# Prefrontal Deficits in Attention and Inhibitory Control with Aging

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**Event-related potentials and behavioral measures were obtained from young and elderly subjects while they performed two different auditory delayed match-to-sample tasks. In each experiment, subjects had to indicate whether an initial and a subsequent test sound were identical in two different conditions: one filled with distracting tone pips and one with no distractors. Electrophysiologically, elderly subjects had reduced attention-related activity over frontal regions. In addition, the distracting stimuli elicited an enhanced primary auditory evoked response in the elderly. The percentage of perseverative errors on the Wisconsin card sorting test, a putative measure of frontal lobe function, was positively correlated with the amplitude of the primary auditory evoked response in elderly subjects. Behaviorally, elderly subjects were impaired by distractors at long but not short delays. Taken together, these results suggest that increased distractibility and impaired sustained attention with aging may be due to altered prefrontal cortex function. These data support the loss of prefrontal suppression over the primary auditory regions with aging.**

It has been proposed that the normal aging process can alter prefrontal cortex (PFCx) functions (Albert and Kaplan, 1980; Parkin and Walter, 1992). Rabbitt (1965) was one of the first researchers to demonstrate experimentally that elderly subjects were less able to ignore task-irrelevant information, a function ascribed to the frontal lobes (Luria, 1973). When older people were tested on a battery of neuropsychological tests, frontal lobe deficits seemed to be a primary component of their cognitive impairments (McDowd and Oseas-Kreger, 1991). In a PET study of recognition memory, older subjects had less activation in frontal and hippocampal regions than younger subjects during encoding (Grady *et al.*, 1995). Further evidence has come from studies in which older subjects exhibit memory deficits characteristic of patients with focal frontal pathology. For example, progressive deficits on tasks sensitive to frontal lobe functions, such as the Wisconsin card sorting test (WCST), have been observed with increasing age (Stuss *et al.*, 1982; Shimamura, 1994). Compared with younger subjects, the elderly have difficulty maintaining set, and are impaired in their ability to maintain and/or retrieve previously learned procedural rules (Haaland *et al.*, 1987).

Neuropathological evidence provides some support for this behavioral data. For example, reductions in neuron count (Creasey and Rapoport, 1985), dendrites (Jacobs and Scheibel, 1993) and synapses are particularly evident in the PFCx with aging (Huttenlocher, 1979; Masliah *et al.*, 1993). Other age-related changes include demyelination in the periventricular white matter contiguous to the anterior horns, suggesting selective subcortical PFCx damage (Gerard and Weisberg, 1986). Also, auditory event-related potentials in normal elderly subjects resemble those produced by patients with PFCx lesions (Chao and Knight, 1996).

Studies of aged nonhuman primates support the finding that the PFCx changes with advancing age (Struble *et al.*, 1985; Bachevalier *et al.*, 1991; Peters *et al.*, 1994). One study found dendritic degeneration in the upper layers of the PFCx as well as degeneration of myelinated axons in the deep layers of cortex and white matter in aged rhesus monkeys (Peters *et al.*, 1994). Other neuropathological changes in the PFCx of aged monkeys include a high density of senile plaques (Struble *et al.*, 1985) and regional catecholamine depletion (Goldman-Rakic and Brown, 1981).

Event-related potentials (ERPs) are voltage fluctuation in the ongoing electroencephalogram (EEG) that are time locked to sensory, motor or cognitive events. The scalp reflections of intracranial synaptic activity, these potentials provide excellent temporal resolution of neural activity underlying cognitive processing in the brain (Coles *et al.*, 1990). Many investigators have utilized this noninvasive technique to make inferences about the timing and anatomical localization of attention and memory processes as well as to quantify neural changes associated with aging. The purpose of the present investigation was to examine whether normal aging altered PFCx function. We utilized a delayed-response task that required both inhibition of irrelevant inputs and control of sustained attention.

