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Cognitive brain activity in Alzheimer's disease: Electrophysiological response during picture semantic categorization

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Abstract

Semantic memory deterioration is a major component of the cognitive decline seen in patients with dementia of the Alzheimer's type (DAT); however, the exact nature of this deficit remains unclear. Some research data support a procedural deficit where there is an inability to access or retrieve the contents of semantic memory, while other data point to a degraded semantic store where the actual content of semantic memory is degraded. Additional information about semantic processing in DAT can be obtained through the use of an event-related potential (ERP) component known as N400. In the present study, ERPs were recorded from 10 young control participants, 10 elderly control participants, and 10 DAT patients in a picture–semantic matching task. Stimuli were presented sequentially as prime–target pairs, with one-half of the targets matching the primes via semantic relationships (e.g., *piano–violin*) and the other half mismatching the prime (e.g., *helmet–violin*). The task was to discriminate between semantically related and unrelated pairs of pictures. In the young and elderly control groups, ERPs generated a larger N400 for unrelated than related target pictures, with a maximum amplitude around 380 ms in the young group and around 480 ms in the elderly group. The amplitude of the N400 was significantly reduced in the DAT patients. However, a separate analysis of congruent and incongruent ERPs trials revealed significant differences only with the incongruent trials. The amplitude of incongruent recordings was larger for the elderly control group than for the DAT patients, while the amplitude for congruent recordings was similar in both groups. These findings are consistent with the neuropathological evidence that Alzheimer's disease is a neocortical disconnection syndrome in which there is a loss of structural and functional integrity of long corticocortical tracts. The semantic activation created by the context is not used efficiently in processing stimuli, which affects access to specific concepts and gradually leads to a breakdown in the structure and organization of semantic memory. (*JINS*, 1998, *4*, 415–425.)

Keywords: Event-related potentials, N400, Picture categorization, Semantic memory, Alzheimer's disease

INTRODUCTION

Semantic memory deterioration is a major component of the cognitive decline seen in patients with dementia of the Alzheimer's type (DAT) (Nebes, 1989). However, the exact nature of this deficit remains unclear. Some research data support a procedural deficit where there is an inability to access or retrieve the contents of semantic memory (Chenery, 1996), while other data point to a degraded semantic storing, with its contents being disrupted (Hodges et al., 1992). According to the network theory of semantic memory postulated by Collins and Loftus (1975), concepts are represented by nodes interconnected by a variety of relationships, such as membership in a common category, functional, and/or property relationships. Whenever a concept is presented, either in the form of its name or picture, its corresponding node in the semantic memory is activated, and this activation spreads automatically to related nodes, increasing the accessibility of the related concepts. Experimental evidence for such a spread of activation comes from studies of semantic priming where behavioral studies have

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shown that the processing of related targets, such as *doctor–nurse*, is enhanced or facilitated in comparison with the processing of unrelated targets, such as *window–nurse* (Neely, 1991). As with words, the processing of a picture can be primed if it is preceded by a semantic associate (Bajo, 1988).

Neuropsychological, computational, psycholinguistic, and brain imaging data suggest the existence of semantic networks, with localized representation of semantic information in the brain. In these networks, similar words or picture meanings are represented by adjacent nodes, while dissimilar meanings are in distant nodes (Spitzer et al., 1995).

Results of studies of semantic priming in DAT patients have reported controversial results, with some reporting intact priming (Hartman, 1991; Nebes, 1989; Ober et al., 1991), others reporting no priming (Huff et al., 1988; Ober & Shenaut, 1988; Salmon et al., 1988), some showing excessive or hyperpriming (Balota & Duchek, 1991; Chertkow et al., 1989; Nebes, 1989), and others showing a mixture of both no priming and intact facilitation (Albert & Milberg, 1989). The type of stimuli used, such as words or pictures, also seems to have an important effect. Margolin (1987) found that DAT patients did not show semantic priming when the prime was a picture of an object, but they did show priming when the prime was a word rather than a picture. There are differences between the processing of words and pictures (Potter & Faulconer, 1975); therefore the follow-up of these results could provide important information about the limitations of semantic functioning in DAT.

