Contribution of Human Prefrontal Cortex to Delay Performance

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Abstract

■ Neurological patients with focal lesions in the dorsolateral prefrontal cortex and age-matched control subjects were tested on an auditory version of the delayed-match-to-sample task employing environmental sounds. Subjects had to indicate whether a cue (S1) and a subsequent target sound (S2) were identical. On some trials, S1 and S2 were separated by a silent period of 5 sec. On other trials, the 5-sec delay between S1 and S2 was filled with irrelevant tone pips that served as distractors. Behaviorally, frontal patients were impaired by the presence of distractors. Electrophysiologically, patients generated enhanced primary auditory cortex-evoked responses to the tone pips, supporting a failure in inhibitory control of sensory processing after prefrontal damage. Intrahemispheric reductions of neural activity generated in the auditory association cortex and additional intrahemispheric reductions of attention-related frontal activity were also observed in the prefrontal patients. Together, these findings suggest that the dorsolateral prefrontal cortex is crucial for gating distracting information as well as maintaining distributed intrahemispheric neural activity during auditory working memory. ■

INTRODUCTION

One of the main functions of the attentional system is to enable cognitive processing to focus on significant stimulus attributes while ignoring or inhibiting irrelevant aspects of the stimulus. The inability to accomplish this segregation results in a vulnerability to distraction and a concomitant inefficiency in dealing with relevant information. Evidence from a variety of experiments suggests that the prefrontal cortex is critical for gating or filtering out irrelevant information. Early research showed that monkeys with bilateral frontal lesions involving the sulcus principalis were severely impaired at delayed discrimination tasks (Jacobsen, 1935). These results were initially interpreted as an immediate memory deficit until subsequent reports revealed that when the animals were kept in darkness during the delay period, their performance improved to near preoperative levels (Malmo, 1942). These observations led Malmo to propose that lesions to the sulcus principalis resulted in attentional deficits that rendered the monkeys unable to inhibit irrelevant visual inputs during the delay.

Neuropsychological evidence suggests that humans with prefrontal damage are also unable to focus attention on task-relevant stimuli (Fuster, 1980; Luria, 1966; Damasio, 1985). Patients with prefrontal damage are susceptible to proactive interference and perform poorly on neuropsychological tests that require response inhibition such as the Wisconsin Card Sorting Test, the Stroop Interference Test, and the Self-Ordered Pointing Test (Shimamura, 1995; Stuss et al.,1982). Recently it has been shown that patients with lesions in the dorsolateral prefrontal cortex were impaired at matching two environmental sounds when distractors intervened between the cue and target (Chao & Knight, 1995). In another study, patients with resections of the dorsomedial and dorsolateral frontal cortex were impaired at detecting multiple visual targets imbedded among distractors (Richer et al., 1993).

Neurophysiological studies have demonstrated a net inhibitory output from the prefrontal cortex to cortical and subcortical regions (Alexander, Newman, & Symmes, 1976; Edinger, Siegel, & Troiano, 1975). In cats, it has been shown that the prefrontal cortex exerts modality-specific suppression of sensory transmission through the thalamic relay nuclei (Skinner & Yingling, 1976; Yingling & Skinner, 1976). When prefrontal-thalamic pathways were blocked, the amplitudes of primary auditory-evoked responses became enhanced. The authors suggested that this represented a disinhibition of neural activity in the primary auditory cortex. Experiments have been conducted to assess whether disinhibition of the primary sensory cortices occur after prefrontal damage in humans. These studies reported electrophysiological evidence of disinhibition of the primary auditory (Knight, Scabini, & Woods, 1989) and somatosensory cortex (Yamaguchi & Knight, 1991) in patients with prefrontal damage.

Event-related potentials (ERPs) are voltage fluctuations in the electroencephalogram (EEG) that are time locked

to sensory, motor, or cognitive events. These volume-conducted scalp measures of synaptic activity are associated with specific cognitive processes such as attention, memory, motor preparation, and linguistic processes (Rugg & Coles, 1995). A frontally distributed negative potential (referred to as the SFN in previous publications) has been recorded in several ERP studies of auditory working memory (Chao, Nielsen-Bohlman, & Knight, 1995; Chao & Knight, 1996; Chao & Knight, 1997a, 1997b). Increasing task demand enhances the amplitude of this frontal negativity, and absence of attention abolishes the potential altogether. For this reason, the SFN has been associated with performance effort and sustained attention.

The goal of the present study was to investigate the role of the human dorsolateral prefrontal cortex in inhibiting irrelevant inputs as well as controlling sustained attention. If the dorsolateral prefrontal cortex is necessary for gating irrelevant inputs, behaviorally, prefrontal patients should be impaired in the presence of auditory distractors. Electrophysiologically, these patients should show evidence of primary auditory cortex activity disinhibition as well. If the dorsolateral prefrontal cortex is also important for sustained attention, electrophysiologically, the prefrontal patients would be expected to generate abnormal SFNs. To address these issues, behavioral and electrophysiological data were recorded from a group of patients with lesions confined to the dorsolateral prefrontal cortex (six left, four right) and age-matched control subjects while they performed an auditory delayed-match-to-sample task.

RESULTS

Behavioral Results

Behavioral data are summarized in Table 1. RT data were subjected to a three-way analysis of variance (ANOVA) with factors of group (control vs. frontals), condition (no distractor vs. distractor), and trial (positive vs. negative) as factors. Significant main effects of group ($F(1, 18) = 11.8, p < 0.003$), condition ($F(1, 18) = 4.8, p < 0.05$), and trial ($F(1, 18) = 40.2, p < 0.0001$) were obtained. Control subjects were faster than frontal patients, and all subjects were faster for the no distractor than for the distractor condition and for positive than for negative trials. Accuracy data were analyzed by a three-way ANOVA with factors of group, condition, and trial. Patients committed more errors than their age-matched counterparts ($F(1, 18) = 15.2$, $p < 0.005$). There was no main effect of condition; however, the interaction between group and condition was significant ($F(1, 18) = 5.1$, $p < 0.04$) because patients committed more errors on the distractor condition than did controls.

