Network Graph Analysis of Category Fluency Testing

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Background: Category fluency is impaired early in Alzheimer disease (AD). Graph theory is a technique to analyze complex relationships in networks. Features of interest in network analysis include the number of nodes and edges, and variables related to their interconnectedness. Other properties important in network analysis are ''small world properties'' and ''scale-free'' properties. The small world property (popularized as the so-called ''6 degrees of separation'') arises when the majority of connections are local, but a number of connections are to distant nodes. Scale-free networks are characterized by the presence of a few nodes with many connections, and many more nodes with fewer connections.

Objective: To determine if category fluency data can be analyzed using graph theory. To compare normal elderly, mild cognitive impairment (MCI) and AD network graphs, and characterize changes seen with increasing cognitive impairment.

Methods: Category fluency results (''animals'' recorded over 60 s) from normals (n = 38), MCI (n = 33), and AD (n = 40) completing uniform data set evaluations were converted to network graphs of all unique cooccurring neighbors, and compared for network variables.

Results: For Normal, MCI and AD, mean clustering coefficients were 0.21, 0.22, 0.30; characteristic path lengths were 3.27, 3.17, and 2.65; small world properties decreased with increasing cognitive impairment, and all graphs showed scale-free properties. Rank correlations of the 25 commonest items ranged from 0.75 to 0.83. Filtering of low-degree nodes in normal and MCI graphs resulted in properties similar to the AD network graph.

Conclusions: Network graph analysis is a promising technique for analyzing changes in category fluency. Our technique results in nonrandom graphs consistent with well-characterized properties for these types of graphs.

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Measures of verbal fluency are a standard part of neuropsychologic testing, and are sensitive to early change in Alzheimer disease (AD).[1–4] Verbal fluency may be tested either as lexical fluency (eg, words beginning with the letter ''F'') or category fluency, such as naming of animals or vegetables. Animal naming is part of the neuropsychologic battery of the uniform data set (UDS) adopted by the National Institutes of Health[5] and childhood and adult norms are well developed.[6,7] Verbal fluency reflects the structure of ''semantic space,'' representations of which are closely aligned with our understanding of how semantic information is organized at the neuronal level, particularly in left hemisphere structures.

Graph theory is a method of representing complex data sets composed of related entities and has been applied to a large number of natural and man-made phenomena such as metabolic pathways, genomics and proteomics, and the structure of the World Wide Web. Networks consist of related objects called *nodes*, connected by *edges* representing a direct relationship (link, route, etc.) between nodes.

Prominent among current network studies are ''small world properties'' and ''scale-free'' properties.[8–11] The small world property was first described by Milgram,[12] who observed that it often took only a few connections to send a letter across the country to someone personally unknown by the initial sender. A similar concept has been popularized as the so-called ''6 degrees of separation.'' It arises when the majority of connections, such as your friends in a social network are local, but a number of connections are to distant friends, who in turn have a similar social network. This creates networks best characterized as having short path lengths and relatively high clustering.[11]

The concept of the scale-free network has been analyzed by Barabasi and colleagues.[8,9] The major characteristic of a scale-free network, compared to a graph with random connections, is the presence of a few nodes with many connections, and many more nodes with fewer connections. An example of this is the Internet, where a few sites such as Google or Yahoo have millions of linked pages, whereas vast numbers of Internet pages have very few links to them.

Few studies of network graphs have focused on neuropsychologic output. We aim to determine if category fluency data can be analyzed using graph theory, and to examine patterns of change in normal adults, mild cognitive impairment (MCI) and AD. We hypothesize that changes in network graphs with increasing cognitive impairment will be consonant with the decreased category fluency observed in early AD. We also address how to interpret observed changes between groups, and whether network graph analysis informs the controversy regarding whether reduced category fluency reflects decreased efficiency in processing semantic concepts, or restricted "semantic space" from memory deficits.

METHODS

Subjects

Subjects were drawn from participants in a longitudinal research registry at the Alzheimer Disease Research Center of University Hospitals of Cleveland-Case Western Reserve University seen between February 2006 and May 2007. All subjects provided signed consent and registry assessments were approved by the University Hospitals Institutional Review Board. There were 38 normals, 33 MCI, and 40 AD subjects. The age, sex distribution, and educational attainments were similar across groups. The AD group was older than the normals ($P < 0.01$), and had higher clinical dementia rating (CDR) total, higher CDR sum of boxes score, lower Mini-Mental State Examination, and named fewer animals than normals or MCI (all $P < 0.001$) (Table 1).

