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A longitudinal study of semantic memory impairment in patients with Alzheimer's disease

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Abstract

Introduction The present study explored the nature of the semantic deterioration normally displayed in the course of Alzheimer's disease. The aim was to disentangle the extent to which semantic memory problems in patients with Alzheimer's disease are best characterized as loss of semantic knowledge rather than difficulties in accessing semantic knowledge.

Method A longitudinal approach was applied. The same semantic tests as well as same items were used across three test occasions a year apart. Twelve Alzheimer patients and 20 matched control subjects, out of a total of 25 cases in each group, remained at the final test occasion.

Results and Conclusions Alzheimer patients were impaired in all the semantic tasks as compared to the matched comparison group. A progressing deterioration was evident during the study period. Our findings suggest that semantic impairment is mainly due to loss of information rather than problems in accessing semantic information.

Key words:

Alzheimer's disease

Sematic memory impairment

Longitudinal study

1. Introduction

Semantic memory impairment is common in Alzheimer's disease (AD) (Adlam et al., 2006; Binetti et al., 1995; Bäckman and Lipinska, 1993; Daum et al., 1996; Hodges et al., 1992; Spaan et al., 2005). Although semantic impairment might not be the first or most sensitive early indicator of AD, all AD patients show semantic memory deficits at later stages of the disease (Hodges and Patterson, 1995).

Semantic memory is culturally shared and can be described as context-free knowledge about the world, objects and facts (Tulving, 1972). Impairment is indicated by problems in naming objects and pictures, in defining objects, and by poor comprehension of oral and written language. Deficiencies in semantic memory are often assessed by tests measuring confrontation naming, categorical verbal fluency or word to picture matching (Bayles and Tomoeda, 1983; Henry et al., 2004; Lonie et al., 2009). Following a series of important papers by Shallice and Warrington (e.g., Shallice, 1988; Warrington and Shallice, 1984), two main hypotheses have been suggested to account for semantic memory impairments, including those observed in patients with Alzheimer's disease (see also Hodges et al., 1992) . One explanation highlights loss of semantic information and it is assumed that semantic representations in memory decline gradually across time (i.e., the degraded store view). A second hypothesis claims that semantic deficits are due to difficulties in accessing or retrieving information stored in semantic long-term memory (i.e., the degraded access view).

In a seminal study, Chertkow and Bub (1990) used an item-to-item specific test and observed error consistency across test trials, providing support for the degraded store view. In this study, the patients were first asked to name pictures and subsequently to perform a ”same category word to picture matching” task. There was a reliable overlap between loss of name production and name comprehension such that pictures named correctly were more likely to be chosen in a word-to-picture matching task than pictures not named correctly (see also Alathari et al., 2004; Bayles et el., 1999; Binetti et al., 1995; Garrard et al., 2005; Hodges and Patterson, 1995; Hornberger et al., 2009; Martin and Fedio, 1983; Salmon et al., 1999a for similar procedures). Several other researchers have described a breakdown in the structure and organization of semantic memory in patients with Alzheimer's disease (for review see Salmon et al., 1999b).

In contrast to the study of Chertkow and Bub (1990), Nebes et al., (1984) argued that there might exist important differences in task demands; for example, conscious and effortful recall of semantic knowledge (such as verbal fluency or picture naming tasks) versus automatic and non-effortful activation of semantic knowledge (such as various priming tasks). In their study, AD patients performed equally as well as controls on automatic priming tasks, despite a substantial impairment when the task required conscious recall of semantic knowledge (for similar views on other forms of memory impairment, see Nilsson et al., 1989; Titov and Knight, 1997.) Based on these findings, Nebes et al. (1984) argued that representations of semantic knowledge are mainly intact in AD and that a semantic deficiency is better accounted for by an impairment in accessing or retrieving semantic information. To date, there have been several studies suggesting that AD patients suffer from retrieval problems rather than loss of knowledge (Bäckman and Lipinska, 1993; Daum et al., 1996; Duong et al., 2006, Laatu et al., 1997; Lipinska and Bäckman, 1996; Nebes et al., 1989).

Evidence to support either the loss or the access theory is often provided by performing cross-sectional studies, error consistencies across tests or item-to-item specific loss. In addition, most research focusing on a decline in semantic memory has involved short time intervals between test occasions. Thus, the possibility of distinguishing between the degraded store and the degraded access view of semantic memory problems in AD patients has been limited. In the present study we addressed these methodological problems by performing a longitudinal study of AD patients repeating the same tasks three times at a yearly rate. Identical tests of semantic memory and identical test items were used on all three test occasions, and thus both task demands and semantic representations tested were the same over time. More recently, longitudinal studies assessing semantic memory have demonstrated a loss of semantic attributes over time (Giffard et al., 2002; Moore et al., 2004). However, the question about access or loss has not been explicitly addressed in these studies.