Additional information about semantic processing in DAT can be obtained by the use of the event-related potential (ERP) component known as N400 (Kutas & Hillyard, 1980). Unlike behavioral measures, ERPs provide continuous, noninvasive, on-line monitoring of brain activity during information processing that is not necessarily contingent upon overt response, and they go beyond behavioral measures by providing continuous multidimensional information about the cognitive activity that goes on between the stimulus onset and the overt response. Priming has also shown to have a substantial effect on this component. Several studies have shown that this negative deflection is enhanced for written endings of sentences with semantically incongruent words relative to sentences with a congruent ending (Kutas & Hillyard, 1980), and that the amplitude of the N400 is an inverse function of the close probability of the target word (Kutas & Hillyard, 1984). This component has also been demonstrated using written words (Harbin et al., 1984), speech sounds (Neville, 1985), and pictures as stimuli (Barret & Rugg, 1990; Bobes et al., 1996; Holcomb & McPherson, 1994), with a larger N400 elicited by semantically unrelated pairs than by semantically related ones. The difference in the ERPs between these two conditions is called the N400 priming effect. Up until now, very few studies have been published using N400 to assess semantic functions in DAT. Recently, Hamberger et al. (1995) used a lexical decision task with sentences as stimuli and found that the N400 amplitude was identically responsive to semantic relatedness in young normal and DAT groups. Behaviorally, the DAT patients produced a significantly greater number of errors; therefore they concluded that their disruption in semantic processing occurs at some point between the elicitation of the N400 and the generation of the reaction time response. However, in a more recent study, Iragui et al. (1996), also using a verbal semantic paradigm with words, reported that the N400 effect was reduced in amplitude in the elderly control group relative to the younger control group and was further attenuated in amplitude, delayed in latency, and somewhat flatter in its distribution across scalp in DAT patients. They suggested that the problem seems to be within the semantic network organization. Since all of the studies of N400 in DAT were performed using printed words as stimuli, it is difficult to determine if the problem with semantic processing is a consequence of disturbances within the semantic system itself, or if it is related to deficits above and beyond deficits in word recognition skills. By using pictures, the linguistic process of decoding printed words can be bypassed, therefore the purpose of the present study was to provide an on-line recording of semantic abilities in DAT patients during an active picture–semantic matching task. Special attention was directed to a possible N400 amplitude reduction. The comparison of N400 amplitude between DAT and two controls groups (young and elderly) was carried out separately for congruent and incongruent trials. Specific contrast was performed to establish whether the N400 amplitude reduction was due to an enhanced negativity for congruent trials or an enhanced positivity for incongruent trials.

METHODS

Research Participants

Ten young control participants (5 men and 5 women, *M* age = 24.4 years, *SD* = 4.2), 10 normal elderly participants (5 men and 5 women, *M* age = 67.8 years, *SD* = 4.7), and 10 patients with DAT (4 men and 6 women, *M* age = 75.4 years, *SD* = 5.2) participated in this study. The control participants were volunteers from the community, and in terms of age the elderly controls did not differ from the patients with DAT. The groups were matched on number of years of education (young control *M* = 9.9 years, *SD* = 4.1; elderly control *M* = 9.6 years, *SD* = 3.2; DAT patients *M* = 8.9 years, *SD* = 3.6). All participants were right-handed. The criteria for inclusion of the normal group were (1) not being demented according to DSM–IV criteria (American Psychiatric Association, 1995), (2) achieving a score equal to or higher than 23 in the Mini-Mental State Examination (MMS) (Folstein et al., 1975), (3) having no background of neurological or psychiatric illness, and (4) scoring within the normal range on a neuropsychological battery that was developed, standardized, and validated in a Spanish-speaking population (Ostrosky-Solís et al., 1997). The battery assessed the domains of attention, memory, language, visual perception, visuospatial process, and executive functions. The battery was administered by a trained certified neuropsychologist. The DAT patient group was recruited from the Center "Francisco Espinoza Figueroa" for Alzheimer's Disease, which is a clinically oriented day care center for DAT patients. The diagnosis of DAT was made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke, Alzheimer's Disease and Related Disorders Association for probable DAT (McKhann et al., 1984), on the neuropsychological test results, and the patient's level of functioning in daily activities. MMS scores ranged from 25 to 30 in both the young controls (*M* MMS = 28.3, *SD* = 2.9) and the elderly controls (*M* MMS = 27.2, *SD* = 3.8) and from 14 to 22 in DAT patients (*M* MMS = 16.5, *SD* = 3.9); duration of illness was between 6 months and 3 years. On the neuropsychological battery, patients scored more than 2 standard deviations below standardized norms on measures of delay recall of verbal and visual material, confrontation naming, verbal fluency, and executive function. Other possible sources of dementia were excluded by appropriate laboratory evaluations, such as computed tomography, electroencephalography (EEG), blood count, serum B12, hepatic, renal, and thyroid function tests. Their scores on the Hachinski Ischemic Rating Scale (Hachinski et al., 1975) were used to aid in excluding multi-infarct dementia. None of the patients were taking psychoactive medication. All participants had normal or corrected-to-normal vision. A total of 15 patients met the criteria selection, but due to excessive artifacts during the EEG recordings, data from 5 patients could not be used.

Semantic Matching Task

Stimuli

The stimuli consisted of 120 related pairs of line drawings taken from the Snodgrass and Vanderwart pool (1980). The stimuli were previously adapted and standardized in a Spanish-speaking population (Aveleyra et al., 1996) and were selected from a pool of 260 drawings on the basis of highest rating scores on the familiarity scale. To obtain the semantically related and unrelated pairs of pictures, a pilot study was performed with a group of 20 young normal participants (*M* age = 26.9 years, *SD* = 5.6) and 20 normal elderly participants (*M* age = 70.4 years, *SD* = 4.3) who did not participate in the ERP experiment. Stimuli were rated for degree of membership in the same semantic category (animals, clothing, vehicles, tools, musical instruments, etc.). Participants were shown a set of 200 matching and nonmatching pictures pairs and were instructed to rate each pair on a scale from 0 (*no membership in the same category*) to 5 (*same category*). Pairs with the highest and lowest strength of semantic association were selected based on the average of participants' judgment. Visually similar pairs were eliminated. A total of 60 matching and 60 nonmatching pairs were finally formed.