## Materials and Methods

### *Subjects*

Twelve young adults (five women and seven men, ranging in age from 20 to 22 years) and 12 elderly adults (five women and seven men, ranging in age from 57 to 71 years) participated in the study. The mean age of the young adults, students recruited from local collages, was 21.3 ± 0.8 years. The average age of the elderly adults — community-dwelling residents recruited from local volunteer groups — was 65.5 ± 4.5 years. The mean number of years of education for the young and elderly were 14.0 ± 1.0 and 14.0 ± 2.4 respectively. Raw scores on the revised Wechsler adult intelligence scale (WAIS-R) vocabulary test were 53.3 ± 8.2 for the young and 53.0 ± 11.0 for the elderly. Raw scores on the WAIS-R digit-symbol test was 69.2 ± 6.8 for the young and 48.3 ± 10.8 for the elderly. All subjects were right-handed and had no history of audiological or neurological disease. None of the subjects was taking any medication at the time of testing. Audiometric thresholds at frequencies of 125, 250, 500, 1000, 2000, 4000 and 8000 Hz were determined in each ear by the method of ascending and descending limits. Elderly subjects had significantly higher thresholds than young subjects [group effect: $F(1,22) = 43.5$, $P < 0.0001$]. To account for this, stimuli were presented binaurally at 60 dB above each subject's mean audiometric threshold. All aspects of the research were explained to the subjects, who signed statements of consent approved by the Institutional Review Boards of the Martinez Veterans Administration Hospital and the University of California at Davis. The subjects were paid for participation.

### *Experimental Procedure*

Each subject participated in two experimental sessions. The sessions took place on separate days. All subjects participated in the behavioral study first. In the behavioral study (experiment I), subjects were tested under

two separate conditions: a no-distractor and a distractor condition. In the no-distractor condition, a 50 ms 500 Hz warning tone was followed 1.2 s later by the initial sound (S1). After a variable silent period (4, 6.9, 8.8, 10.7 or 12.6 s), the test sound (S2) was presented. The silent period varied in a pseudorandom fashion, with each delay period occurring 16 times. Subjects were instructed to press a 'yes' button if S1 and S2 were identical and a 'no' button if they were different. Same or different trials were presented in random order. There were 80 trials, of which 50 were positive (S1 and S2 matched) and 30 were negative (S1 and S2 did not match). In the distractor condition, the stimulus parameters were identical to the no-distractor condition, except that the interval between the initial and test sounds was filled with 3–18 distractor tones, depending on the delay interval. Eleven possible distractor tones, ranging from 325 to 1156 Hz, 100 ms in duration (zero rise/fall time), were synthesized digitally on a personal computer. The distractor tones were randomly presented, beginning 1 s after the end of S1 and ending 1 s before onset of S2. The interstimulus interval (ISI) between the distractor tones was 400 ms. The sounds that served as S1 and S2 stimuli were drawn from a repertoire of 256 possible digitized environmental noises such as a dog bark or dishwasher noises. The duration of environmental sounds was 700 ms. (The rise/fall time varied depending of the shape of the sound.) The order of the no-distractor and distractor conditions was counterbalanced across subjects.

In the electrophysiological study (experiment II), an EEG was recorded from subjects while they performed a variation of the behavioral task described above. In order to simplify experimental procedures for signal averaging constraints of EEG recording, we employed only one delay (5 s) between S1 and S2. In the no-distractor condition, a 50 ms 500 Hz warning tone was followed 1.2 s later by S1. After a silent period of 5 s, S2 was presented. In the distractor condition, the 5 s delay period between S1 and S2 was filled with irrelevant, distracting tone pips. In experiment II, the distractors were 100 ms, 4000 Hz tone pips (zero rise/fall time). The tone pips were presented randomly at interstimulus intervals (ISIs) ranging randomly from 50 to 210 ms. High frequency auditory potentials evoked by the tone pips were recorded. There was a total of 200 trials, of which 20% were negative and 80% were positive. Positive and negative trials and distractor and no-distractor trials were presented in random order and the order of the two conditions was counterbalanced across subjects.

The experiments were conducted with the subjects seated comfortably in a reclining chair in a sound chamber (43 dB attenuated) with controlled background luminance (0.4 foot lamberts). All stimuli were presented binaurally at 60 dB above each subject's hearing level.

