Semantic Memory Deficits in Low-educated Patients with Alzheimer's Disease

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Background/Purpose: Although a deficit of semantic memory is evident in the dementia of the Alzheimer's type (DAT), the underlying neuropsychologic mechanism remains controversial. Breakdown of the semantic network during the course of DAT and an inability to access semantic information have been postulated as possible explanations, but supporting data are limited, particularly in low-educated patients. This study examined semantic memory in low-educated patients with different degrees of dementia severity.
Methods: In total, 197 adult subjects were recruited, including 165 DAT patients and 32 normal controls. Subjects were divided into four subgroups according to their dementia severity. All subjects completed an episodic memory task, the Six-Object Memory Test, and semantic memory tasks including the Object Naming Test, the Remote Memory Test and the Semantic Association of Verbal Fluency Test. One-way ANOVA and ANCOVA with a *post hoc* Scheffe's procedure were used to evaluate differences between groups.
Results: All patients, irrespective of the degree of dementia, showed impaired performance on the Six-Object Memory Test [$F(4, 163) = 69.95$, $p < 0.0001$ for immediate recall; $F(4, 163) = 41.34$, $p < 0.0001$ for delayed recall]. On the semantic memory tasks, patients with moderate to severe dementia showed impaired performances on the Object Naming Test [$F(4, 180) = 28.25$, $p < 0.0001$] and the Remote Memory Test [$F(4, 167) = 26.22$, $p < 0.0001$ for recall; $F(4, 167) = 34.80$, $p < 0.0001$ for recognition], while all patients performed defectively on the Semantic Association of Verbal Fluency Test [$F(4, 194) = 70.43$, $p < 0.0001$].
Conclusion: Our results thus partially support the hypotheses that a loss of semantic structure and an inability to access semantic knowledge occur in the pathogenesis of DAT. [*J Formos Med Assoc* 2006;105(11): 926–935]

Key Words: Alzheimer's disease, low education, semantic memory

Memory deficit is the most prominent and earliest recognized feature of dementia of the Alzheimer's type (DAT).[1–3] It is now well established that impairment of episodic memory is a major feature of DAT patients.[4,5] In addition, a deficit of semantic memory in these patients has also been reported.[6–9] However, this deficit is usually overshadowed by the impairment of episodic memory. Studies of semantic memory problems in DAT patients proposed that the impairment of semantic memory is also evident in early-stage DAT, and that this deficit might be more valuable in discriminating between DAT and other kinds of dementia.[4,10–13] However, the underlying neuropsychologic mechanism responsible for this deficit in DAT is still a matter of debate.[13,14]

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Loss of semantic knowledge is a result of a breakdown in the semantic network during the course of DAT,[15–18] even in the early stage.[10,18] Impaired access to semantic information, however, has also been postulated to account for the deficit of semantic memory in DAT patients.[19–22] Important data supporting the structural hypothesis mainly come from Hodges et al.[6,9,23] They used clinical tests such as visual confrontation naming and semantic association of verbal fluency to examine the semantic memory deficits in DAT patients. The results of these tests showed a breakdown in the hierarchical structure of patients' semantic knowledge. Recently, based on multidimensional scaling (MDS), Chan et al[24–26] examined the semantic memory function in patients with DAT, and their results further support the structural hypothesis. However, other studies found that a retrieval deficiency in DAT patients might contribute to their poor performance in the semantic memory tasks.[14,22,27] Nebes and Hallighan[28,29] reported that not all DAT patients exhibited normal semantic memory, and they attributed some patients' impaired performance on the semantic memory tests to an overload of attentional demands for retrieval.

An incompatible degree of severity of dementia in patients with DAT in previous studies might account for the inconsistent findings. For instance, several studies reported remarkable semantic memory problems in DAT patients, without mentioning the severity of their dementia.[10,18,23] Other studies concluded that early DAT patients evidenced semantic memory deficits, without comparing them to patients in other stages of the disease.[12,30] Our review found only two studies which investigated semantic memory performance in patients with different degrees of severity,[4,31] and both reported that not all questionable-to-mild DAT patients (MMSE[32] > 17) had semantic memory deficits. Therefore, the heterogeneous samples of DAT patients used in previous studies may have led to the inconsistencies in the reported findings on semantic memory deficits.