More specifically, our test battery comprised three tasks. The first involved word reading. Based on previous studies, it was expected that word reading ability should be more or less intact in AD and represents a highly automatized ability (Cummings et al., 1986; Diesfeldt, 1992; Nebes et al., 1984; Nelson and O'Connell, 1978; O'Carroll and Gilleard, 1986; Schwartz et al., 1980; Sharpe and O'Carroll, 1991). The second task was word comprehension. This task was assumed to involve conscious processing of semantic knowledge. A third task, also highlighting conscious and presumably effortful retrieval of semantic knowledge, was a semantic attribute judgment task. The loss hypothesis predicts that the same semantic information would fail to be comprehended across different tasks within one test occasion and across test occasions. The access hypothesis predicts random absence of specific semantic information across tasks within one test occasion as well as across test occasions. The approach to test these hypotheses by examining item-by-item consistency across tests has been used in previous studies (e.g., Garrard et al., 2005; Hodges et al., 1996). Our longitudinal design extends this approach by examining item-by-item consistency within the same AD patients across time.

To summarize, the purpose of the present study was twofold: to examine how AD patients differ from matched controls in semantic memory performance over time, and to study if the pattern of semantic memory impairment in patients with Alzheimer's disease is best characterized as loss of semantic knowledge or difficulty in accessing semantic knowledge.

2. Method

2.1. The initial samples of participants

Initially 25 patients were included in the study, all diagnosed with possible Alzheimer's disease (duration of disease m = 3.4 years). The diagnoses were established according to DSM-IV and based on neuroradiological (e.g., CT scan), neurological, neuropsychological and medical evaluations at the University Hospital in Linköping and at the Vrinnevi Hospital in Norrköping. A comparison group of 25 people matched by age, gender and education were also included in the study.

Drop-out. The participants were tested on three occasions, one year apart (±1 month). During the course of the study, three of the AD patients died and ten showed severe cognitive declines, thus being untestable in some or all tests administered during the test occasions. At the third and final test occasion, twelve out of 25 AD patients completed the full test battery. The matched comparison group consisted of 20 participants at the third and final test occasion. Drop-out was due to reasons unrelated to the purpose of the study.

2.2 The final sample of participants

The mean age in the AD group (n = 12) at the first test occasion was 77 years (SD = 5.5) and their mean level of education was 8.2 years (SD=2.1). The mean age in the comparison group (n=20) was 73 years (SD=4.7) and their average level of education was 9.7 years (SD=3.5).

(Table 1 about here)

ANOVAs revealed that neither age, $F(1, 28) = 3.74$, $p > .05$, nor level of education, $F(1, 27) = .40$, $p > .05$, differed significantly between the two groups. Different df between the F-tests was due to missing values of age and education in the comparison group. There were 75% and 60% females respectively in the AD group and the comparison group. When tested on the Mini-Mental State Examination (MMSE; Folstein et al., 1975) at the first test occasion, the control group scored within the normal range (> 25), and significantly better than the AD group, $F(1, 30) = 34.06$, $p < .01$. The AD patients ranged from mild to severe dementia with a mean of 20.8. None in the AD group and comparison group had any documented history of neurological or psychiatric illness, alcoholism, or learning disabilities. The participants were tested one at a time, either at the University Hospital in Linköping or in their homes.

2.3 Tests

2.3.1. Word reading. The word reading test did not require reading skills beyond the elementary school level. Word reading was assessed by having the participants read out loud a total of 32 single words presented one at a time on a computer screen. The words were high-frequency nouns, printed in lower-case letters (Geneva font, 24-point). There were 16 regular and 16 irregular words from ten semantic categories (animals, fruits and vegetables, tools, vehicles, clothing, music instruments, plants, professions, body parts and kitchen utilities).

2.3.2 Word reading comprehension. To assess reading comprehension (i.e., the first semantic test), the participants were, after having read each single word in the word reading test, immediately asked to indicate the corresponding picture from a set of four pictures. The four alternatives comprised the target word (e.g. apple), a close semantic foil (e.g., peach), a distant semantic foil (e.g., grapes) and a visually alike foil from another semantic category (e.g., bomb). The correct pictures were presented in a randomized order for each trial. All pictures were black and white contours.