Electrophysiological Results

Middle-Latency Auditory-Evoked Potentials

Figure 1 shows the middle latency auditory-evoked potentials (MAEPs) elicited by the tone pips that served as distractors. All subjects generated wave V, Na, Pa, Nb, and Pb potentials. The Na component was larger in amplitude ($t = 2.5, p < 0.03$) and longer in latency ($t = 2.7$, $p < 0.02$) in frontal patients compared to age-matched controls (see Figure 1 and Table 2). Although there was a trend for patients to generate larger amplitude Pa components than control subjects, this difference was not significant ($p = 0.06$). However, Pa amplitude was significantly correlated with the frontal patients' task performance ($r = 0.86, p < 0.05$). That is, patients with the worst behavioral performance also generated the largest Pa components.

Long-Latency Event-Related Potentials

The N1 was quantified as peak amplitude from 50 to 150 msec and subjected to an ANOVA taking group (frontals

Table 1. Mean Reaction Time in Milliseconds and Mean Error Rate for Control Subjects and Frontal Patients (± *SD*).

			Performance	
Group	*Condition*	*Trial*	*Reaction Time (msec ± SD)*	*Accuracy (error rate ± SD)*
Control	No Distractor	Positive	822 ± 46	2.4 ± 0.3
		Negative	949 ± 58	0.6 ± 0.6
	Distractor	Positive	814 ± 46	2.6 ± 0.6
		Negative	919 ± 45	1.2 ± 0.8
Frontal	No Distractor	Positive	1018 ± 50	3.4 ± 0.6
		Negative	1290 ± 76	7.6 ± 3.2
	Distractor	Positive	979 ± 51	8.3 ± 2.4
		Negative	1188 ± 69	8.2 ± 2.6

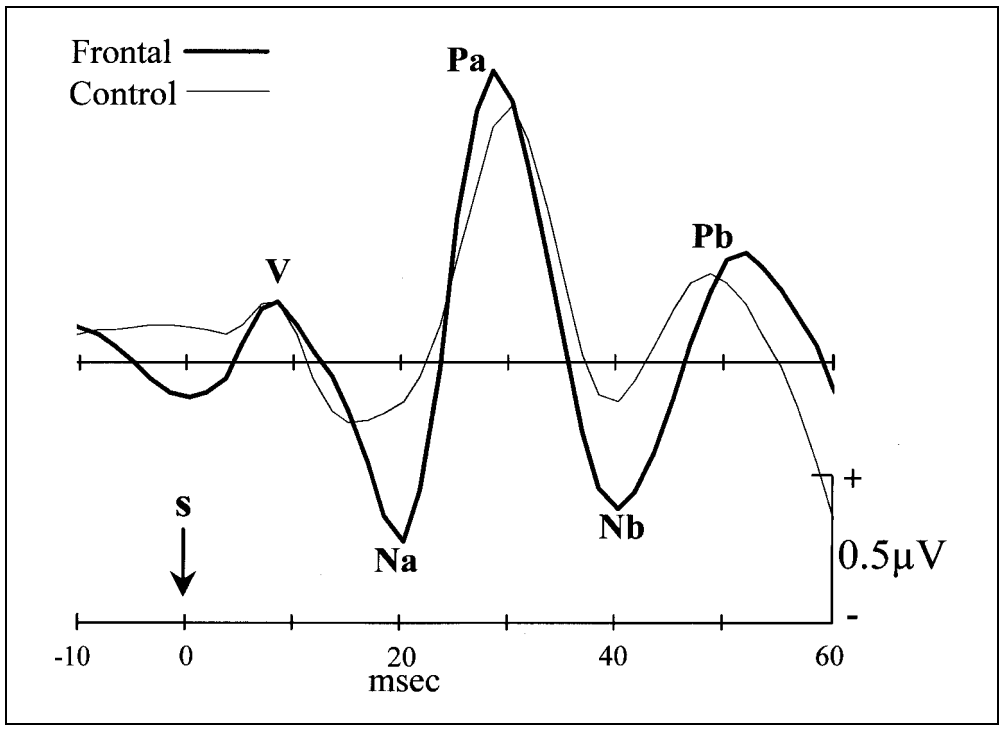

Figure 1. MAEPs are shown for controls (n = 7, thin line) and frontal patients (n = 7, thick line). The MAEPs are shown from the Cz' electrode site. Although a 10-msec baseline is shown here, the recording epoch actually included a 50-sec prestimulus baseline.

vs. controls) and electrode as factors. The N1 potential was reduced over the lesioned hemisphere with reductions maximal over posterior sites (for location: controls vs. frontals: $F(21, 240) = 3.79$, $\varepsilon = 0.22$, $p < 0.007$; at restricted posterior temporal sites: $F(1, 12) = 13.1$, $p < 0.005$). See Figure 5. When the amplitude of the N1 at lateral electrodes was subjected to a separate ANOVA to evaluate scalp distribution and laterality, there was a significant interaction between group and hemisphere ($F(1, 12) = 12.0$, $p < 0.005$). Latency of the N1 component was unaffected by lesions.

Figures 3 through 5 show grand-averaged ERPs elicited by S1 and correctly detected S2 with and without distractors. The averages include a fronto-central N1/P2 complex characteristic of auditory ERPs, a frontally distributed negative potential, and P300 components.

Subjects generated a frontally distributed negative potential (referred to as the sustained frontal negativity, or the SFN, in previous reports) that peaked at 515 msec poststimulus onset. SFN latency was analyzed in an ANOVA taking group (frontals vs. controls), condition (no distractor vs. distractor), and stimulus type (S1, S2

Table 2. MAEP Latency (milliseconds ±*SD*) and Amplitude (Peak microvolts ±*SD*) for Frontal Patients and Control Subjects.

Component	*Group*	*Latency*	*Amplitude at Cz′*
Na	control	15.86 ± 1.68	–0.21 ± 0.14
	frontal	18.43 ± 0.53[a]	–0.47 ± 0.24[a]
Pa	control	29.29 ± 2.56	0.83 ± 0.29
	frontal	28.14 ± 1.07	0.85 ± 0.29
Nb	control	39.00 ± 3.83	–0.31 ± 0.29
	frontal	40.14 ± 3.02	–0.64 ± 0.41
Pb	control	47.00 ± 1.73	0.32 ± 0.48
	frontal	48.14 ± 1.46	0.32 ± 0.52
Wave V	control	4.71 ± 2.29	0.18 ± 0.15
	frontal	7.14 ± 2.41	0.19 ± 0.11

[a] $p < 0.05$.

