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Event-related brain potentials during semantic categorization in normal aging and senile dementia of the Alzheimer's type

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Abstract

To assess the effects of normal aging and senile dementia of the Alzheimer's type (SDAT) on semantic analysis of words, we examined the N400 component of the event-related potential (ERP) elicited during the processing of highly constrained (opposites) and less constrained materials (category-category exemplars) in 12 young control subjects, 12 elderly control subjects and 12 patients with SDAT. We employed a priming paradigm in which a context phrase was spoken and a target word (congruent or incongruent) was presented visually. The N400 effect was reduced in amplitude and delayed in the elderly control group relative to that of the younger subjects, and was further attenuated in amplitude, delayed in latency and somewhat flatter in its distribution across the scalp in the SDAT patients. These findings are consistent with less efficient processing and integration of lexical items with semantic context in normal aging, which is further exacerbated by SDAT. Differences in the N400 range associated with the opposite and category conditions were observed only in the young subjects, suggesting less use of controlled attentional resources or perhaps weaker associative links with age.

Keywords: Event-related potentials; Aging; Alzheimer's disease; Semantic priming

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1. Introduction

The facilitative effect ('priming') of context on word recognition has been demonstrated in numerous studies using reaction time (RT) measures in young adults. Generally, a word (e.g. 'doctor') is recognized with greater speed and/or accuracy if it is preceded by a semantically related sentence or single word (e.g. 'nurse') than by an unrelated context (e.g. 'table') (Collins and Loftus, 1975; Neely, 1977; Neely, 1991). Since accessing single words and integrating their meaning with the ongoing discourse are operations fundamental to successful language comprehension, a number of recent studies have used priming procedures to examine semantic processes in aging and dementia, usually measuring lexical decision (deciding whether a letter string is or is not a word) or pronunciation times. Most have found that semantic priming remains stable across the adult life-span, even in the presence of deficits in explicit memory tested via recognition or recall (Howard et al., 1981; Cohen and Faulkner, 1983; Howard, 1983; Burke and Yee, 1984; Byrd, 1984; Cerella and Fozard, 1984; Bowles and Poon, 1985; Chiarello et al., 1985; Madden, 1986; Mueller et al., 1980; Rabinowith, 1986; Burke et al., 1987; Balota and Duchek, 1988; Stern et al., 1991); however, some investigators have observed significant age-related delays in priming (Eysenck, 1975; Petros et al., 1983; Howard et al., 1986). Similar variability characterizes results of investigations in patients with senile dementia of the Alzheimer's type (SDAT), with some authors reporting reduced priming (Ober and Shenaut, 1988; Albert and Milberg, 1989) and others failing to observe any significant effects of dementia on the size of the semantic priming effect (Nebes et al., 1984; Nebes et al., 1986; Chertkow et al., 1989; Nebes et al., 1989; Balota and Duchek, 1991). Some of these discrepancies may be accounted for by differences

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in patient populations and by methodological problems including floor and ceiling effects, reliance of subjects on intentional or explicit memory strategies, and insufficient statistical power to demonstrate group differences. In addition, the lexical decision task has come under attack as a good index of priming given that decision-related processes unrelated to lexical access per se have been shown to influence lexical decision times (Balota and Chumbley, 1984; Lupker, 1984; Seidenberg et al., 1984; Balota and Lorch, 1986). The inferences based on pronunciation latency measures have also been questioned because of their susceptibility to task-specific factors presumably unrelated to lexical access (Balota and Chumbley, 1984). In fact, Norris (1986) claimed that it was possible to account for semantic context effects on RT in lexical decision and pronunciation tasks without resorting to the notion of lexical access.

Semantic priming paradigms have been used to investigate not only lexical access but also semantic memory. In a typical experiment, subjects are exposed to pairs of words; subsequently, they are given the first word of each pair and asked to say the first word that comes to mind. Under these circumstances, priming is inferred from the greater likelihood of their saying the second word originally experienced in related than in unrelated pairs. SDAT patients reportedly show less priming relative to normal controls in such tasks (Huff et al., 1988; Nebes, 1989). However, Nebes (1989) suggested that failure of SDAT patients to prime in an associate production task of this sort could be due to a faulty lexical retrieval mechanism, thus saying little about the integrity of the semantic network. Supporting his argument are observations that SDAT patients also fail to show normal priming in word stem completion tasks, where a priming effect is likewise contingent on successful word retrieval (Shimamura et al., 1987; Salmon et al., 1988; Heindel et al., 1989; Keane et al., 1991) (but see Grosse et al., 1990; Partridge et al., 1990; and Christensen and Birrell, 1991, for different results). In this task, subjects are initially exposed to a series of words; subsequently, they are presented with the first 3 letters of each word (i.e. stem) and asked to say the first word that comes to mind. Priming is reflected in a greater tendency to complete the stems with words that had previously been studied. While some investigators have failed to observe any age-related changes in word stem completion priming (Light and Singh, 1987), the results of several studies with larger numbers of and/or older subjects have revealed a significant reduction in word-stem completion priming with increasing age (Chiarello and Hoyer, 1988; Davis et al., 1990). As performance in word-stem completion tasks may be affected by encoding strategies (Partridge et al., 1990), explicit memory (Randolph, 1991) and the severity of dementia (Christensen et al., 1992; but see also Nebes' argument above (Nebes, 1989)), differential contributions of these factors may account for the variable pattern of findings in both aging and SDAT.

As performance measures reflect only the outcome of the registration, storage and retrieval processes involved in language and memory, complementary techniques that allow a view of the processes taking place as stimuli are actually being analyzed have been sought. One such technique involves recording event-related brain potentials (ERPs) from the human scalp as subjects perform various tasks (Hillyard and Picton, 1987; Kutas and Van Petten, 1988; Halgren, 1990). One robust characteristic of the ERP elicited as subjects read or listen to meaningful material is the N400 component; its amplitude has been shown to be sensitive to semantic and associative relationships among the major lexical items both in sentences and word pairs, being smaller for related than for unrelated words. The N400 is typically larger for words that are semantically incongruous with a preceding context than for words that are semantically congruous (Kutas and Hillyard, 1980; Kutas and Hillyard, 1983). In fact, all words elicit an N400 whose amplitude is an inverse function of a word's expectancy within its current context (Kutas and Hillyard, 1984). The N400 is elicited by spoken words, printed words, signed language, and perhaps photographs of faces (Barrett and Rugg, 1990) or drawings of familiar objects (Barrett and Rugg, 1990; Nigam et al., 1992). By contrast, syntactic, orthographic or physical violations in written or spoken prose passages, and complex, abstract sounds or drawings do not trigger much N400 activity; nor do a variety of melodic or rhythmic violations in musical sequences (Besson and Macar, 1987; Verleger, 1990; Paller et al., 1992).