Visits were performed in person, attended by the subject and surrogate informant. Visits included a complete neurologic examination and a battery of neuropsychologic tests, including the CDR scale[13] and the Consortium to Establish a Registry for AD version of the Mini-Mental State Examination.[14,15] Diagnosis of AD was made in accordance with NINCDS/ADRDA criteria[16] and MCI by Petersen et al criteria.[17] Diagnosis was assigned through a consensus conference approach.

TABLE 1. Demographic and Neuropsychologic Features of Groups [Mean (SD)]

	Normal	Mild Cognitive Impairment	Alzheimer Disease
N	38	33	40
M:F	19:19	12:21	15:25
Age	72.9 (9.7)	75.2 (10.3)	78.4 (8.1)*
Education	15.9 (2.6)	14.9 (2.6)	13.9 (3.0)
MMSE	29.0 (1.1)	27.6 (2.2)**,†	19.1 (5.8)**
CDR global	0.14 (0.23)	0.56 (0.16)**,†	1.2 (0.52)**
CDR sum of boxes	0.37 (0.69)	2.15 (1.45)**,†	6.93 (2.86)**
Total animals	21.1 (4.6)	16.1 (4.0)**,†	9.7 (5.53)**

*$P < 0.01$ compared with normals.
**$P < 0.001$ compared with normals.
†$P < 0.001$ compared with AD.
CDR indicates clinical dementia rating; MMSE, Mini-Mental State Examination.

Category fluency testing was performed under the supervision of a neuropsychologist (P.K.O.) in accordance with the methods specified by the UDS. In this paradigm, subjects are given 60 seconds to produce a list of animals. The exact instructions are given in Appendix A.

Definitions and Data Procedures

The results were handwritten at the time of testing and only the total score was submitted to the National Alzheimer Coordinating Center, whereas source documentation was retained. Data were extracted from the source documents and quality controlled by 2 independent raters for unusual spellings, and elimination of plural spellings. Obvious variants of the same term were combined ("man" and "human"), but alternative forms of the same species were retained ("cow" and "calf"). In contrast to procedures for counting the total number of items generated, duplicates were not deleted.

A separate network graph was compiled for each group of subjects. The networks were assembled by using animal names as nodes. Edges were created when 2 animal names (such as cat and dog) were named in succession by at least 1 subject. Multiple occurrences of the same combination were ignored, so that no extra weighting is given for frequent combinations compared with unique combinations (eg, cat-dog vs. mouse-aardvark). Figure 1 shows the construction of a sample graph.

The Cytoscape 2.5.1 visualization program was used to generate network graphs using the edge weighted, spring embedded, node unweighted layout.[18] Data were

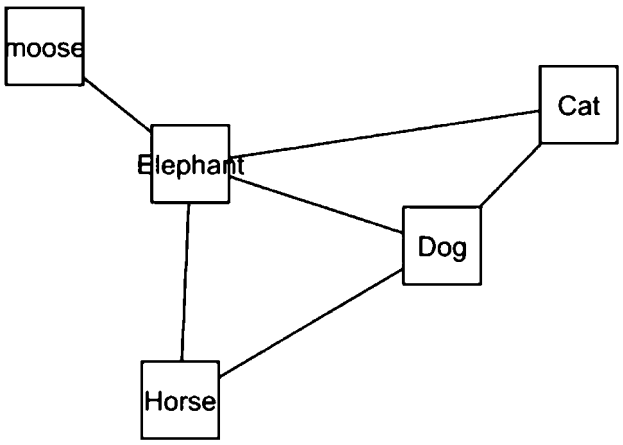

FIGURE 1. Example of graph construction. If 3 individuals gave results of cat, dog, and elephant; cat dog, horse, and elephant; and dog, cat, elephant, and moose, the resultant graph would have 5 nodes and 6 undirected edges of cat-dog, dog-elephant, dog-horse, horse-elephant, cat-elephant, and elephant-moose. The highest node degree is elephant with 4 edges connecting it to other nodes. The average path length for elephant is 1.0 as it is 1 edge to every other node. The characteristic path length for horse would be (1+1+2+2)/4 = 1.5. See text for other examples in calculating node and graph properties.

also analyzed by the Cytoscape plugin NetworkAnalyzer, a program for graph analysis.[19] Statistical analyses were performed with SPSS for Windows 15.0 (SPSS Inc, 2007).

