



# Electrophysiological insights into the nature of the semantic deficit in Alzheimer's disease

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(Received 2 May 1995; accepted 30 October 1995)

**Abstract**—Event-related brain potential (ERP) and reaction-time measures were used to determine if the specificity of a category prime differentially affects the amount of semantic priming seen in patients with dementia of the Alzheimer type (DAT) compared with normal elderly and young controls. Subjects were primed with an auditory category name followed by the visually presented name of an imageable object and indicated whether the object was a category member; the category was either superordinate to, at, or subordinate to the basic level. All groups showed similar priming effects in response to the category manipulation, as evidenced in both reaction time and the amplitude of the N400 component of the ERP. Overall, DAT subjects showed the smallest ERP priming effects and young controls the largest. The present study did not provide evidence for a strong version of a strictly “bottom-up” breakdown of the semantic networks in subjects with DAT, suggesting a role for factors such as task difficulty and memory search strategies in online categorization tasks of this type. Copyright © 1996 Published by Elsevier Science Ltd.

**Key Words:** ERP; dementia.

## Electrophysiological insights into the nature of the semantic deficit in Alzheimer's disease

There is considerable evidence for an impairment of performance on tests that utilize semantic memory in patients with dementia of the Alzheimer type (DAT) [see Ref. 22 for review]. For example, DAT patients show impairment on verbal fluency tests [8, 36] in which subjects are required to produce words that begin with a specified letter or words that are members of a restricted category, such as animals. In fact, DAT subjects demonstrate a disproportionately severe reduction in category as opposed to letter fluency, suggesting a breakdown in semantic processing [8, 24]. Moreover, these patients do not benefit from meaningful classification schemes to help guide their word-finding searches and typically produce numerous general categories (e.g., fruits, vegetables) and few specific exemplars (apples, lettuce) on a “supermarket” fluency task [34, 45, 59]. Patients with DAT also

show impairment in object naming, producing numerous semantic errors (e.g., superordinate and within-category associative errors) [1, 25]. Superordinate naming errors imply that only broad category membership knowledge is accessed. Indeed, errors at the perceptual and phonological stages of object naming are relatively rare except in the most advanced stages of the disease.

Despite the wealth of data, the nature of the semantic memory deficit in Alzheimer's disease remains unclear. Some authors have argued that the basic structure of semantic knowledge is not affected, but rather that the deficit of DAT is the result of an impairment in accessing the information [38]. Other researchers have theorized that these impairments do result from a general breakdown in the hierarchical organization of semantic knowledge [10, 13, 25, 26]. That is, whereas demented patients may retain general semantic information above a given concept, they progressively lose knowledge of the concept's specific attributes that constitute its meaning [26].

Hodges *et al.* [26] tested this hypothesis with a battery of tests, including category fluency, naming, sorting by superordinate to subordinate attributes of the items, word-to-picture matching, and verbal definitions to Alz-

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heimer's patients and normal elderly controls. For the category fluency task, subjects were asked to produce as many exemplars as they could of animals, birds and household items. Two lower order categories were included, namely breeds of dogs and types of boats. A disproportionate reduction in patients' abilities to generate exemplars from lower order categories relative to superordinate categories was found. The sorting task required that pictures be classified under various category headings at three levels in the hierarchy of semantic knowledge (e.g., general versus specific; level 1: living versus man-made; level 2: land animals versus water animals versus birds; level 3: size, habitat, and fierceness of various land animals). The DAT patients achieved near perfect scores when asked to sort items as living or man-made, but became increasingly worse than controls at sorting items as the levels became more specific. The authors also found a relative preservation of superordinate knowledge on the definitions test. Taken together, the authors concluded that these results supported a "bottom-up" breakdown in the hierarchical organization of semantic memory in DAT.

Similar conclusions were drawn by Chertkow *et al.* [12], who asked DAT patients questions about pictures and words depicting objects. Questions regarding the general category (e.g. "Is this a tool or clothing?") were answered equally well by DAT patients and controls, but the patients were significantly more impaired in answering subordinate-level questions based on perceptual and functional attributes of the items (e.g., [item = saw], "Is the tip made of metal or wood?").

It has been demonstrated that DAT patients have difficulty on tasks which require an intentional search for information within semantic memory [13]. Many of the tasks used in studies claiming to provide evidence of semantic impairment in DAT (e.g., fluency tasks, card sorting, vocabulary tests) put high demands on this ability. Some researchers have used semantic priming tasks, in which processing of a stimulus can be facilitated when it is preceded by a related or predictive event, to diminish the need for subjects to rely on the use of an active memory search. Studies of semantic priming in DAT have yielded conflicting results; whereas some authors have shown that DAT patients demonstrate less priming than normal controls [46], others have shown normal or greater than normal semantic priming in those with DAT [12, 40]. If a systematic breakdown of semantic information is indeed at the core of this deficit, with specific information about objects being lost before the more general information, then one would expect to see this reflected in priming tasks. Persistent priming effects should result from structurally intact representations.

#### *Event-related brain potentials and DAT*

Given the vast range of deficits seen in Alzheimer's disease, it would be useful to employ a technique that

minimizes the task demands on the subject, yet gives a measure sensitive to semantic processing. One such measure is event-related brain potentials (ERPs). ERPs offer a real-time measure of cognitive processing [32]. ERPs are a measure of electrical activity in the brain, are relatively non-intrusive, and provide continuous information about the sequence and timing of brain activity. ERPs such as the P300, have been successfully used in studies of DAT [51, 52]. The P300 is thought to measure the subjective expectancy for a particular stimulus or stimulus class, being larger in cases where an attendant stimulus is rare or in some way different to what is expected [54]. Looking for gross differences in the latency and amplitude of the P300 to help differentiate those with DAT from normals, or other disorders such as pseudodementia, researchers have found that P300 latency and clinical status are correlated; demented subjects are characterized by longer P300 latencies [48, 51]. However, although the P300 may be useful in differentiating groups of demented from non-demented subjects, findings indicate that this measure may not be sufficiently sensitive to differentiate demented persons on an individual basis for clinical diagnosis, or in separating types of clinical dementias [49].

Several investigators have also examined the consequences of aging and dementia on the ERP word repetition effect [21, 57]. This effect refers to the greater positivity in the ERPs elicited by words repeated (old) relative to that occurring to items presented for the first time in the experiment (new). A consistent finding has been that the size of the ERP repetition effect in response to visually-presented words does not decline with age or DAT [21, 57]. Even in subjects with pronounced explicit memory deficits, the ERP repetition effect remains robust [57]. This is important for the present experiment because it is assumed that the repetition effect consists of multiple ERP components, including the N400 (see below).