***ERP Recording***

An EEG was recorded from Ag/AgCl electrodes placed at Fp1, Fpz, Fp2, F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, T3, T4, T5, T6, O1, Oz and O2 according to the international 10–20 system. One additional electrode was placed 2 cm in front of Cz (Cz′) to record higher frequency middle latency auditory evoked potentials (MAEPs) elicited by the distracting tone pips. All electrodes were referred to a balanced non-cephalic, sterno-vertebral reference electrode. Vertical and horizontal eye movements were recorded from electrodes placed below and on the outer canthus of the eye. Trials contaminated by excessive eye movements or electromyographic artifacts over 100 μV were automatically rejected before averaging. The EEG was first continuously digitized at 600 Hz/channel to analyze the high frequency auditory evoked potential recorded from Cz′ and then decimated by averaging together three consecutive sampling points to reduce the effective sampling rate to 200 Hz to analyze the slower ERP components from the remaining 21 electrode sites. The EEG from Cz′ was filtered at 10–300 Hz and those from the other 21 electrodes were filtered at 0.1–100 Hz.

***Data Analysis***

Data averaging was performed off-line after sorting by stimulus type (warning tone, distracting tones, S1 presentation, S2 presentation without distractors, S2 presentation with distractors), trial (positive or negative) and response type (correctly or incorrectly identified trials). Epochs containing eye movement or an electromyographic (EMG) artifact over 100 μV were automatically rejected from the averaged data. Peak latency and amplitude were measured for wave V (4–8 ms), Na (15–20 ms), Pa (25–35 ms), Nb (35–45 ms) and Pb (45–60 ms), as well as for a sustained frontal negativity (SFN) (500–600 ms) and posterior P3 (300–500 ms). These components were identified from individual subjects and grand averaged waveforms. Peak and mean amplitude measures for the middle latency components were referred to a 50 ms prestimulus baseline while longer latency components were referred to a 200 ms prestimulus baseline. Latency measures were referred to stimulus onset.

Analysis of variance (ANOVA) and *t*-test measures were made by

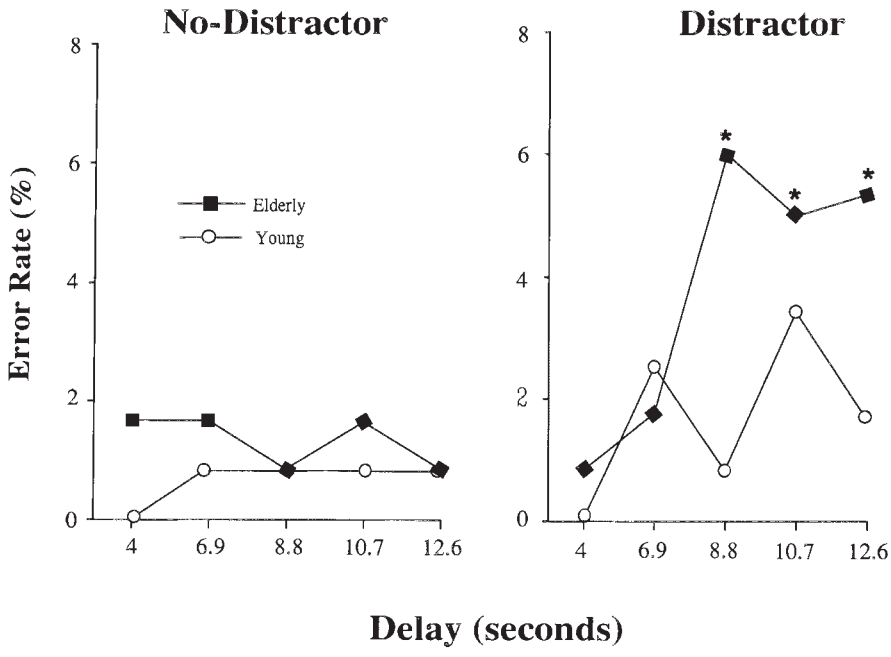


**Figure 1.** Mean percentage error for each group over positive trials in the no-distractor and the distractor conditions of experiment I. Planned comparisons revealed that elderly subjects performed worse ($P < 0.05$) than young subjects at the longer delays (>8 s) of the distractor condition than in the no-distractor condition, as indicated by the asterisks.

condition. Scalp potentials were normalized for comparisons of scalp distributions across conditions and repeated-measures ANOVAs were carried out with the Greenhouse–Geisser correction. In these cases, original degrees of freedom, the Greenhouse–Geisser coefficient, ε, and corrected probability levels are reported.