The acquisition of semantic knowledge depends mostly upon formal education. Thus, there is an implied relationship between the extent of formal education an individual receives and semantic knowledge acquisition. Most DAT patients included in studies of semantic knowledge had at least a high-school education. However, whether DAT patients with only an elementary school education also exhibit semantic memory dysfunction and whether their defective pattern is compatible with patients with higher education levels have not been investigated. The goal of this study was to avoid the methodologic failures of previous studies in exploring the feasibility of the function and structural hypotheses of semantic memory dysfunction in DAT. Accordingly, we recruited a cohort of low-educated DAT patients with different degrees of dementia, as evaluated by the Clinical Dementia Rating Scale (CDR).[33–35] The following specific questions were thus investigated: (1) whether semantic memory function of DAT patients with low education levels is similar to their episodic memory function, i.e. vulnerable to the disease process; (2) whether a deficit of only semantic retrieval reflects a loss of access to semantic knowledge, or of both semantic retrieval and recognition that might implicate a breakdown of the semantic function system; (3) whether a retrieval deficit becomes evident in the early stage of DAT, i.e. in the questionably or mildly demented patient, or in the late stage, i.e. in the moderately or severely demented patient; (4) whether semantic retrieval and recognition deficits become evident in the early stage of DAT, i.e. in the questionably or mildly demented patient, or in the late stage, i.e. in the moderately or severely demented patient.

Methods

Subjects

A total of 197 subjects, including 165 patients with DAT and 32 healthy control subjects participated in this study. All participants signed a written informed consent prior to enrollment. The diagnosis of DAT was made by neurologists at the National Taiwan University Hospital (NTUH) or at the Chang-Gung Memorial Hospital (CGMH) according to the criteria proposed by the National Institutes of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),[36] which comprised the study inclusion and exclusion criteria.

DAT patients were recruited when they visited the neurology clinics of two medical centers in northern Taiwan, i.e. NTUH and CGMH. Patients with a history of suspected psychiatric problems, cerebrovascular insults, traumatic brain injuries, or other major medical illnesses (e.g. cancer, thyroid dysfunction, etc.) were excluded.

The 165 DAT patients were divided into the following four subgroups on the basis of their CDR scores: *questionable* ($n=55$, CDR = 0.5), *mild* ($n=60$, CDR = 1.0), *moderate* ($n=39$, CDR = 2.0), and *severe dementia* ($n=11$, CDR = 3.0). The mean age, years of education, and MMSE scores of DAT patients and healthy control subjects are shown in Table 1.

Memory measures

Because of the low educational level of our subjects ($M=6.42$, $SD=4.89$), the use of conventional episodic memory tasks such as the Logical Memory Test of the Wechesler Memory Scale–Revised[37] and semantic memory tasks such as the priming task[29] and the DRM paradigm[38,39] was considered inappropriate. Therefore, all subjects were assessed by a battery of neuropsychologic tests known as the Short-Form Higher Cortical Function Examination.[40] This battery was designed for the Taiwanese population with low education level. In this battery, we selected memory subtests to evaluate subjects' semantic memory performance. In brief, these subtests were as follows.

Episodic memory

Six-Object Memory Test: Six familiar objects—soap, an eraser, scissors, a coin, a battery, and a candle—were presented to the subjects. In each of the trials, subjects were asked to name these objects and to remember them. Five trials were needed to complete the learning phase of the test. Once subjects answered correctly in two consecutive trials, no

Table 1. Mean age, years of education and MMSE scores of patients and controls

	Total		Controls		Subgroups of AD patients: Questionable		Mild		Moderate		Severe		*F*
	n	M ± SD	*n*	M ± SD	*n*	M ± SD	*n*	M ± SD	*n*	M ± SD	*n*	M ± SD	
Age	197	71.99 ± 8.76	32	69.81 ± 5.56	55	71.02 ± 10.67	60	72.97 ± 8.55	39	72.56 ± 8.03	11	75.82 ± 7.91	1.43
Education	197	6.42 ± 4.89	32	8.88 ± 4.37	55	6.56 ± 4.39	60	6.57 ± 5.59	39	4.28 ± 3.95	11	5.36 ± 4.78	4.30*
MMSE	79	21.01 ± 7.59	32	28.03 ± 2.01	17	21.29 ± 3.22	14	16.79 ± 5.74	14	10.57 ± 3.20	2	9.00 ± 0.00	79.07†

$^*p<0.05$; $^†p<0.0001$. M ± SD = mean ± standard deviation; MMSE = Mini-Mental State Examination.

further trials were presented. After a 10-minute delay, subjects were then asked to report a free recall of the six objects without prior warning. The maximum correct score of learning was 30, and that of delayed recall was 6.

Semantic memory

Object Naming Test: [41] This test consisted of naming 16 familiar objects without cueing (e.g. comb, ring, key, cup, chopsticks, etc.). The maximum correct score was 16.