None of these studies has used ERP measures to investigate semantic memory changes directly in dementia. One ERP component that may prove useful in this regard is the "N400"; it has been suggested to be a marker of semantic processing. Kutas and Hillyard [30] showed that the N400 effect is large sentence final words that are anomalous and much smaller or nonexistent to congruent sentence completions as a function of their expectancy [31]. The sensitivity of the N400 to semantic relationships has been demonstrated in word pair experiments using lexical decision tasks [2, 27], and category membership verification tasks [4, 43]. In these experiments, the N400 effect is larger to unrelated words than to related words, presumably because these words did not receive a facilitating effect from previous words, perhaps necessitating a more extensive search of the lexicon [33]. A number of studies have demonstrated that the N400 amplitude varies with semantic priming manipulations. For example, Kutas and Van Petten [32] demonstrated that the N400 effect is larger when the task directs attention to semantic relationships than when the task does not enforce pro-

cessing of the semantic relation between word pairs [see also Ref. 27]. Brown and Hagoort [5] demonstrated that masking prime words in a lexical decision task failed to elicit an N400 effect. They interpreted this result as evidence that the N400 reflects semantic integration processes and not merely automatic lexical access. Thus, the N400 effect is elicited in a variety of tasks as an index of semantic relation, and appears to involve some attentional processing.

### *Goals of current study*

The present study was designed to determine if the specificity of a category prime differentially affects the amount of semantic priming seen in patients with DAT compared with normal elderly controls. Subjects were presented with categories from three levels in the hierarchy of semantic knowledge and asked to determine whether or not specific exemplars fit into these categories. Average latency and amplitude of the N400 component for each of these conditions was examined for Alzheimer's patients and normal elderly controls. Based on prior behavioral findings suggesting a "bottom-up breakdown" of semantic memory in those with DAT [26], it was hypothesized that the patient group would not differ significantly from the elderly control group in N400 amplitude (reflecting the degree of semantic processing) for the most superordinate categories (e.g., living) but differences would be apparent for the subordinate categories (e.g., animal), with DAT patients performing increasingly worse for those categories that focus on more specific attributes of exemplars (e.g., land animal). Results from these two groups were also compared with data from a young control group in order to tease apart the effects of aging from the effects of dementia.

Reaction time data were recorded in addition to the ERPs and the above stated hypotheses apply to the reaction time data as well. In other words, it was expected that the two control groups would show behavioral priming effects for all three levels of category membership, whereas the patient group was expected to be slower than the control groups, and to show less priming for the more specific categories as implied by the conclusions of Hodges *et al.* [26].

## **Method**

### *Subjects*

The patients were participants in the Alzheimer's Disease Research Center (ADRC) of the University of California, San Diego. The diagnosis of DAT was made by a senior staff neurologist according to criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [35]. Patients with a history of severe head injury, alcoholism, cardiovascular disease, or psychiatric illness were not included.

Twelve patients with a diagnosis of DAT were tested (seven males, five females). The mean age of these patients was 72.4 (range = 67–81 years), and the average years of education was 14.3 (range = 10–20 years). The mean Dementia Rating Scale (DRS) score for this group was 121, which is considered to be in the mild to moderate range of dementia severity (range = 98–135).

Twelve normal elderly subjects (three males, nine females) were matched for age (mean = 73.1; range = 63–86 years) and education (mean = 15.8; range = 12–18 years) to the DAT subjects. DRS scores were significantly different for these two groups [ $t(10) = -6.06$ ,  $P < 0.01$ ] with demented patients performing worse than their age-matched controls.

The young control subjects were recruited from the UCSD undergraduate and graduate student populations. There were four males and eight females in this group. The average age of the young subjects was 21.3 (range = 18–27 years), and years of education ranged from 13 to 19 years.

### *Materials*

Stimuli were based, in large part, on the test items used by Hodges, Salmon and Butters [26] (see appendixes 1 and 2 for a complete list of stimuli). Each subject was presented with 186 trials. Half of the target words were related to the preceding category headings, and half were unrelated. Three lists of targets were counterbalanced so that each word appeared at each category level across subjects. These words in each list were matched for the mean frequency of usage in the English language (mean frequency of each list = 24.32).

### *Procedure*

Stimuli were generated by an IBM-PC computer and were presented on a computer monitor. The experimenter said the name of a category, which was followed (in approximately 1000 msec) by the name of an imageable object in the center of the computer monitor. This word was displayed for a duration of 1500 msec. Subjects sat in a comfortable recliner chair. The subject's task was to decide whether or not the object was a member of the category, and to press one of two buttons to signal "yes" (the object was a member of the category), or "no" (the object was not a member of the category). The responding hand was counterbalanced across subjects such that half of the subjects in each group responded "yes" with the right thumb, and half responded "no" with the right thumb.

A practice run consisting of 18 trials was administered to all subjects before the experimental run.

Sixteen channels of electrophysiological data were amplified using Grass amplifiers set at a bandpass of 0.02–100 Hz. All electrode impedances were under 5 k $\Omega$ . The 16 channels of EEG were continuously digitized at 167 Hz and stored on hard disk. Behavioral responses were recorded along with the ERPs. Averages of artifact-free ERP trials were calculated for each stimulus type (i.e., related or unrelated to the category, the level of the preceding category name) for each appropriate behavioral response category (i.e., correct or incorrect response). ERPs were computed for epochs extending from 100 msec before stimulus onset to 1400 msec after stimulus onset. Trials contaminated by blinks, movements, excessive muscle activity, or amplifier blocking were rejected off-line before averaging; approximately 5% of the trials were lost due to such artifacts for all age groups. Epochs, with correctable blinks (i.e., without amplifier blocking) were corrected using an adaptive filtering algorithm developed by Dale (1994) and included in the relevant ERP averages.

### Recording the EEG

Tin electrodes (Electro-Cap International) were located at 13 scalp sites (all referenced to the left mastoid process during recording). Eye blinks and eye movements were monitored by one electrode placed below the infraorbital ridge of the right eye and a bipolar recording from electrodes by the outer canthus of each eye. The scalp sites included standard international 10–20 system locations: frontal left (F7) and right (F8); temporal left (T5) and right (T6); occipital left (O1) and right (O2); and a central midline site (Cz). Three pairs of electrodes approximately over Broca's area (Bl and Br), Wernicke's area (Wl and Wr) and primary auditory cortex (L41 and R41) were also used. Data was re-referenced offline to the algebraic average of activity at left and right mastoids.

## Results

### Data analysis

Computer programs were used to measure and analyze the peak latencies and mean voltages of responses in the latency windows of the N400 and a later positive component. Statistical analyses were performed with repeated-measures analyses of variance (ANOVAs) with group (DAT, normal elderly, young), condition (related or unrelated), category level (approximately superordinate, basic, or subordinate), and hemisphere (i.e., left versus right) as variables. *Post-hoc t*-tests (two-tailed) were performed to examine specific differences among and within groups. Repeated measures with greater than 1 d.f. (degree of freedom) were evaluated with *P* values adjusted using the Greenhouse Geisser epsilon correction factor.

### Reaction time

All three groups made significantly more errors at level 1 (superordinate categories) than for either of the other two levels [main effect of level,  $F(2,60) = 9.23$ ,  $P < 0.001$ ]. The main effect of group was also significant for the total number of correct responses [ $F(2,30) = 14.94$ ,  $P < 0.001$ ]. The young and elderly control subjects did not differ in terms of their number of incorrect responses, and made significantly fewer mistakes than did the DAT subjects ( $P < 0.001$ ). The young controls achieved an average of 95% correct at level 1, 97% at level 2, and 98% at level 3. The mean percentage correct for the elderly controls was 94 for level 1, and 96 for levels 2 and 3. For the DAT subjects, the average percentage of correct responses at level 1 was 73, 84 at level 2, and 83 at level 3.

