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# Age-related qualitative differences in auditory cortical responses during short-term memory

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## Abstract

**Objective:** To examine the affects of aging on auditory cortical activity during a short-term memory task.

**Methods:** Young and elderly subjects performed a working memory task using acoustically presented digits while evoked potential components (N100, P200) generated by auditory cortex were recorded. Reaction time and N100/P200 amplitudes and latency were analyzed as a function of memory load.

**Results:** N100 amplitude to probes decreased as a function of memory load in young subjects, but increased as a function of memory load in the elderly. Young subjects also exhibited changes in N100 latency during memorization of list items, a result not found in elderly subjects.

**Conclusions:** We conclude that normal aging is associated with a qualitatively different pattern of N100 responses during memory retrieval, and a static N100 response during encoding. The findings suggest that aging is accompanied by functional reorganization of the neural network that supports retrieval in auditory working memory. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

**Keywords:** Evoked potential; Aging; N100; Scanning; Working memory

## 1. Introduction

Healthy aging is accompanied by gradual decline in several aspects of long-term and working memory function (Craik and Jennings, 1992). During aging there are reductions in certain neurotransmitter levels and receptor number, the formation of  $\beta$ -amyloid deposits, neuronal shrinkage, and synapse loss (Terry et al., 1986; Masliah et al., 1993; DeKosky and Palmer, 1994; Mrazek et al., 1994; Haroutunian et al., 1999; Raz, 2000), all of which may contribute to age differences in memory function.

The gradual time course of these structural changes during aging is compatible with functional reorganization of the neural circuitry involved in memory. Evidence for such age-related reorganization of memory systems has recently been reported in several combined behavioral and PET studies. Relative to young subjects, elderly subjects exhibit reduced activity in several regions during encoding of memory items and incomplete regional activation during recall (Grady et al., 1995). Elderly subjects also engage additional brain areas when performing at comparable levels to young subjects (Cabeza et al., 1997a; Madden et al., 1999; McIntosh et al., 1999; Reuter-Lorenz et al., 2000),

and have different functional correlations between brain regions (Cabeza et al., 1997b; McIntosh et al., 1999). Collectively, these findings demonstrate that the performance of young and elderly subjects, even at equivalent levels of proficiency, may be accompanied by different regional patterns of neural activity.

A memory scanning paradigm developed by Sternberg (1966) has often been used to relate event related potentials (ERPs) to working memory function (e.g. Starr and Barrett, 1987). Subjects memorize a brief list of memory set items (e.g. digits) and a few seconds later indicate if a probe number was a member of the memory set by pressing one of two reaction time (RT) buttons. RTs linearly increase with memory load (i.e. the number of items in the memory set). Scanning time, in ms/memory item, is defined by the slope of the RT  $\times$  memory load function. If the stimuli are presented acoustically, ERP components (N100, P200) generated by the synchronized activity of neurons in the primary and secondary auditory cortices can be recorded (Naatanen and Picton, 1987; Zouridakis et al., 1998). The N100 and P200 components are sensitive to physical parameters of the stimuli, but also are affected by cognitive factors such as attention (Hillyard et al., 1973) and stimulus change (Naatanen, 1990). Recently, Conley et al. (1999) using a memory scanning paradigm in young subjects

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showed that N100 amplitude to probes decreased in a linear manner with increasing memory load. Memory load was linearly related to both RT and N100 amplitude, findings which suggest that auditory cortex may participate in the scanning of items stored in working memory.

The purpose of this experiment was to assess the N100 during a working memory task in a group of healthy elderly subjects, and to compare these findings with those of healthy young subjects. Previous reports have shown increases in scanning time in the elderly, as compared to young subjects (e.g. Anders et al., 1972). We hypothesized that, relative to young subjects, elderly subjects during memory scanning would exhibit decreases in N100 amplitude to probes with increasing memory load, but with a longer scanning time and a steeper N100 amplitude vs. memory load function. In the present report we found scanning time to be significantly increased in the elderly. However, elderly subjects exhibited linear *increases* of N100 amplitude to in-set probes in association with increasing memory load, a pattern opposite from that observed in young people. The results suggest that auditory cortical activity during short-term memory functions is qualitatively different between normal young and elderly subjects.

## 2. Methods

### 2.1. Subjects

There were two groups of subjects in this experiment. One group was composed of college students (Young group), and the other consisted of elderly people from the community (Elderly group). All subjects signed informed consent forms, and the experiments were performed in accordance with a protocol approved by the UC Irvine institutional review board.

In the young group ( $n = 12$ ; 12 female) subjects were recruited from the UC Irvine student population. The mean age of the young group was  $20.0 \pm 0.4$  (range 18–22) years. Mean level of education was 14.0 (range: 12–16) years. Students received course credit for their participation in the study. Subjects were excluded if they had a history of epilepsy, head trauma, or major psychiatric condition. Ten subjects were right-handed, one left-handed, and one subject reported that she was ambidextrous, but used her right hand to press the buttons during the experiment. All had hearing within the normal range for their age, and could clearly respond to the stimuli presented in the experimental session.

Subjects in the elderly group ( $n = 12$ ; 9 female) were recruited from a control population at the UC Irvine Alzheimer's Disease Research Center. Mean age of the elderly group was  $67.8 \pm 1.3$  (range 60–79) years. Nine out of the 12 subjects were between the age of 60 and 70. Mean level of education was  $16.9 \pm 0.8$  (range 12–23) years. Subjects were healthy at the time of experimentation, had mini-

mental status scores  $\geq 28$  (out of 30 possible points), and did not suffer from serious chronic illnesses. All of the subjects had average to above average scores on a battery of neuropsychological tests. As with the young subjects, participants in the elderly group did not have a history of epilepsy, head trauma, or major psychiatric condition. Nine subjects were right handed, 3 were left handed. All elderly subjects were able to clearly discriminate the auditory stimuli and perform the task at high levels of accuracy.