Network Definitions

In a network of N nodes and K edges, the following terms may be defined for each node, and averaged over all nodes.

Degree: Node degree, k, is the number of nodes to which a given node has a direct connection.

Example: In Figure 1, the node degree of "elephant" is 4.

Average node degree: Over all nodes in a graph average node degree of the graph is

$$\langle k \rangle = \frac{2K}{N}$$

Example: In Figure 1, the average node degree by manual counting is $[(1 \times 1) + (1 \times 4) + (1 \times 3) + (2 \times 2)]/5 = 1.4$ or from the formula above $\langle k \rangle = (2 \times 6)/5 = 1.4$.

Clustering coefficient: The clustering coefficient is a measure of connectedness of neighbors of a node to each other, and is related to the number of triangles between a node and any 2 neighbors.

The clustering coefficient is calculated as the ratio of the existing edges E_i to the total number of possible edges between a node and its immediate neighbors and is by the formula. Clustering coefficients vary from 0 to 1. A given node's clustering coefficient = 0 when none of the nodes attached to it and linked to each other. The clustering coefficient = 1 when all of the neighbors are linked to each other. The formula for the clustering coefficient for a node is

$$cc(i) = \frac{2E_i}{k_i(k_i - 1)}$$

The average clustering coefficient for the graph is

$$CC = \frac{1}{N}\sum_{i=1}^{N} CC(i)$$

Example: In Figure 1, the node labeled "dog" has node degree k (i) = 3 ("horse," "elephant," and "cat"), and E_i is 2 (existing edges between "horse"-"elephant," and "elephant"-"cat"). Using the equation above cc (dog) = 0.66. Similarly, because "horse" has node degree 2, and 1 existing edge between its neighbors (edge between "elephant" to "dog"), its clustering coefficient is 1.0. The clustering coefficient for "moose" is undefined, as it results in division by zero. For the other nodes, the clustering coefficient for "cat" equals 1.0, and for "elephant" is 0.33.

Over all 5 nodes in the graph, the average clustering coefficient is 0.6.

Path length: The path length, l, between any 2 nodes is the smallest number of edges in the path connecting them. The characteristic path length of a graph, L, is the average of all the shortest path lengths between all nodes in the graph.

Example: In Figure 1, the path length from "moose" to "elephant" is 1, and "moose" to "cat" is 2. For "moose" the average path length is 1("moose"-"elephant") + 3 × 2(2 each for "moose"-"horse"; "moose"-"dog"; "moose"-"cat")/4 = 1.75.

The characteristic path length of the graph is the average of the shortest average path lengths over all nodes.

Example: In Figure 1, the average for all shortest paths between pairs of nodes is 1.4.

The diameter of a graph is the maximal distance between any pair of its nodes.

Example: In Figure 1, the diameter is 2, as this the maximum shortest path between any 2 nodes.

Data Analysis Plan for Network Comparisons

As network graph variables are interrelated, it is important to normalize and compare networks with standard models. Initial analysis compared each network graph with a random graph of equal N and average node degree for each group. The Spectral NET program[20] was used to generate the random graphs used for comparisons.

The small world properties of each graph were evaluated by several methods as the literature contains several definitions based on the Watts and Strogatz model.[11] Bassett and Bullmore[21] combined path length and clustering coefficient to create a normalized measure for small world properties; Sporns and Zwi[22] compute a similar measure scaled to network size. The formulas for

TABLE 2. Network Statistics by Group, and Comparison With Random Graph Simulations and Determination of "Small World" Properties