Procedure

Stimuli were presented sequentially in prime–target pairs with one-half of the targets matching the primes via semantic relationships (e.g., *piano–guitar*) and the other half mismatching the prime (e.g., *helmet–guitar*). The pairs of pictures were presented in a pseudorandom order. The 120 pictures of equal size (black lines on a white background) were presented on a VGA monitor and were 8 cm high × 8 cm wide. The black line drawings occupied about one-third of the background and were roughly equivalent in size. Participants sat at 1 m from the screen, and the pictures subtended a vertical and horizontal visual angle of about 4.6°. The task was to discriminate between semantically related and unrelated pairs. Figure 1 shows the time course of stimulus presentation and examples of semantically related and unrelated pairs. Participants sat in a comfortable chair in front of the computer monitor, and they were instructed to minimize body and eye movements. The EEG recording was synchronized with the onset of the second picture. A typical trial proceeded as follows: the letter string "XXXX" was presented as a warning signal, then a picture (S1) was presented for 1 s, followed by a 300-ms blackout; a second picture (S2) was presented (1-s duration) after the blank interval, and the screen was again blanked. After the blank screen, the word "RESPONDA" ('answer') appeared, and the participants responded verbally (*yes* or *no*) if the stimulus was related to the previous one. The EEG recordings were synchronized with respect to S2. The response was delayed until EEG recording was finished in order to reduce artifacts; thus reaction time was not measured.

Electrophysiological Recording

Electrophysiological data acquisition and analysis were carried out on a Neuroscan system (Herndon, VA, USA). Scalp electrical activity was recorded from 32 monocular derivations of the 10–20 International System. An electrode cap (Electro-Cap International) was used. All electrodes were referenced to linked ear lobes. An additional bipolar derivation recorded electrooculograph (EOGH) activity and was used to reject sweeps contaminated with eye movements. Electrode impedance was always below 5 KΩ. The signal was filtered between 0.5 and 30 Hz (3 dB down). In each trial 256 points of digitized EEG (12-bit resolution) were recorded at a sampling rate of 256 Hz, totaling 1 s, and stored on a magnetic disk for off-line analysis. A prestimulus baseline of 100 ms was obtained in each trial, and data acquisition continued 900 ms after stimulus (S2) onset. Only trials on which a correct behavioral response was made were used to form the averages. Trials on which EOGH activity exceeded a peak to peak amplitude of −50 to +50 μV or on which saturation of one or more channels of the analog-digital converter occurred were also excluded (about 15% of trials were lost due to such artifacts). For every participant, averaged ERPs for each recording site were obtained for each stimulus condition and were submitted to low-pass

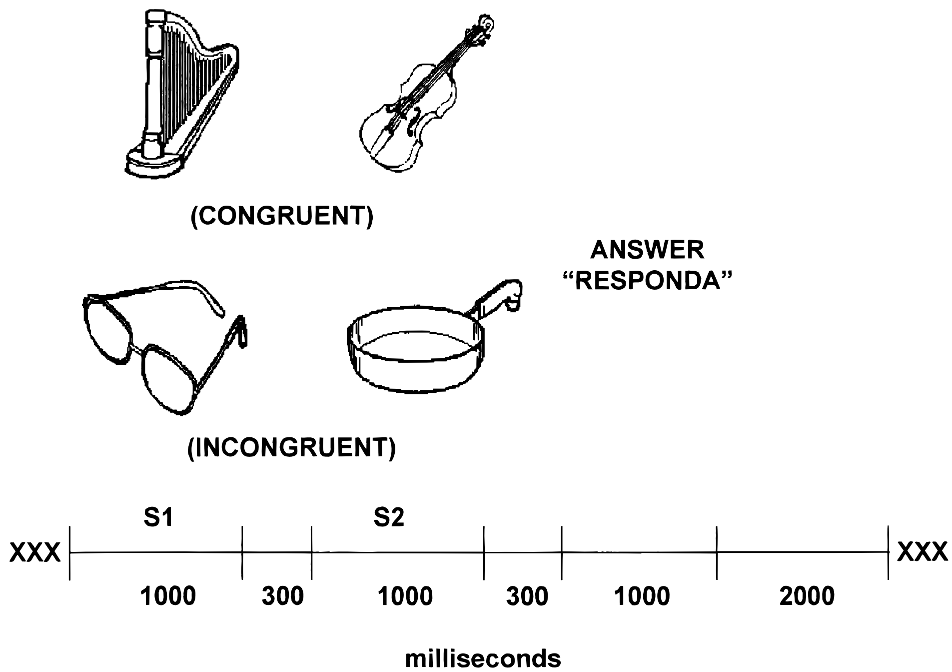

Fig. 1. Examples of semantically congruent and incongruent picture pairs and time course of stimulus presentation and data acquisition (in ms).

digital filtering (zero phase distortion) with an upper cut-off of 10 Hz. The average amplitude of ERP waveforms was measured for each individual in predefined time windows (defined below). All data points were corrected (prior to plotting or measurement) by subtracting the average prestimulus amplitude value. In other words, all amplitude values were measured with respect to the average amplitude of the prestimulus value corresponding to each ERP. The peak latency and peak mean amplitudes of the N400 were quantified by computer in both congruent and incongruent conditions and in the difference waveforms derived from a point-by-point subtraction of the congruent and incongruent ERPs. Latencies were measured relative to stimulus onset. The peak of the N400 was identified on the maximum negativity between 300 and 550 ms poststimulus.