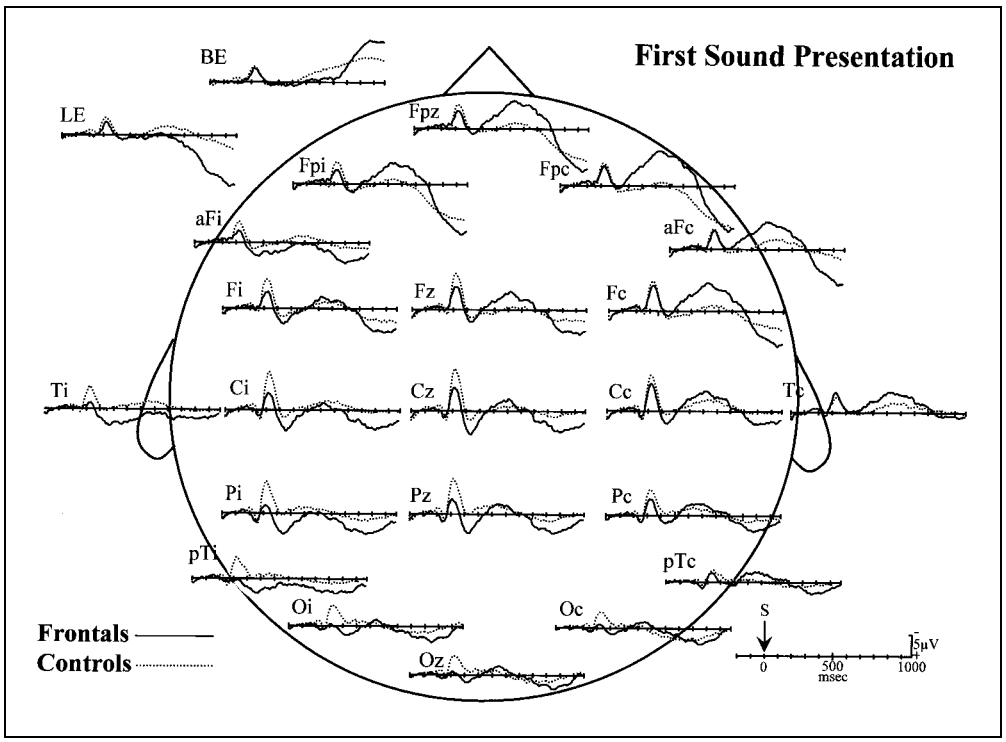

Figure 2. The group-averaged event-related potentials from control (dotted line) and frontal patients (solid line) to the target stimuli (S1). The patient data are presented as a function of electrode site ipsilateral or contralateral to lesion (e.g., Ci includes C3 from left-lesioned patients and C4 from right-lesioned patients). Note the focal reduction of the frontal negative component over the site of lesion in patients.

with distractors, and S2 without distractors) as factors. There was a significant main effect of stimulus type ($F(4, 48) = 7.7, p < 0.0001$) because S1 elicited the shortest-latency SFNs, whereas S2 with distractors elicited the longest-latency SFNs. There was a significant interaction of group X stimulus type ($F(4, 48) = 6.5, p < 0.0001$) because frontal patients generated longer-latency SFNs to S1 than did control subjects.

The SFN was quantified as peak amplitude from 500 to 600 msec and subjected to an ANOVA taking stimulus type and scalp sites as factors. The analysis revealed that all stimulus types elicited a sustained negative wave that

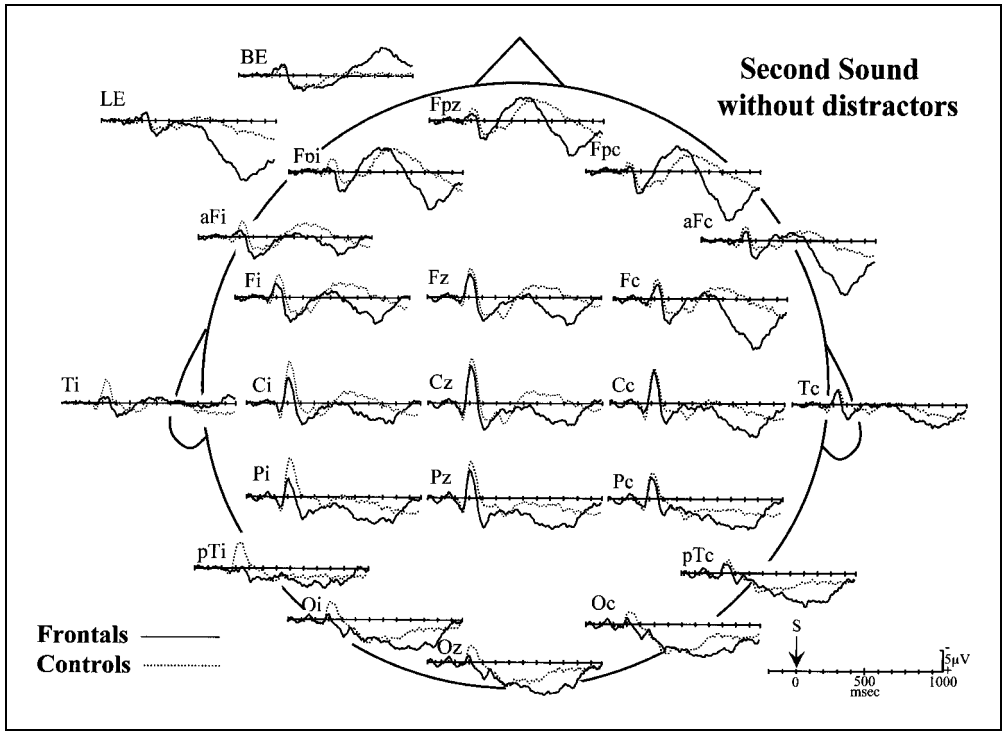

Figure 3. The group-averaged event-related potentials to correctly detected cue (S2) without distractors (positive trials).