	Normals	MCI	AD
Nodes (N)	173	124	83
Edges (K)	532	398	269
Clustering coefficient ($CC_{network}$)	0.21	0.22	0.31
Average node degree $\langle k \rangle$	6.15	5.82	6.48
Characteristic path length ($L_{network}$)	3.27	3.18	2.68
Network diameter	9	9	6
Erdös-Renyi simulation			
Probability of connectedness $P = \langle k \rangle / N = CC_{random}$	0.0355	0.047	0.078
Characteristic path length $L_{random} = \ln N / \ln[(2K/N)-1]$	3.14	2.85	2.59
Regular lattice ($\langle k \rangle = 6$)			
$\gamma_{lattice}$	0.6	0.6	0.6
$\lambda_{lattice}$	14.7	10.5	6.92
$\lambda = (L_{network}/L_{random})$*	1.04	1.12	1.06
$\gamma = (CC_{network}/CC_{random})$*	5.92	4.68	4.02
$\sigma = \gamma/\lambda$*	5.50	4.20	3.79
λ_{scaled}**	0.019	0.043	0.035
γ_{scaled}**	0.31	0.31	0.44

*Adapted from *Neuroscientist*. 2006;12:512–523.
**Adapted from *Neuroinformatics*. 2004;2:145–162.
AD indicates Alzheimer disease; MCI, mild cognitive impairment.

this are given in Table 2. As the small world property implies that a graph is intermediate between a lattice (where nodes are connected to all neighbors) and a graph with random connections, both random and lattice models of equal N and $< k > = 6$ were generated to compare with our results with averages taken over 10 exemplars.

RESULTS

Representative views of networks generated by our procedures are shown in Figure 2. Table 2 shows network metrics as described in the methods. With increasing cognitive impairment, characteristic path lengths decline and clustering coefficients rise.

Compared with random graphs, the observed clustering coefficients are much higher whereas characteristic path length is approximately the same. This is consistent with the presence of small world properties and there is a reduction in small world properties of the MCI and AD groups relative to the normal group.

Figure 3 shows the relationship of the interrelated variables of node degree, clustering coefficient, and characteristic path length for each node.

To test the importance of lower frequency nodes, which seem to be less frequent with increasing cognitive impairment, we performed 2 additional analyses. The rank correlation of the 25 most commonly named items for normal-MCI was 0.8, normal-AD was 0.83, and MCI-AD 0.75 ($P \leq 0.001$ for all comparisons) (Table 3). We also filtered networks by eliminating low-degree nodes. Removing nodes with a node degree < 3, the normal group had 96 remaining nodes, mean clustering coefficient 0.29 and characteristic path length 2.625. Similar analysis of the MCI group showed 69 residual nodes, clustering coefficient 0.359, and characteristic path length 2.342. These results are similar to the results for the AD group, as shown in Table 2.

In a scale-free network, a log-log plot of a node's degree, k, versus its probability [$P(k)$], results in a straight line over much of the distribution. Excluding nodes with clustering coefficients of zero, all group networks show scale-free properties with slope for normal = 0.968 ($R^2 = 0.645$); MCI = 0.854 ($R^2 = 0.528$): AD = 0.805 ($R^2 = 0.659$) (Fig. 4).

DISCUSSION

Our study had 3 components: (1) networks can be created from category fluency data, in this case, the cooccurrence of animals named, resulting in a "undirected information network." (2) The validity of this approach depends on the networks having properties associated with nonrandom networks, as described below. (3) Review our results relative to theories about semantic memory deficits in AD.

The initial aim is amply demonstrated in the results and highly encouraging with regard to using graph theory to model neuropsychologic data. Our findings extend previous investigations of category fluency by using graph theory methods to map semantic space and directly