## Results

### *Performance Data*

In experiment I, elderly subjects made more errors than young subjects [aging effect: $F(1,22) = 9.15$, $P < 0.05$]. Both groups committed more errors in the distractor condition [condition effect: $F(1,22) = 12.56$, $P < 0.005$] and at the longer delays [delay effect: $F(1,22) = 3.95$, $P < 0.05$]. Although there were no group differences at the first two delay periods of the distractor condition, planned comparisons revealed that elderly subjects performed significantly worse ($P < 0.05$) than young subjects at the longer delay periods (> 8.8 s) of the distractor condition than the no-distractor condition (see Fig. 1). All subjects responded faster to positive trials [trial effect: $F(1,22) = 12.76$, $P < 0.005$] and shorter delays [delay effect: $F(4,88) = 2.62$, $P < 0.05$]. Reaction time also interacted significantly with trial by condition: [$F(1,22) = 13.14$, $P < 0.005$] and condition by delay: [$F(4.88) = 4.27$, $P < 0.005$]. In experiment II, elderly subjects again committed more errors than young subjects [aging effect: $F(1,22) = 5.66$, $P < 0.05$] and both groups made fewer errors on negative trials [trial effect: $F(1,22) = 39.18$, $P < 0.0001$].

### *MAEPs*

All subjects generated wave V, Na, Pa, Nb and Pb components to the tone pips that served as distractors. Wave V was significantly larger in amplitude [wave V: $t(22) = 3.2$, $P < 0.001$] and longer in latency [wave V: $t(22) = 2.1$, $P < 0.05$] in young subjects, while the Pa component was significantly larger in amplitude [$t(22) = 4.1$, $P < 0.0001$] in elderly subjects (see Fig. 2 and Table 1).

Because enhanced MAEPs have been associated with frontal lobe dysfunction and problems in gating irrelevant inputs (Knight *et al.*, 1989; Yamaguchi and Knight, 1990; Chao and Knight, 1995a and submitted for publication), the elderly subjects were given the WCST in another session as an approximate measure of frontal lobe function. Two dependent measures, Pa amplitude and perseverative errors on the WCST, showed positive and significant correlation ($r = 0.58$, $P < 0.049$). That is, the elderly subjects who committed the most perserverative errors on the WCST also tended to generate a larger Pa component.

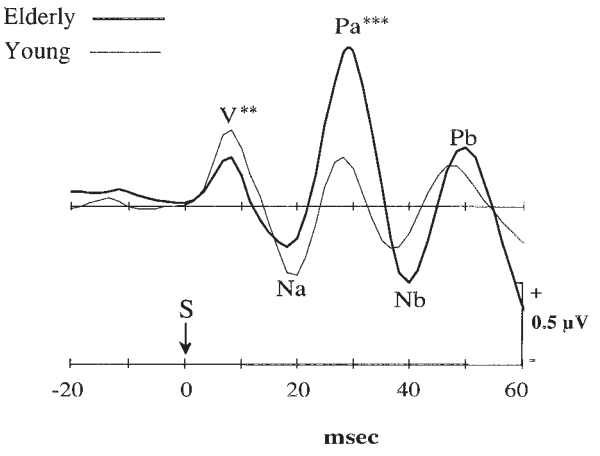


**Figure 2.** Group averaged MAEPs from elderly (thick line) and young subjects (thin line) shown at the Cz′ electrode site. ** $P < 0.001$; *** $P < 0.0001$.

### *Long Latency ERP Components*

Figure 3 shows the grand averaged ERPs elicited by S1 and correctly detected S2 with and without distractors at central electrode sites. The averages include a fronto-central N1/P2 complex and a central N2 component characteristic of auditory ERPs as well as SFN and P300 components.

The N1 component was quantified as peak amplitude from 50 to 150 ms. An analysis of variance (ANOVA), taking group (young versus elderly) and electrode sites as factors, revealed that the N1 was significantly larger in elderly subjects [$F(1,22) = 7.23$, $P < 0.05$].

