD patient as part of their annual UCSD ADRC evaluation. The BNT required subjects to name 30 objects (e.g., tree, pretzel) depicted in outline drawings. On the letter fluency test, subjects were asked to generate orally in 1 min as many words as possible that began with the letters "F," "A," and "S," respectively. On the category fluency test, subjects were asked to generate orally as many different kinds of animals, fruits, and vegetables as possible, with 1 min allowed for each category. The DRS was administered a second time to each AD patient approximately 1 yr later ($M = 13.5$ mo). Thus, an average of 9 mo passed between the administration of the triadic comparison task and the administration of the second DRS.

The Pathfinder analysis

It has been proposed that semantic knowledge is organized as a parallel or serial network (Collins & Loftus, 1975) in which concepts are linked with various weights that are assumed to reflect their relatedness (i.e., psychological distance or proximity). The Pathfinder analysis is a scaling procedure designed to systematically construct

a model of the semantic network from empirically derived concept proximity data (Dearholt & Schvaneveldt, 1990).

A Pathfinder network consists of a set of nodes, with each node representing a concept. Concepts are connected within the network by links, which have various lengths that represent their strength of association as determined by proximity data. Two concepts will be directly connected in the network only if the length of their direct link is shorter than the sum of the links that indirectly connect them through other concepts in the network. For example, Figure 1 shows a hypothetical pathfinder network for the concepts A, B, and C. In this network, A and B have a link length of 1, B and C have a link length of 2, and A and C have a link length of 7. A and B, and B and C, are directly connected in the network because the lengths of their direct links (1 and 2, respectively) are shorter than the sum of the lengths of any indirect links between them. However, A and C are not connected because the indirect path A-B-C (3) is shorter than the direct path A-C (7).

The Pathfinder analysis allows the user to choose the level of complexity in the network (i.e., number of links) by adjusting two functions in the calculation. The first function, r , defines the path length and the second function, q , determines the maximum number of links in the path. From the same set of data, the Pathfinder analysis can generate the simplest network with a minimum number of links, the most detailed network with the maximum number of links, or a network with a number of links between the minimum and the maximum. The choice of the complexity of a network should be based upon the theoretical assumptions and practical purposes of the study. Minimal complexity (i.e., a minimum number of links) was chosen for the present study in order to provide simple and clear networks that can be easily compared for the purpose of detecting abnormalities in the semantic memory of AD patients. Thus, for all analyses, r was set to ∞ and q to $n - 1$.

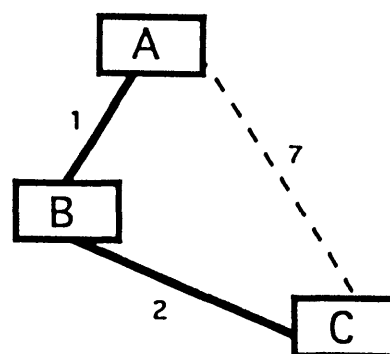


Fig. 1. A hypothetical Pathfinder network for three concepts labelled A, B, and C. Concepts A and B, and Concepts B and C, are connected with link lengths of 1 and 2, respectively. Concepts A and C are not directly connected because their link length (7) is longer than the sum of the indirect links (3) which connect them through Concept B. (Note: solid lines represent direct links.)

The structural similarity between two Pathfinder networks can be examined by calculating the Closeness measure (Goldsmith & Davenport, 1990). This measure, also called the Similarity Index, describes the extent to which the same concept in two networks is surrounded by the same neighborhood of concepts. To compute the Similarity Index, the neighborhood concepts (i.e., directly connected concepts) for each concept in the two graphs are listed and compared. A quotient is then calculated for each concept by dividing the number of neighborhood concepts common to both networks by the total number of neighborhood concepts in the two networks. For example, if the neighborhood concepts of Concept A in network 1 are B and C, and the neighborhood concepts of Concept A in network 2 are B and D, there are a total of three neighborhood concepts (i.e., B, C, and D) for Concept A, but only one (i.e., B) is commonly linked to Concept A in both networks. Therefore, the quotient for Concept A is 1/3 or .33. The Similarity Index for the two networks is obtained by averaging the quotients of all concepts. The value of the Similarity Index can range from 0.0 for totally dissimilar graphs to 1.0 for identical graphs.