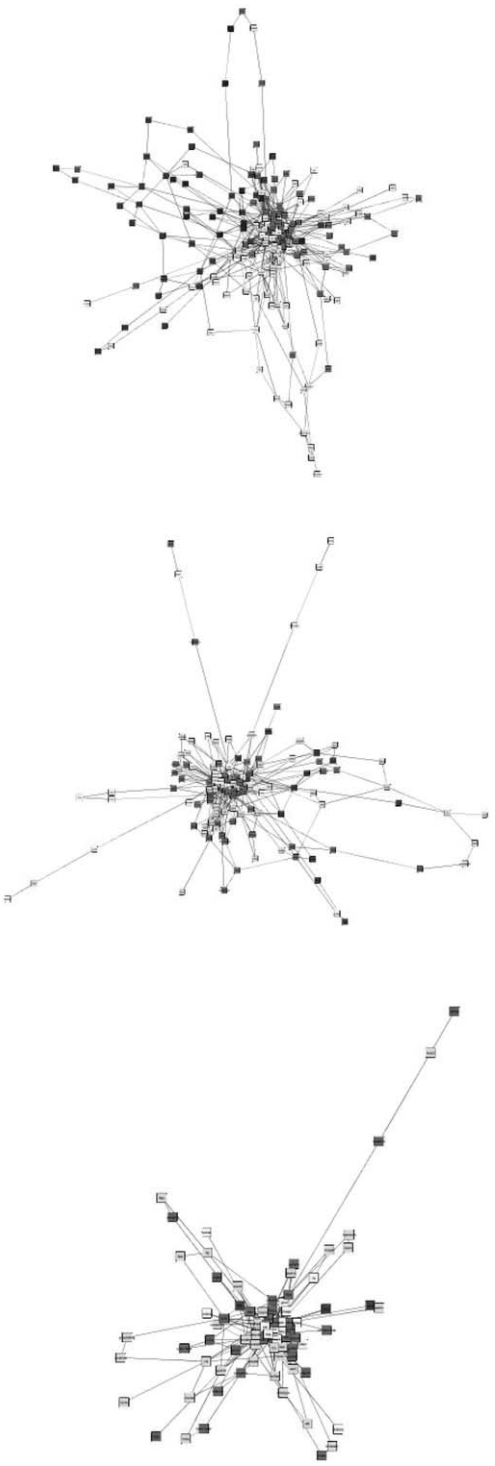

FIGURE 2. Representative views of networks. Top panel: normals (173 nodes; 532 edges). middle panel: mild cognitive impairment (124 nodes, 398 edges). Bottom panel: Alzheimer's disease (83 nodes, 269 edges). Visualization is performed with the Cytoscape 2.5.1 unweighted spring-embedded algorithm.[18]

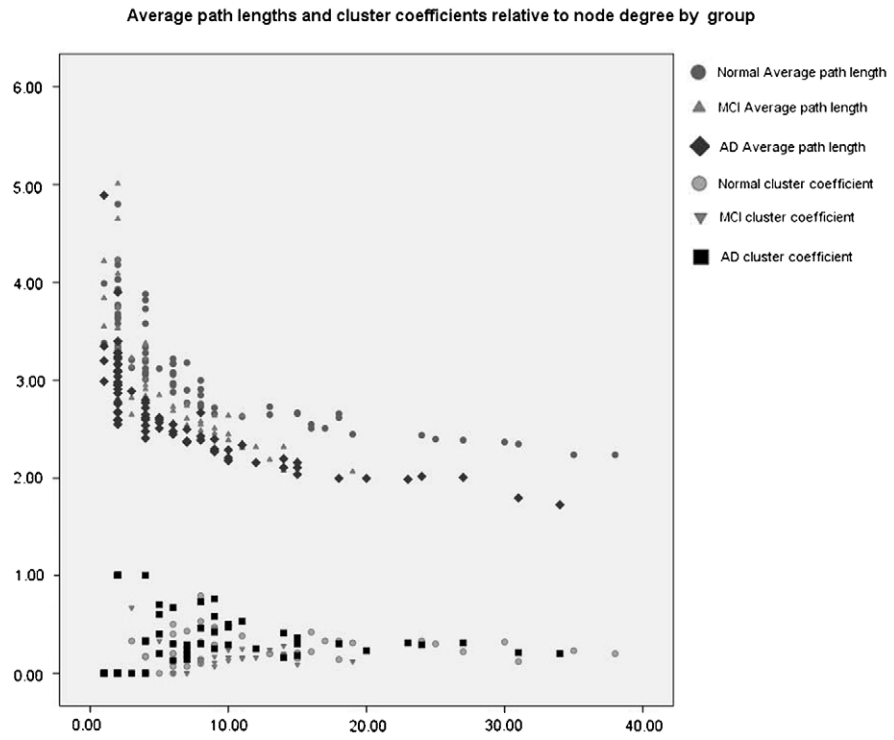

FIGURE 3. Change in network parameters as a function of cognition: clustering coefficients and characteristic path length versus node degree. Each point represents the topological properties of a node, which is a named animal species.

compare networks generated by different populations using network parameters.