### 2.2. Memory task

The memory task was modified from a working memory task designed by Sternberg (1966). All stimuli in the experiment were presented in the auditory modality. Stimuli were digitized from a male voice and were adjusted to be 500 ms in duration. Stimuli were presented at a normal conversation level ( $\sim 60$  dB nHL) from two speakers placed  $\sim 0.75$  m in front of the subject. Subjects were seated in a comfortable chair and held a small button box in their dominant hand while performing the task.

A schematic diagram of a memory trial is shown in Fig. 1. Each trial contained a start cue, followed by a list of sequentially presented digits (1–9). The list of digits was the memory set, and contained either 1, 3, or 5 digits. After the memory set was presented there was a 3.0 s delay period. Following the delay period a single digit (probe) was presented. The subject was instructed to determine if the probe digit was a member of that trial's memory set. If the probe matched an item in the memory set (in-set probe) the subject depressed an upper response button with the thumb of their dominant hand. If the probe failed to match any of the memory set digits (out-of-set probe) the subject pressed a lower response button with the thumb of their dominant hand. Subjects were instructed to respond rapidly while maintaining high levels of accuracy.

Each block contained 20 memory trials, with an inter-trial interval of 3.0 s. The specific digits within the memory set varied randomly across trials. Blocks lasted 2.5, 3.5, and 4.5 min for 1, 3, and 5 item set sizes, respectively, and were separated by a short rest period ( $\sim 1$  min). All trials within a

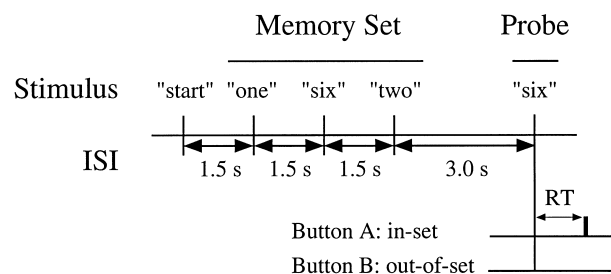


Fig. 1. Schematic diagram of a single trial. Each block contained 20 trials, with a 3.0 s inter-trial interval. Each trial commenced with the word 'start,' followed by the memory set list. A 3.0 s interval separated the final list item and the probe digit.

given block had the same number of items in the memory set, and the subject was informed of the set size before each block. This blocked design permitted the evaluation of ERP components during memorization as a function of set size. The particular digits for each block of 20 trials were randomly determined with the following restrictions. (1) Digits within a given memory set were presented only once. (2) The probability of in-set and out-of-set probes was 0.5. Thus, each block contained 10 in-set and 10 out-of-set probes. (3) A maximum of 3 trials in a row with in-set or out-of-set probes was permitted. (4) In-set probes were drawn approximately equally from each serial position in the memory set (3 item set  $P = 0.33/\text{position}$ ; 5 item set  $P = 0.20/\text{position}$ ). One item blocks were given first, followed by the 3 item and then the 5 item blocks. Elderly subjects were given 2 blocks/set size (40 trials total/set size). Because additional time was available for young subjects, they were given 3 blocks/set size (60 trials total/set size) to further increase the S/N ratio for ERPs.

### 2.3. Number classification task

As in an earlier study in young subjects (Conley et al., 1999) we employed a control number classification task for comparison with the results from the memory task. The results from young subjects in the current study replicated the main findings from Conley et al. (1999). For this reason it was judged unnecessary to repeat the number classification task in young subjects. However, in order to be certain that any effects observed in elderly subjects were attributable to memory demands of the task rather than non-specific features of the memory paradigm, we conducted the same number classification task in a group of elderly subjects.

Eleven subjects were recruited from the healthy control population at the UC Irvine Alzheimer's Disease Research Center. These subjects did not participate in the memory task described above. The selection and exclusion criteria were as described above. Mean age of the elderly control group was  $72.7 \pm 1.9$  (range 62–80) years, and years of education was  $16.5 \pm 1.0$  (range 12–22). Age and education level of subjects in the number classification task were not significantly different from the elderly group that performed the memory task, and all had mini-mental status scores  $\geq 27$ .

Subjects were given an identical series of trial blocks as described above for Expt. 1. The only difference between the memory and number classification task was the instruction given to the subjects. Subjects were asked only to listen to the list of numbers in the memory set. When the probe was presented the subject's task was to determine if the probe digit was 'even' or 'odd.' For even numbers subjects pushed the upper response button, odd numbers the lower button. As in the memory task both speed and accuracy were emphasized. Subjects were given two blocks of 20 trials (40 trials total) for the 1, 3, and 5 item set sizes. One item blocks were given first, followed by the 3 and 5 item blocks.

### 2.4. Electrophysiological recordings

Subjects were seated inside a sound attenuating, electrically shielded chamber. Seven Ag/AgCl recording electrodes at sites Fz, Cz, Pz, C3, C4, T3, T4 were placed on the scalp according to the 10–20 system (Jasper, 1958). Young subjects were also given an additional electrode at the Oz site. Two electrodes were placed above and below the left eye to monitor eye movements, and one electrode was placed on the forehead to serve as the ground. Electrodes placed on the left and right mastoid served as references in a linked mastoid configuration. For all recordings electrode impedances were  $\leq 5 \text{ k}\Omega$  and checked occasionally during the recording session. The EEG and EOG were digitally amplified with a bandpass of DC–100 Hz and a digitization rate of 500 Hz. EEG, EOG, and stimulus trigger pulses were collected continuously. All data were further processed and analyzed off-line. An eyeblink correction algorithm was used to correct for artifacts (Gratton et al., 1983). Individual sweeps were sorted and averaged according to stimulus type. Sweeps to probes were automatically rejected if activity on a scalp site exceeded  $100 \mu\text{V}$  or the subject made an incorrect response or failed to respond. Individual sweeps to probe stimuli were then visually inspected for artifacts before being accepted into the average. Sweeps to memory set items were rejected if the voltage on any channel exceeded  $75 \mu\text{V}$ . A lower rejection threshold was used for memory set items ( $75 \mu\text{V}$ ) vs. probes ( $100 \mu\text{V}$ ) because individual sweeps for memory set items were not examined visually for artifacts due to the large number of sweeps. Separate averages were constructed for each serial position in the 3 and 5 item memory sets. The average potential for the 3 and 5 item set sizes was then created by averaging the 3 serial position subaverages in the 3 item set, and the 1st, 3rd, and 5th serial positions in the 5 item set.