Results

Each subject completing the triadic comparison task generated proximity data, the frequencies with which each pair of concepts was chosen as most alike. If two concepts were chosen frequently as most alike, they were considered to be strongly related. Because 12 stimuli were used in the task, the proximity data for all possible combinations of two animals could be represented in a 12×12 half matrix. A group semantic network for the NC subjects was generated by averaging their proximity data to create a single matrix for the group, and then subjecting this matrix to the Pathfinder analysis. This procedure produced a NC standard semantic network, shown in Figure 2, that consisted of 12 nodes and 12 connections. Within the network, strongly associated concepts were connected directly, whereas moderately or weakly associated concepts were not. Thus, as can be seen in Figure 2, closely related concepts like *dog* and *cat* were connected directly, but *dog* and *cow* were connected only indirectly through *pig* and *horse*.

Each AD patient's proximity data were subjected to the Pathfinder analysis separately to produce one semantic network for each patient. The structural similarity between each AD patient's semantic network and the standard NC network was determined by deriving a Similarity Index (as described in the Methods section), which assessed the proportion of common neighborhood links present in the two networks. When the semantic network of an AD patient was very similar to the standard network, the Similarity Index approached 1. Conversely, the Similarity Index approached 0 when an AD patient's semantic network was very different from the standard net-

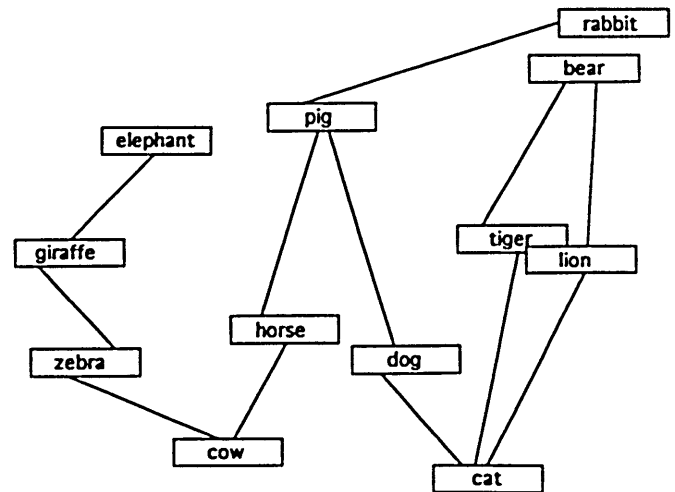


Fig. 2. The standard network generated by the Pathfinder analysis from the average proximity data of 12 NC subjects. Each concept is represented by a single node in the network, and two concepts are linked only if their direct path is shorter than all their indirect paths. The derived network is the simplest model that could be developed from this particular set of proximity data (see text).

work. The average Similarity Index for the 12 AD patients was .48 ($SD = .11$; range .32-.73).

To examine the relationship between semantic network deterioration and rate of cognitive decline, the network Similarity Indices of the AD patients were correlated with the decline in their DRS scores over the subsequent year. A DRS difference score (i.e., $DRS_{yr\ 2} - DRS_{yr\ 1}$) was calculated for each AD patient. Consistent with the notion that the rate of cognitive decline varies greatly among AD patients, these difference scores ranged from 1 to -21 ($M = -8.25$, $SD = 7.67$). A simple linear regression analysis with the DRS difference scores as the dependent variable and the Similarity Indices as the independent variable was highly significant [$F(1, 10) = 51.52$, $p < .001$] with $r^2 = .84$ (see Figure 3).

To determine if the Similarity Index was unique in predicting rate of decline, or was a better predictor than other measures of semantic memory, simple regression analyses were performed to examine the relationship between the DRS difference score and other tasks which assess semantic memory, including the Boston Naming Test, the letter and category fluency tasks, and the Supermarket fluency task (i.e., naming items found in a supermarket for 1 min) of the DRS. The results of these analyses, shown in Table 2, revealed that these measures were not significantly correlated with rate of subsequent decline. In addition, rate of decline was not significantly correlated with initial level of dementia as measured by yr 1 DRS score.