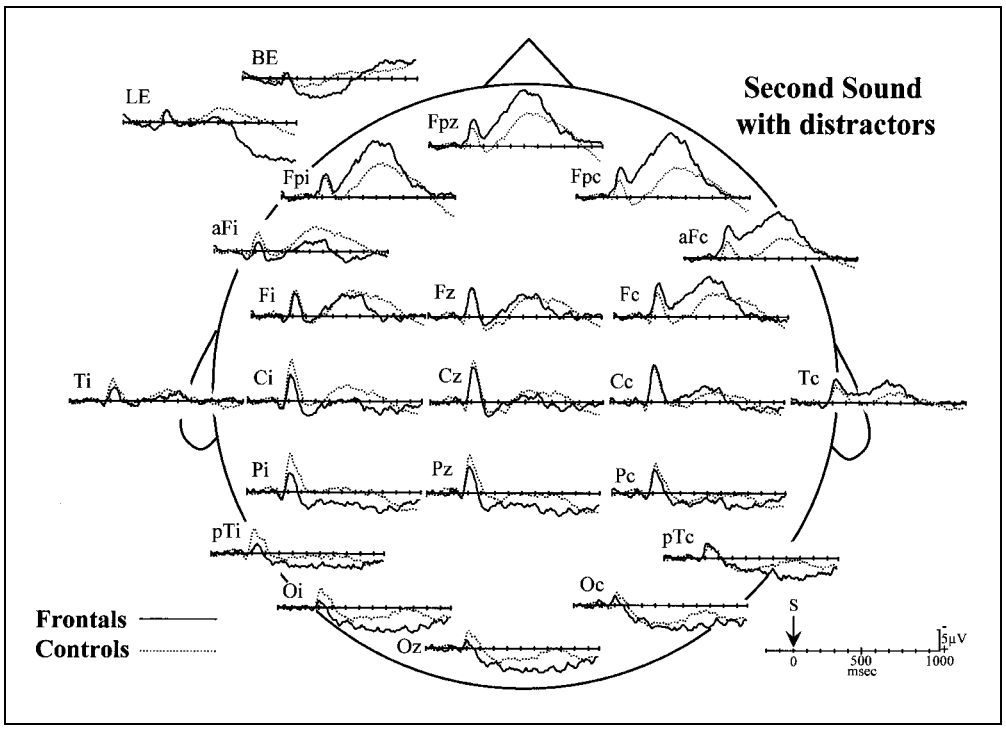

Figure 4. The group-averaged event-related potentials to correctly detected cue (S2) with distractors (positive trials).

was maximal in amplitude over frontal electrode sites (for scalp distribution, $F(20, 240) = 16.0$, $\varepsilon = 0.20$, $p < 0.001$). We further examined SFN amplitude in a separate ANOVA taking group, trial, condition, and stimulus type as factors over eight frontal electrode sites (Fp1, Fpz, Fp2, F7, F3, Fz, F4, and F8). This analysis yielded a significant main effect of stimulus type ($F(2, 24) = 4.9$, $\varepsilon = 0.86$, $p = 0.02$) and significant interactions between stimulus type and group ($F(2, 24) = 6.2$, $\varepsilon = 0.86$, $p = 0.01$) and between electrode and group ($F(7, 84) = 4.0$, $\varepsilon = 0.35$, $p = 0.02$).

The main effect of stimulus type was due to the fact that S1 elicited the smallest-amplitude SFNs, whereas S2 with distractors elicited the largest-amplitude SFNs. Newman-Keuls comparisons revealed that all three types of stimuli (S1, S2 without distractors, S2 with distractors)

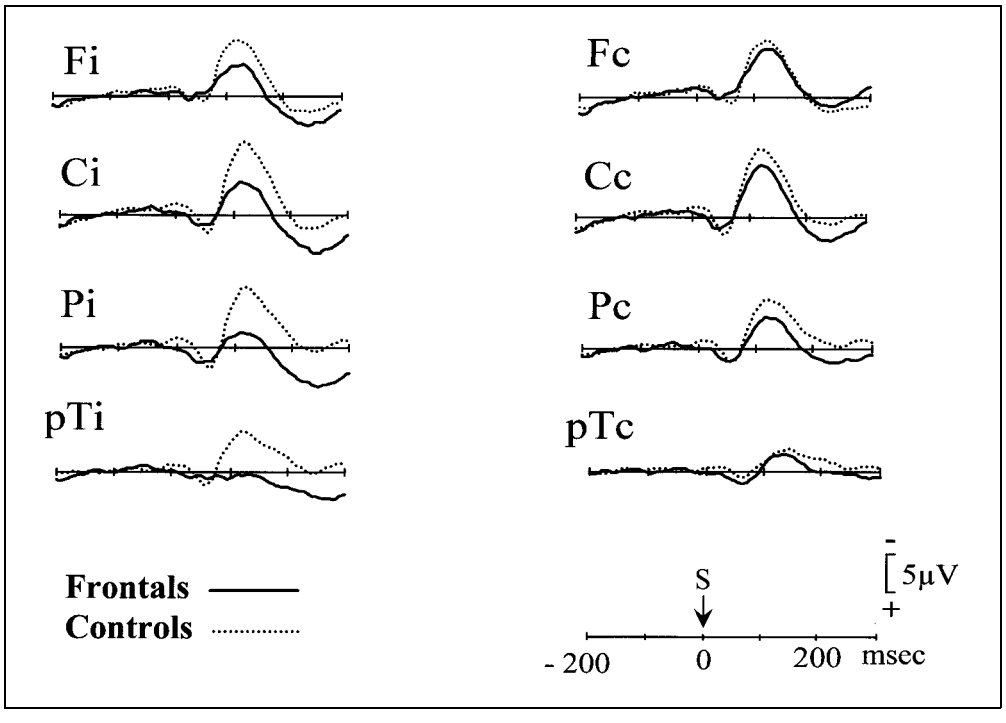

Figure 5. The auditory N1 potential is shown at lateral electrode sites for controls (dotted line) and frontal patients (solid line). Note the reduction in N1 amplitude at ipsilateral electrode sites in frontal patients, especially over posterior temporal sites.

were significantly different from each other ($p < 0.05$). The interaction between stimulus type and group was due to the fact that patients did not show the systematic increase in SFN amplitude for S1, S2 without distractors, and S2 with distractors that control subjects did (see Figure 6). Patients generated the largest SFNs to S1 and to S2 with distractors and reduced amplitude SFN to S2 without distractors. The interaction between electrode and group reflects the fact that the SFN was reduced in amplitude over the side of the lesion in the patients. The lateral frontal electrodes were subjected to a second ANOVA to evaluate the laterality of the SFN in frontal patients. The analysis revealed a main effect of hemisphere ($F(1, 6) = 6.4, p < 0.05$). Further analysis revealed that the SFN was both reduced over the site of lesion (frontals vs. controls at Fi: $t = 2.1, p < 0.05$) and increased over the non-lesioned cortex (frontals vs. controls at Fc: $t = 2.6, p < 0.05$; see Figures 7 and 8).