### *Sustained Frontal Negativity*

Subjects generated a SFN that peaked 549 ms after stimulus onset. SFN latency was subjected to an ANOVA, taking group, trial (positive versus negative) and stimulus type (S1, S2 without distractor, S2 with distractor) as factors. The analysis yielded significant effects of trial [$F(1,22) = 6.12$, $P < 0.05$] and stimulus type [$F(1,22) = 6.13$, $P < 0.05$], and a significant interaction between trial and stimulus type [$F(1,22) = 5.65$, $P < 0.05$].

An ANOVA with stimulus type and scalp sites as factors revealed that all stimulus types elicited a SFN that was maximal in amplitude over frontal electrode sites [scalp distribution effect: $F(20,400) = 34.47$, $\varepsilon = 0.22$, $P < 0.0001$]. There was also a main effect of stimulus type [$F(2,44) = 3.79$, $P < 0.05$]. Newman–Keuls comparisons revealed that SFNs elicited by S1 stimuli were significantly ($P < 0.05$) different from SFNs elicited by S2 without distractors and by S2 with distractors. The SFN was smaller in amplitude over frontal electrode sites in elderly subjects than in young subjects [group × electrode interaction: $F(20,400) = 4.29$, $\varepsilon = 0.22$, $P < 0.005$; see Figs 3 and 4]. Further examination of the effects of aging on SFN amplitude in a separated ANOVA taking group, trial and stimulus type as factors over eight frontal electrode sites (Fp1, Fpz, Fp2, F7, F3, Fz, F4 and F8) yielded significant main effects of aging [$F(1.22) = 14.57$, $P < 0.0005$] and a significant interaction between stimulus type and age group [$F(2,44) = 6.92$, $\varepsilon = 0.71$, $P < 0.01$].

The amplitude of the SFN generated by elderly subjects was correlated with Pa amplitude and percentage of perseverative errors on the WCST. Both of these components were marginally significant (SFN versus Pa: $P = 0.053$; SFN versus WCST: $P = 0.057$).

### *P300 Component*

Although this task was not specifically designed to elicit the

**Table 1**
MAEP latency (ms ± SD) and amplitude (peak μV ± SD) for the two subject groups

| Component | Group | Latency | Amplitude at Cz′ |
|---|---|---|---|
| Na | young | 18.50 ± 0.52 | –0.36 ± 0.16 |
| | elderly | 17.42 ± 2.94 | –0.24 ± 0.14 |
| Pa | young | 28.00 ± 2.22 | 0.28 ± 0.23 |
| | elderly | 28.83 ± 2.12 | 0.86 ± 0.45*** |
| Nb | young | 36.75 ± 2.01 | –0.35 ± 0.22 |
| | elderly | 38.92 ± 2.68* | –0.57 ± 0.50 |
| Pb | young | 47.83 ± 1.64 | 0.37 ± 0.37 |
| | elderly | 46.58 ± 1.73 | 0.26 ± 0.34 |
| Wave V | young | 7.75 ± 1.14* | 0.37 ± 0.14** |
| | elderly | 6.10 ± 2.50 | 0.18 ± 0.14 |

*$P < 0.05$; **$P < 0.001$; ***$P < 0.0001$.