Discrimination behavior was analyzed using the signal detection theory measures d' and the $\log_{10}$ of β (Swets, 1964). The use of d' permits an assessment of the accuracy of performance without contamination from variations in criteria (biased response), which could be important between control and patient groups.

Statistical Analysis

Behavioral and ERPs measures were submitted to analysis of variance (ANOVA). For the ERP measures, amplitude and latency values were subjected to repeated measures ANOVAs, using group (normal young, normal elderly, and DAT patients) as the between-subject variable and congruity (congruent vs. incongruent) and electrode site (12 levels, including the sites where the negativity was the largest) as the within-subject repeated measures. The Greenhouse–Geisser procedure was used, when appropriate, to mitigate violations of the sphericity assumption in repeated measures designs (Keselman & Rogan, 1980). Additional ANOVAs and planned comparisons (described below) were carried out. To determine if significant interactions of electrode site with group reflected differences in scalp distribution between groups, the data were normalized as outlined by McCarthy and Wood (1985). Only significant interactions on the normalized amplitude measures are reported.

RESULTS

Behavior

All of the participants were able to discriminate between congruent and incongruent pictures, as reflected by the mean d' (Table 1), which was significantly different from zero for all groups studied (t tests, $p < .001$). The mean d' differed between groups was confirmed by an ANOVA [$F(2,27) = 10.04$, $p < .001$]. Planned comparisons demonstrated that the d' for the DAT group was significantly lower than both control groups ($p < .001$), whereas the difference between the young and elderly controls was not significant. The mean percent of hits was also very high for the two control groups and lower for the DAT group, but always above 50%. These data differed between groups as confirmed by an ANOVA [$F(2,27) = 14.43$, $p < .005$]. Response bias (log β), also shown in Table 1, was not statistically different among the three groups.

Table 1. Behavioral results: Mean values of d', hits percentage, and $\log_{10}\beta$

	Group		
	Young control	Elderly control	DAT
Result	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
d'	4.32 (.47)	4.54 (1.38)	2.54 (1.21)
Hits percent congruent	98.8 (2.12)	94.3 (7.97)	78.7 (10.85)
Hits percent incongruent	98.8 (1.8)	95.4 (6.13)	84.2 (15.1)
$\mathrm{Log}_{10}\beta$	−2.43 (4.69)	−4.22 (7.09)	0.21 (3.6)

ERPs

Grand average ERPs elicited by congruent and incongruent pictures for young, elderly, and DAT patients are shown in Figure 2. The morphology of the ERPs was characterized by an early negativity, with a peak latency about 100 ms, largest anteriorly, followed by a positive deflection peaking at approximately 200 ms, also largest at anterior sites. This deflection was followed by a second negative deflection, broadly distributed across the scalp, peaking around 350 to 400 ms (N400), which was larger for incongruent than for congruent pictures (shaded areas in Figure 2), and finally a broadly distributed positive deflection at approximately 600 ms.

No significant effects in the amplitude nor the latency of the ERPs were found before 300 ms for any factor. Thus, attention will be focused on the late ERP component. For both control groups, after the 300 ms, the recordings associated with incongruent pictures were markedly more negative than those associated with the congruent pictures; however, for the DAT patients, this component was diminished in amplitude. This negativity appeared in the average difference waveform as a single peak, with onset about 325 ms at Cz and lasting up to 550 ms, with its maximum at about 425 ms. For the young and elderly groups, the amplitudes in incongruent trials were more negative than in the congruent trials; however, for the DAT patients, both amplitudes for congruent and incongruent recordings overlapped, and small differences could be observed only at the Fc4 site. At temporal sites, a small difference between the two types of recordings was also seen, but the ERPs from incongruent trials were more positive than those from congruent trials. The amplitude distribution in the DAT group of the incongruent trials resembled that of the congruent recordings. Figure 3 shows the average difference waveforms obtained by subtracting the ERPs associated to congruent trials from the ERPs associated with the incongruent trials in the three groups studied. The 12 sites selected included the locations where the negativity was largest.

The mean amplitude of the difference waveform was calculated over a 325-ms window that was centered for each group on the corresponding N400 peak: that is, between 325–400 ms in the young control group, and between 350–550 ms in the elderly control and DAT groups. An ANOVA of these data indicated a significant main effect of group [$F(2,27) = 14.58$, $p < .001$], but planned comparisons showed that a difference only existed between the DAT patients and the two normal groups; amplitude for the young controls did not differ from that for the elderly controls.