The observations that N400 amplitude is modulated by the degree of semantic congruence between a word and its sentence context or the degree of semantic association between lexical (or meaningful) items have led to the proposition that, with all other factors held constant, the N400 may provide a good index of the semantic support that a word has received from its context (Bentin et al., 1985; Kutas and Hillyard, 1984). Thus, the elicitation of N400 by incongruous or unpredictable words and smaller N400s (or outright positivities) by congruous or highly expected words reflects an appreciation by the individual of the semantic relationship between the eliciting word and context in which it occurs. To the extent that these effects have been investigated, this appreciation requires that the individual be attending to or actively processing the materials.

These findings make the N400 a likely candidate for a metric to assess how semantic analysis is affected by normal aging and various neurological disorders. Harbin et al. (1984) first investigated the effects of aging on the N400 by flashing sequences of 5 words to young (mean age 21 years) and elderly (mean age 71 years) adults. Individuals were asked to decide whether or not the fifth word matched the semantic category of which the preceding 4 words were members. The N400 elicited by mismatching words had a longer latency in the elderly than in the younger participants. Gunter et al. (1992) reported similar effects of aging on the N400 effect elicited by congruous and incongruous sentence endings; they also noted a reduction in the amplitude of the N400 effect with age (mean age of elderly group 56 years). Friedman et al. (1989), using a picture matching task, found longer N400 latencies in older (age 68–80 years) than in younger (age 20–38 years) adults.

The present study was designed to replicate and extend these investigations by exploring the effects of age on processing of highly constrained (e.g. opposites) and less constrained materials (e.g. category-category exemplars). In addition, we used N400 effects as a probe to assess the integrity of semantic processes in patients with SDAT. Contextual constraint was manipulated because the amplitude of N400 is reduced with increasing degree of constraint. Opposite and categorical relations also map onto the distinction between prediction-based and expectation-based strategies for utilizing contextual information, respectively (Becker, 1980). We employed a paradigm wherein the context was spoken and the target word (congruent or incongruent) was presented visually. In a preliminary investigation, this procedure proved to be suitable for use in patients with mild to moderate dementia. Performance on standard neuropsychological tests was also correlated with various ERP measures in both the SDAT patients and the elderly controls.

2. Methods

2.1. Subjects

Twelve young control subjects (8 men and 4 women, 18–30 years old, mean ± SD 24 ± 3.5 years), 12 elderly control subjects (7 men, 5 women, 62–81 years old, mean ± SD 72 ± 5.4 years), and 12 patients with mild to moderate SDAT (8 men, 4 women, 57–83 years old, mean ± SD 70 ± 7.8 years) participated in the experiments. The groups were matched on handedness and number of years of education. The control subjects were free from neurological, psychiatric and significant medical diseases. None of the participants were taking psychoactive medications and SDAT patients were not enrolled in experimental drug protocols.

The elderly controls and the SDAT patients were selected from the registry of the Alzheimer's Disease Research Center (ADRC) of the University of California, San Diego (UCSD). The diagnosis of probable SDAT was made following the criteria developed by the National Institute of Neurological and Communicative Diseases and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (McKhann et al., 1984) by two neurologists and one neuropsychologist. Mini-Mental State Examination (MMSE) scores ranged from 29 to 30 in elderly controls and from 18 to 26 in SDAT patients.

Monocular corrected visual acuity was better than 20/25 in young subjects, better than 20/30 in elderly normal subjects, and better than 20/35 in SDAT patients.

2.2. Neuropsychological assessment

Both the elderly controls and patients underwent extensive neuropsychological evaluation at the UCSD ADRC as part of the longitudinal study of dementia (Salmon and Butters, 1992). Their overall degree of cognitive impairment was based on scores on the Mini-Mental State Examination (Folstein et al., 1975) and the Dementia Rating Scale (Mattis, 1976). A subset of their test scores assessing language and memory functions were selected for correlation with ERP measurements, namely: confrontation naming (Boston Naming Test; Kaplan et al., 1983); two tests of verbal fluency (letter (Butters et al., 1987) and category fluency tests (Borkowski et al., 1967)); the Vocabulary Test from the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981); the Number Information Test, a test of explicit memory that assesses semantic knowledge (Goodglass et al., 1984); two tests of episodic recent memory, the digit span test of the Wechsler Memory Scale-Revised (Wechsler, 1987), and retrieval from short-term memory on the Buschke-Fuld Selective Reminding Test (Buschke and Fuld, 1974); retrieval from long-term memory and number of intrusions on the Buschke-Fuld Selective Reminding Test (Buschke and Fuld, 1974).

2.3. Event-related potential recordings

2.3.1. Procedures

Subjects sat in a comfortable reclining chair in an electrically-shielded room, facing a television monitor. The screen was occluded except for a rectangular slit in the center through which the words were viewed. Each word consisted of white letters against a dark background. The monitor was 100 cm from the subject; words subtended a 0.3° visual angle vertically and 0.3–2.9° visual angle horizontally.

Subjects participated in 4 separate blocks of 80 context-target pairs each for a total of 320 trials. Half of the phrases defined antonymic relationships, that is, opposites (e.g. 'the opposite of tall') and half indicated category membership relations (e.g. 'a type of flower'). Half of the target words were congruent with the sense of the preceding phrase (see Table 1 for sample stimuli) while the remaining half were not.

On each trial, a context phrase was spoken aloud by the investigator. Approximately 1 s later, the target word was flashed in the center of a television monitor for a duration of 265 ms. About 1.5 s after the presentation of a target word, the subject was required to indicate whether or not the target word was appropriate given the sense of the preceding phrase by saying 'yes' or 'no'. Subsequently, regardless of the correctness of the prior answers, the sub-

Table 1

Examples of category and opposite stimuli, each with either congruent or incongruent target words

Stimulus	Target word
Category congruent	
'A musical instrument'	Piano
'A kitchen utensil'	Knife
'A kind of tree'	Oak
Category incongruent	
'A striped animal'	Steam
'A hot cereal'	Skull
'A kind of cloth'	Hunger
Opposite congruent	
'The opposite of white'	Black
'The opposite of good'	Bad
'The opposite of empty'	Full
Opposite incongruent	
'The opposite of evening'	Season
'The opposite of give'	Center
'The opposite of thick'	Stage

ject reported the word (s)he actually read. The intertrial interval was approximately 3 s.

2.3.2. Electrophysiological data collection

The electroencephalogram (EEG) was recorded using Ag/AgCl electrodes attached with collodion at 13 scalp sites and the right mastoid, each referred to an electrode over the left mastoid. Each scalp site was re-referenced off-line to an average of the left and right mastoid recordings. Vertical eye movements were monitored via an electrode placed on the right inferior orbital ridge, referred to the left mastoid; horizontal eye movements were monitored via a right to left bipolar montage at the external canthi. Subjects were asked to keep their eye and body movements and blinks to a minimum. Electrode impedances were less than 5 kΩ.