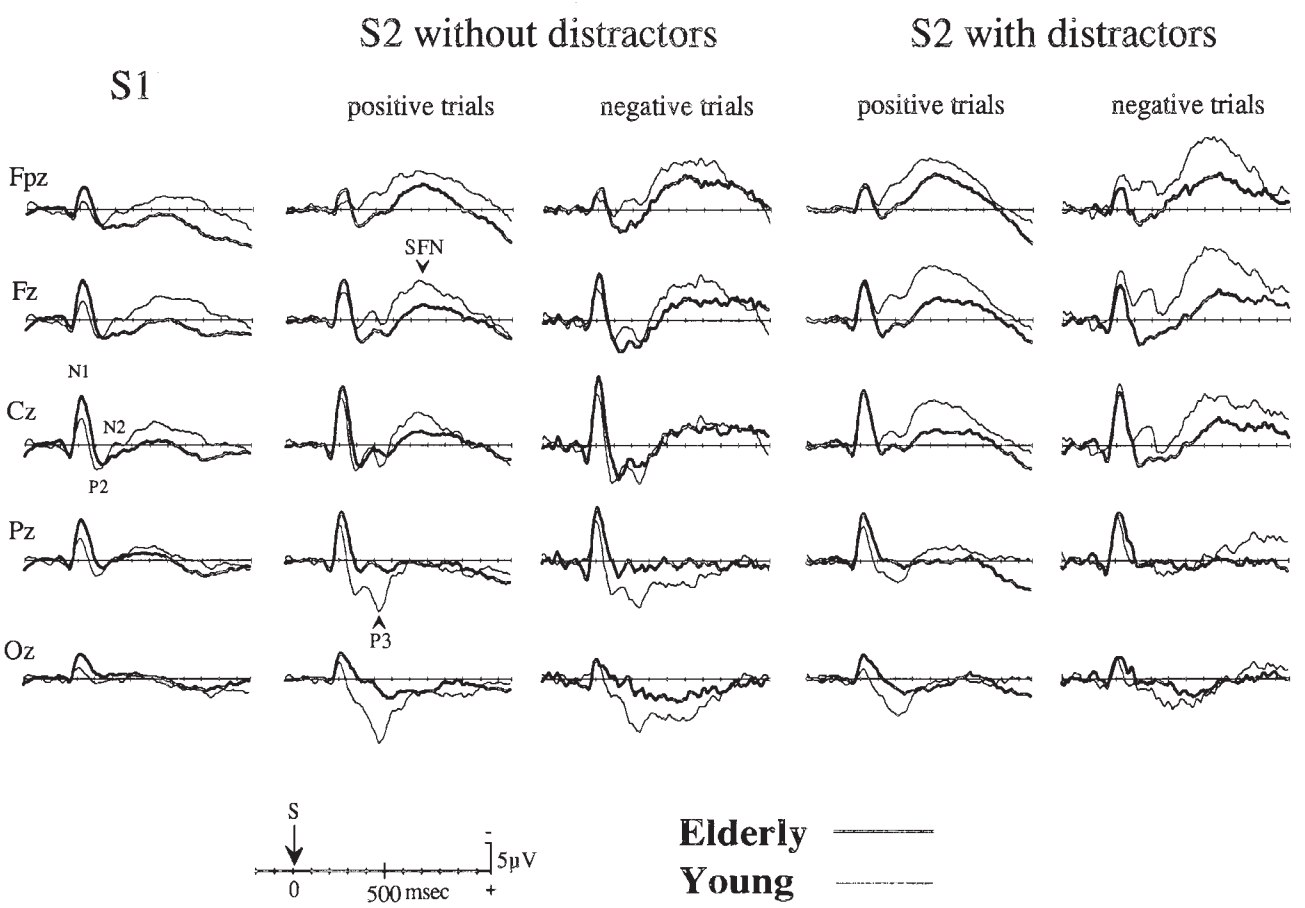


**Figure 3.** Grand averaged waveforms for correctly identified S1, S2 without distractors and S2 with distractors at central electrode sites. Note the enhanced N1 and reduced SFN and P3 components in the elderly compared with the young.