To explore the interaction among various language tasks in predicting the rate of cognitive decline, a stepwise multiple regression analysis was performed with DRS difference score as the dependent variable and the Similar-

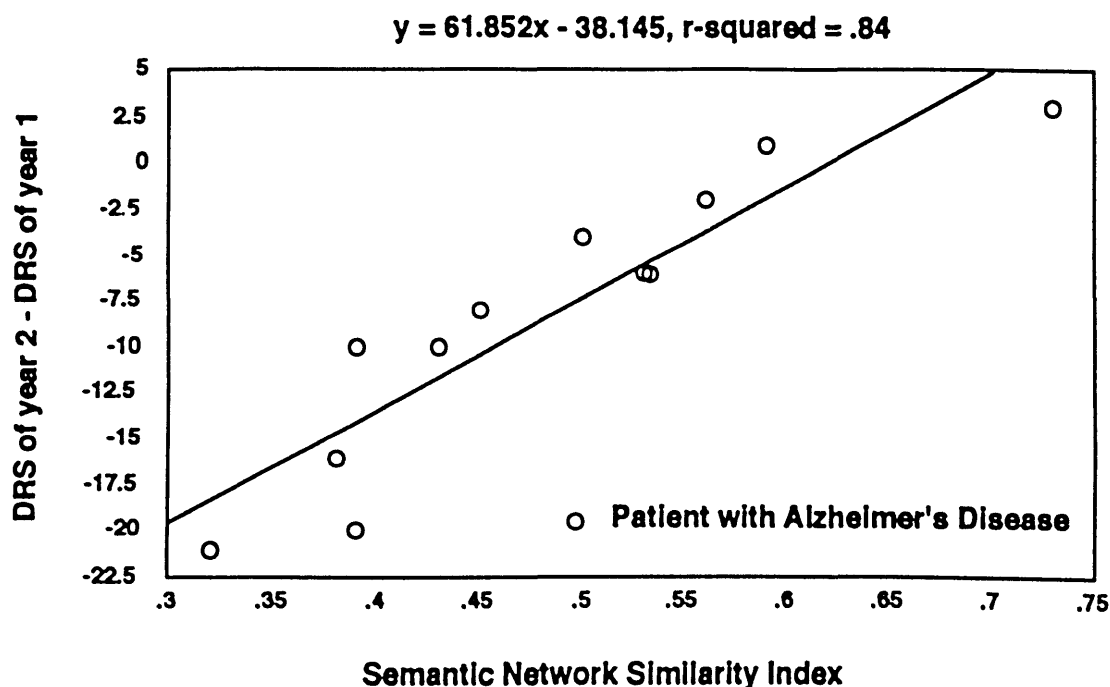


Fig. 3. The semantic network Similarity Index of 12 AD patients plotted as a function of rate of cognitive decline as measured by the difference between the DRS scores obtained near the time of semantic knowledge testing (Year 1) and 1 yr later (Year 2). The simple linear regression analysis comparing these variables, shown at the top of the Figure, was highly significant ($p < .001$).

ity Index, BNT score, letter and category fluency scores, Supermarket fluency score, and yr 1 DRS score as the independent variables. The multiple regression was highly significant [$F(1, 10) = 51.52, p < .05; r^2 = .84$], with only the Similarity Index retained in the equation.

Discussion

The present results demonstrate that an index of the abnormality of the semantic network obtained from a multivariate scaling analysis can accurately predict the subsequent rate of global cognitive decline in patients with probable AD. Eighty-four percent of the variance in the

rate of AD patients' decline on the DRS over a 1-yr interval was accounted for by a Similarity Index which quantified the amount their semantic network deviated from a standard NC network. The Similarity Index was more effective in predicting subsequent cognitive decline than initial DRS score or traditional measures of language and semantic memory, such as confrontation naming and verbal fluency. Indeed, naming and fluency scores were not significantly correlated with rate of cognitive decline in the present study, and did not account for a significant proportion of the variance in rate of decline beyond that explained by the Similarity Index. Despite the apparent strength of the present results, they should be considered tentative until replicated, particularly given the small sample size and the unpredictable influence of the interval between semantic memory testing and DRS administration.