Seven of the 13 scalp electrodes were placed according to the International 10–20 system (Jasper, 1958) at Cz, F7, F8, T5, T6, 01, and 02 sites. In addition, symmetrical left and right anterior temporal electrodes (BL, BR) were placed halfway between F7-T3 and F8-T4, respectively (the left hemisphere site corresponded approximately to Broca's area). Symmetrical right and left posterior temporal (WL, WR) electrodes were placed laterally to the vertex by 30% of the interaural distance and posteriorly to the vertex by 12.5% of the nasion-inion distance (over the left hemisphere, this electrode lay approximately over Wernicke's area). Symmetrical left and right midtemporal electrodes were placed 33% of the interaural distance laterally to the vertex (L41, R41).

The EEG and EOG were amplified using Grass P511 amplifiers with 8 s time constant. The high frequency half amplitude cut-off was 300 Hz (–6 dB). The amplified signals were digitized on-line at a sampling rate of 167 Hz and stored on magnetic tape for subsequent averaging.

2.4. Data analysis

Separate ERP averages were obtained for correctly detected congruous and incongruous target words for both the opposite and category stimuli. Each waveform consisted of a 1500 ms epoch including 100 ms prior to stimulus onset. Trials contaminated by eye blinks or movements, excessive muscle activity or amplifier blocking were rejected by computer algorithm prior to averaging (about 10% of trials were lost due to such artifacts). The peak latency and peak mean amplitudes of the N400 were quantified by computer both in the ERPs to congruous and incongruous words per se and in the difference waves derived from a point-by-point subtraction of the congruous from the incongruous word ERPs. Latencies were measured relative to stimulus onset, and amplitudes were measured relative to 100 ms prestimulus baseline voltage. The peak of N400 was identified as the maximum negativity between 200 and 800 ms poststimulus. Mean amplitudes were measured over specified latency windows. Fractional area latencies were measured as the latency at which the mean negative amplitude between 200 and 800 ms area reached 50% of its total value.

Amplitude and latency values were subjected to repeated measures ANOVA with the 3 experimental groups (normal young, normal elderly, SDAT patients) as between subject variable and 3 within subject variables: target type (congruous or incongruous), stimulus type (opposites or categories), and electrode site ($N = 13$). For some analyses, homologous left and right electrodes were collapsed as anterior to posterior sites (6 levels) and the 6 right and 6 left hemisphere electrodes were averaged to yield mean right and left hemisphere scores (two levels). The probabilities reported for interactions are those obtained after Greenhouse-Geisser correction (Keselman and Rogan, 1980). When necessary, significant interactions were reassessed with repeated measures ANOVAs of normalized amplitudes as outlined by McCarthy and Wood (1985); only interactions that were significant on the normalized amplitude measures are reported. Amplitude and latency measures were also subjected to multivariate linear regression analyses; values of Cz, WL and WR for category and opposite conditions served as dependent variables ($N = 6$) and the neuropsychological scores as independent variables ($N = 11$).

3. Results

3.1. Congruity detection

The percentages of correct behavioral responses are shown in Table 2. Responses were considered correct

Table 2

Percentage of accurate responses as a function of stimulus condition (opposites and categories) and response type (‘yes’ for congruous, ‘no’ for incongruous)

	Young	Old	AD
Congruous opposite	100	100	95.2
Congruous category	100	99.8	91.5
Incongruous opposite	100	99.5	69.1
Incongruous category	99.9	99.7	72.6

only if the subject accurately judged the congruity of the word relative to the context and then said the word aloud. Young and elderly controls responded correctly on virtually every trial. By contrast, SDAT patients performed significantly worse than the elderly controls (main effect of group: $F(1, 11) = 11.41$, $P = 0.003$), showing greater impairment for incongruous than congruous words ($F(1,11) = 11.02$, $P = 0.007$). There were no significant differences as a function of stimulus type.

3.2. Event related potentials

The grand average ERPs ($n = 12$/group) elicited by congruous and incongruous words for young, elderly and SDAT patients in the opposite and category conditions are shown in Fig. 1A,B, respectively. Individual variability can be seen in Fig. 2 where ERPs from right Wernicke’s site for each subject are shown. As evident in these figures, ERPs to all target words were characterized by a posteriorly distributed N1 component and an anteriorly-distributed P2 component. These early sensory components were followed by a broad negativity peaking around 350–400 ms (N400) that was larger for incongruous than congruous words (shaded areas in Figs. 1 and 2) and appeared to be riding on a sustained positivity that followed P2 and persisted for the remainder of the epoch in the young and elderly control subjects. Fig. 3 depicts the difference waves derived from point by point subtraction of congruous from incongruous word ERPs for opposite and category stimuli, separately. Visual inspection of these data suggests that the N400 congruity effect has a lower amplitude together with longer onset and peak latencies in the normal elderly than in young controls. SDAT patients exhibited a still greater diminution in amplitude and delay in the latency of the N400 difference ERP.

3.3. N400 potential

3.3.1. Latency

The latency of the congruity effect was measured in the difference waves (i.e. difference between congruous and incongruous ERPs) (see Fig. 3). In the younger control subjects the N400 effect began around 200 ms and peaked around 400 ms (370 ± 58 ms). In the older control subjects, the N400 effect began around 300 ms and peaked at 420 ± 90 ms; in SDAT patients, the N400 effect began around 400 ms and peaked at 530 ± 160 ms. Both peak latencies and fractional area latencies, differed significantly across the 3 subject groups (peak latency: $F(2,33) = 14.96$, $P = 0.001$; fractional area latency: $F(2,33) = 17.09$, $P = 0.001$). Post hoc analysis revealed that each group was significantly different from the other two groups.

3.3.2. Amplitude

To allow a direct comparison of data from all 3 groups, the mean amplitudes of the ERPs were first measured in original ERPs across a broad window between 200 and 800 ms post-stimulus onset. By this measure the N400 was significantly larger for incongruous than congruous target words in both young and elderly controls (main effect of target word: young controls, $F(1,11) = 13.86$, $P = 0.003$; elderly controls, $F(1,11) = 5.58$, $P = 0.038$) but not in the SDAT patient group (see Fig. 1).

The time course of the N400 congruity effect was analyzed further by measuring the mean amplitudes in difference waves across 3 latency windows of 200–400, 400–600 and 600–800 ms, and including latency window as a variable in the ANOVA. This analysis revealed a significant group by window interaction ($F(2,33) = 9.58$, $P = 0.001$). In the younger group, the N400 effect was maximal in the 200–400 ms window, decreasing thereafter. In the older subject group, the N400 congruity effect was maximal in the 400–600 ms window. In the SDAT patients, a small negativity appeared at 400–600 ms, which extended (with lower amplitude) into the 600–800 ms window (see Fig. 4).