### 2.5. Data analysis

Behavioral measures included RT, calculated relative to the onset of probe stimuli, and accuracy. Accuracy was expressed as the percent of correct responses out of all trials with a response. The number of trials without a button press was also noted. Slopes of RT vs. set size were calculated for each subject by fitting a best-fit curve through their mean RT values at each set size.

The EEG was digitally filtered using FFT and inverse FFT procedures. Bandpass filters were set at 1–16 Hz (12 dB/octave) to attenuate slow shifts. Peak latencies were calculated relative to stimulus onset. The amplitudes of all stimulus evoked potentials were defined relative to a 100 ms prestimulus baseline period. For both items and probe stimuli the N100 and P200 components were measured. N100 amplitude and latency was defined as the maximum negativity between 80 and 180 ms, while P200 amplitude and latency was the maximum positivity between 150 and

250 ms. All values reported below were measured from the Cz electrode site, unless otherwise specified.

## 2.6. Statistical analysis

ERP and behavioral data were analyzed using repeated measures analysis of variance (ANOVA). The Greenhouse-Geisser correction was applied to control type I error. When the Greenhouse-Geisser was utilized the adjusted  $P$  values were reported. Differences of  $P < 0.05$  were considered significant. Behavioral analysis included the factors of group (young, elderly), set size (1, 3, 5 item memory sets), and probe type (in-set vs. out-of-set). Factors used to evaluate ERP amplitude and latency included group, set size, and electrode site (Fz, Cz, Pz, C3, C4, T3, T4). In-set and out-of-set probes were analyzed separately. To directly compare the results from the number classification task with the memory task, probes in number classification were also divided according to in-set and out-of-set status. Note that 'even' and 'odd' numbers were present for both in-set and out-of-set averages. Topographic differences across electrode site were assessed using normalized values (McCarthy and Wood, 1985). Significance for post hoc testing was set at  $P < 0.05$ . Post hoc testing employed Tukey tests or trend analysis, to test for statistically significant linear and quadratic associations, when appropriate.

## 3. Results

### 3.1. Memory task: behavior

#### 3.1.1. Accuracy

Mean accuracy was 99.1 and 98.5% in the young and elderly groups, respectively. These differences were not statistically significant. The percent of trials without a response was not significantly different between groups, with 0.7 and 2.3% of the trials having no response in the young and elderly groups, respectively.

#### 3.1.2. Reaction time

RT as a function of set size is illustrated in Fig. 2. We performed a repeated measures ANOVA between groups using the factors set size (1, 3, 5 items) and probe type (in-set vs. out-of-set). Overall RT differences between the groups did not attain significance. There was a significant effect for set size ( $F(2, 44) = 71.8$ ;  $P < 0.0001$ ), indicating that for both groups RT increased with greater set sizes. There was also a significant interaction between group and set size ( $F(2, 44) = 15.2$ ;  $P < 0.0001$ ), which indicates a greater increase in RT with increasing set size in the elderly group. This result was verified by a significant difference between groups in the RT vs. set size slopes ( $F(1, 22) = 17.0$ ;  $P < 0.001$ ). The mean slope of subjects in the elderly group (106.2 ms/item) was more than twice the value seen in young subjects (46.9 ms/item). There were no significant RT differences between in-set and out-of-set

probe types, but there was a significant group  $\times$  probe type interaction ( $F(1, 22) = 5.9$ ;  $P < 0.03$ ). This was due to a faster RT for in-set (818.7 ms) vs. out-of-set (886.1 ms) probes in young subjects, while the elderly group exhibited similar RTs for both probe types (959.2 ms in-set, 953.5 ms out-of-set).

### 3.2. Memory task: evoked potentials to items and probes

Grand average potentials recorded from Cz in the 1 item set from the young and elderly groups are presented in Fig. 3. Memory set items elicited N100 and P200 components before returning to baseline levels (Fig. 3A). Probe stimuli elicited N100 and P200 components, as well as additional components having longer latencies (N200 and P300) (Fig. 3B). In the present report analysis will be restricted to the N100 and P200 components, although significant amplitude and latency differences were also observed for the N200 and P300 components.

### 3.3. Memory task: evoked potentials to probes

#### 3.3.1. In-set probes

**3.3.1.1. N100.** Plots of the mean in-set N100 amplitudes for each set size are shown in Fig. 4A. Grand average potentials for each set size are superimposed in the young (Fig. 4C) and elderly (Fig. 4E) groups. There were no significant differences between groups in overall N100 amplitude. Importantly, there was a significant group  $\times$  set size interaction ( $F(2, 44) = 10.8$ ;  $P < 0.001$ ). For young subjects N100 amplitude *decreased* with increasing set size. In the elderly group N100 amplitude *increased* with increasing set size. Trend analysis indicated a significant linear relationship between N100 amplitude and set size in both groups ( $P < 0.01$ ). The N100 amplitude  $\times$  set size slope was positive in the young group (slope =  $0.98 \mu\text{V}/\text{item}$ ;  $r = 0.99$ )

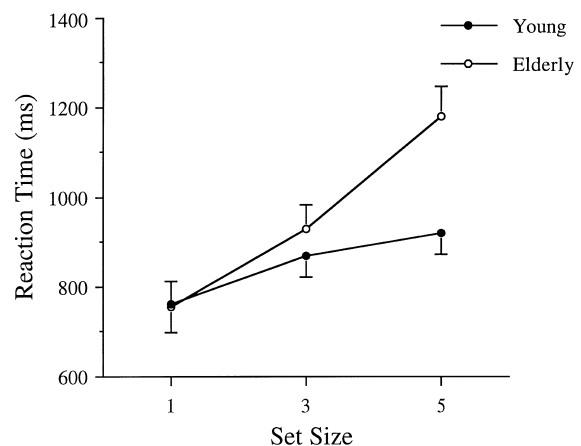


Fig. 2. Plot of RT versus set size for young and elderly subjects. Both groups exhibited linear increases in RT with greater set size, but elderly subjects demonstrated a significantly larger RT increase across set size as compared with young subjects. Scanning rates were 46.9 ms/item and 106.2 ms/item in the young and elderly, respectively.