The effectiveness of this index of the integrity of semantic knowledge in predicting rate of cognitive decline in AD patients is consistent with previous studies that have shown a relationship between rate of decline and severity of language dysfunction (Knesevich et al., 1986; Mortimer et al., 1992). However, the present Similarity Index appears to have a clear advantage in this regard over traditional language measures. The Similarity Index accounted for over 80% of the variance in AD patients' subsequent rate of decline, whereas previous studies found that BNT scores (Knesevich et al., 1986) and composite verbal abilities scores (Mortimer et al., 1992) were only mildly predictive, accounting for less than 60% of the variance in patients' cognitive deterioration. Similar lan-

Table 2. The results of simple linear regression analyses comparing rate of cognitive decline with the network Similarity Index, Boston Naming Test, DRS Supermarket fluency task, letter fluency task, category fluency task and first year DRS scores

	R	R ²	F-test	Significance level
Network Similarity Index	.91	.84	51.52	$p < .001$
Boston Naming Test	.17	.03	.29	N.S.
Supermarket fluency task	.15	.02	.22	N.S.
Letter fluency task	.04	.00	.01	N.S.
Category fluency task	.23	.05	.54	N.S.
First year DRS	.14	.02	.19	N.S.

guage measures (i.e., confrontation naming and verbal fluency) used in the present study were not significantly related to rate of deterioration. However, this may have been due to the smaller sample size and greater variability in patients' initial severity of dementia compared to previous studies.

The Similarity Index may be more effective than traditional language measures for predicting rate of cognitive decline because it is based on an appraisal of semantic memory that places few demands on retrieval, initiation, and phonological output. Since these nonsemantic processes are minimized in the triadic comparison task, the multivariate graphic analysis used to analyze the comparison data can provide a relatively pure measure of the integrity of the semantic network that underlies language. In addition, these procedures can provide a richer visualization of the organization of semantic knowledge than traditional tests and univariate analyses because the network derived with multivariate graphic analysis is based on simultaneous examination of the relationships among multiple concepts.

The success of a measure of the abnormality of semantic networks in predicting the rate of cognitive decline in AD patients may lie in the relationship between the disruption of semantic memory and cortical deterioration. Recent theoretical frameworks have viewed semantic memory as a systematically organized network of inter-related concepts and representations (Collins & Loftus, 1975; Rumelhart & McClelland, 1986), which are presumably stored in a distributed fashion in the association cortices (Marshall, 1988; McCarthy & Warrington, 1990). As the association cortices gradually deteriorate in AD, 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 present results, in conjunction with recent findings about the progression of neuropathological changes in AD, may have important clinical implications for assessing the course of the disease. Although the temporal progression of the neuropathological changes of AD are not fully known, studies have suggested that the hippocampus and related structures are usually affected very early in the course of the disease. As the disease progresses, frontal, temporal, and parietal association cortices become increasingly involved (Hyman et al., 1984; Pearson et al., 1985; Braak & Braak, 1991; Arriagada et al., 1992; Bancher et al., 1993; De Lacoste & White, 1993). Consistent with the severe hippocampal formation damage and consequent memory loss that occurs very early in the course of AD, episodic memory tasks are highly sensitive for detecting the disease in its earliest stages (e.g., Welsh et al., 1991). However, because the hippocampal formation is heavily damaged very early in AD, perhaps before a clinical diagnosis is made, the global cognitive decline that occurs after the clinical diagnosis has been found

to be related to deterioration of the association cortices (Terry et al., 1991). Thus, tests of "higher cortical functions," may be more effective than episodic memory tests for staging the progression of dementia over time (Welsh et al., 1991), and, as indicated by the present results, may be quite effective for estimating the rate of future global cognitive decline.

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