Because the onset of the N400 effect varied across the subject groups, the amplitude of the N400 effect was also measured in difference waves as the mean voltage across a 300 ms window beginning at the onset of the effect for each group (that is, between 200–500 ms in the younger subjects, between 300–600 in the older control subjects, and between 400–700 ms in SDAT patients). An ANOVA of these data indicated a significant main effect of group ($F(2,33) = 9.19$, $P = 0.001$) reflecting the fact that the N400 effect was largest in the younger group, smallest in the SDAT patient group, and intermediate in amplitude for the elderly controls.

3.3.3. Scalp distribution (Figs. 3 and 5)

The scalp distribution of N400 was different across the 3 groups (group by electrode interaction: $F(12,396) = 4.32$, $P = 0.001$). In the younger control subjects, the N400 effect was larger over posterior than anterior sites (main effect of electrode: $F(12,132) = 15.74$, $P = 0.001$), larger over the right than left hemisphere (main effect of hemisphere: $F(1,11) = 4.49$, $P = 0.048$), and largest at the vertex. The older control subjects’ difference ERPs were characterized by a similar scalp topography, although the anterior-to-posterior amplitude gradient was less pro-

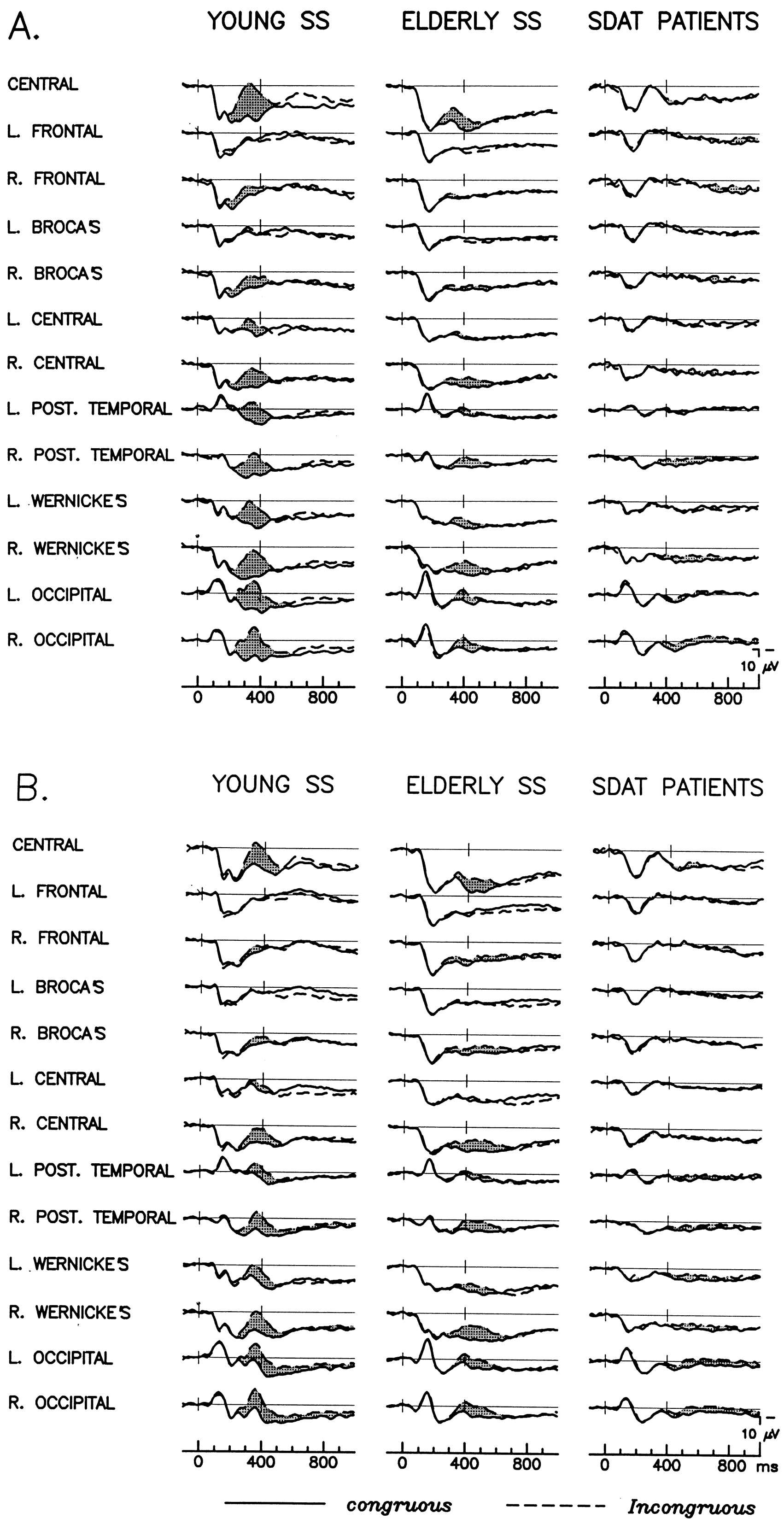


Fig. 1. Grand average ERPs in the young ($N = 12$), elderly ($N = 12$) and Alzheimer patient ($N = 12$) groups, elicited by visually-presented words in the opposite (A) and category conditions (B). At each site, the ERPs to congruous (solid line) and incongruous (dashed line) words are superimposed. Note the shading reflects the congruity effect. In this and all subsequent figures negativity is upwards. SS, subjects.