The DAT subjects had the slowest reaction times overall with a mean latency of 1077 msec (S.D. = 139 msec), followed by the normal elderly controls with a mean latency of 923.6 msec (S.D. = 93 msec), and the young controls were faster with a mean latency of 861.03 msec (S.D. = 313 msec). This group difference is significant

[ $F(2,30) = 3.43$ ,  $P < 0.05$ ]. *Post-hoc* comparisons revealed that the young control subjects were significantly faster than the old control subjects, and the old controls were significantly faster than the DAT subjects ( $P < 0.01$ ).

All three groups had faster reaction times for related than for unrelated conditions at all three levels of categorization. The ANOVA revealed a significant group by relatedness interaction [ $F(2,30) = 3.51$ ,  $P < 0.05$ ]. *Post-hoc* comparisons showed that this relatedness effect was significant only for the DAT patients ( $P < 0.01$ ), and only at levels 2 and 3, but not at level 1 ( $P < 0.01$ ). The overall effect of level was reliable [ $F(2,60) = 45.43$ ,  $P < 0.01$ ], with all three groups being slower to respond to level 1 trials than to trials at either of the other two levels (Fig. 1).

In order to examine whether or not the apparently greater priming effects seen in DAT patients could be accounted for simply by their overall slower reaction times, a regression analysis was conducted using a total reaction time measure (unrelated + related trials) to predict priming scores (unrelated – related trials) [11]. Regression equations were calculated for each of the three category levels based on reaction time data from the young controls. These equations were used to predict priming scores for each elderly control subject and each DAT subject. These predicted scores were compared to actual priming scores, and one-way *t*-tests were conducted on the differences obtained for each group separately. The regression equations from the young were reasonable predictors of the elderly control subjects' performance ( $P > 0.25$ ). The relationship between total time and priming for the young was also found to be a reasonable predictor of performance at level 1 for the DAT subjects ( $P = 0.12$ ); however, at levels 2 and 3, the equations were not good predictors, underestimating the size of priming effects for the DAT subjects ( $P < 0.05$ ).

### Event-related potentials

*Young control subjects.* ERPs to words that are members of preceding categories compared to ERPs to words that are not members of preceding categories for category levels 1, 2, and 3 are shown in Figs 2a, b, and c for the young controls, elderly controls, and DAT subjects, respectively. An initial analysis contrasted the mean potential amplitudes over consecutive 100 msec latency intervals for the recordings from all scalp electrodes. This analysis revealed that ERP amplitudes were significantly more negative for words not preceded by related categories than for words preceded by related categories between 200 and 500 msec (Fig. 2a).

Further analyses were conducted on difference waves formed by subtracting the ERPs for primed from unprimed trials. For these analyses, the ERP over Wernicke's area (Wl) and its right hemisphere homologue (Wr) were the focus, as this is where N400 effects are

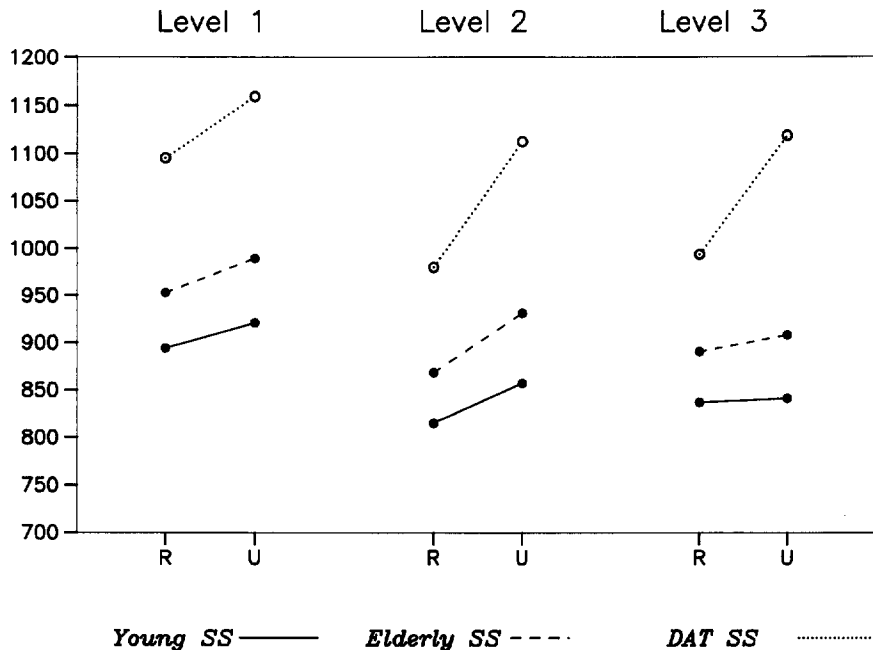


Fig. 1. Mean reaction time (in msec) for young, elderly control and DAT subjects to semantically related (R) and unrelated (U) words as a function of category level (1: superordinate; 2: basic; 3: subordinate).

typically maximal and most clear. A  $2 \times 3$  ANOVA (hemisphere  $\times$  category level) was conducted to examine the within-subject differences at these two sites for the mean amplitude between 300 and 500 msec post-stimulus. The hemisphere  $\times$  level interaction was significant [ $F(2,22) = 4.98, P < 0.02$ ]. Follow-up tests revealed that level 1 was reliably more negative over the left than the right hemisphere ( $P < 0.05$ ). The asymmetry of the N400 effect was only marginally significant for levels 2 and 3 ( $P < 0.08$ ). Whereas level 2 showed the same pattern as level 1 (left hemisphere more negative than the right), the pattern was reversed for level 3, with Wr more negative than Wl.

When priming effects over the two hemispheres were examined separately (using Wl and Wr to represent the left and right hemispheres, respectively), it was revealed that level was marginally significant over the right hemisphere ( $P > 0.09$ , with level 3  $>$  level 2  $>$  level 1 in terms of priming effect size). The effect of level is not significant over the left hemisphere.