Validation of the initial aim depends on the demonstration of properties associated with nonrandom networks. The most important features of networks are "small world" properties and scale-free properties. The small world concept is salient for social networks as described in the Introduction, but has implications for biologic networks including connectivity of cat and macaque cerebral cortex, brainstem reticular system, and networks derived from electroencephalogram (EEG) and functional magnetic resonance imaging studies.[23–25] Formally, it refers to graphs intermediate between an ordered lattice structure where all nodes are connected to all neighbors, and a random graph; as such, it may represent an optimal "wiring" strategy.[11]

The concept of the scale-free network has been analyzed by Barabási and colleagues.[9,10] In contrast to a graph where connections are random, in a scale-free network, there are a few nodes with many connections, and many more nodes with fewer connections. All of the group networks show scale-free properties, best demonstrated in plots of the node degree distribution following a so-called "power law."

As a starting point for our exploratory analysis, our results are consistent with these 2 properties, and begin to allow comparison with networks derived from other measures, and indirect comparisons with other studies involving category fluency.

Implications for Semantic Networks in AD

The 2 major theories for decreased category fluency in AD involve reduced search efficiency and decreased semantic access.[26,27] Decreased semantic memory is an early finding in AD and can be conceived as a form of "pruning" of semantic space, consistent with the results of Chertkow and Bub.[27] The mechanisms underlying category fluency involve multistep processing, including autopriming and the need to recall and suppress previously mentioned items.[28] There is conflicting evidence about priming effects in AD, and it has been difficult to fully dissociate decreased semantic access from decreased processing efficiency.[28]

The high correlation of commonly named items, and the preservation of graph properties in all groups suggest that basic category fluency mechanisms are similar across groups. The reduction in graph complexity (fewer nodes and shorter path lengths) beginning in MCI compared with normal and more pronounced in AD supports the concept that decreased semantic access is an early finding in MCI as in AD, as reported in several studies.[29–31]

Reduced processing efficiency could be related not only to increased inter-item timing (which we did not measure) but also due to decreasing in clustering and switching in AD, as reported by Troyer et al and others.[32,33] The final graphs do not lend themselves easily to measuring clustering and switching, but additional studies based on graph theory may address this issue as well.

TABLE 3. Most Commonly Named Animals Ranked by Frequency

Normals	N = 38	MCI	N = 33	AD	N = 40	All Groups	N = 111
Dog	35	Dog	33	Dog	40	Dog	108
Tiger	35	Cat	32	Cat	37	Cat	102
Cat	33	Lion	24	Horse	20	Lion	72
Lion	33	Elephant	20	Cow	19	Elephant	64
Elephant	30	Cow	17	Lion	15	Tiger	63
Cow	27	Horse	16	Elephant	14	Cow	62
Horse	25	Tiger	15	Tiger	14	Horse	58
Giraffe	25	Snake	14	Pig	11	Bear	42
Pig	21	Giraffe	13	Bear	10	Pig	42
Bear	20	Bear	13	Monkey	8	Giraffe	41
Monkey	17	Monkey	13	Bird	8	Monkey	38
Goat	12	Pig	12	Deer	8	Snake	33
Mouse	12	Zebra	11	Snake	7	Mouse	30
Snake	12	Donkey	11	Mouse	7	Bird	28
Deer	11	Mouse	11	Sheep	6	Zebra	27
Hippo	11	Bird	10	Rabbit	5	Deer	23
Zebra	11	Rabbit	9	Donkey	5	Goat	23
Bird	11	Goat	8	Zebra	5	Whale	23
Alligator	11	Alligator	7	Hippo	5	Rabbit	22
Chicken	11	Sheep	7	Mule	5	Hippo	22
Buffalo	10	Chicken	7	Fish	5	Alligator	21
Rat	9	Squirrel	7	Giraffe	5	Chicken	21
Rhino	9	Lamb	6	Camel	5	Squirrel	20
Squirrel	9	Kangaroo	6	Kangaroo	4	Kangaroo	19
Kangaroo/ raccoon	9	Deer	6	Squirrel	4	Fish	17

Correlations normal-MCI $r = 0.8$ ($P < 0.001$); normal-AD $r = 0.83$ ($P < 0.001$); MCI-AD $r = 0.75$ ($P < 0.001$).
AD indicates Alzheimer disease; MCI, mild cognitive impairment.