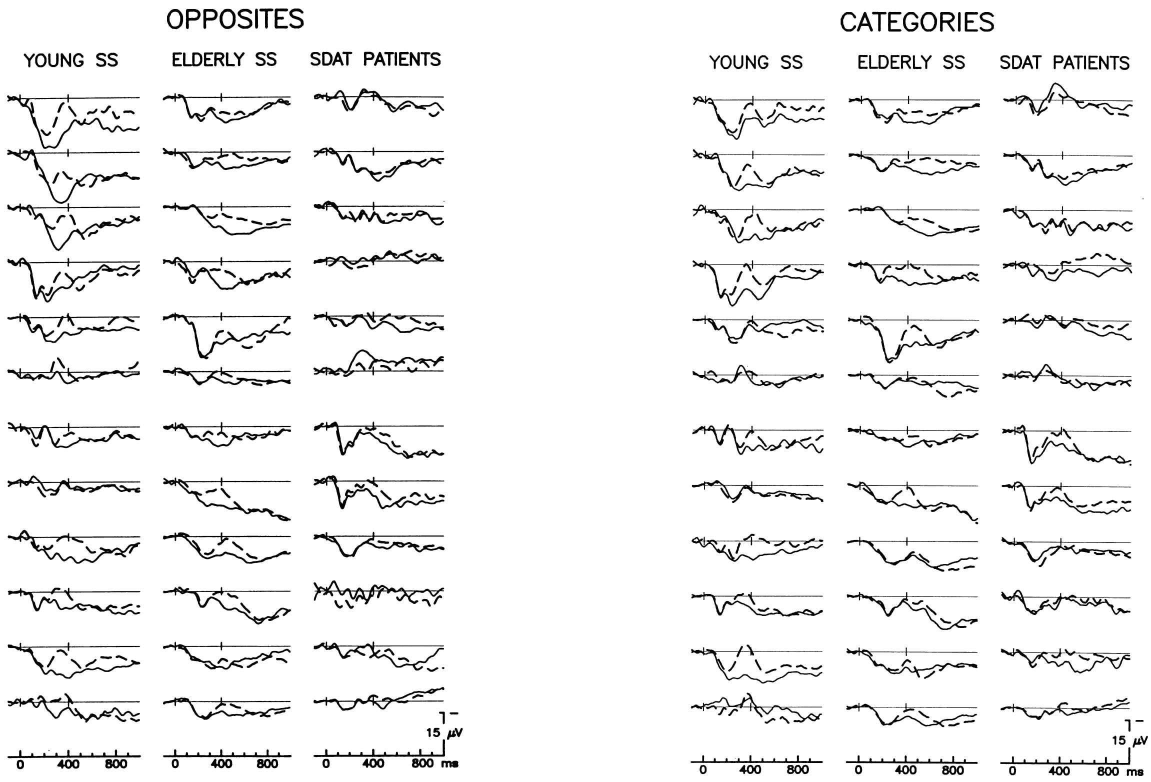


Fig. 2. Average ERPs recorded over the right hemisphere homologue of Wernicke's area in each subject elicited by opposite (A) and category (B) stimuli. Superimposed are responses to congruous words (solid lines) and responses to incongruous words (dashed lines).

nounced (main effect of electrode: $F(12,132) = 4.03$, $P = 0.032$), while the hemispheric difference was somewhat more pronounced (main effect of hemisphere: $F(1,11) = 9.36$, $P = 0.01$). By contrast, SDAT patients did not show any significant anterior-to-posterior amplitude gradient; again, the N400 was larger over the right than left hemisphere (main effect of hemisphere: $F(1,11) = 4.42$, $P = 0.002$).

3.3.4. Stimulus type

The mean amplitude of the N400 difference ERP between 200 and 800 ms also showed significant group × stimulus type interactions ($F(2,33) = 4.98$, $P = 0.029$) indicating that, for younger subjects only, the N400 effect for opposites was significantly larger than that for categories (main effect of stimulus type: $F(1,11) = 6.35$, $P = 0.0285$); no significant differences between stimulus types were found in either the older subject group or the SDAT patient group, although there was a similar trend in the older control subjects. As can be seen in Fig. 6, the ERPs to incongruous target words for the two stimulus types were almost identical. In contrast, ERPs to congruous words differed noticeably but only in the younger subjects: the ERPs elicited by category members had a small N400, whereas those to opposites were positive in the same epoch. Thus, it was the greater positivity elicited by congruous words in the opposite condition that led to a larger N400 effect for opposites than category members. In the older subject group, the amplitude difference in the ERP to congruous words from the two stimulus conditions was smaller than in the younger controls. In the SDAT patient group the ERPs to congruous target words from the opposite and the category conditions were indistinguishable.

3.3.5. Slow positive drift

The N400 of all these groups appeared to be superimposed on a prolonged positivity that began after P2 and persisted for the duration of the epoch (see Fig. 1). In the younger subjects, this slow positivity peaked at about 550 ms. In elderly control subjects, the positivity did not have a definite peak and appeared to partially overlap the N400. The ERP of SDAT patients had almost no slow potential over posterior sites.

3.4. Neuropsychological data

Table 3 presents the means and standard deviations of neuropsychological test scores of elderly controls and SDAT patients. There were significant group differences on scores from all the tests. Each test score was significantly correlated with every other test score ($R = 0.91$, $P = 0.003$) with the exception of the number information test ($R = 0.81$, $P = 0.09$), digit span ($R = 0.83$,

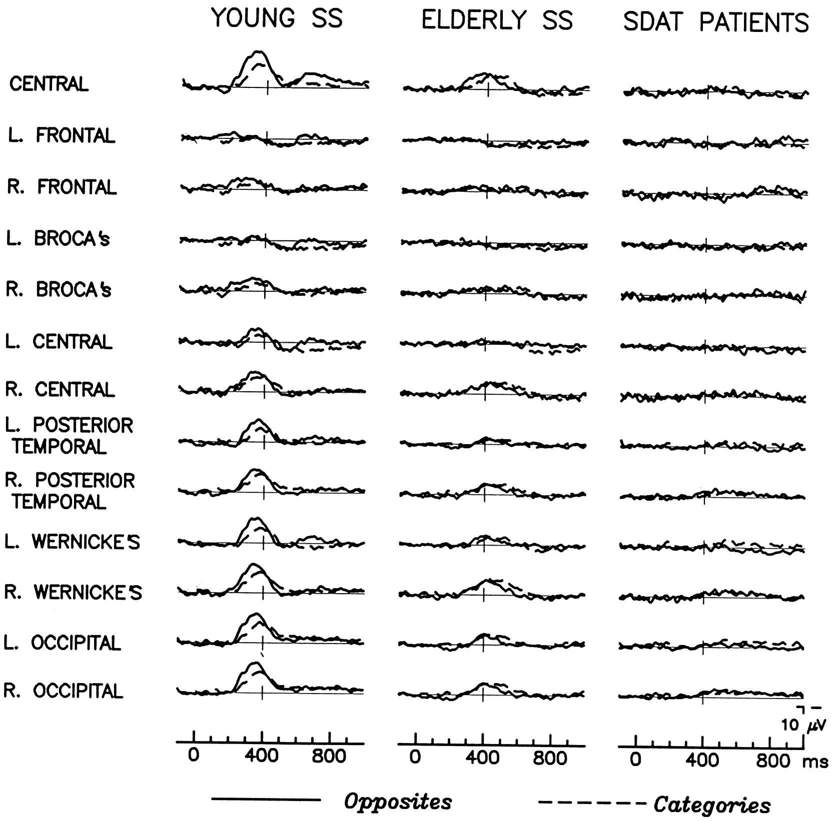


Fig. 3. Grand average difference ERPs elicited by opposite (solid lines) and category stimuli (dashed lines) for each of the subject groups. Difference ERPs were derived by a point-by-point subtraction of the congruous word ERPs from the incongruous word ERPs.

$P = 0.054$), and the number of intrusions in the selective reminding test ($R = 0.74$, $P = 0.26$).

Simple multiple linear regression analyses with neuropsychological test scores (listed in Table 3) predicted the fractional area latency measured at WL and WR for opposites ($R = 0.90$, $P = 0.015$ and $R = 0.88$, $P = 0.02$, respectively). There were no significant correlations between neuropsychological tests and fractional area latencies in the category condition.