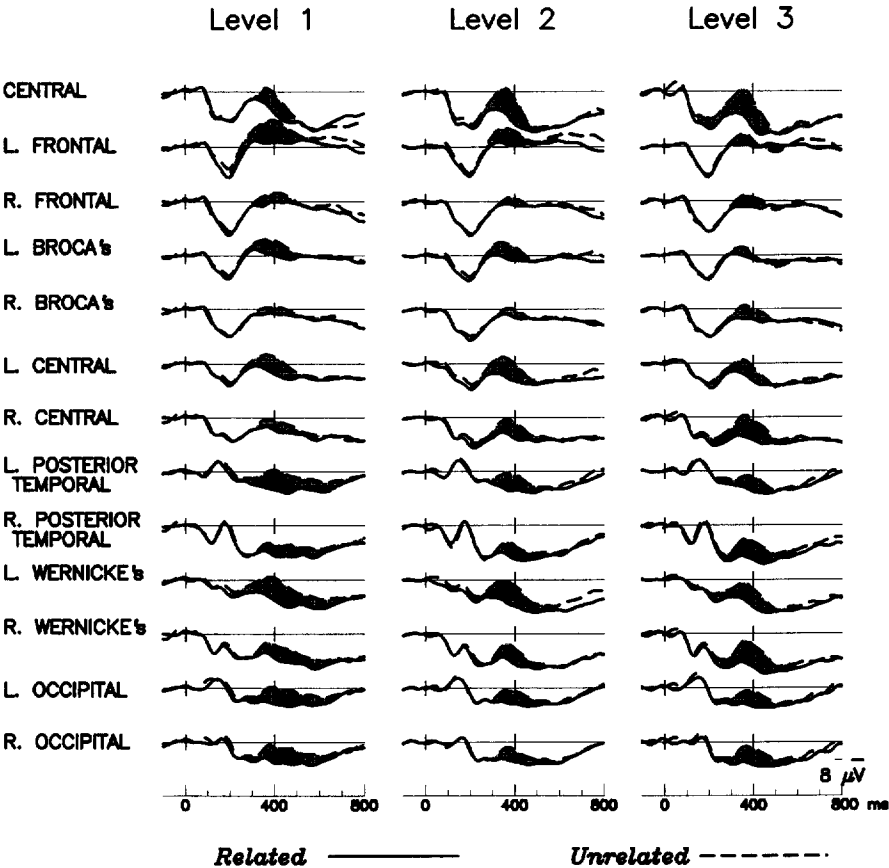
**Elderly control subjects.** As for the young controls, unrelated words elicited greater negativity over the right hemisphere peaking around 400 msec. However, over the left hemisphere the effect of congruity was manifest in a positivity with a slightly longer latency (see Fig. 2b).

Thus, the elderly controls show an N400 congruity effect that is maximal at posterior electrode sites and strongly lateralized to the right hemisphere. An examination of mean potential amplitudes over consecutive 100 msec latency intervals between 200 and 1000 msec revealed that the effect of relatedness is significant between 300 and 500 msec post-stimulus presentation. A  $2 \times 3$  within subjects ANOVA (hemisphere  $\times$  level) was used to examine the mean amplitude differences between

these two sites between 300 and 500 msec post-stimulus. The hemisphere  $\times$  level interaction was significant [ $F(2,22) = 5.21, P < 0.02$ ]. Follow-up tests reveal that levels 1 and 3 are significantly different across the hemispheres ( $P < 0.01$ ), with more negativity associated with the right hemisphere than the left. The main effect of hemisphere is also significant [ $F(1,11) = 6.45, P < 0.05$ ], with greater negativity over the right hemisphere than the left. The effect of level was not significant for data from either hemisphere.

**DAT subjects.** For the DAT subjects, as in the normal elderly controls, it appears that the N400 priming effects are lateralized to the right hemisphere, with a slightly later positivity occurring to unrelated words over the left hemisphere (see Fig. 2c). An examination of mean potential amplitude for primed and unprimed stimuli across the recording epoch revealed that, collapsed across electrode sites, there was no main effect of relatedness. The relatedness  $\times$  hemisphere effect was, however, significant, reflecting the right hemisphere N400 effect and the presence of a positive congruity effect over the left hemisphere.

A  $2 \times 3$  ANOVA (hemisphere  $\times$  category level) was conducted on the mean amplitude of the difference waves within the latency window of 300–500 msec at Wl and Wr, as was the case for the young and elderly control subjects. The hemisphere  $\times$  level interaction was significant [ $F(2,22) = 3.87, P < 0.05$ ]. Follow-up tests on this interaction effect revealed that level 2 ( $P < 0.05$ ) and level 3 ( $P < 0.01$ ) were significantly more negative over the right than the left hemisphere. The main effect of hemisphere was significant [ $F(1,11) = 11.11, P < 0.01$ ], with the mean amplitude significantly more negative over the right than over the left. Over the right hemisphere,



(B)

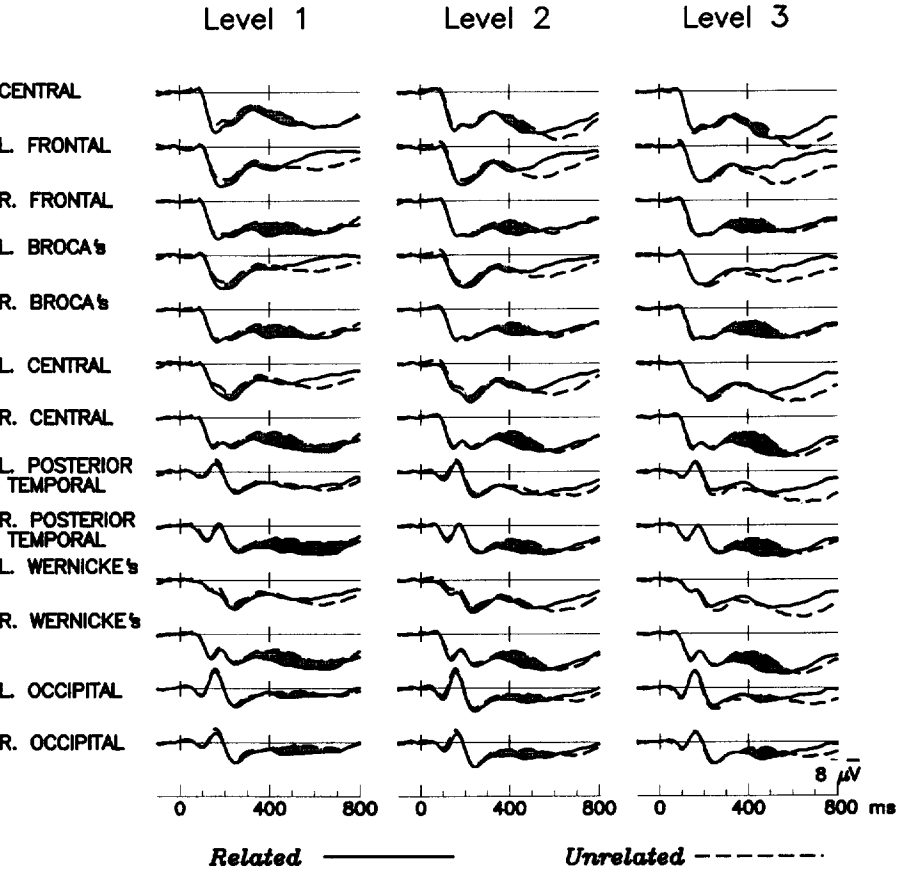


Fig. 2(A, B).