In order to examine scalp distribution, mean amplitude values were corrected as indicated by McCarthy and Wood (1985) and subjected to a repeated measures ANOVA with group (young control, elderly control, and DAT) and electrode site (Fz, Cz, Pz, Oz, Fc3, Cp3, T3, Tp7, Fc4, Cp4, T4, Tp8). A significant interaction of Group × Electrode Site [$F(22,297) = 2.9$ $p < .019$] was found. Planned comparisons showed that central and parietal sites did not differ between the normal groups (young and elderly), and that significant changes between the normal groups were limited to Fc3, Fc4, Fz, T3, and Oz. However, both normal groups were different from the DAT group, who showed a significantly smaller amplitude across all scalp electrodes. Moreover, the topographic distribution differed for the young control group, who showed a bilateral distribution with activation at frontal and centroparietal sites, whereas in the elderly control group the N400 effect was largest at the right centroparietal area. DAT patients did not show any significant amplitude gradient and only showed a very small N400 effect at Fc4.

The latency of the congruity effect was measured in the difference waves. In the young control group, the N400 began around 325 ms and peaked around 400 ms (383.98 ± 38.3 ms). In the elderly control group, the N400 effect began around 350 ms and peaked around 470 ms (486.37 ± 64.02 ms); for the DAT patients, the N400 began around 350 ms and peaked around 490 ms (497.7 ± 45.3 ms). Statistical analysis showed that there was a significant difference between groups [$F(2,27) = 14.57$, $p < .001$], but planned comparisons showed that difference existed only between the young group and the other two groups, while the latency for the elderly group did not differ from that for the DAT patients.

The mean amplitude of the congruent and incongruent recordings for the time window from 325 to 550 ms at the 12 selected sites are shown in Figure 4 for the three groups studied. The amplitude values corresponding to the congru-

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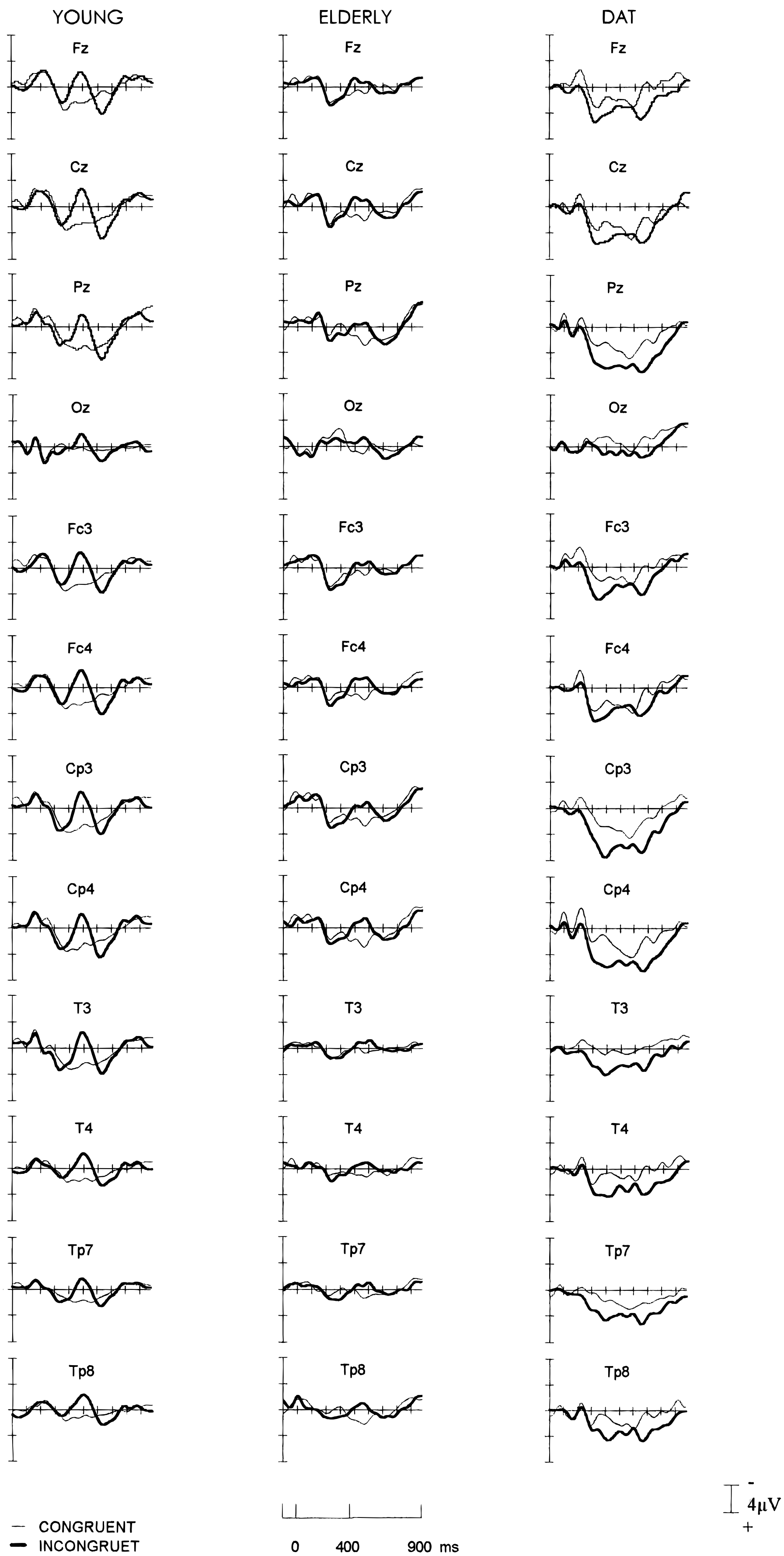

Fig. 2. Grand average ERPs elicited by congruent and incongruent pictures for the young group ($N = 10$), elderly group ($N = 10$), and DAT patients ($N = 10$). At each site, the ERPs associated with congruent trials (thin line) are overlaid on ERPs elicited by incongruent trials (thick lines). The shading reflects the congruity effect. In this and all subsequent figures negativity is upwards.