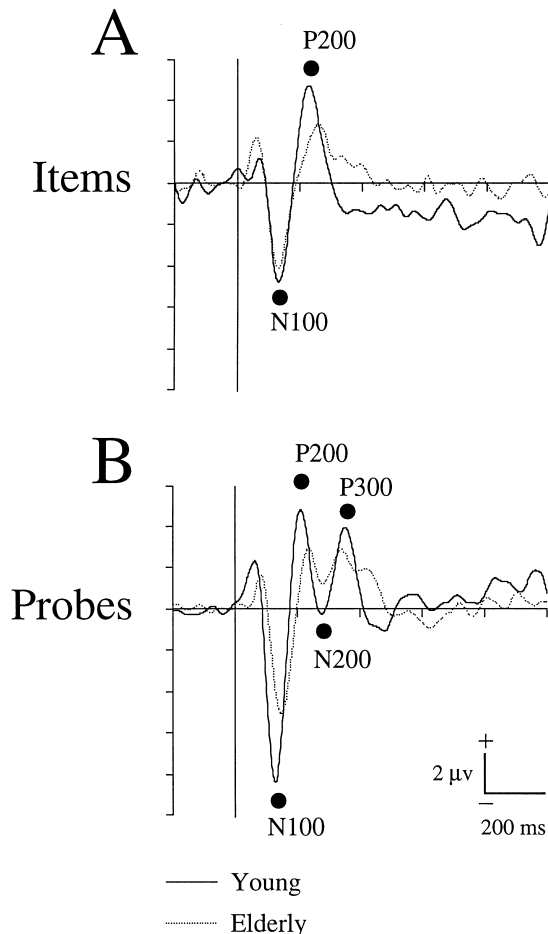


Fig. 3. Grand average evoked potential tracings in the young and elderly for memory set items (A) and probes (B). Data are shown from  $-200$  ms to  $+1000$  ms relative to stimulus onset, which is indicated by the vertical line. Examples are from the 1 item set size, bandpass filtered at 1–16 Hz. (A) Memory set items elicited prominent components at  $\sim 100$  ms (N100) and  $\sim 200$  ms (P200) after stimulus presentation, and a subsequent slow negative component that was most apparent in young subjects (Pratt et al., 1989). (B) In addition to the N100 and P200 components, probe stimuli also elicited N200 and P300 components.

and negative (slope =  $-1.0 \mu\text{V}/\text{item}$ ;  $r = 0.96$ ) in the elderly. A positive slope value denotes less negative (smaller) N100 amplitudes with increasing set size; a negative slope indicates more negative (greater) N100 amplitudes with increasing set size.

**3.3.1.2. N100 topography.** The interaction between groups across set size may be attributable to differences in the strength and/or location of the neuronal generator sources. We conducted 3 repeated-measures analyses of variance (ANOVAs), a single ANOVA per set size, using all 7 electrode sites (Fz, Cz, Pz, T3, C3, C4, T4) to test if the group  $\times$  electrode site interaction was significant. The pattern of results for the 3 set sizes were similar. There was a significant effect of electrode site ( $P < 0.0001$ ), with the largest amplitude at Cz, followed by Fz and Pz, and progressively smaller amplitudes at the lateral sites. The

group  $\times$  electrode site interactions were not significant for 3 and 5 item set sizes. For the 1 item set size there was a small, but significant group  $\times$  electrode site interaction ( $F(6, 132) = 2.7$ ;  $P < 0.05$ ). Normalized amplitudes in the 1 item set size were comparable at all sites with the exception of C3 (young  $0.51 \pm 0.09$ ; elderly  $0.85 \pm 0.04$ ). The results do not support the hypothesis that different neural generator sites produced the N100 component in the young and elderly subjects for 3 and 5 item set sizes, but there may be age differences in generator sites for the 1 item set size. N100 latency was significantly faster in the young (129.4 ms) vs. elderly (140.1 ms) subjects ( $F(1, 22) = 6.8$ ;  $P < 0.02$ ) and did not vary significantly with set size.

**3.3.1.3. P200.** There was a significant difference in P200 amplitude between groups ( $F(1, 22) = 6.7$ ;  $P < 0.02$ ). Mean P200 amplitudes in the young and elderly groups were 5.6 and 2.5  $\mu\text{V}$ , respectively. P200 amplitude did not vary across set size, and the group  $\times$  set size interaction was also not significant. The absence of P200 amplitude changes across set size suggests that the group differences in P200 amplitude were independent of the preceding N100 amplitude. P200 latency did not vary significantly between groups or across set size.

### 3.3.2. Out-of-set probes

**3.3.2.1. N100.** N100 amplitudes in response to out-of-set probes as a function of set size are presented in Fig. 4B. Grand average potentials for each set size are shown for the young (Fig. 4D) and elderly (Fig. 4F) groups. There was a significant group difference in overall N100 amplitude ( $F(1, 22) = 4.7$ ;  $P < 0.05$ ), and a main effect across set size ( $F(2, 44) = 5.2$ ;  $P < 0.02$ ). Contrary to what was found for in-set probes, the group  $\times$  set size interaction was not significant. Although the average N100 amplitudes decreased significantly with set size, especially in the young group, this pattern varied across individual subjects of each group. Thus, there were no age differences in the N100 response to out-of-set probes as a function of set size. This result shows that the group difference in N100 dynamics across set size was specific to in-set probes. N100 latency was significantly faster in the young (128.8 ms) vs. elderly (144.1 ms) subjects ( $F(1, 22) = 26.8.0$ ;  $P < 0.0001$ ), and N100 latency did not vary significantly over set size.