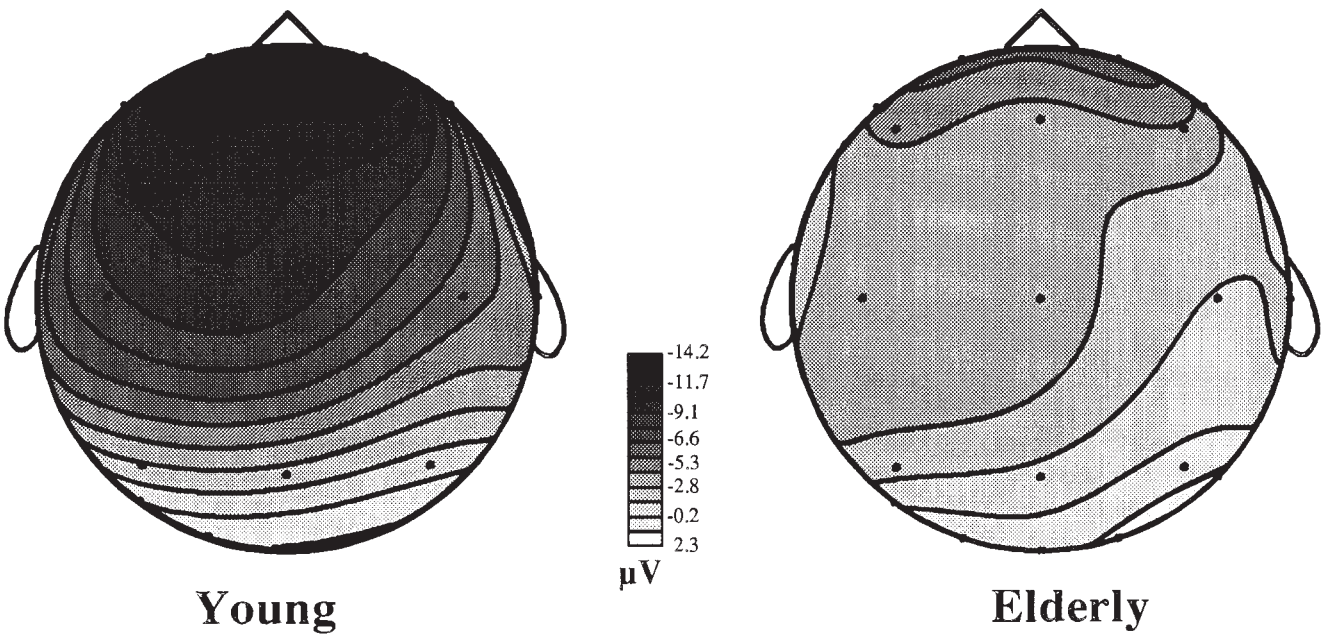


**Figure 4.** Scalp distribution of the SFN elicited by correctly identified S2 stimuli without distractors for young and elderly subjects. The darker shade represents maximal negative voltages and the lighter represents maximal positive voltages. Note that the SFN is reduced over frontal sites in the elderly.

P300 component, young subjects generated a P3 that peaked at 344 ms and elderly subjects generated a P3 that peaked at 442 ms after onset of S2 stimuli [aging effect: $F(1,22) = 264.1$, $P < 0.0001$]. An ANOVA taking stimulus type, trial and electrode sites as factors yielded a significant main effect of stimulus type [$F(1,22) = 30.57$, $P < 0.0001$]. Newman–Keuls comparisons revealed that S1 was significantly ($P < 0.05$) different from S2 without distractors and S2 with distractors. Aging reduced the amplitude of P3 [$F(1,22) = 7.83$, $P < 0.05$].

## Discussion

The present study found electrophysiological evidence of a decline in efficiency of the inhibitory mechanism in elderly subjects. With advancing age, most auditory evoked potentials become smaller in amplitude (Jerger and Hall, 1980; Rowe and Kahn, 1987) and delayed in latency (Fujikawa and Weber, 1977; Thomsen *et al.*, 1978; Allison *et al.*, 1984). Accordingly, wave V, which originates from the inferior colliculus (Stockard and Rossiter, 1977), was reduced in amplitude and longer in latency in elderly subjects. In contrast, the Pa component of the MAEP, likely representing primary auditory cortex activation (Kraus *et al.*, 1982; Woods *et al.*, 1985, 1987; Pelizzone *et al.*, 1987), was enhanced in elderly subjects. This indicates that sensory inputs were less suppressed in the elderly than in the young.

Other investigators have also found that the amplitude of the Pa component grows linearly with age, becoming significantly larger in older subjects (Woods and Clayworth, 1986; Jerger *et al.*, 1988; Chambers and Griffiths, 1991; Chambers, 1992). Woods and Clayworth (1986) suggested that the enhancement of the Pa component with age may result from reduced inhibitory control of afferent stimulation. This explanation has also been offered by other investigators for the age-related amplitude increase in middle latency brain potentials in the visual and somatosensory modalities (Straumanis *et al.*, 1965; Drechsler, 1978).

The PFCx exerts suppression over multiple subcortical and cortical regions (Edinger *et al.*, 1975; Alexander *et al.*, 1976). Blocking a PFCx–thalamic mechanism results in increased primary auditory evoked responses in the cat (Skinner and Yingling, 1976; Yingling and Skinner, 1976). In humans, damage to the dorsolateral PFCx results in enhanced MAEP amplitudes (Knight *et al.*, 1989; Chao and Knight, 1995a and submitted for publication). Taken together, these data suggest that the increased MAEPs in elderly subjects was due to a loss of PFCx suppression over inputs to primary auditory regions.