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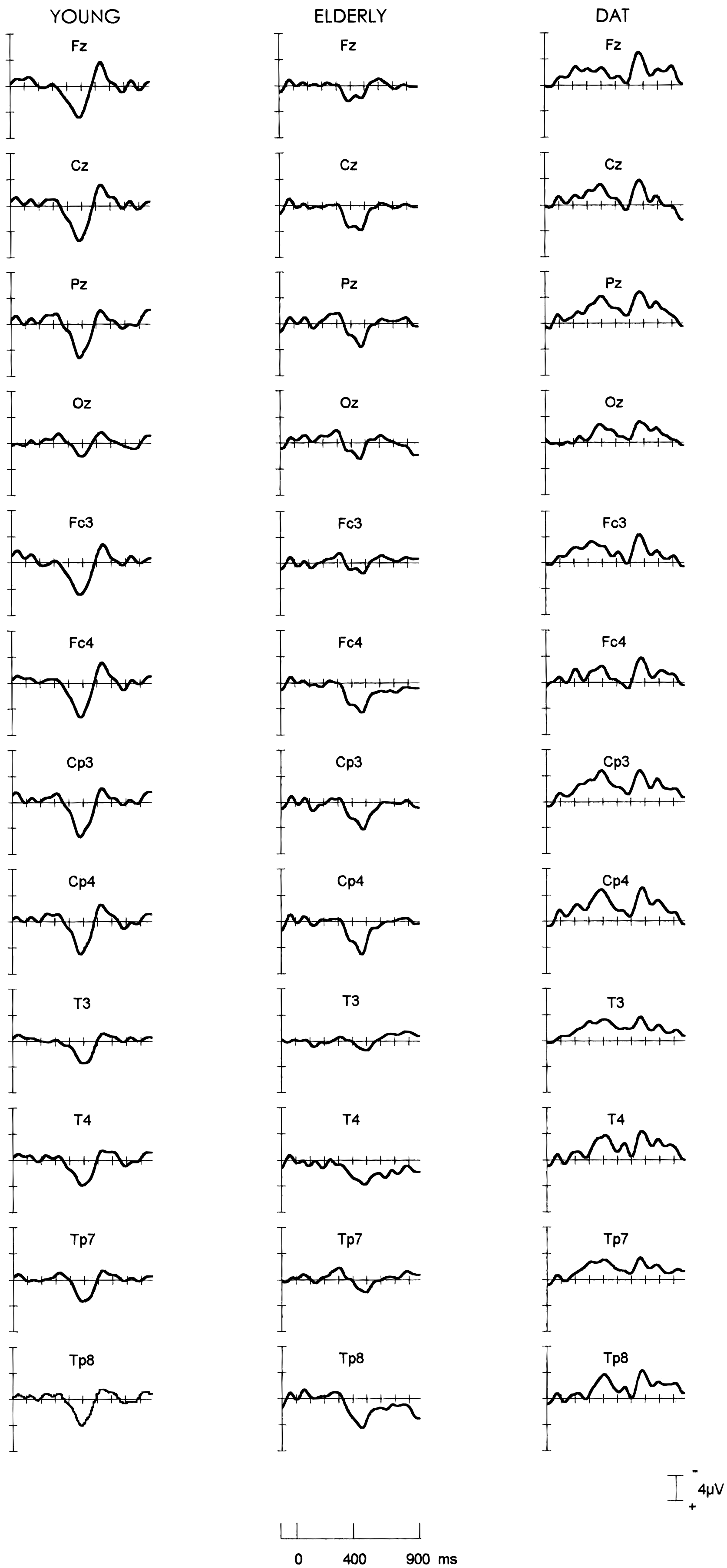

Fig. 3. Grand average difference ERP waveforms obtained by subtracting ERPs associated with congruent trials from ERPs associated with incongruent trials.

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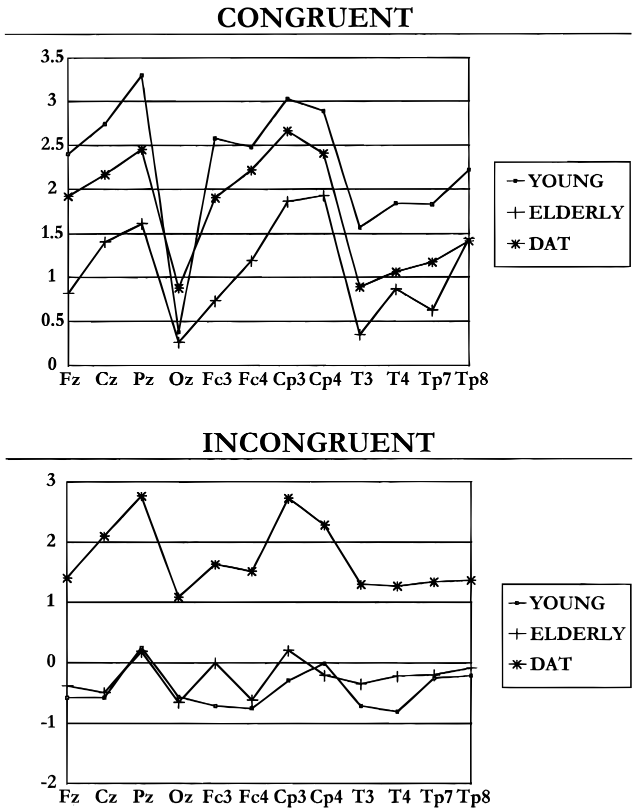