2.3.3. Semantic attribute judgment test. To further assess semantic knowledge of the 32 nouns presented in the reading test, a semantic attribute judgment test was administered. The attributes used in this test were elicited from 20 elderly and 20 middle aged persons, who were asked to generate attributes to the target words. Three attributes generated more frequently and three attributes generated only a few times were chosen to represent each target word. Each target word in the test was presented together with a list of twelve attributes. Six of these attributes were semantically related (three essential attributes and three less essential attributes) to the target word and six were semantically unrelated attributes. The task was to select the attributes that were semantically related to the target word. The participants were not informed on how many attributes they were supposed to indicate.

2.4. Statistical analysis

To examine overall cognitive functioning, word reading skill, and semantic memory (i.e., word comprehension and attribute judgment test), we compared mean performances in MMSE, word reading, and both semantic tests using ANOVAs with group as a between subject factor and time as a within subject factor. These analyses address differences in semantic memory deterioration over time in AD as compared to controls. To examine the pattern of semantic deterioration in AD patients in more detail two types of analyses were performed. First, the number of semantic attributes expressed as proportions for comprehended or not comprehended words were compared using t-tests. Following these analyses, a consistent pattern of differences in the proportions of attributes between comprehended compared to not comprehended words would indicate that semantic memory impairment in AD is primarily due to loss of semantic knowledge rather than problems in accessing information. Second, a more direct test of the degraded store vs. degraded access hypotheses was performed by examining item-by-item consistency using the frequencies with which words were comprehended or not across time. In this case, Chi-square tests should indicate to what extent words comprehended at the first test occasion were more likely to be comprehended at later test occasions. A high degree of inter-test item consistency should provide further support for loss of semantic knowledge rather than access impairment.

3. Results

At the first and second test occasion there were no significant differences obtained between the groups in word reading ($F(1, 30) = 1.71$, $p > .05$; $F(1, 30) = 2.79$, $p > .05$). However, a significant difference, mainly due to ceiling effects, was observed at the third and final test occasion, ($F(1, 30) = 9.38$, $p < .05$). Thus, at the third occasion the AD patients made a total of twelve reading errors (out of 384 words) while the comparison group made no errors. These findings suggest that word reading is not the primary problem for AD patients and that possible deficits in word comprehension should mainly be attributable to semantic problems.

3.1 Semantic memory over time

Three ANOVA s with group as a between subject factor and test occasion as a within subject factor were performed separately for the MMSE screening test and the two semantic memory tests.

(Table 2 about here)

In the MMSE screening test there were main effects of group $F(1, 30) = 62.05$, $p < .001$ and time, $F(2, 60) = 15.99$, $p < .001$. There was also an interaction between group and test occasion, $F(2, 60) = 24.50$, $p < .001$, indicating a gradual decrease in cognitive functioning among the AD patients over time. The proportion of words comprehended in the reading comprehension test by the AD group was significantly lower than the proportion for the comparison group ($F(1, 30) = 30.78$, $p < .001$), and there was a main effect of time ($F(2, 60) = 8.56$, $p < .01$). There was also an interaction between group and test occasion, suggesting a decrease in the number of comprehended words among AD patients while controls remained at the same level across time ($F(2, 60) = 11.02$, $p < .001$). In the semantic attribute judgment test there was a main effect of group ($F(1, 30) = 39.25$, $p < .001$), a main effect of time ($F(2, 60) = 5.21$, $p < .05$), and also an interaction between group and test occasion ($F(2, 60) = 4.28$, $p < .05$).

In sum, there was an interaction between group and test occasion for word comprehension, indicating a gradual decrease in semantic functioning in the AD group. There was also an interaction effect of group and test occasion on the semantic attribute test, suggesting that the Alzheimer group identified fewer semantic attributes as a function of time. Since we established that there was significant difference between the AD group and the control group in semantic memory performance across tests and over time, we will now focus on the nature of semantic deficits in the AD group.

3.2 Loss or access problems? Overlap between tests

To analyze the nature of the semantic memory impairment displayed in the AD group, all words read correctly by AD patients were tracked across tests at each occasion and across time within each test of semantic memory.

3.2.1 Overlap between tests – first test occasion. As can be seen in Table 3, the proportion of semantically related attributes selected was significantly higher for words comprehended in the reading comprehension test, ($t(382) = 2.46$, $p < .05$). In addition, there was no difference for highly related semantic attributes, ($t(382) = 1.75$, $p > .05$), while the difference reached significance for attributes less essential for each semantic target word ($t(382) = 2.09$, $p < .05$). Thus, for words that were comprehended, AD patients indicated less attributes only weakly associated with the semantic target. One reasonable explanation of this finding is that the semantic status of a word comprehended in the reading task is richer than the corresponding representation for a word not comprehended.