Subjects generated P3a and P3b components to S2 stimuli; however, they did not generate P300 components to S1 (for stimulus type effect: $F(2, 24) = 5.8, p = 0.01$). Newman-Keuls comparisons revealed that S1 was significantly different from S2 with and without distractors ($p < 0.05$). Subjects generated a fronto-central P3a component that peaked 339 msec after onset of S2 stimuli. There were no significant differences between the amplitude or the latency of the P3a component between patients and controls. Subjects also generated a parietal-occipital P3b to the S2 stimuli. The P3b component peaked at 407 msec after stimulus onset in control subjects, whereas the P3b peaked at 570 msec post-stimulus onset in prefrontal patients. There was no significant difference in P3b amplitude between patients and controls; however, the difference in P3b latency was significant between patients and controls ($F(1, 12) = 13.0, p < 0.005$).

DISCUSSION

In the current study, patients with unilateral lesions confined to the dorsolateral prefrontal cortex exhibited heightened interference effects, performing poorly on trials in which distractors were interposed between the cue and target. This is in accord with animal experiments that have demonstrated that lesions to the sulcus principalis render monkeys increasingly susceptible to irrelevant stimuli (Bartus & Levere, 1977; Zola-Morgan & Squire, 1986),

MAEPs are stimulus-dependent neural activity that originate from auditory pathways and primary auditory cortical regions (Kraus, Ozdamar, & Stein, 1982; Pelizzone et al., 1987; Woods, Clayworth, & Knight, 1985; Woods, Clayworth, Knight, Simpson, & Naeser, 1987). These components typically occur within 60 msec after stimulus onset. Prefrontal patients generated enhanced Na components of the MAEP compared to normal controls in the current study. Because there were no significant differences between patients' and controls' audiometric thresholds or in the amplitude of wave V, which originates in the inferior colliculus (Stockard & Rossiter, 1977), peripheral factors could not have been responsible for the enhanced Na component in frontal patients. Previous studies have reported that patients with comparable-size lesions in the parietal and temporal lobes generate normal or reduced amplitude MAEPs (Kraus, Ozdamar, & Stein, 1982; Woods, Clayworth, Knight, Simpson, & Naeser, 1987). This suggests that nonspecific brain lesion effects are not likely to be responsible for the observed increase in Na amplitude in frontal patients.

The prefrontal cortex exerts suppression over multiple cortical and subcortical regions (Alexander et al., 1976; Edinger et al., 1975). Blocking a prefrontal-thalamic mechanism resulted in increased primary auditory

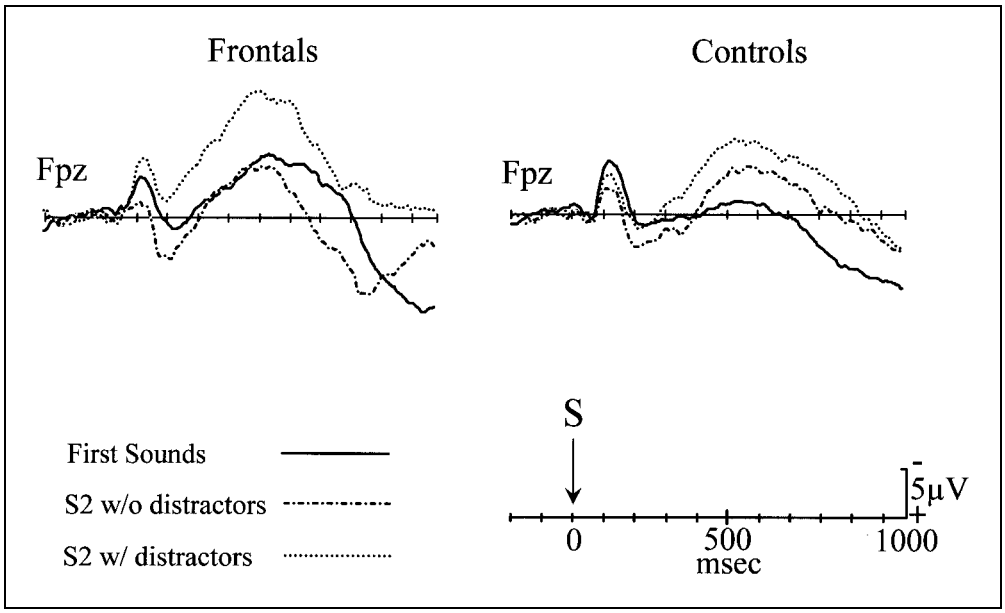

Figure 6. The effect of different stimuli on the frontal negative component is shown here. The waveforms elicited by S1 (solid line), correctly detected S2 without distractors (dashed line), and correctly detected S2 with distractors (dotted line) are plotted here at Fpz. Note the systematic reduction in negativity from S2 with distractors to S2 without distractors to S1 in control subjects.

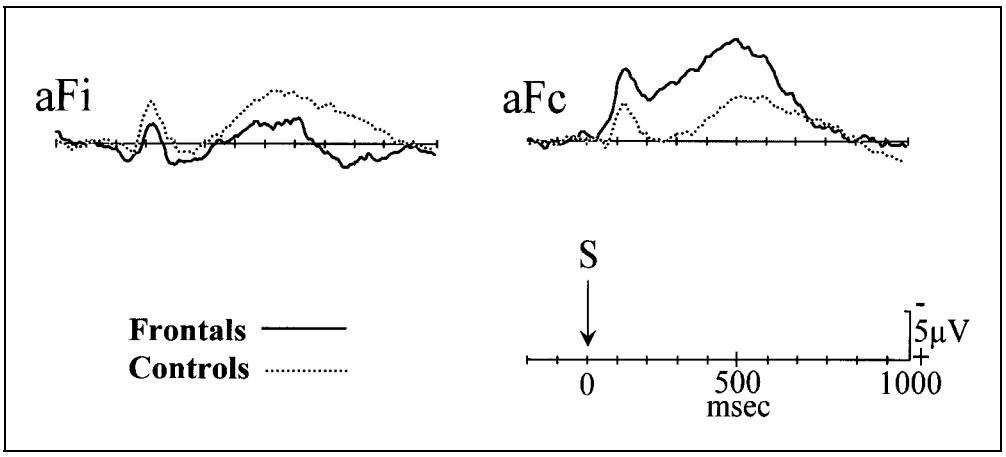

Figure 7. The frontal negative component at two frontal electrode sites. The data are presented from Fp1 (left trace) and Fp2 (right trace) in controls. In the patients, aFi shows data from Fp1 in left-lesioned patients and Fp2 in right-lesioned patients. Note that the negative component is reduced at the site ipsilateral to the lesion and enhanced at the site contralateral to the lesion in the patients.