Fig. 4. Distribution across the scalp of the mean amplitude voltage values calculated in the time windows between 325 and 550 ms in the three groups studied. Congruent and incongruent values are shown separately.

ent trials were similar in the three groups, whereas the amplitude for incongruent trials for the DAT patients were clearly more positive than that for both of the control groups. Thus, a reduction in N400 amplitude for the DAT group is due to a reduction of the negativity in the incongruent trials.

All these findings were confirmed with an ANOVA performed on the amplitude values. In this analysis, group (young, elderly and DAT) was considered as a between-subject factor, and congruity (congruent *vs.* incongruent) and electrode site (12 levels, including the same sites described) were employed as within-subject factors. As reported by the ANOVA, the main effect of group was not significant. Congruity [$F(1,27) = 28.64$, $p < .001$] and electrode site [$F(11,297) = 7.6$, $p < .001$] were significant, the first of which reflects the more negative value for incongruent recordings with respect to congruent ones. The interaction of Group × Congruity was also significant [$F(2,27) = 13.16$, $p < .001$]. Planned comparisons showed that a significant effect of congruity existed for the young and elderly control groups. However, this effect was not significant for the DAT group, which confirmed that the N400 amplitude was diminished in this group. The interaction of Congruity × Electrode Site [$F(11,297) = 4.41$, $p < .001$] was also significant. Planned comparisons showed that the congruent recordings did not differ among the three groups; but there was a significant difference in the DAT group with respect to the other two groups in the incongruent condition. The three-way interaction was also significant [$F(22,297) = 1.69$, $p < .027$]. Planned comparison showed that amplitude of N400 were different between the DAT and young groups at all sites recorded, whereas the difference between the DAT and elderly groups were significant at Cz, Pz, Cp3, Cp4, T3, T4, and Tp8. Comparison between the elderly and young groups showed significant differences at all sites except Oz, Cp4, and Tp8.

DISCUSSION

Behavioral measures revealed that the mean d' for discriminating between congruent and incongruent pictures was very high and significantly different from zero for the three groups (young control, elderly control, and DAT patients). The mean percent of hits was also very high and similar for congruent and incongruent trials. However, the d' for the DAT group was significantly lower than for both control groups, whereas the difference between young and elderly groups was not significant.

Unlike off-line measures, the recording of ERPs provided an opportunity to observe the activity that is related to the semantic processing that occurs between the onset of the stimulus and before the behavioral response. Thus the analysis of the N400 effect, supplemented by a separate analysis of the ERPs to the congruent and incongruent trials, provided information regarding the structural organization of the semantic system and how DAT patients are accessing related and unrelated concepts. As in other studies that have used pictures as stimuli (Barret & Rugg, 1990; Bobes et al., 1996; Holcomb & McPherson, 1994), the N400 was significantly larger for incongruent than congruent pictures for both the young and elderly controls. This negativity was seen clearly in the difference waveforms and was very similar in morphology for the young and elderly controls. However, a significant interaction of Group × Electrode site showed that central and parietal sites did not differ between the young and elderly groups, and that significant changes were limited to frontal, frontocentral, and occipital sites. Longer latencies were found in the elderly group than in the younger group. The scalp distribution was also different. In the younger controls it was more frontally distributed and larger over the left than the right hemisphere, whereas in the elderly controls it was largest over the right centroparietal region. Other studies have reported similar effects of aging on the latency of the N400 by using pictures (Friedman et al., 1989), written words (Harbin et al., 1984; Iragui et al., 1996), and sentences (Gunter et al., 1992).

Neuropsychological studies have shown that memory deficits are a major component of the cognitive decline seen in normal aging. Although the structure of semantic memory and spreading activation between related concepts within the semantic memory are generally unaffected by age, there is evidence that semantic access, or the time required to ac-

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cess a representation in memory, is delayed with increasing age (Madden, 1989). The lack of significant aging effects in the N400 amplitude effect between young and elderly participants could mean that semantic processing mechanisms that are reflected by the N400 waveform remain intact with increasing age. However, the delay latency of N400 could be due to a slower information processing, as it has been pointed out before (Friedman et al., 1989; Gunter et al., 1992; Harbin et al., 1984; Iragui et al., 1996). The differences in scalp distribution could be related to the neural changes in brain structure and function accompanying normal aging. Age-related neuronal loss has been documented in association cortex compared to primary sensory and motor cortex (Braak et al., 1989; Timiras, 1988), although some regions show larger age differences than others (Berg, 1988; Kemper, 1984). The most pronounced losses in the neocortex are in the frontal polar cortex and the premotor cortex and association regions in the temporal lobe. The temporal limbic region and the parietal and visual cortex also show losses in cell count with age but to a lesser degree (Braak et al., 1989; Kemper, 1984). Therefore, the different scalp distribution observed in this experiment could be due to selective losses of cortical inputs and synaptic organization. Thus, with aging there are different cortical networks that participate in the generation of the N400 evoked response; younger individuals can rely on bilateral anterior and posterior areas of the brain to generate the response, whereas older individuals must rely on more restricted centroparietal neural networks.