A study comparing category naming in AD patients and normal controls by Chan et al[34] used multidimensional scaling and pathfinder analysis to compute network similarity. Their tasks are conceptually related to ours, and there is homology in the clustering of animals. However, their paradigm differed in details from our prompted list for category naming making direct comparisons difficult.

Comparison With Other Network Models of Controlled Word Association

Semantic networks are of interest because of the centrality of language to our daily experience. The history of semantic network models can be traced back to Collins and Quillian's[35] tree-structured hierarchical model proposed in 1969. In their model, concepts are represented as nodes in a tree-structured hierarchy, with connections determined by class-inclusion relations.

Steyvers and Tenenbaum[36] explored controlled word association datasets involving semantics such as word associative networks, Roget's thesaurus and the WORDNet database. In the model closest to our analysis, using an undirected associative word network, they reported a characteristic path length of 3.04 and clustering coefficient of 0.186, which are strikingly close to our results for normal individuals. All of these semantic networks showed both small world and scale-free properties; word association networks are based on pooled responses from population samples, a methodology akin to ours.

Network Studies and AD

Stam et al[23] studied spatial patterns of EEG synchronization likelihoods in normal elderly and AD patients and showed small world network patterns in both groups. In their study, nodes are physical EEG electrodes and synchronization likelihood forms edges with the use of threshold values, each individual creates a "personal network" averaged across groups. Our network graphs are not based on an anatomic template, and analysis and conclusions are derived from pooled group output. Although their network parameters change opposite to ours, the differences in paradigms accounts for the differences and we agree with the conclusion of decreased processing efficiency in AD.

CONCLUSIONS

The network graphs shown do not imply maps of anatomically discrete brain areas involved in object naming. Grossman et al[37] and Damasio et al[38] demonstrate activation of multiple left hemisphere structures with animal naming. Concept retrieval for animal naming activates portions of the right temporal lobe.[37] Patterns of words produced may serve to prime the brain to produce semantically related words and a spreading activation model across semantic networks has been proposed.[38,39]

Other aspects of these networks may be related to clustering and switching among semantic subcategories, and measures of group similarity. This would include assortivity, the likelihood of consecutive items belonging