evoked responses in cats (Skinner & Yingling, 1976; Yingling & Skinner, 1976). In humans, damage to the dorsolateral prefrontal cortex results in enhanced MAEP amplitudes (Knight et al., 1989; Chao & Knight, 1997a). Taken together, these data suggest that the current enhancement of Na amplitude in frontal patients was due to a loss of prefrontal cortical suppression over inputs to primary auditory regions.

The N100 component measures overlapping neural activity in auditory association cortex (Woods, 1995). In the current study, patients with dorsolateral prefrontal lesions generated smaller N100 components than age-matched controls. This result may relate to the finding that patients with prefrontal lesions are impaired in their ability to focus attention on task-relevant stimuli (Fuster, 1980; Damasio, 1985; Woods & Knight, 1986). Results from dichotic listening experiments have shown that focusing attention on tones in one ear can lead to a systematic enhancement of evoked potentials to all stimuli in that ear (Hillyard, Hink, Schwent, & Picton, 1973). When this auditory selective-attention effect was examined in patients, abnormalities were detected in patients with both left and right prefrontal damage (Knight, Hillyard, Woods, & Neville, 1981). In the current study, the N100 component was markedly reduced over posterior sites in the lesioned hemisphere of the patients. Similar

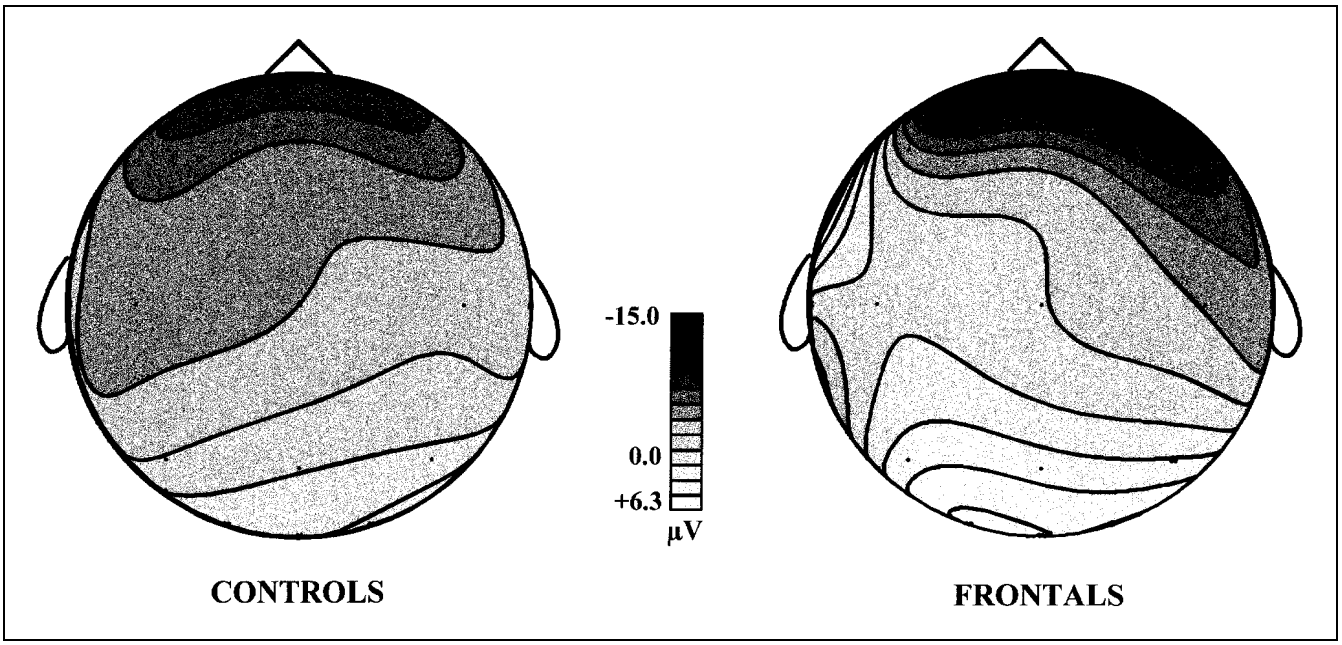

Figure 8. The topographical map of the frontal negative component (time window 525 to 575 msec) elicited by S2 with distractors. For this figure, all the patient's lesions have been reflected onto the left hemisphere. Note that the frontal negative component is enhanced over the nonlesioned hemisphere and is focally reduced over the lesioned hemisphere in the patients. All electrodes were referred to a balanced noncephalic, sterno-vertebral reference.

effects of ipsilateral reduction of neural activity in visual association cortex activity have been observed after prefrontal damage (Knight, 1997). These findings provide evidence that the prefrontal cortex provides facilitory input to neural activity in distant intrahemispheric association cortex regions.