The N400 effect was significantly reduced in the DAT patients. These results agree with the findings of Iragui et al. (1996), who found that the N400 elicited by mismatching words (opposites and category examples) was absent in DAT patients. They suggested that due to either less use of controlled attentional resources or weaker associative links, the semantic analysis becomes more difficult and/or less efficient with dementia. In contrast Hamberger et al. (1995), using a sentence context with a sense–nonsense decision task to the terminal words, did not find an abnormal N400 effect in DAT patients. Conflicting results might be due to different task demands. In the Hamberger et al. (1995) experiment, the sense–nonsense decision might rely more on associative–lexical priming than on semantic priming. Associative priming, which is presumed to be based on the build-up of facilitatory connections between word forms rather than meaning, occurs when words are semantically unrelated, but are high in associative value. Using an oral reading task, Glosser and Friedman (1991) found that DAT patients showed effects of priming for word pairs that were associatively related, but not for semantically related pairs. In the present study, by using pairs of pictures, the linguistic process of decoding printed words was bypassed, and the task required matching pictures according to semantic, not perceptual, relationships. The stimuli used were not visually similar, and based on the results of our pilot study, all were high frequency examples of the same semantic category. The fact that category decisions are faster with pictures than with words has led to the hypothesis that pictures are more directly connected to the semantic memory (Paivio, 1986; Potter & Faulconer, 1975). Our data seem to point out that DAT patients are more affected on semantic than associative priming.

The amplitude of N400 effect (subtraction of the ERPs of congruent from incongruent trials) was significantly reduced in DAT patients. This reduction could be due to either an increased positivity in incongruent trials (smaller N400 to incongruent trials), an increased negativity in congruent trials (larger N400 in congruent trials), or both. Therefore, a separate analysis of congruent and incongruent ERPs trials was carried out. The amplitude measurements in the N400 time window were similar in the elderly controls and DAT patients for the congruent trials. However, in the incongruent trials, the amplitude in this time window was significantly smaller in amplitude for the DAT patients relative to the elderly controls.

Thus, the results of this study indicate that DAT patients showed both normal and abnormal patterns of ERPs: they showed normal ERPs for congruent trials, but they exhibited abnormal ERPs for incongruent trials. The interpretation of this pattern of results depends on the type of hypothesis about the functional meaning of the N400 that is accepted. According to Holcomb (1993), the amplitude of the N400 is small for related targets because the lexical detector for the target benefits from the spread of activation associated with the processing of the prime. If the target is preceded by an unrelated prime, there is no such benefit, and more resources are required to detect the target. The utilization of these extra resources might be what is reflected by the larger N400 amplitude. Under this hypothesis, in the DAT group the smaller N400 to incongruent pictures could be due to a weakened network, which would limit the quantity of resources available to detect and generate the N400. Another possible and related interpretation is that, in normal individuals, the activation of a stimulus suppresses activation of highly associated concepts, but not of unrelated concepts; when an unrelated stimulus is presented in the incongruent condition, an N400 is elicited because the second stimulus is processed against the background of this suppression. In DAT patients, there may be abnormal suppression of all stimuli because of a weakened network; thus, an N400 ERP to an incongruent stimuli is not observed.

The weakened network of the DAT patients could be due to damage in the cortical association areas. Neuropathological studies have shown that DAT patients evidenced marked pathology in temporal, parietal, and frontal association cortices. The senile plaques and neurofibrillary tangles of DAT prominently involve the origins and termination of long corticocortical associative fibers of the brain (Brun, 1988; Lewis et al., 1987; Morrison et al., 1986). Neurophysiological studies have found that there are changes in brain functional connectivity in DAT, and that EEG decreases between parietal and frontal areas due to degeneration of the fibers that connect these two areas (Leuchter et al., 1992). It has been suggested that DAT is a "neocortical disconnection syndrome," where associative areas lose afferent and efferent connections through white matter tracts. This disconnection occurs at the cortical level, and it is associated with the death of pyramidal neurons, which provide corticocortical projections (Leuchter et al., 1992; Lewis et al., 1987; Morrison et al., 1986; Pearson et al., 1985). Since ERP is presumed to be primarily a reflection of the sum of postsynaptic activity of pyramidal cells in the cortical layers (Iragui et al., 1996), it is possible that the impaired ERP priming of our patients might be due to deficient cellular connectivity and synaptic relations, which would lead to deterioration in the associative links within the semantic network. The complex connections that link the brain areas are affected by the disease, and functionally the semantic activation created by the context cannot be used efficiently in processing incongruent stimuli, thus affecting access to specific concepts and gradually leading to a breakdown in the structure and organization of semantic memory.

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