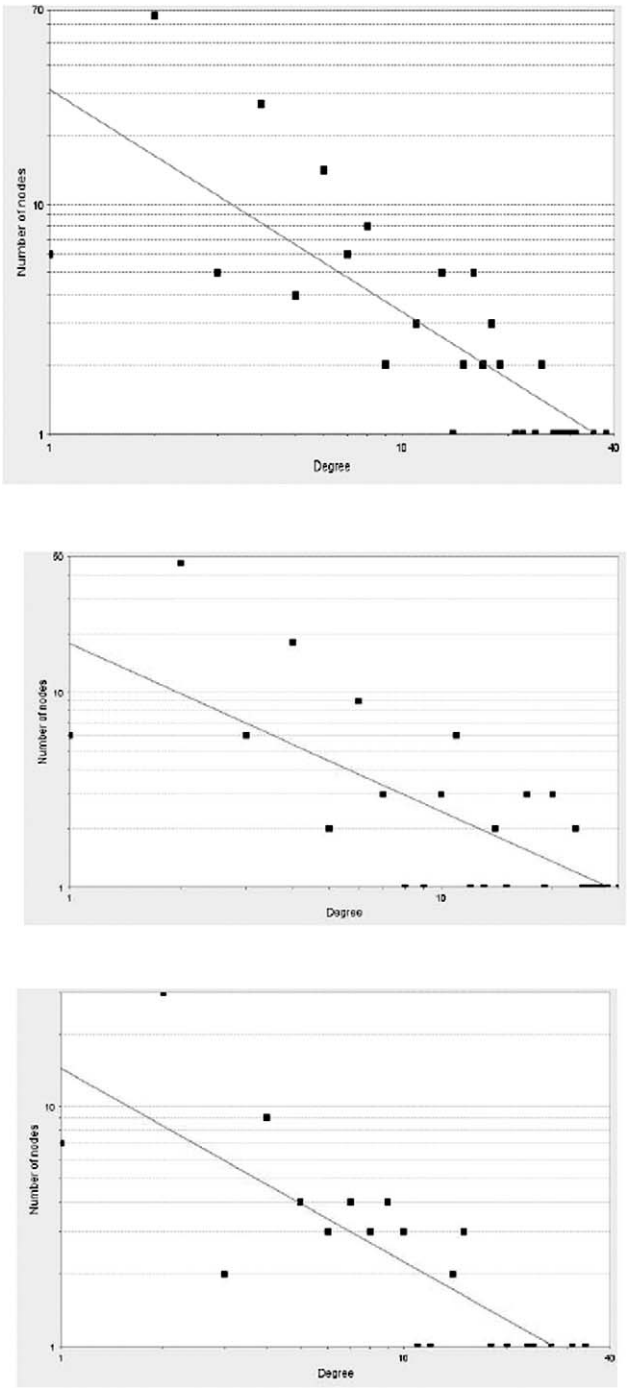

FIGURE 4. Power law distributions for k versus $P(k)$ (scale-free properties). Top panel: normals slope = -0.968 ($R^2 = 0.645$); middle panel: mild cognitive impairment: slope = -0.854 ($R^2 = 0.528$); lower panel: AD; slope = -0.805 ($R^2 = 0.659$).

to a semantic subcategory[40] and collaborative filtering and recommender systems, which provides predictive models based on the likelihood of subjects from different groups producing similar chains of animal names. However, analysis of these measures is beyond the scope of this paper.

Other limitations relate to the nature of the graphs themselves. Our network graphs consist of unweighted and undirected edges for simplicity of analysis. Pairs of items that occur frequently (eg, ''cat-dog'' or ''dog-cat'') are represented as a 2 nodes and a single edge. Analysis of weighted edge networks is important and suggests directions for further study. Network measures are dependent on group size, and our conclusions should be replicated in larger study populations. The interrelatedness of graph measures such as node degree, clustering coefficients and path lengths, is a complex topic and warrants a conservative approach to interpretation of results. Overall, network graph analysis may provide a new way to examine brain and language output as a function of cognitive impairment, and may be adapted to compare similar tasks across disease states.

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APPENDIX A

Description:
This is a widely used measure of semantic memory(verbal fluency, language). The subject is asked to name different exemplars of a given semantic category, and the number of unique exemplars named is scored.
The procedure is adapted from CERAD administration and scoring procedures for Verbal Fluency (Morris et al, 1989)

Administration of Category Fluency test
[SAY]: ''I am going to give you a category and I want you to name, as fast as you can, all of the things that belong to that category. For example, if I say 'articles of clothing', you could say 'shirt', 'tie', or 'hat'. Can you think of other articles of clothing?''
Allow up to 20 seconds for the subject to produce two responses. Circle the number corresponding to the subject's responses, and read the associated instruction.

Response Code
Instructions
0 (no response)
''You could have said 'shoes' or 'coat' since they are articles of clothing''
1 (One or more incorrect responses)
''No, _____is (are) not an article of clothing. You could have said 'shoes' or 'coat' since they are articles of clothing''
2 (One or more correct responses, no incorrect responses)
''That's right''. You could also have said 'shoes' or 'coat'
3 (One or more correct responses, one or more incorrect responses)
''_____is (are) correct, but _____ is (are) not an article of clothing. You could also have said 'shoes' or coat'
4 (two or more correct responses)
''That's right''

[Say] ''Now I want you to name things that belong to another category: Animals. You will have one minute. I want you to tell me all the animals you can think of in one minute. ready? Begin.

Start timer as you say ''Begin''. Write actual responses as legibly as possible on the *Worksheet for Category fluency-Animals* (master form provided in the tabbed section entitled ''UDS Neuropsych test forms''). Stop the procedure at 60 seconds. One prompt (''Tell me all of the animals you can think of'') is permitted if the participant makes no response for 15 seconds or expresses incapacity (e.g. ''I can't think of any more''). It is also permissible to repeat the instruction or category if the subject specifically requests it.

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