All subjects generated a frontally distributed negative potential (referred to as the SFN in previous publications) to S1 and S2 stimuli. In previous studies of auditory working memory, increasing task demand resulted in an enhancement of the frontal negativity, whereas absence of attention abolished the potential (Chao & Knight, 1996; Chao & Knight, 1997a, 1997b; Chao, Nielsen-Bohlman, & Knight, 1995). For this reason, the frontal negative component has been associated with performance effort and sustained attention. In the current study, there was a focal reduction of the frontal negativity over the region of damage in the patients. The precise intracellular mechanisms underlying generation of ERP components are not known; however, evidence from numerous studies suggests that scalp-recorded negative slow waves originate primarily in the upper cortical layers due to depolarization in the dendritic trees of pyramidal neurons (Birbaumer, Elbert, Canavan, & Rockstroh, 1993; Caspers, Speckmann, & Lehmenkuhler, 1980; Speckmann et al., 1984; Lutzenberger, Elbert, & Rockstroh, 1987). The fact that the frontal negativity component was focally reduced over the region of the damage suggests that the dorsolateral prefrontal cortex is largely responsible for the generation of the frontal negative component. The frontal negative component was not reduced at midline or at contralateral sites in patients; rather it was enhanced over the nonlesioned hemisphere as well as over frontal polar regions. Enhancement of the frontal negative component over nonlesioned regions may be indicative of compensatory activity in these areas of the brain.

In conclusion, this study has shown that patients with unilateral lesions in the dorsolateral prefrontal cortex are impaired in their ability to filter out task-irrelevant information during delay periods. Enhancement of the primary auditory cortical response to task-irrelevant distractors suggests that prefrontal damage disrupts early inhibitory modulation of inputs to the primary auditory cortex. This disruption may result in increased noise in the system and, thus, contribute to the behavioral deficits observed in these patients. In addition, prefrontal lesions also resulted in decrements of neural activity to task-relevant stimuli in prefrontal and auditory association cortices. This suggests that damage to the prefrontal cortex not only affects the patients' ability to ignore irrelevant inputs but also affects their ability to focus attention on significant stimulus attributes. These findings provide evidence that the prefrontal cortex not only exerts inhibitory modulation over primary cortices but also provides facilitory input to neural activity in distant intrahemispheric association cortical regions. Damage to these systems may underlie the working memory deficits observed after prefrontal damage.

METHODS

Subjects

Ten patients with CT or MRI-confirmed unilateral lesions involving the dorsolateral prefrontal cortex (six left-sided, four right-sided) were selected from the outpatient population in the U.C. Davis Department of Neurology. The average lesion volume was 42.1 cm^3. All lesions were at least 6 months old and centered in Brodmann areas 9, 44, 45, and 46. Figure 9 shows the reconstruction of all ten patients.

All but one left prefrontal patient displayed mild-to-moderate nonfluent aphasia at the time of testing. Comprehension was intact in all patients. Two patients had moderate weakness in their right upper extremity. All patients used the hand ipsilateral to their lesion to press buttons to give their responses.

Behavioral measures were obtained from 10 patients (6 males, 4 females; mean age: 69.3 $\pm$ 8.8 years) and 10 age-matched control subjects (6 males, 4 females; mean age: 68.3 $\pm$ 7.4 years). Middle- and long-latency auditory ERPs were obtained from 7 of the 10 patients (3 patients did not wish to participate in the EEG study; 4 males, 3 females, mean age of patients run in EEG study: 69 $\pm$ 9.5 years) and 7 age-matched control subjects (4 males, 3 females, mean age: 68.9 $\pm$ 9.1 years). All of the control subjects were right handed and had no history of audiological or neurological disease. 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. All subjects were paid for their participation.

ERP Recording

The EEG was recorded from Ag/AgCl electrodes placed at Fp_1, Fpz, Fp_2, F_3, Fz, F_4, C_3, Cz, C_4, P_3, Pz, P_4, T_3, T_4, T_5, T_6, O_1, Oz, and O_2 according to the international 10–20 system. One additional electrode was placed 2 cm in front of Cz (Cz′) to record MAEPs (latency 8 to 70 msec). All electrodes were referred to a balanced noncephalic, 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 artifact over 100 μV were automatically rejected before averaging. The EEG was first continuously digitized at 600 Hz per channel to analyze MEAPs 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. EEG