(C)

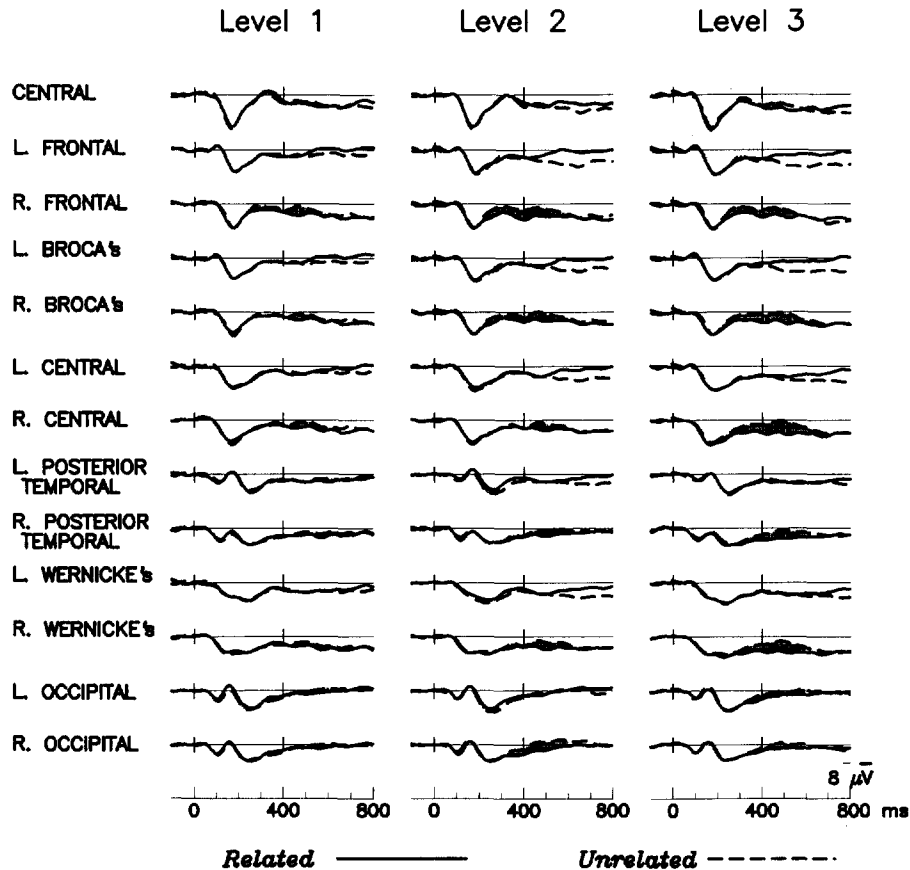


Fig. 2(C).

Fig. 2. Grand average ERPs elicited by semantically related (solid) and unrelated (dashed) words for each of the three category levels (1: superordinate; 2: basic; 3: subordinate). The shaded areas represent the N400 effect. Panel (A) shows data for the young control subjects, Panel (B) shows data for the elderly control subjects and Panel (C) shows data for the DAT subjects. Negative is up in this and all following figures.

the effect of level is significant ( $P < 0.05$ ;  $3 > 2 > 1$ ); levels 1 and 3 are significantly different ( $P < 0.02$ ), with level 2 falling in between. The effect of level is not significant over the left hemisphere.

**Comparison of group.** Difference ERPs reflecting congruity effects for each of the three groups are shown superimposed for each of the three levels of categorization in Fig. 3, and difference waves for each of the three levels are shown superimposed for each of the three groups separately in Fig. 4. These difference waves are shown for individual subjects within their groups in Fig. 5.

A  $3 \times 3 \times 2$  ANOVA (group  $\times$  level  $\times$  hemisphere) was conducted on the mean amplitude of the difference waves between 300 and 500 msec. Means and standard deviations of these measures are shown in Table 1. The main effect of group is significant [ $F(2,33) = 9.42$ ,  $P < 0.001$ ]. Group differences vary between the two hemispheres [group  $\times$  hemisphere:  $F(2,33) = 6.46$ ,  $P < 0.01$ ]. Over the right hemisphere, both the young and elderly control subjects demonstrate significantly more priming than the DAT subjects ( $P < 0.02$ ), but are not reliably different from each other. Over the left hemisphere, the young control subjects showed an N400 effect that the other

two groups do not ( $P < 0.001$ ). The level  $\times$  hemisphere interaction is significant [ $F(2,66) = 5.80$ ,  $P < 0.01$ ]. The three levels are significantly different over the right hemisphere ( $3 > 2 > 1$ ). Levels 1 and 2 are reliably different ( $P < 0.01$ ), and levels 2 and 3 are marginally different ( $P = 0.05$ ). The effect of level is not reliable at Wernicke's left.

Because the three groups showed differences in the onset and duration of their N400 effects, these analyses were conducted using different time windows for each group to compare the distribution of their effects more directly. Means and standard deviations for these measures are shown in Table 1. For each group, a 300 msec window was chosen in which their priming effects appeared maximum (young: 250–550 msec, elderly: 300–600 msec, DAT: 400–700 msec). These analyses yielded the same results as those reported above. Mean amplitude of the priming effects within these time windows for each of the three category levels are shown in Fig. 6.

N400 latency effects were also examined, using a computer algorithm that calculated the maximum negative peak in the time windows of the N400 effects for each group (young: 250–550 msec, elderly: 300–600 msec, DAT: 400–700 msec). Peak latency differences emerged

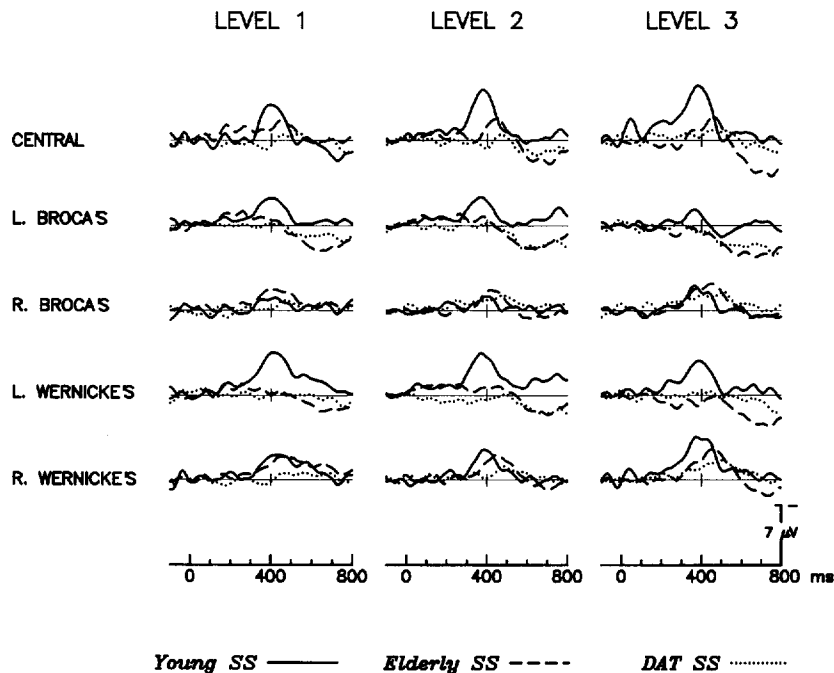


Fig. 3. Comparison of difference ERPs (point by point subtraction of unrelated minus related waveforms) for young, elderly control and DAT subjects separately for each category level.