4. Discussion

In line with previous findings, the ERPs to congruous words were associated with a sizable N400 in young subjects that was large over centroparietal regions of the right scalp (Kutas and Hillyard, 1980; Kutas and Van Petten, 1994). On the whole, the present observations in elderly controls also accord well with previous reports of decrease in amplitude and delay in the latency of the N400 effect with advancing age (Harbin et al., 1984; Gunter et al., 1992). In addition, we observed that in SDAT patients (1) the N400 effect was both further attenuated in amplitude and delayed in latency, and (2) the distribution of the N400 effect across the scalp was flatter (i.e. more equipotential) along the anterior-posterior axis. However, it should be noted that assessing changes in the scalp distribution of the N400 effect in the elderly and SDAT groups is limited somewhat by the large decrease in its overall amplitude in these two groups. This confound was ameliorated insofar as possible by applying the normalization procedure of McCarthy and Wood (1985) but the apparent change in distribution should nonetheless be taken with caution until replicated.

To our knowledge, this is the first study of the N400 congruity effect in Alzheimer's dementia. Several laboratories, however, have examined the consequences of aging and dementia on the ERP word repetition effect (Karayanidis et al., 1983; Friedman et al., 1992; Friedman et al., 1993a; Friedman et al., 1993b; Hamberger and Friedman, 1992; Rugg et al., 1994). The ERP repetition effect refers to the greater positivity elicited by items repeated in the course of the experiment relative to that elicited by items presented for the first time. This is of relevance here because it has been presumed that the ERP repetition effect reflects the modulation of multiple ERP components, including the N400. In contrast to our observations on the N400, however, the most consistent finding on the ERP repetition effect has been the absence of a statistically significant difference in its size (Karayanidis et al., 1983; Friedman et al., 1992, Friedman et al., 1993a, Friedman et al., 1993b; Hamberger and Friedman, 1992; Rugg et al., 1994) or onset latency (Rugg et al., 1994) across young

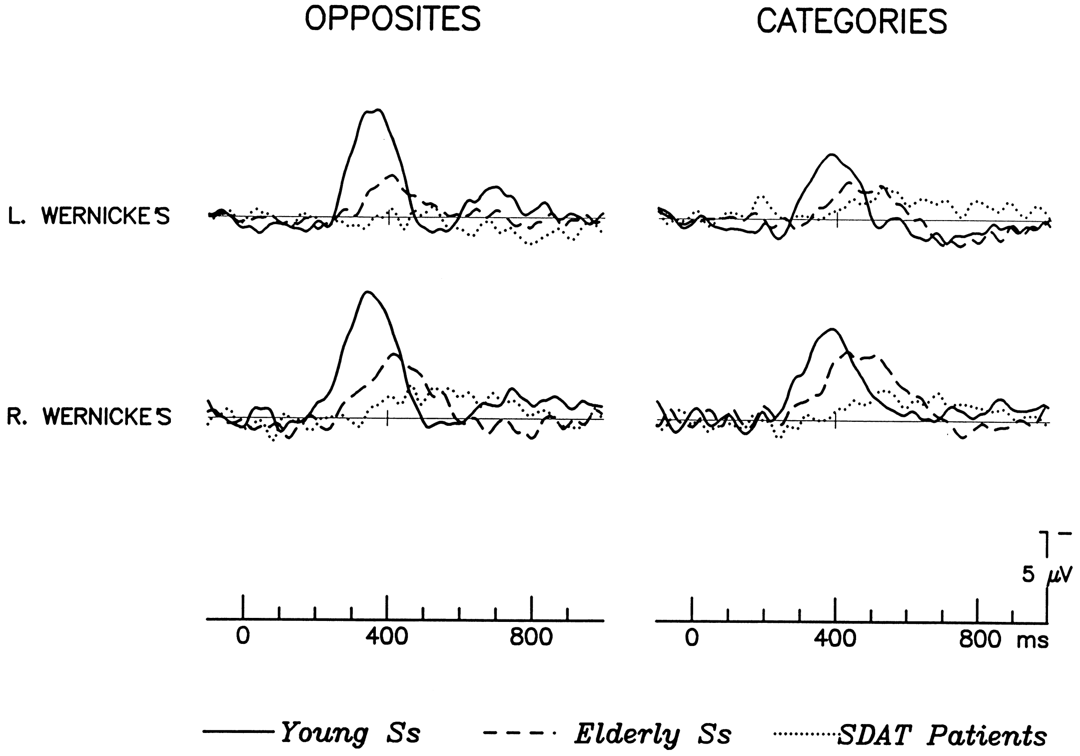
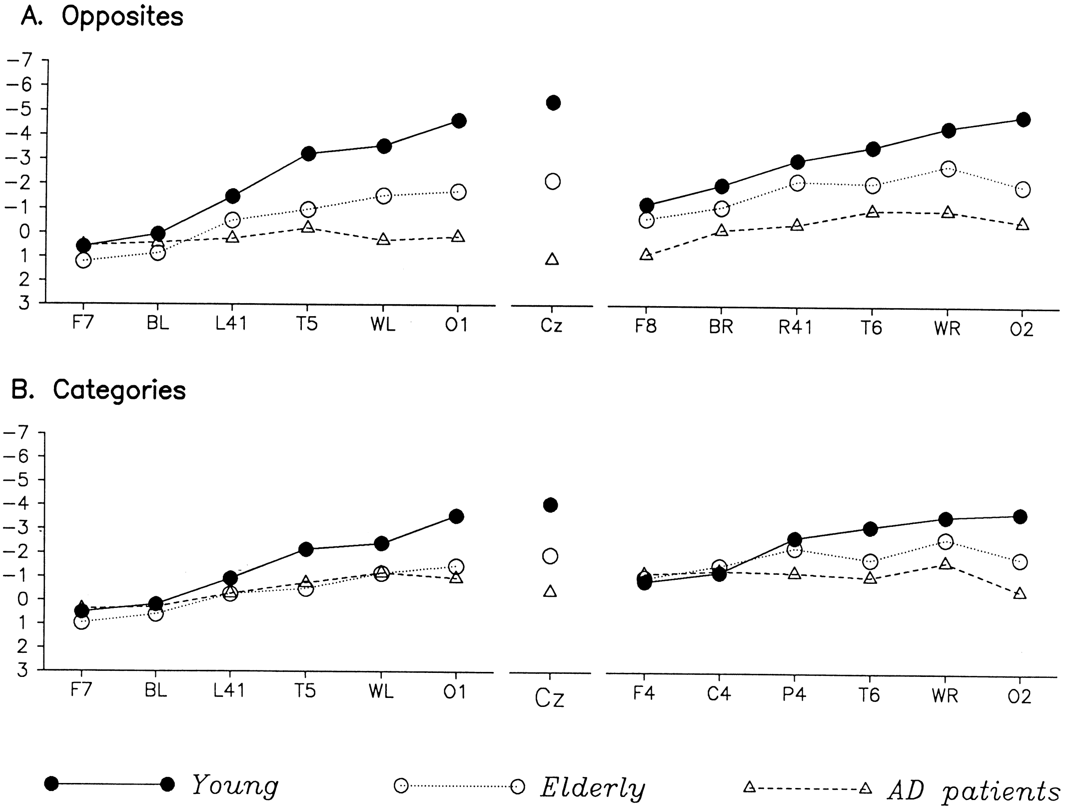