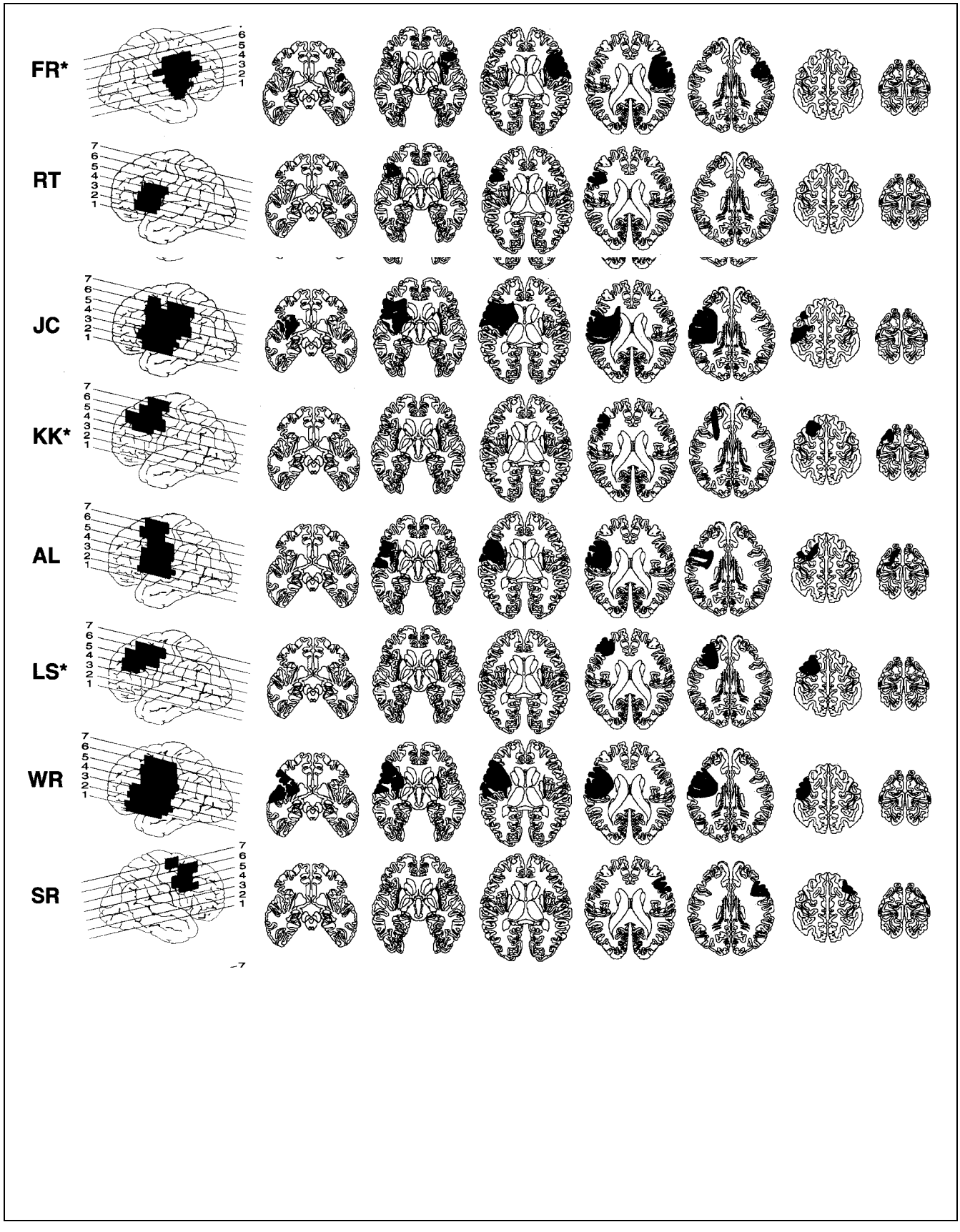

Figure 9. Individual axial and lateral lesion reconstructions showing the extent of damage in all 10 frontal patients. The lines on the lateral reconstruction refer to the seven axial sections presented. Patients with an asterisk after their initials did not participate in the electrophysiological part of the study.

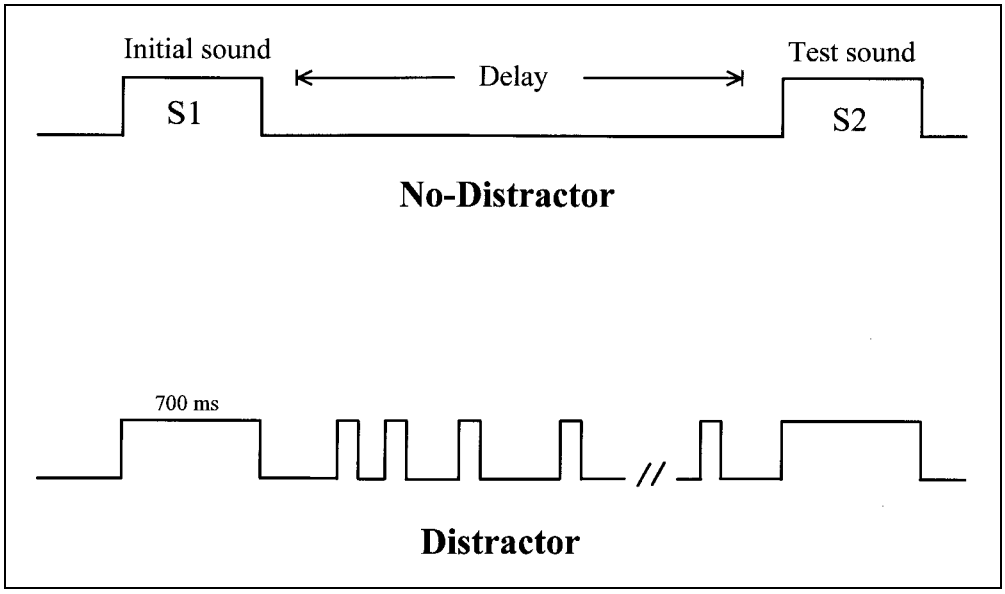

Figure 10. Schematic diagram of the paradigm.

from Cz′ was filtered at 10 to 300 Hz, and the EEG from the other 21 electrodes was filtered at 0.1 to 100 Hz.

Procedures

The experiments were conducted with the subjects comfortably seated in a reclining chair in a sound chamber (43 dB attenuated) with controlled background luminance (0.4 footlamberts). Subjects were presented with a 50-msec, 500-Hz warning tone followed 500 msec later by an initial sound (S1). After a delay of 5 sec, a test sound (S2) was presented. Subjects were instructed to press a "Yes" button if the S1 and S2 were identical and a "No" button if they were different. Control subjects used their right hand to respond. Patients used the hand ipsilateral to their lesion.

There was a total of 200 trials. Twenty percent of the trials were negative (S1 and S2 did not match) and 80% were positive. On half the trials, the delay period was filled with irrelevant, distracting tone pips (distractor condition; see Figure 10 for a schematic diagram of the paradigm). Same or different and distractor or no-distractor trials were presented in random order. The stimuli presented were drawn from a repertoire of 256 possible digitized sounds. The sounds consisted of nonspeech human sounds (e.g., sneeze or cough), animal vocalizations (e.g., a dog barking), musical instruments (e.g., piano or guitar), and noises that occur in the environment (i.e., dishwasher noises or garage door opening). The tone pips of 4000 Hz were constructed by means of digital synthesis on a personal computer. The duration of S1 and S2 sounds was 700 msec (rise/fall time varied depending of the shape of the sound) and the duration of the distracting tone pips was 100 msec (zero rise/fall time). The tone pips were presented at interstimulus intervals (ISIs) that ranged randomly from 50 to 210 msec. The pure-tone audiometric threshold from 125 to 8000 Hz was determined by the method of ascending and descending limits in each ear in subjects (see Table 2). There was no difference between the mean threshold of the patients and control subjects ($F1, 18 = 2.83, p = 0.11$). The stimuli were presented binaurally at 60 decibel above each subject's hearing level.

Data Analysis

Data averaging was performed off-line after sorting by presentation type (warning tone, S1 presentation, S2 presentation without distractors, S2 presentation with distractors) and by response type (correctly or incorrectly identified trials). Epochs containing eye movement or electromyographic (EMG) artifact over 100 μV were automatically rejected from the averaged data. The rejection rate of trials due to eye movement was about 10%. Peak latency and amplitude were measured for wave V (4 to 10 msec), Na (15 to 20 msec), Pa (25 to 35 msec), Nb (35 to 45 msec), Pb (45 to 60 msec), as well as a sustained frontal negativity, or SFN, (500 to 600 msec), P3a (300 to 400 msec), and P3b (300 to 700 msec) 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-msec prestimulus baseline, whereas longer-latency components were referred to a 200-msec prestimulus baseline. Latency measures were referred to stimulus onset.

ANOVA and *t*-test measures were made by 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.

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