**3.3.2.2. P200.** P200 amplitude was not significantly different across set size for out-of-set probes. P200 amplitude was significantly different between groups for out-of-set probes ( $F(1, 22) = 12.6$ ;  $P < 0.01$ ). P200 latency was significantly different between groups ( $F(1, 22) = 12.6$ ;  $P < 0.01$ ), with mean latencies of 205.7 and 228.2 ms in young and elderly groups, respectively. There were no significant latency differences across set size.

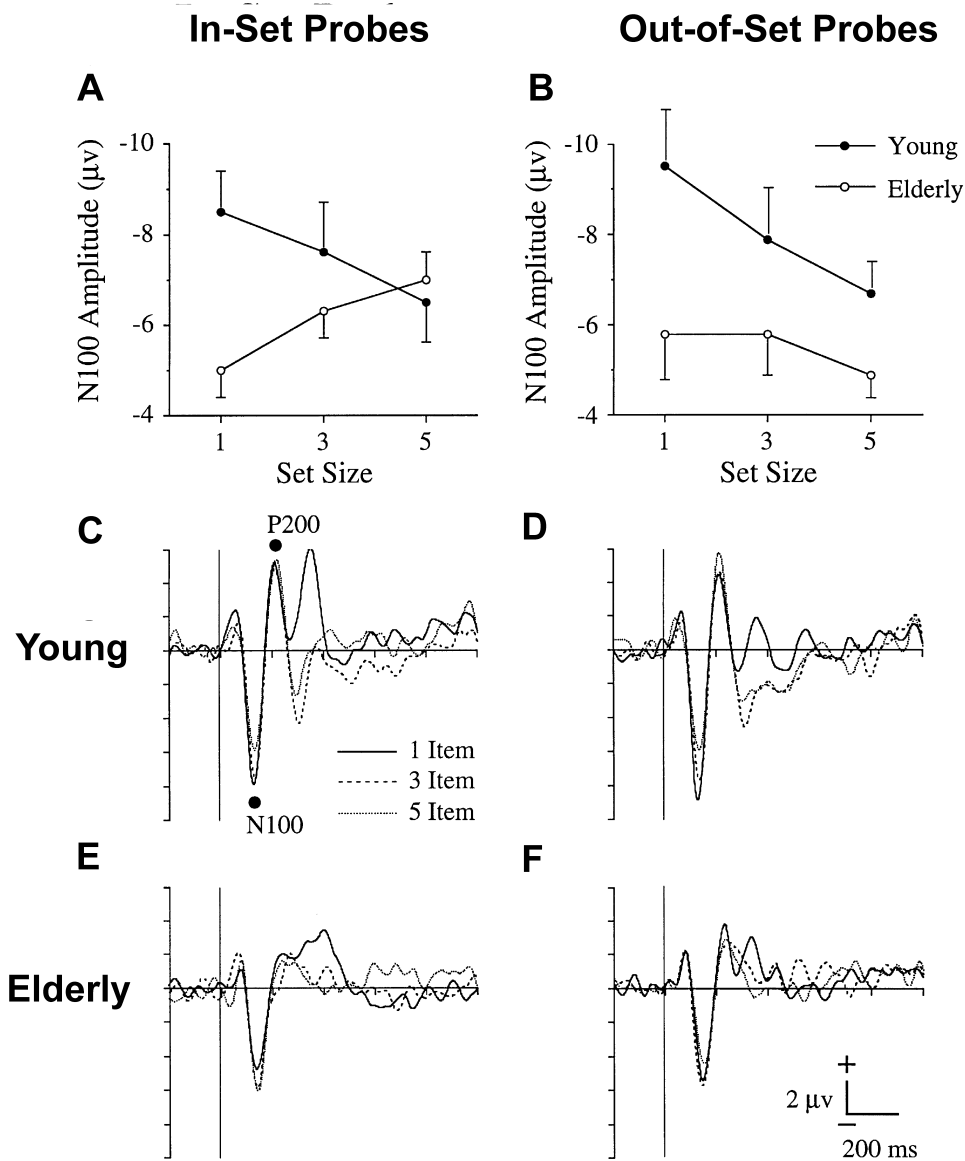


Fig. 4. Evoked potentials to probes in young and elderly subjects. (A) Mean N100 amplitude to in-set probes as a function of set size. There was a significant group  $\times$  set size interaction. (B) Mean N100 amplitude to out-of-set probes as a function of set size. The group  $\times$  set size interaction did not attain significance, but only young subjects had a significant linear decrease in N100 amplitude with increasing set size. Grand average evoked potential tracings in young subjects for in-set (C) and out-of-set (D) probes. Grand average evoked potential tracings in elderly subjects for in-set (E) and out-of-set (F) probes. Tracings in C–F were bandpass filtered at 1–16 Hz.

### 3.4. Memory task: evoked potentials to memory set items

#### 3.4.1. N100

Grand average potentials to items in the 1 and 5 item sets are illustrated in Fig. 5A,B. Results shown in Fig. 5 suggest N100 amplitude differences between set sizes for the young (Fig. 5A) and elderly (Fig. 5B) groups, as well as a latency difference between set sizes for young subjects. Mean N100 amplitudes to items for each set size are presented in Fig. 5C.

There were no significant group differences in N100 amplitude. There was a significant main effect for set size

( $F(2, 44) = 7.0$ ;  $P < 0.01$ ), with decreasing N100 amplitudes for larger set sizes in both groups. The decrease in N100 amplitude with set size was not attributable to refractory effects because N100 amplitudes in response to the first item of each list decreased as a function of set size ( $F(2, 44) = 3.7$ ;  $P < 0.04$ ). Also, there were no significant differences in N100 amplitudes between the 1st, 3rd, and 5th serial positions in the 5 item set. Taken together, the results suggest that N100 amplitude decreases across set size were related to memory load.