Remote Memory Test: This test consisted of five questions about important life events in Taiwanese society, including mainly general knowledge about local culture. These questions were as follows: "What do people do at the Tomb Sweeping Festival?", "What date is the Mid-Autumn Festival?", "Which month is the so-called ghost-month?", "When do people display the spring festival poetic couplets?", and "What is the traditional food in mid-winter?" The maximum correct score for both recall and recognition versions was 15.

Semantic Association of Verbal Fluency Test: This test, developed by Hua et al,[42] consisted of three different semantic categories—fruit, fish, and vegetables. Subjects were asked to report as many items within a category as possible in 1 minute. The score was a summation of correct responses in the three categories.

Data analysis

One-way ANOVA and ANCOVA with a *post hoc* analysis using Scheffe's procedure, and Pearson's correlation were used to evaluate differences between groups. Statistical significance was defined as a probability value of less than 0.05. Commercially available software (SPSS version 11.0; SPSS Inc., Chicago, IL, USA) was employed.

Results

One-way ANOVA revealed a significant difference in education and MMSE scores between controls and the four DAT groups [$F(4, 197) = 4.30$, $p < 0.05$ for education; $F(4, 79) = 79.07$, $p < 0.0001$ for

Table 2. Episodic memory performance of low-educated patients and controls

	Total		Controls		Subgroups of AD patients								F
					Questionable		Mild		Moderate		Severe		
	n	M ± SD	*n*	M ± SD	*n*	M ± SD	*n*	M ± SD	*n*	M ± SD	*n*	M ± SD	
Six-Object Memory Test													
Immediate recall	163	19.29 ± 8.32	32	28.06 ± 1.46	38	23.18 ± 4.20	51	18.16 ± 5.51	32	12.63 ± 7.36	10	3.50 ± 5.64	65.95*
Delayed (10 min) recall	163	3.13 ± 2.51	32	5.88 ± 0.42	38	4.05 ± 1.93	51	2.65 ± 2.25	32	1.06 ± 1.79	10	0.00 ± 0.00	41.34*

*$p < 0.0001$. M ± SD = mean ± standard deviation.

MMSE]. *Post hoc* analysis of pair-wise differences in mean years of education between the four subgroups using Scheffe's procedure showed a significant difference only between the healthy control group and the patient group with moderate severity of dementia. In addition, the difference of MMSE scores was significant between any two of these four groups, with the exception of the difference between the moderate and the severe groups. One-way ANOVA revealed no significant differences in mean age among groups.

Episodic memory

Six-Object Memory Test. As shown in Table 2, one-way ANOVA revealed a remarkable difference between the healthy controls and all four DAT subgroups for both immediate and delayed recall scores [$F(4, 163) = 69.95$, $p < 0.0001$ for immediate recall; $F(4, 163) = 41.34$, $p < 0.0001$ for delayed recall]. *Post hoc* analysis with Scheffe's procedure revealed significant differences in the analysis of delayed recall between each pair of DAT groups and controls, with the exception of moderate and severe DAT groups ($p = 0.60$) (i.e. control group > questionable group > mild group > moderate group = severe group). Because of the significant difference in educational level between healthy controls and the four DAT groups [$F(4, 197) = 4.30$, $p < 0.05$], ANCOVA with years of education was used as a covariate to analyze memory performance. The results revealed the same pattern as found in the analysis by one-way ANOVA.

Spearman's correlational study (Table 3) revealed that there was a significant negative correlation between dementia severity and both immediate and delayed recall ($r = -0.78$, $p < 0.0001$ for immediate recall; $r = -0.69$, $p < 0.0001$ for delayed recall).

Semantic memory

Object naming. As shown in Table 4, one-way ANOVA revealed a significant difference in object naming results between healthy controls and the four DAT groups [$F(4, 180) = 28.25$, $p < 0.0001$]. *Post hoc* analysis with Scheffe's procedure showed a different pattern from that of the episodic memory performance with only the moderate and the severe groups performing significantly worse than the other three groups on this test (i.e. control group = questionable group = mild group > moderate group = severe group). Because of the significant difference in educational level between healthy controls and the four DAT