(Table 3 about here)

This finding seems to suggest that loss of semantic information rather than retrieval problem underlies semantic deficiency in AD patients.

3.2.2. Overlap between tests – second and third occasion. The pattern of results across tests within the second and third test occasion was similar to that obtained in the first test occasion (Table 3). The proportion of attributes indicated, both as a total amount (second occasion; $t(382) = 3.22$, $p < .01$; third occasion; $t(382) = 3.22$, $p < .01$) and for essential (second occasion; $t(382) = 3.02$, $p < 0.01$; third occasion; $t(382) = 3.02$, $p < .01$)) as well as less essential attributes (second occasion; $t(382) = 2.53$, $p < .05$; third occasion; $t(382) = 2.53$, $p < .05$) differed significantly between target words comprehended in the reading task compared to target words not comprehended.

3.3. Loss or access problems? Overlap across time

To further clarify whether semantic memory problems in AD patients are due to loss of semantic knowledge or problems with access to semantic knowledge, expected and observed frequencies were tested over time for words comprehended. Loss would be implied by consistency in the pattern of words not comprehended within each test across time. Problems in accessing semantic information would again be implied by an inconsistency in the pattern of performances.

3.4 Words comprehended – over time

If a word was comprehended at the first test occasion, it was to a large extent also comprehended at the second occasion. If the word was not comprehended at the first occasion, it was very likely that there was no comprehension for the word at the second occasion either (see Table 4). This result was significant ($\chi^2(1, N = 384) = 55.76$, $p < .001$). This finding was replicated when comparing word comprehension performance between the second and the third test occasion, ($\chi^2(1, N = 384) = 37.91$, $p < .001$) as well as between the first and third occasion, ($\chi^2(1, N = 384) = 29.93$, $p < .0001$).

(Table 4 about here)

4. Discussion

The purpose of this study was to (a) study how AD patients differ from matched control subjects in semantic performance over time, and to (b) study whether the semantic impairment in AD patients is best explained by a hypothesis of loss of semantic knowledge or a hypothesis of difficulties in accessing the semantic knowledge.

Overall we found that AD patients were impaired in the semantic tasks compared to the comparison group (i.e., MMSE, reading comprehension and attribute judgment test). The difference between the two groups was apparent already at the first occasion of testing. Impairment in word comprehension is assumed to be related to the word-finding problems normally displayed by AD patients, and the hypothesis that semantic knowledge is gradually degraded in AD patients (Martin, 1992). Reading comprehension is repeatedly found to be impaired in AD patients, and it also seems to be associated with levels of dementia (Cox et al., 1996; Bayles et al., 1990). Petersen et al. (1988) performed a PET study and concluded that it is possible to read single words without any activation of the areas in the brain that are supposed to underlie semantic association. That is, one can technically read without necessarily knowing the meaning of the words. This might account for the finding that AD patients can still read single words seemingly equally well as the comparison group.

Is the semantic memory impairment best explained by loss of semantic knowledge or by difficulties in accessing the semantic knowledge? The first way of exploring this issue involved a semantic attribute judgment task and a reading comprehension test. The assumption was that if semantic knowledge was lost, the AD patients would be likely to choose fewer attributes to a word not comprehended than to a semantic target word comprehended. In contrast, if semantic impairment is accounted for by a retrieval (access) problem, fewer attributes would sometimes be chosen to words comprehended and sometimes to words not comprehended. The results show that there were significantly more attributes chosen for the words comprehended than for the words not comprehended. To further analyze this pattern, all the words (n=384) from the reading ability test were tracked through the reading comprehension test across all three test occasions. The results indicated that words comprehended at the first occasion were also comprehended at the second and third test occasions. If it was a matter of poor access of semantic memories, it is unlikely that the pattern would be as consistent as shown in the tests conducted.

Although the pattern of findings across tests as well as in the longitudinal evaluation in this study was remarkably consistent, it should be noted that the drop-out rate from the initial to the last test occasion about two years later was more than 50% (i.e., 13 out of 25 AD). This is common and almost inevitable in longitudinal research on AD patients spanning several years, highlighting the need for replications in research addressing the progression in patients with chronic neurodegenerative disorders.

Taken together, the findings from our study suggest that semantic impairment displayed during the course of Alzheimer's disease is due to loss of information rather than problems in accessing semantic information. This conclusion was confirmed not only by examining item-by-item consistency between tests but more importantly replicated across time within the same sample of AD patients.

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