N100 latencies were not significantly different between groups; however, latencies were significantly different

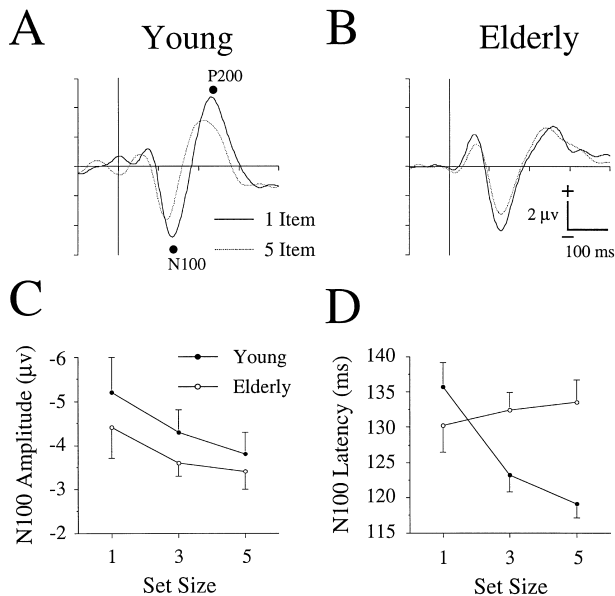


Fig. 5. Evoked potentials to memory set items in young and elderly groups. Grand average sweeps in young (A) and elderly (B) subjects. (C) Mean N100 amplitude to items as a function of set size in the young and elderly groups. There was a significant reduction in N100 amplitude with greater set size in both groups. (D) N100 latency for items as a function of set size. There was a significant reduction in N100 latency with greater set size for the young, but not the elderly group.

across set size ( $F(2, 44) = 5.2$ ;  $P < 0.02$ ). This effect was due to a significant group  $\times$  set size interaction (see Fig. 5D) ( $F(2, 44) = 11.4$ ;  $P < 0.0001$ ). Again, the latency change was not due to refractory effects because the group  $\times$  set size interaction was still present when N100 latency from the first item was analyzed ( $F(2, 44) = 5.6$ ;  $P < 0.01$ ). The young group exhibited monotonic latency decreases with increasing set size, having latencies of 135 ms (1 item), 123 ms (3 item), and 119 ms (5 item). Post hoc testing in young subjects showed that N100 latencies in the 1 item set were significantly longer than the 3 and 5 item sets (both  $P < 0.01$ ). Latencies in the 3 and 5 item sets were not significantly different. N100 latencies in the elderly group were not significantly different between any pair of set size means. Significant differences in N100 latency were seen between groups for 3 item ( $P < 0.05$ ) and 5 item sets ( $P < 0.01$ ), but not for the 1 item set size.

In the 5 item set N100 latencies did not differ significantly across serial position, but there was a significant group difference ( $F(1, 22) = 17.0$ ;  $P < 0.001$ ).

### 3.4.2. P200

Comparison between the groups indicated a significant overall difference in P200 amplitude ( $F(1, 22) = 7.3$ ;  $P < 0.02$ ). There was also a significant difference over set size ( $F(2, 44) = 7.0$ ;  $P < 0.01$ ). Unlike the N100, there was not a significant difference across set size when only the first stimulus in each list was analyzed. This suggests that the

difference in P200 amplitude across set size may be due to refractory effects associated with repeated presentations of the list stimuli, rather than a response to memory set size.

There was a small difference between groups in overall P200 latency ( $F(1, 22) = 6.0$ ;  $P < 0.03$ ). There were no significant latency differences across set size, but the effect approached significance ( $P < 0.06$ ).

### 3.5. Number classification vs. memory task: behavior

For the following analysis the group of elderly subjects given the memory task was compared with a separate group of elderly subjects who performed the number classification task. The purpose of this comparison was to determine if the ERP changes across set size in the elderly group are due to nonspecific aspects of the stimulus sequence.

#### 3.5.1. Accuracy

Accuracy was not significantly different between tasks, with a mean of 99.6% correct in the number classification task and 98.5% correct in the memory task. The percent of trials without a response was also not significantly different between tasks, with 2.6 and 2.3% of the trials having no response in the number classification and memory tasks, respectively.

#### 3.5.2. Reaction time

The RTs as a function of set size for the number classification and memory tasks are shown in Fig. 6A. We performed a repeated measures ANOVA between the memory and number classification task groups using the factors Set Size (1, 3, 5 items) and Probe Type (in-set vs. out-of-set). There was a significant effect for set size ( $F(2, 42) = 31.5$ ;  $P < 0.0001$ ), but this was due to a significant interaction between set size and task ( $F(2, 42) = 35.2$ ;  $P < 0.0001$ ). RT increased with set size in the memory task, but was similar across set size in the number classification task. There were no significant differences between tasks or probe types.

### 3.6. Number classification vs. memory task: evoked potentials

#### 3.6.1. Probes

N100 amplitude as a function of set size is shown for in-set (Fig. 6B) and out-of-set (Fig. 6C) probes. For in-set probes there was a significant N100 amplitude difference across set size ( $F(2, 42) = 3.4$ ;  $P < 0.05$ ), but no significant overall difference between tasks. Importantly, there was a significant task  $\times$  set size interaction ( $F(2, 42) = 4.8$ ;  $P < 0.02$ ). The results from the between group comparison were clear and unambiguous: most of elderly (8/12) subjects in the memory task exhibited monotonic N100 amplitude increases across set size for in-set probes, while none of the elderly subjects in the number classification task had monotonic increases across set size. This interaction shows that N100 amplitude for in-set probes increased with set size, but