Table 3. Spearman's correlation between dementia severity and memory performance

	CDR	Object naming	Semantic association of verbal fluency	Remote memory – recall	Remote memory – recognition	Six-Object Memory Test – immediate recall	Six-Object Memory Test – delayed (10 min) recall
CDR	1.00						
Object naming	–0.58*	1.00					
Semantic association of verbal fluency	–0.77*	0.60*	1.00				
Remote memory – recall	–0.62*	0.71*	0.67*	1.00			
Remote memory – recognition	–0.62*	0.51*	0.62*	0.54*	1.00		
Six-Object Memory Test – immediate recall	–0.78*	0.65*	0.76*	0.66*	0.65*	1.00	
Six-Object Memory Test – delayed (10 min) recall	–0.69*	0.43*	0.65*	0.50*	0.42*	0.80*	1.00

**p* < 0.0001. CDR = Clinical Dementia Rating Scale.*

Table 4. Semantic memory performances of the low-educated patients and controls

	Total		Controls		Subgroups of AD patients								
					Questionable		Mild		Moderate		Severe		F
	n	M ± SD	n	M ± SD	n	M ± SD	n	M ± SD	n	M ± SD	n	M ± SD	
Object naming	180	14.18 ± 3.44	32	15.91 ± 0.39	45	15.09 ± 1.82	54	15.09 ± 2.19	39	12.31 ± 4.43	10	7.00 ± 3.86	28.25*
Semantic association of verbal fluency	194	21.31 ± 11.01	32	34.34 ± 7.95	55	26.05 ± 7.57	60	19.32 ± 6.37	38	10.92 ± 7.00	9	3.11 ± 4.04	70.43*
Remote memory – recall	167	11.54 ± 4.58	32	14.81 ± 0.74	38	13.18 ± 2.75	51	11.71 ± 3.61	36	8.94 ± 5.13	10	3.30 ± 5.19	26.22*
Remote memory – recognition	167	13.14 ± 3.60	32	15.00 ± 0.00	38	14.61 ± 1.24	51	13.65 ± 2.02	36	11.53 ± 4.34	10	4.80 ± 5.14	34.80*

$p < 0.0001$. M ± SD = mean ± standard deviation.

groups [$F(4, 180) = 22.93$, $p < 0.01$], ANCOVA with years of education was used as a covariate to analyze memory performance. The results revealed the same pattern as found with the analysis by one-way ANOVA.

Remote memory. A significant main effect was found for groups in both the recall and the recognition versions [$F(4, 167) = 26.22$, $p < 0.0001$ for recall; $F(4, 167) = 34.80$, $p < 0.0001$ for recognition]. In the recall version, *post hoc* analysis with Scheffe's procedure showed that controls had significantly better scores than all four DAT groups, except for a lack of difference between the control and the questionable group or between the questionable group and the mild group (i.e. control group = questionable group, questionable group = mild group > moderate group > severe group). The performance pattern on the recognition version was similar to that of the Object Naming Test with the moderate and the severe groups performing significantly worse than the other three groups on this test (i.e. control group = questionable group = mild group > moderate group = severe group). Again, because of the significant difference in educational level between healthy controls and the four DAT groups [$F(4, 167) = 21.27$, $p < 0.01$ for recall; $F(4, 167) = 27.73$, $p < 0.01$ for recognition], ANCOVA with years of education as a covariate was used to analyze memory performance. The results revealed the same pattern as found with the analysis by one-way ANOVA.

Semantic association of verbal fluency. One-way ANOVA showed a significant main effect for the groups [$F(4, 194) = 70.43$, $p < 0.0001$]. A similar pattern of episodic memory performance was evident, with significant differences between each pair of DAT groups and controls, with the exception of moderate and severe DAT patients (i.e. control group > questionable group > mild group > moderate group = severe group). Because of the significant difference in educational level between healthy controls and the four DAT groups [$F(4, 197) = 56.98$, $p < 0.01$], ANCOVA with years of education as a covariate was used to analyze their memory performance. The results still revealed the same pattern as found with the analysis by one-way ANOVA.

An additional correlational study was conducted to examine the relationship between dementia severity and the semantic memory deficits using Spearman's rank-order correlation. The results (Table 3) also revealed a significant negative correlation between dementia severity and all the semantic memory tests ($r = -0.58$, $p < 0.0001$ for object naming; $r = -0.77$, $p < 0.0001$ for semantic verbal fluency; $r = -0.62$, $p < 0.0001$ for remote memory–recall; $r = -0.62$, $p < 0.0001$ for remote memory–recognition].

In brief, our results showed that the patients with moderate and severe dementia performed poorly on two of the semantic memory tests, i.e. the Object Naming Test and the Remote Memory Test, respectively. In contrast, one aspect of semantic memory performance, the Semantic Association of Verbal Fluency Test, was defective in each stage of Alzheimer's disease.