Fig. 4. Comparison of grand average difference ERPs recorded at Wernicke's area (L Wernicke's) and the right hemisphere homologue (R Wernicke's) in the young (solid line), elderly (dashed line), and Alzheimer patient (dotted line) groups for both stimulus conditions.

subjects, SDAT patients, and age-matched elderly control subjects. Thus, unless there were counteracting potentials of opposite polarity, the presumed N400 component of the ERP repetition effect must differ from the N400 congruity effect in its psychological and neural bases; the former was unaffected by normal aging or dementia whereas the latter was severely compromised for written words in both groups.

It is important to note that the elderly subjects in this study were a highly select population living independently who performed well on the same extensive battery of psychometric tests given to the SDAT patient group. Equally important to keep in mind is that the clinical diagnosis of SDAT remains presumptive until it is confirmed by neuropathological examination. Although postmortem examination is not yet available in our patients, autopsies have confirmed SDAT in 92% of subjects clinically diagnosed employing the criteria of the UCSD ADRC (Galasko et al., 1994), indicating a high level of accuracy.

Before discussing the additional implications of our findings on the cognitive or neural changes that accompany normal aging and dementia, we should consider alternative explanations. The N400 seen in an average ERP is that which emerges from the noise when multiple single trials are averaged together. Thus, one potential explanation for amplitude reduction in a specific component between groups would be based on greater within-subject variability in the latency of that component on a trial-by-trial basis. Assuming constant amplitude of the signal and no other overlapping potentials, averaging will result in an apparent amplitude reduction of the average signal if the trial-to-trial latency variability is greater than the width (frequency) of the signal. The signal-to-noise ratio of the N400 potential on a single trial was too low to allow us to test whether this was in fact the case in our data from the elderly and SDAT patients. However, the hypothesis is reasonable by analogy to results with other cognitive ERPs under similar circumstances. Typically, both elderly individuals and SDAT patients show significantly reduced P300s, at least in part due to greater variability in the latency of the P3 across trials (Pfefferbaum et al., 1984). In fact, increased single trial variability (in amplitude as well as latency) seems to be a hallmark of ERPs from abnormal populations. Thus, greater latency variability in the N400 across single trials probably does contribute somewhat to the amplitude reduction in our elderly participants and SDAT patients. Certainly, slowed and more variable synaptic transmission could lead to greater variability in neuronal firing and synchrony. However, the N400 effects were significantly smaller not only when measured at the peak, but also in the mean amplitude, which is less sensitive to jitter than peak measures. That is, the overall area under the N400 difference curve was smaller in SDAT patients than in elderly controls and in the elderly controls than the younger subjects; this is less consistent with an account based solely on


A. Opposites

B. Categories

Fig. 5. Distribution across the scalp of the mean amplitude of the N400 effect in young, elderly, and SDAT patients.

increased latency variability. In any case, latency variability is not an answer per se but yet another phenomenon that needs to be explained in neural and mental terms. What physiological/anatomical considerations lead to the increased variability in N400 activity and what is the functional (processing) consequence of such increased variability, if it occurs?

While there is a consensus that normal aging is associated with changes in cognitive ability as a direct reflection of specific changes in the brain, the nature of the brain changes remains controversial. Loss and/or shrinkage of large neurons in neocortex and hippocampus (Coleman and Flood, 1987; Terry et al., 1987; Peters, 1993) and subcortical nuclei (Kemper, 1993) as well as dendritic loss with decreased arborization of the cortical neuropil (Scheibel and Scheibel, 1975; Flood, 1993) have been reported. Thus, age-related functional changes may be related to selective losses of cortical inputs and synaptic organization (Barnes, 1994). Since the ERP is presumed to be primarily a reflection of the sum of postsynaptic activity of pyramidal cells in the cortical layers, decreased arborization and/or modified synaptic connectivity could account for many of the ERP changes observed with age. Evidence from laboratory animals, however, reveals degenerative changes in some regions of the hippocampus and functional sparing of other areas (Barnes, 1993), thus contradicting the view that aging is a process of general deterioration (Rapp and Amaral, 1992; Finch, 1993).

Neocortical changes may also account for N400 changes in SDAT patients. Neuropathologically, neocortical damage in SDAT involves predominantly association cortex which becomes progressively deafferented of cortical and subcortical inputs and devoid of some locally projecting intrinsic cortical neurons (Henderson and Finch, 1989). The degree of synaptic loss in frontal, parietal and temporal association cortex has been found to correlate with the severity of cognitive impairment (Terry et al., 1991). Neurophysiologically, brain electrical activity mapping has revealed changes in parietal and temporal areas in SDAT (Duffy et al., 1984; Duffy et al., 1993; Albert et al., 1990; Prichep et al., 1994). EEG coherence is decreased between parietal and frontal areas, presumably due to degeneration of long corticocortical fibers that connect parietal association and frontal cortices (Leuchter et al., 1992). PET has indicated hypometabolism within association cortex, with relative sparing of primary motor and sensory areas (Duara, 1992) which was more pronounced in the temporal-parietal than in the frontal regions. These same areas have been reported to contain single units that respond to word stimuli (Ojemann and Creutzfeldt, 1987; Bechtereva et al., 1989). Furthermore, significant associations have been found in SDAT patients between semantic memory deficits and hypometabolism in left cingulate, superior temporal and frontal association areas (Perani et al., 1993). Since the scalp N400 is absent in patients with posterior temporal lesions (Puce et al., 1991), it is possible