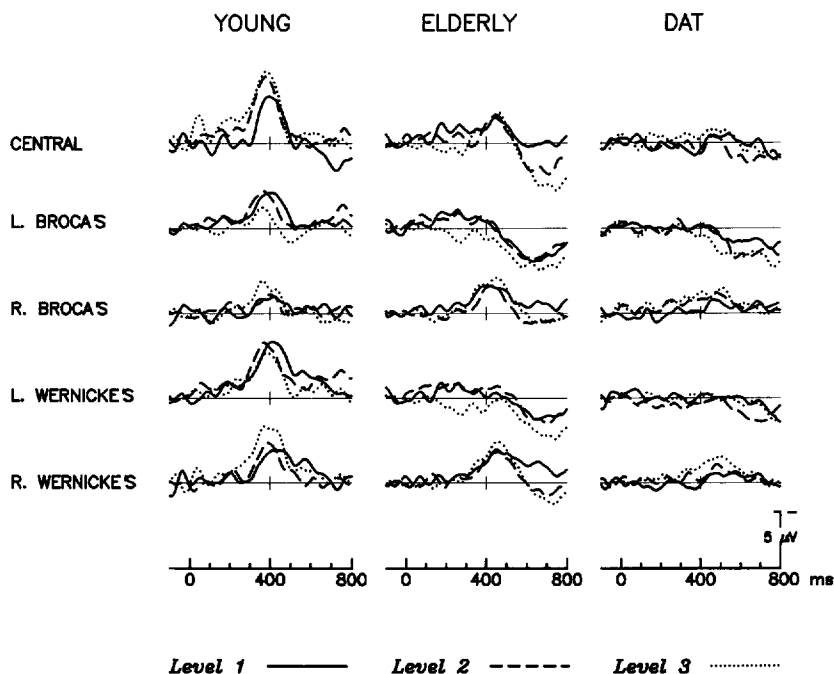


Fig. 4. Comparison of difference ERPs (unrelated minus related waveforms) for all three category levels, separately for each group.

between groups over the right hemisphere, but not over the left. At Wernicke's the young showed earlier peak latency N400 effects than the elderly controls, who were earlier than the DAT subjects [ $F(2,22) = 10.05$ ,  $P < 0.001$ ]. Follow-up tests revealed that the control groups' N400 effects peaked significantly earlier than the patient group at level 3 only ( $P < 0.05$ ).

Subsequent to the N400 effects, a later positive component was examined within the window of 600 and 800 msec. The group effect was significant for the amplitude of this region of the ERP [ $F(2,33) = 5.69$ ,  $P < 0.01$ ]. Whereas the elderly controls and the DAT subjects showed this positivity over the left hemisphere, the young did not. This component did not vary with level.



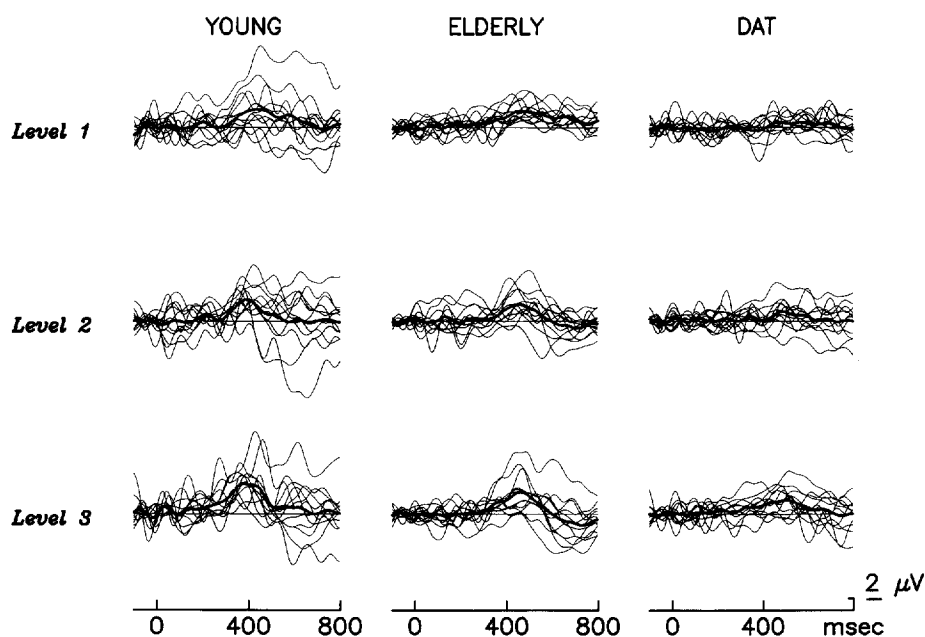


Fig. 5. Difference ERPs showing the congruity effect for the 12 individual subjects in each group for each category level. The electrode site shown is the right hemisphere homologue to Wernicke's area. The thicker line represents the grand average difference ERP for each group.

Table 1. Mean amplitude of the N400 effect

Category	Hemisphere	Young	Elderly	DAT
1	Left	-3.16 (3.70)	-0.08 (2.18)	0.02 (0.98)
	Right	-1.77 (3.09)	-1.93 (1.06)	-0.61 (1.18)
2	Left	-2.83 (2.67)	-0.39 (3.11)	0.90 (1.63)
	Right	-1.72 (2.13)	-1.53 (1.98)	-0.79 (2.09)
3	Left	-2.20 (2.36)	0.89 (2.03)	0.16 (1.67)
	Right	-3.08 (2.20)	-2.08 (2.32)	-1.52 (1.97)

## Discussion

The present study provides evidence of some appreciation of semantic relatedness by young, normal elderly, and Alzheimer's subjects alike. For all three groups, data support the conclusion that categories can prime at least some category members in a similar manner. Electrophysiologically, this effect is seen as a difference in the ERPs between related and unrelated target words after the auditory presentation of a category name. On average, the N400 component, whose amplitude is thought to be a function of both the subjective conditional probability and the strength of the semantic relationship between a target word and preceding context [31], was larger for unrelated targets than for targets that were semantically related to the prime.

Although all three groups evidenced an N400 priming effect, the amplitude of the N400 effect was largest for the young control subjects, followed next by the elderly controls, and was the smallest for the Alzheimer's patients. A similar pattern held for the latency of the N400 effect, which was earliest and sharpest in the young subjects and quite late and broad in the DAT patients,

with normal elderly being intermediate. The reduction and prolongation of the N400 effect with advancing age and with dementia probably reflects a decrease in the amount of semantic analysis and integration and increase in the duration and variability of the processes.