Further evidence linking frontal lobe dysfunction and enhanced MAEPs comes from the finding that elderly subjects with the highest percentage of perseverative errors on the WCST, a putative measure of frontal lobe function, also tended to generate larger MAEP components. Patients with lesions in the dorsolateral PFCx also generate enhanced MAEPs and show behavioral evidence of difficulty in gating task-irrelevant stimuli (Chao and Knight, 1995a,b and submitted for publication).

Compared with younger subjects, elderly subjects had significantly reduced amplitude SFNs. Evidence from numerous studies suggests that a slow wave activity recorded from the scalp originates primarily in the cortex from excitatory post-synaptic potentials (EPSPs) and inhibitory post-synaptic potentials in the dendritic trees of cortical pyramidal neurons (Caspers *et al.*, 1980; Speckmann *et al.*, 1984; Elbert and Rockstroh, 1987; Lutzenberger *et al.*, 1987). Although the precise intracellular mechanisms underlying the generation of ERP components are not know, scalp recorded negative slow waves have been proposed to be manifestations of synchronized EPSPs in the upper cortical layers (Birbaumer *et al.*, 1993). It has been suggested that diminished negativity at the front of the scalp in older subjects may be associated with structural changes in the brain (Pfefferbaum *et al.*, 1979, 1980; Ford and Pfefferbaum, 1980, 1985). A recent study found evidence of degeneration of dendrites in the upper layers, especially layer 1, of the frontal cortex in aged rhesus monkeys (Peters *et al.*, 1994). Aged humans may undergo similar upper layer cortical changes which underlie the bilateral reduction of the SFN in elderly subjects in the present study. It is also possible that aging results in a loss of modulatory catecholaminergic, dopamergic or serotonergic inputs to the PFCx.

Behaviorally, elderly subjects committed more errors at the longer delays in the interference condition than in the no-distractor condition in experiment I. This is consistent with reports that elderly subjects demonstrate memory impairments at long retention intervals (Craik, 1977) and with increasing numbers of intervening items (Sekuler and Ball, 1986; McDowd and Oseas-Kreger, 1991). In experiment II, where the delay between S1 and S2 was only 5 s, there was no significant group by condition interaction. This is consistent with the findings of Bartus and his colleagues (1978), which showed that while aged monkeys are impaired in the delayed response task at progressively longer delays, they do not show deficits when the delay is 5 s or shorter.

One of the main functions of the attentional system is to enable cognitive processing to focus on stimulus attributes and ignore or inhibit irrelevant aspects. The inability to accomplish this segregation results in a vulnerability to distraction and a concomitant inefficiency in dealing with relevant information. There are likely multiple subcomponents to the overall process of effective attention. Some researchers have suggested that older subjects are more susceptible to distractibility due to a decline in the efficiency of inhibitory mechanisms (Hasher and Zacks, 1988). Weakened inhibitory control results in a variety of effects, such as a more 'cluttered' and therefore smaller working memory (Hasher and Zacks, 1988) and greater vulnerability to distraction (McDowd *et al.*, 1995). In the present study, elderly subjects were not impaired by a long retention interval in the no-distractor condition in experiment I; however, they were significantly impaired by long retention intervals in the interference condition. This suggests that the decline in the efficiency of suppressive control in elderly subjects contributed to impaired sustained attention in these subjects as well. Electrophysiological evidence suggests that age-related PFCx changes my be responsible for this loss of suppressive capacity in the elderly. Elderly subjects generated reduced amplitude SFNs compared with young subjects. The SFN has been associated with effortful processing and sustained attention (Chao *et al.*, 1995; Chao and Knight, 1996). Scalp topographical (Chao *et al.*, 1995; Chao and Knight,1996) and lesion data (Chao and Knight, 1995a and submitted for publication) support a role of the dorsolateral PFCx in generation of the SFN. Taken together, these data suggest that integrity of the PFCx is critical for gating irrelevant information which is a crucial component for the maintenance of sustained attention.

## Notes

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