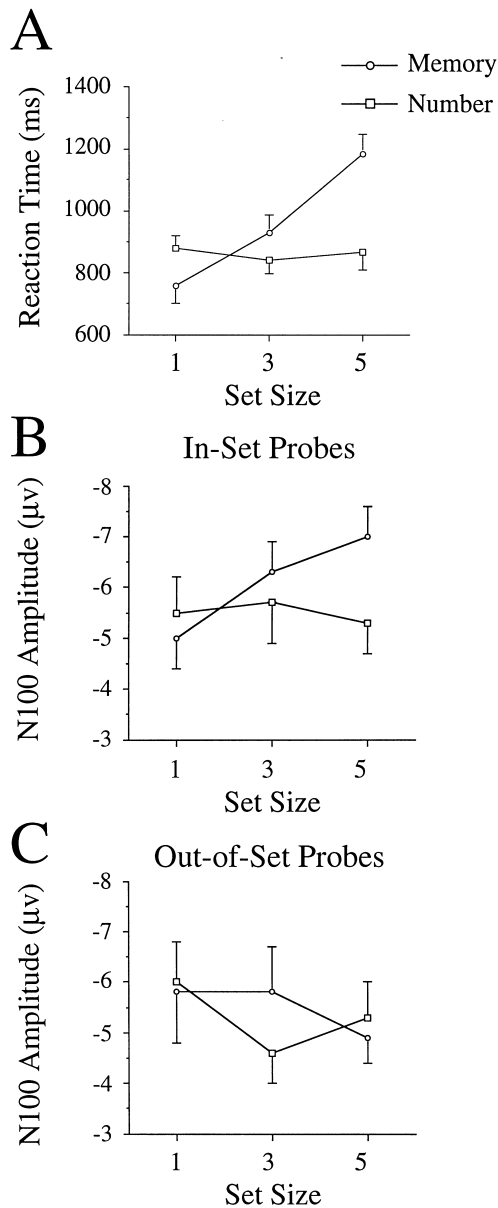


Fig. 6. Comparison of memory and number classification tasks in elderly subjects. (A) RT as a function of set size in both tasks. RT significantly increased with set size in the memory task, but in the number classification task. (B) N100 amplitude across set size for in-set probes in both tasks. There were significant N100 amplitude increases in the memory task, but not in the number classification task. (C) N100 amplitude as a function of set size for out-of-set probes. There were no significant differences in N100 amplitude between tasks for out-of-set probes.

only in the memory task. For out-of-set probes there were no significant differences between tasks, set size, or task  $\times$  set size interaction.

N100 latency was not significantly different between tasks or set size, and the task  $\times$  set size interaction was also not significant.

P200 amplitude for in-set probes was not significantly different between tasks, set size, or the task  $\times$  set size interaction. There was a small difference between tasks for out-

of-set probe amplitude ( $F(1, 21) = 4.9$ ;  $P < 0.04$ ), with larger P200 amplitudes for the memory ( $4.1 \mu\text{V}$ ) vs. number classification ( $1.7 \mu\text{V}$ ). P200 amplitudes across set size and the task  $\times$  set size interaction were not significantly different.

P200 latency was not significantly different between tasks, or across set size, and the task  $\times$  set size interaction was also not significant.

### 3.6.2. Memory set items

N100 amplitudes elicited by items were not significantly different between tasks or set size. The task  $\times$  set size interaction was also not significant. There were no significant N100 latency differences for task, set size, or task  $\times$  set size.

P200 amplitudes were also not significantly different between task, set size, or task  $\times$  set size. P200 latency was not significantly different between tasks, set size, or task  $\times$  set size.

## 4. Discussion

Results from the present study indicate that the pattern of amplitude changes in N100 component of auditory evoked potentials during an auditory working memory task is qualitatively different between young and elderly subjects. During retrieval of in-set probes N100 amplitude decreased with increasing memory load in young subjects, but increased with memory load in elderly subjects. The N100 amplitude  $\times$  set size functions for each group were linear but in opposite directions. Age differences of N100 latency, but not amplitude, were also present during memorization. N100 latency decreased with increased memory load in young, but not elderly, subjects. We observed the traditional linear changes in reaction time as a function of memory load in both groups (Sternberg, 1966; Anders et al., 1972), with elderly subjects requiring longer scanning times for each item contained in working memory as compared with young subjects.

### 4.1. N100 activity during memory retrieval

Previous studies in the target detection paradigm have shown that the N100 is generated in primary and/or secondary auditory cortex in young (Pantev et al., 1995; Verlindt et al., 1995; Zouridakis et al., 1998) as well as elderly (Anderer et al., 1998) subjects. The P200 is generated in secondary auditory cortex (Scherg and Von Cramon, 1986; Rif et al., 1991; Siedenberg et al., 1996). Selective attention experiments have shown that scalp N100 amplitudes can be influenced by additional components that overlap with the time period of the traditional N100 (Naatanen, 1990). At the present time we favor the interpretation that the N100 amplitude changes in both young and elderly subjects are due to changes in activity within primary/secondary auditory cortex because there is no compelling evidence for additional generator sites or components in the memory

scanning paradigm. However, detailed studies to determine the generator sites of the scalp N100 in the auditory memory scanning task have not been conducted for either young or elderly subjects. In the current study topographic differences between groups were only present in the 1 item memory set. If there were systematic differences in the neural generators between groups this topographic difference would also be expected in the 3 and 5 item memory set sizes.

In addition to cognitive factors, such as attention and memory, the amplitude of the N100 is sensitive to changes in physical attributes of stimuli, such as intensity or inter-stimulus interval (Näätänen and Picton, 1987). Hearing loss, especially for high frequencies, is a typical consequence of aging, but is unlikely to account for N100 amplitude changes in elderly subjects. First, there were no group differences in N100 amplitude for memory set items and in set probes, and only a small difference for out-of-set probes. Because N100 amplitude is sensitive to stimulus intensity (Näätänen and Picton, 1987) reductions in hearing threshold in the elderly group would have resulted in smaller overall N100 amplitudes in the elderly. In addition, the group  $\times$  set size interaction for in-set items also cannot be accounted for by hearing loss in the elderly group. This point is best illustrated by the N100 amplitudes for the 5 item in-set probes, where the elderly group had larger N100 amplitudes as compared with young subjects (see Fig. 4A). Prolonged N100 latencies to probes in the elderly also cannot be attributed to hearing loss because there were no significant group differences in N100 latency to memory set items.