Discussion

Episodic memory

The DAT patients in this study had a low level of education, which makes them quite different from patients included in most Western studies.[35,43–45] Previous studies from the West usually selected subjects with an educational level above senior high school (12th grade), and included few illiterate patients. Our results further confirm, however, that defective episodic memory is the most prominent feature of patients with DAT, even in the early stage, regardless of educational level.

Semantic memory: a different pattern from episodic memory

Unlike episodic memory deficits seen in early DAT patients, our results showed no deficits on most semantic memory tests until the middle stage of the disease (i.e. patients with moderate severity of dementia). These results differ from previous studies of semantic memory problems in DAT patients. Hodges et al[23] used tests similar to those used in this study to examine semantic memory deficits in DAT patients. They found that DAT patients had significantly poorer performance on a naming task and suggested that a breakdown in the semantic process occurs in the early stage of DAT. They also designed various types of semantic memory tests to examine semantic function in DAT patients to support this conclusion.[9] Two possible reasons might account for the inconsistencies between the findings of Hodges et al and the present study. First, the previous study by Hodges and co-workers did not systematically investigate the issue of association between dementia severity and semantic memory deficits. In fact, in their analysis of different levels of dementia in DAT patients, Hodges et al[4] found that there were not necessarily any semantic memory deficits in early DAT patients. Our results confirmed this finding. Second, in the present study, different tests were used to examine the patients' semantic memory. It is possible that the semantic memory tasks used in this study, which were designed for subjects with a low level of education, are less complicated than the tasks used for the highly educated subjects in the Western studies. Our review of the literature revealed no reported studies of the influence of low education on semantic memory function. Generally speaking, low-educated people should have a less complicated semantic network than their more highly educated counterparts. Accordingly, the semantic networks of low-educated subjects might be more vulnerable to DAT. However, our data did not support this hypothesis. Although the present study did not compare the performance of low- and highly-educated DAT patients on semantic memory tests, the results did reveal that even low-educated patients preserved semantic memory in the early stage of dementia.

Our patients performed poorly on the Semantic Association of Verbal Fluency Test even in the early stage of DAT. This result seems to be consistent with previous studies.[46,47] However, the reason for a difference in the performance pattern as compared to results of other semantic memory tasks remains unclear. One possible explanation for this discrepancy is that the Verbal Fluency Test is not a pure test of semantic memory function. Instead, it may also measure other kinds of cognitive abilities, such as executive function.[48–50] Thus, a poor performance on this task might reflect multiple cognitive dysfunctions, other than semantic memory deficits. In fact, Tippett et al[51] recently reported that DAT patients failed in some semantic memory tasks partially due to impairment of their semantic selection ability.

Semantic memory deficit: loss of structure or inability to access?

Our patients in the early stage of DAT did not exhibit a remarkable semantic memory deficit. It thus appears that semantic system function of these patients was at least within normal limits, despite their low educational backgrounds. Accordingly, this finding cannot be explained by a loss of semantic structure, as hypothesized by some researchers,[4,9,23–26] or an inability to access semantic knowledge, as hypothesized by others.[19–22] However, evidence of a remarkable deficit of semantic memory function, reflected by impaired performances on free recall and/or recognition tasks in our patients with mid- to late-stage DAT, seems to partially support either of these two hypotheses.

There were several limitations to this study. First, there are many different methods available for the investigation of semantic memory deficits in DAT patients, including MDS methods,[24] the priming test,[29] and the DRM paradigm.[37,38] Because these conventional tests might be too difficult for use in assessing the semantic memory tasks of a low-educated population, we used clinically available semantic memory tasks that were more consistent with our low-educated patients' abilities. This selection, however, limited the ability of this study to clearly differentiate whether the naming deficits of patients were related to the semantic impairment, retrieval or the lexical deficits. Further work is needed to examine DAT patients with the object identification test or the word-object matching test to clarify this issue, or to develop a semantic memory task specifically tailored to a low-educated adult population. Furthermore, although the syndrome of dementia is associated with a global deterioration of cognitive function, we did not analyze the influence of other cognitive deficits, such as executive dysfunction and language function, on the semantic memory problems in DAT patients.

In summary, this study showed that all low-educated DAT patients exhibited defects in episodic memory and that there was a positive correlation between the severity of dementia and the severity of memory impairment. However, those patients with moderate and severe dementia manifested semantic memory problems, including deficits of recollection and recognition. These results seem to only partially support the hypotheses of a loss of semantic structure or of an inability to access semantic knowledge in patients with DAT. Further studies with semantic memory tasks specifically tailored to such a low-educated population to re-examine this controversial issue is necessary.

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