Whereas it has been argued that the semantic deficit in DAT is caused by breakdown of a semantic network, the present study does not support a strong form of this view, according to which DAT patients should show either no semantic priming at all or a pattern of priming that is qualitatively different from that of normal elderly controls. Neither our ERP nor RT data fit this pattern. Several investigators have suggested that DAT patients fail to categorize words and pictures because they no longer retain knowledge of their meanings [1, 26]. Support for this point of view is derived from studies that manipulate the reliance of subjects on pre-existing knowledge of associations between concepts. In the present study, the category level manipulation was used to examine this hypothesis. It was hypothesized that the patient group would demonstrate a pattern of performance reflecting a loss of specific category knowledge. The DAT patients were expected to show less semantic priming

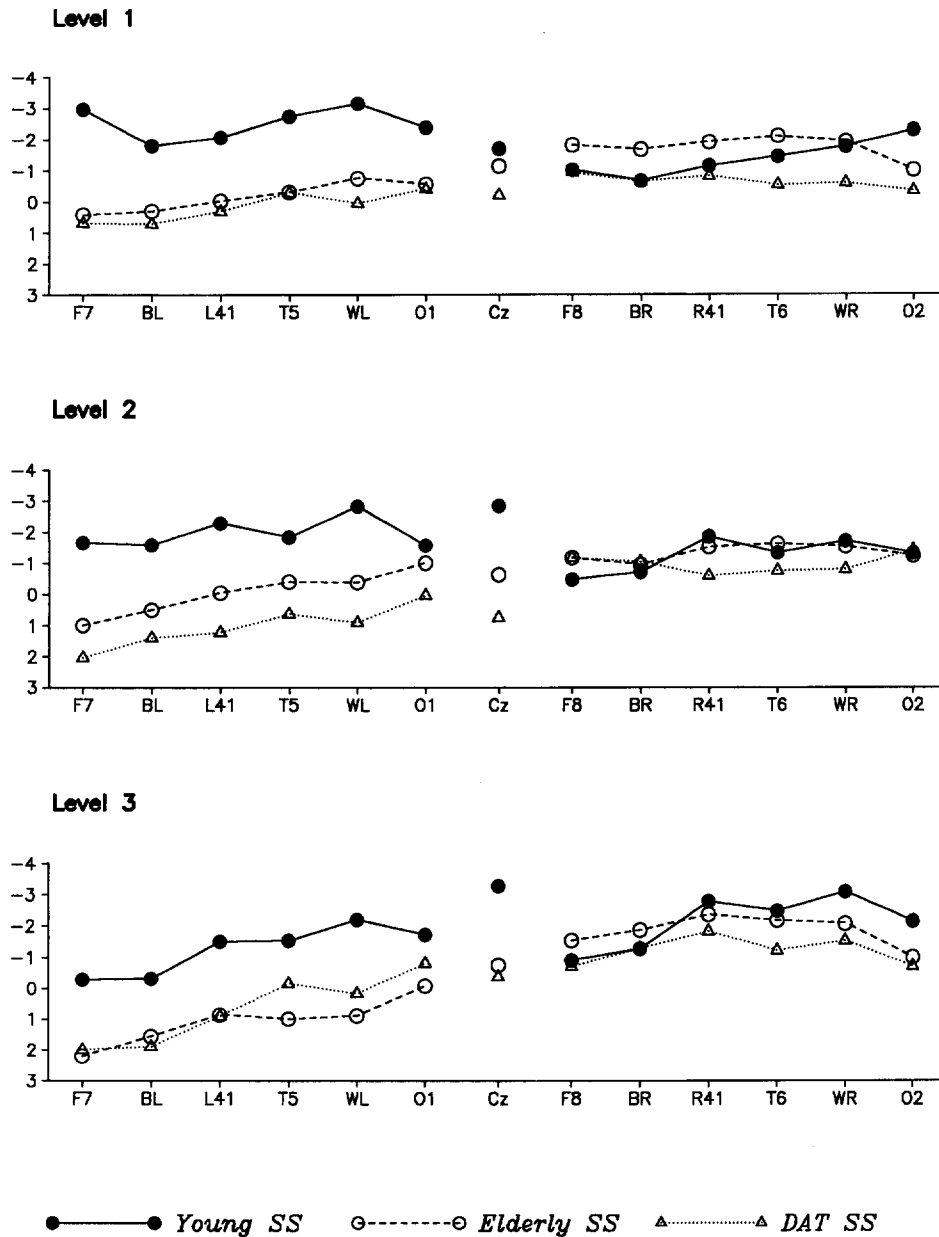


Fig. 6. Comparison of the distribution of the N400 effect across groups for each category level, separately. In each graph, the data reflect mean amplitude in  $\mu\text{V}$  of the difference ERP at all 13 electrode sites (young: 250–550 msec; elderly control subjects: 300–600 msec; DAT subjects: 400–700 msec).

(decreased N400 amplitude and smaller reaction time differences between unrelated and related target words) for the more specific categories than the normal controls, but to perform like the control subjects for the most general categories. Instead, the effect of category level resulted in a similar pattern for all groups. All of the groups showed larger N400 congruity effects on basic and subordinate category levels than on the superordinate categories. Moreover, the broadest level of categorization led to the slowest reaction time responses and the most errors for all groups. The fact that DAT patients were affected by the category level manipulation in the same manner as the control groups suggests that at least some of the structure of a semantic network must be intact in

the mildly demented such as the subjects that partook in the present experiment.

These results indicate that narrowing the set size of possible category members facilitated timed categorization performance for the young, elderly, and the demented alike. This finding of facilitated performance by constraining the set size is in agreement with results demonstrating that DAT patients seem less impaired on tasks including stimuli with high contextual constraint. For instance, in some cases sentence constraint seems to affect DAT patients more than normal controls and may act to minimize the severity of anomia found in DAT [44]. These findings highlight the need to take into account the processing demands of the task. Tasks that prove difficult

for the normal elderly may become increasingly more difficult for the demented.

The patients were the only group to demonstrate significant reaction time priming effects. This was not due to a speed-accuracy trade-off, for these subjects showed faster responses for the basic and subordinate categories than for the superordinate categories, but also had the highest percentage correct for these more specific categories. It has been argued that increased priming effects in those with DAT or in some cases normal aging may be an artifact of their overall slower reactions [40]. Many studies have shown that there is a generalized cognitive slowing with age on reaction-time tasks [3, 9, 58] and the present results do show a pattern which reflects a slowing for the normal elderly, and even more so for the patient group. Even so, the patient group showed more priming in reaction time for basic and subordinate category levels than could be accounted for by slowing alone. In addition, an examination of the ERP data illustrates that the differences are not merely the result of response slowing; there are quantitative differences in the amount of semantic processing demonstrated by the two groups as reflected in the amplitude of the N400 component.

Aside from the integrity of semantic memory there is evidence suggesting that other factors, such as attention, can influence the pattern of priming in both normal elderly and in DAT. Ober *et al.* [47] used pronunciation and lexical decision tasks with short (250 msec) prime-target stimulus-onset asynchronies, to examine the effects of various category relations on semantic priming in those with DAT and older and younger control subject. They found no significant group differences in the magnitude of semantic priming for a variety of prime-target relationships (i.e., highly associated category co-members, subordinate-superordinate or superordinate-subordinate pairs, atypical-typical, typical-atypical, and atypical-atypical pairings). Similarly, Nebes *et al.* [38] found that DAT patients and control subjects showed equivalent facilitation in naming latency when a word was preceded by a semantic associate with stimulus-onset asynchronies of approximately 500 msec. Both of these studies concluded that DAT patients' semantic priming appears to be more normal when assessed with measures that rely on automatic as opposed to attentional processing. In fact, DAT patients do have difficulty on tasks which require an intentional, active search for information within semantic memory [13]. In the present study, the task directed subjects' attention to the meaning of words, and may thus have facilitated the performance of the patients and affected quantitative differences in the degree of priming between the groups. For example, the high percentage of related primes (50%) may have contributed to the use of more controlled processing of semantic relationships. Indeed, an examination of the ERPs, in particular the level  $\times$  hemisphere  $\times$  priming interaction, suggests that subjects may have been using more than one process in performing the task. The more specific categories elicited the largest N400 effect over the

right hemisphere, and the least negativity over the left hemisphere for all groups. In a study of automatic and attentional processing and semantic priming, Holcomb [27] found a positive slow wave that followed the N400 effect was elicited by the attentional manipulation. Perhaps in the present study, the effects seen over the right hemisphere reflect more incidental activation within semantic memory, whereas the left hemisphere effects were affected to a greater degree by an intentional use of attentional strategies. Specifically, the left hemisphere positivity seen in the elderly controls and DAT subjects may be related to violations of expectancies leading to an active search of semantic memory. Such a positivity, although hinted at in the data from the young may be partly masked by their large N400 activity over the left hemisphere.