Results from the number classification task in the elderly suggest that N100 increases to in-set probes are related to the mnemonic demands of the memory task. More detailed studies would be needed to rule out factors such as task difficulty, or possibly arousal, that might also differ between the memory and number classification tasks. Because N100 amplitudes were unchanged across set size in the number classification task, age differences in N100 amplitude in the memory task are unlikely due to age differences in the recovery function of auditory cortex to repeated stimuli (Papanicolaou et al., 1984).

The present results in conjunction with Conley et al. (1999) permit the following conclusions regarding N100 amplitudes during memory scanning. (1) Amplitude changes in probes as a function of set size are observed when subjects are required to remember list items. N100 amplitudes were invariant across set size in the number classification task for both young (Conley et al., 1999) and elderly subjects. (2) In-set probes selectively demonstrate a memory load effect in the elderly. In young subjects the N100 amplitude to both in-set and out-of-set probes were affected by memory load. (3) N100 amplitude changes are not strictly related to RT in the elderly because RT increased linearly with memory load to both in-set and out-of-set probes, while N100 amplitude changed linearly with memory load only to in-set probes. Furthermore, the

notion that N100 amplitude is associated with RT requires a principled reason why N100 should increase with memory load in the elderly but decrease with memory load in the young, even though both groups exhibit RT increases with memory load.

#### *4.2. Mechanisms for age-related differences in auditory cortical function during retrieval*

Recent PET studies have defined several age-related changes in cortical function during memory, face matching, and other tasks. First, aging is associated with reduced activation of brain regions that were also active in young people (Grady et al., 1994, 1995, 1998; Nagahama et al., 1997; Esposito et al., 1999). Second, there was activation of brain areas that were not engaged in young subjects (Grady et al., 1992; Cabeza et al., 1997a; Esposito et al., 1999; Madden et al., 1999; McIntosh et al., 1999; Reuter-Lorenz et al., 2000). Third, changes were seen in the correlated activity among regions, with differences in coactivation in aging (Cabeza et al., 1997b; McIntosh et al., 1999). Any, or all, of these possibilities may be relevant to the age differences in N100 dynamics.

Age-related changes in primary/secondary auditory cortex is an obvious explanation for the age differences in N100 amplitude across set size. Age differences in temporal lobe volumes, especially association areas, have been described (Sullivan et al., 1995; Raz et al., 1997). Studies that specifically examined primary and secondary auditory cortex have only shown slight changes in neuron density with age (Coleman and Flood, 1987). The auditory cortex undergoes little structural change with aging, however, subtle alterations may be sufficient to induce changes in N100 response to memory load.

Neurons within the auditory cortex are reciprocally connected in a hierarchical fashion with association areas (Pandya and Yeterian, 1985; Felleman and Van Essen, 1991). These connections would allow the N100 to be influenced by regions outside of the auditory cortex; regions that may in turn affect the response of neurons within the auditory cortex that ultimately generate the N100. The findings that memory load and attention (Hillyard et al., 1973) influence N100 amplitude are consistent with this notion.

The prefrontal cortex is one candidate brain region that may influence N100 activity. The prefrontal cortex is particularly vulnerable to detrimental changes due to aging (West, 1996). Age-related deficiencies in prefrontal cortex have been supported by psychological (Hochanadel and Kaplan, 1994), neuroimaging (Nagahama et al., 1997), and anatomical (Raz et al., 1997) studies. Electrophysiological changes in the elderly using a working memory paradigm have been reported in a late slow wave component that may be generated in frontal cortex (Chao and Knight, 1997a). In addition, neuroimaging, and single unit recordings have demonstrated the importance of the prefrontal

cortex for working memory (Goldman-Rakic, 1995; Jonides et al., 1997).

The functional relationship between prefrontal cortex and auditory cortex in the cat was explored by Alexander et al. (1976), who reported marked reductions in the response of auditory cortical neurons to auditory stimuli following prefrontal stimulation. The prefrontal cortex could influence auditory cortex either directly, or via thalamic gating of afferents to auditory cortex (Yingling and Skinner, 1975, 1976). In the current study reductions in N100 amplitude with increasing memory load in young subjects may be attributable to memory load-dependent increases in inhibition from prefrontal cortex over auditory cortex. Consistent with this notion, studies in young subjects have shown increased activity in prefrontal cortex with increases in memory load (Braver et al., 1997; Jonides et al., 1997; Rypma and D'Esposito, 1999).

Increases in N100 amplitude across set size for in-set probes in the elderly may be the result of altered inhibition from prefrontal cortex to auditory cortex. One possibility is that reductions in prefrontal inhibition may be exacerbated by increases in set size, a process that could result in a net increase in N100 amplitude with greater memory load. Chao and Knight have suggested reductions in prefrontal inhibition to explain the increased amplitude of midlatency auditory ERPs in both elderly subjects and patients with prefrontal cortex lesions (Chao and Knight, 1997b, 1998).

#### 4.3. Auditory cortex activity during memorization

We also observed N100 amplitude and latency changes during memorization. Young subjects had clear reductions in N100 amplitude with increases in set size. In the elderly N100 amplitude reductions across set size in the memory task were similar to young subjects. However, in the elderly group these changes were not consistent enough across subjects to be considered significantly different from results in the control task. We conclude that if there are reductions in N100 amplitude across set size during memorization in the elderly the effect is subtle. More importantly, latency reductions with increased set size were seen in young, but not elderly subjects. The significance of N100 latency with respect to memory is unclear, but the marked group difference may relate to differences during encoding between young and elderly people (Grady et al., 1995). We speculate that the changes in N100 latency during encoding may be associated with subsequent RTs during retrieval. Reaction time and N100 latency were not significantly different between groups for the 1 item set size. There were small differences between groups in RT and N100 latency for the 3 item set, and large differences on both these measures in the 5 item set. Thus, when viewed across set sizes, N100 latency differences between groups during encoding roughly paralleled RT differences between groups during retrieval.

In conclusion, the results from this study of the N100

potential provide evidence that aging is accompanied by reorganization of auditory cortical responsiveness, particularly during the scanning of working memory.

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