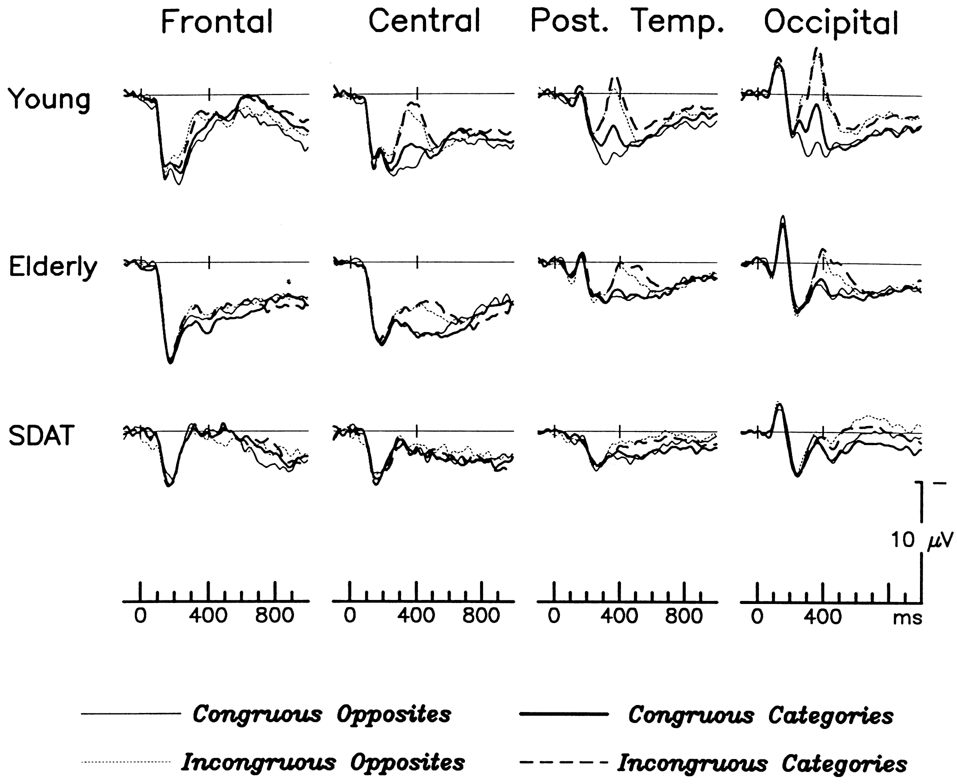


Fig. 6. Grand average ERPs recorded at right frontal, central, temporal and occipital sites on each of the groups. ERPs elicited by congruous and incongruous stimuli in the opposite and category conditions are superimposed.

that the involvement of association areas plays a role in the changes of N400 that we observed in SDAT patients. PET functional mapping of brain areas involved in semantic processing in normal subjects has also implicated temporal, parietal and frontal association areas (Peterson et al., 1988; Wise et al., 1991; Démonet et al., 1992; Howard et al., 1992; Grasby et al., 1993).

Table 3

Means (standard deviations) of neuropsychological test scores

	Older controls	SDAT patients
MMSE	29.50 (0.90)	22.25 (3.41)
DRS	140.64 (3.14)	113.73 (9.16)
BNT	28.50 (1.46)	22.33 (5.99)
LF	46.25 (5.26)	26.33 (11.16)
CF	21.58 (8.18)	9.50 (4.10)
VT (WAIS-R)	60.25 (4.86)	45.18 (8.63)
NIT	22.75 (1.71)	16.75 (5.94)
DS (WMS-R)	17.83 (3.88)	11.91 (3.94)
BSRT (total)	41.25 (5.55)	18.18 (6.76)
BSRT (LTM)	33.17 (9.78)	5.27 (3.27)
BSRT (intrusions)	1.0 (1.41)	2.55 (2.54)

MMSE, Mini-Mental State Examination; DRS, dementia rating scale; BNT, Boston Naming Test; LF, letter fluency; CF, category fluency; VT, vocabulary test; WAIS-R, Wechsler Adult Intelligence Scale-Revised; NIT, Number Information Test; DS, digit span; WMS-R, Wechsler Memory Scale-Revised; BSRT, Buschke-Fuld Selective Reminding Test; LTM, long-term memory.

While there exists no consensus as to the exact mental operation that is indexed by the N400, there is a moderately large body of data demonstrating that within psycholinguistic experiments it is associated with some aspect of lexical processing especially in relation to the eliciting word's meaning. In particular, N400 amplitude has proven to be very sensitive to all of the factors (frequency, repetition, semantic priming, semantic context) that are known to influence the speed of lexical access and word recognition; moreover, it is an exquisite index of the semantic relation between a word and its context (Kutas and Van Petten, 1988). Thus, even though the N400 may not in itself reflect lexical access, it has been found to be sensitive to experimental manipulations that presumably affect the speed of lexical processing. Delay of lexical access in aging and dementia is supported by behavioral studies that have found elderly subjects to be consistently slower than young controls and SDAT patients to be slower than age-matched elderly control subjects; this pattern holds both for lexical decision and pronunciation latency tasks (Howard et al., 1981; Howard et al., 1986; Petros et al., 1983; Bowles and Poon, 1985; Chiarello et al., 1985; Nebes et al., 1986; Nebes et al., 1989; Light and Singh, 1987).

Studies in healthy young subjects also have demonstrated that the amplitude of the N400 in semantic priming word pair and sentence experiments is modulated by the relationship between the target word and information in semantic memory set up by the context. The size of these effects is further modulated by attention; N400 effects are much larger when the task requirements draw attention to the meaning of words and relations between them (for a review, see Kutas and Van Petten, 1994). The fact that the N400 effect was diminished in the elderly subjects and virtually absent in SDAT suggests that this semantic analysis may become more difficult and/or less efficient with age and even more so with dementia. Different theories of aging have put the onus on reduced working memory capacity, reduced or poorer control of attentional resources, and less efficient inhibitory processes (Light and Capps, 1986; Cohen, 1988; Hasher and Zachs, 1988; McDowd and Oseas-Kreger, 1991; Tipper, 1991). Our data are consistent with all of these proposals.

The reduced sensitivity of this semantic integration process in these groups was also evident in the lack of a difference in the processing of category and opposite members. These two stimulus conditions differ in how much they rely on association versus semantic overlap; the associative strength of opposites (a function of the number of subjects who would give the target in response to the prime in an association norm test) is quite high relative to that of category members which tend to share more semantic characteristics with their category name. Recent evidence suggests that priming between words that are strongly associated may differ from that between words that are not associated but share semantic features (Lupker, 1984; Chiarello et al., 1990; Moss and Marslen-Wilson, 1993). Associative priming is presumed to be based upon the build-up of facilitatory connections between word forms rather than meanings. For the younger subjects, the primary difference between ERPs elicited by opposites and categories was in the presence of larger, earlier positivity for congruent opposites than congruent category members. Neither the elderly nor the SDAT patients showed this effect. Thus, although both groups showed diminished N400 congruity effects for opposites and categories, they seemed to be somewhat more affected for associative than semantic priming. An alternative interpretation, however, would be that the opposites elicited larger ERP effects in the younger group because they led to the conscious expectation of a particular word which was confirmed, as opposed to the much larger set of choices in the case of categories (Becker, 1980). On this view, the difference is not necessarily due to associative versus semantic priming. Rather, the lack of a difference in the congruent ERPs for the opposites and categories in elderly subjects and SDAT patients would be a consequence of less efficient use of attentional resources to generate explicit predictions (i.e. specific expectations). Additional experiments, perhaps probing the two hemispheres separately with materials that afford associate priming only, semantic priming only, and both may be necessary to help choose among these alternatives (Chiarello and Richards, 1992; Chiarello et al., 1992).

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