Hemispheric differences in semantic priming have been noted by other investigators, although primarily for lateralized stimulus presentations. For example, using low proportions of related primes and an SOA of 600 msec in both pronunciation and lexical decision tasks, Chiarello and Richards [17] obtained reliable priming only in the left visual field/right hemisphere. Moreover, the priming effects were as large for poor as for good category exemplars. They argued that semantic information may be represented in both hemispheres, but that a broader range of meanings for words may be activated in the right than in the left cerebral hemisphere. In subsequent experiments, Chiarello *et al.* [17] argued for the left hemisphere's predominance in semantic integration processes. Employing various stimulus onset asynchronies, Burgess and Simpson [7] found that, while automatic processing occurred in both hemispheres, only the left hemisphere was involved in more controlled processing. Nakagawa [37] found that hemispheric differences in semantic priming interacted with the anterior attention network. The anterior attention systems includes areas of the mid-prefrontal cortex, and may be important for attending to word meaning and inhibiting irrelevant information during the processing of language. Nakagawa's work suggests that the left hemisphere may depend more heavily on the availability of the anterior attention system than the right, thus it may have the ability to shape the process of semantic priming more actively. The differential contributions of the left and right hemispheres to semantic priming have hardly been examined in the elderly and AD patients, but they are potentially very important. If there are two semantic memory stores with different characteristics and if these are tapped differently by various tasks or differentially affected by aging and dementia, this may account for some of the discrepancies in the literature on the sequelae of DAT on semantic memory.

The potential hemispheric differences in semantic processing notwithstanding, it is clear that investigating semantic memory and how it is impacted by DAT is a complicated endeavour. No single measure and no single task has privileged access to semantic memory processes,

their organization and disintegration. The pattern of effects with some measures and some tasks can only be explained by a breakdown in semantic memory, whereas for other tasks and measures the best account seems to be in terms of slowing or quantitative (but not qualitative) changes. Our data fall into this latter category. On the one hand, our DAT patients showed very little and delayed N400 congruity effects; however, insofar as a patient showed an N400 effect it behaved similarly in response to experimental manipulations as in the elderly and young controls. On the other hand, DAT patients also showed prolonged reaction times and the largest behavioral priming effects, which could not be accounted for by the magnitude of the behavioral slowing *per se*. Thus even within this single study the two dependent variables provide a somewhat different picture of the effect of DAT on semantic processing.

The strongest form of the breakdown of semantic memory with DAT would be task and measure independent and would have predicted better priming for general than for specific category items. However, both the significant reduction and prolongation of the N400 congruity effect and the abnormal amount (in this case too much) of priming in the DAT patients are consistent with a weaker form of the breakdown in semantic memory hypothesis, which is modulated by a variety of other factors, such as attention, depending on the task.

One must take into account task difficulty and the cognitive processes that come into play in different semantic priming tasks in order to help answer such questions. It has been argued that the ERP repetition effect, which remains robust even in those with DAT, reflects the modulation of multiple ERP components, including the N400 [57]. The presumed N400 component of the ERP repetition effect must differ from the N400 congruity effect in its psychological and neural bases; the former appears unaffected by dementia whereas the latter appears to be severely compromised in those with DAT (see also Iragui, Kutas and Salmon, *in press*). Such dissociations among implicit memory mechanisms may help clarify the nature of the semantic deficit in DAT. Future studies should address the role of attention on semantic priming for the young, normal elderly and demented in greater depth. It would also be useful to examine priming as a function of different kinds of semantic relationships between targets and primes in each of these groups, and the roles of inhibition and additivity. The true nature of the semantic deficit in Alzheimer's dementia will remain a mystery until we understand better the normal process of how meaning in language connects with our understanding of the world.

*Acknowledgements*—This research was supported, in part, by a McDonnell-Pew Center for Cognitive Neuroscience Graduate Fellowship awarded to Tanya J. Schwartz, and by grants from NIA (AGO8313) and NICHD (HD22614). Subjects were paid by funds from VA Merit Review Grant No. 307. We gratefully acknowledge Frank Haist for his comments on previous ver-

sions of this manuscript, and Ron Ohst for programming support.

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## Appendix 1

### Categories

- Level 1: Living
  - Man-made
- Level 2: Animals
  - Plants
  - Household items
  - Musical instruments
- Level 3: Land animals
  - Water
  - Trees
  - Flowers
  - Furniture
  - Electrical appliances
  - Wind instruments
  - String instruments

**Appendix 2***Target words*

refrigerator	nurse	broiler	voter	palm
iron	maid	television	monk	drill
desk	adviser	bureau	relative	rose
dresser	sponsor	bed	therapist	map
bass	civilian	mandolin	clergyman	lily
violin	hunter	trumpet	corn	gown
horn	planet	trombone	leaf	poppy
bassoon	stomach	cow	brick	cabin
cat	portrait	dog	treaty	pansy
lion	candle	salmon	skirt	attic
clam	doll	shark	curtain	brick
lobster	battery	redwood	fountain	apple
birch	soap	fir	statue	rope
dogwood	tire	lilac	shirt	elm
marigold	label	daffodil	airplane	screw
carnation	candy	telephone	physician	oak
toaster	pioneer	oven	livestock	flag
heater	grandmother	table	diplomat	trout
crib	spectator	stool	teenager	chapel
cabinet	female	ukulele	journalish	snail
viola	sailor	banjo	ocean	rocket
flute	neighbour	saxophone	cowboy	
bugle	psychologist	harmonica	person	
rabbit	envelope	camel	radar	
bear	airport	monkey	suitcase	
shrimp	pen	octopus	coin	
turtle	plaster	eel	canvas	
pine	submarine	maple	tractor	
spruce	concrete	willow	fork	
tulip	tray	orchid	boot	
daisy	ticket	violet	cottage	
vacuum	ant	drill	man	
radio	fish	stove	feather	
chair	canyon	sofa	peer	
lamp	actor	bookcase	freshman	
guitar	veteran	cello	human	
fiddle	land	clarinet	mouse	
oboe	lover	recorder	sergeant	
bagpipe	merchant	horse	button	
deer	crown	goat	taxi	
fox	pipe	oyster	pan	
whale				