Lesions of frontal cortex diminish the auditory mismatch negativity

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Summary Event-related brain potentials to non-attended auditory stimuli were recorded from patients with dorsolateral prefrontal cortex (DPCFX) lesions and from age-matched control subjects as they performed a visual reaction time task. Auditory stimuli consisted of monaural sequences of repetitive standard tones (1000 Hz) and occasional deviant tones of a higher frequency (1300 Hz). In comparison with control subjects, DPCFX patients showed increased P1 amplitudes (mean peak latency 80 msec), consistent with reduced frontally mediated gating of sensory input to the auditory cortex. The mismatch negativity (MMN) elicited by deviant tones was reduced in DPCFX patients over a broad latency range (120–210 msec), especially over the lesioned hemisphere and for tones delivered to the ear ipsilateral to the lesion. The results suggest that DPCFX and DPCFX-temporal projections play a critical role in involuntary orienting to physical changes in sequences of non-attended auditory stimuli.

Key words: Attention; Auditory; Event-related potentials; Frontal; Cortex; Orienting; Hemisphere; Evoked potential; Mismatch negativity; Visual

Physically deviant auditory stimuli occurring in a sequence of repetitive standard stimuli elicit a mismatch negativity (MMN) in the auditory event-related brain potential (ERP; for a review, see Näätänen 1992). The MMN typically overlaps with the N1 (peak latency 90–120 msec) and subsequent P2 (180–200 msec) deflections. Since N1 and P2 waves are also elicited by frequent standard stimuli, the MMN is best seen in difference waves obtained by subtracting standard-tone ERPs from deviant-tone ERPs.


Näätänen and collaborators (e.g., Näätänen et al. 1989; Näätänen 1990, 1992) have proposed that the MMN is generated by a mismatch between the physical features of deviant stimuli and a neuronal sensory-memory trace ("neuronal model"; Sokolov 1975) produced by repetitive standard stimuli. A complete representation of the physical features of a repetitive stimulus is presumably stored in this memory trace, since a change in any feature (frequency, intensity, duration, location, etc.) elicits an MMN (Näätänen 1992). The MMN is elicited by physical stimulus changes even when the subject's attention is directed to other auditory (e.g., Näätänen et al. 1978; Alho et al. 1989) or visual stimuli (Sams et al. 1985b; Alho et al. 1992; Woods et al. 1992). Therefore, the MMN seems to be associated with the automatic analysis of stimulus features (Näätänen 1992). However, the mismatch process that generates the MMN might be the initial stage in a chain of brain processes that leads to involuntary orienting of attention to changes in the acoustic environment (Näätänen 1979; Sams et al. 1985b; Näätänen and Picton 1987; Lyytinen et al. 1992).

Using scalp current density analysis, Giard et al. (1990) identified an additional MMN generator in frontal cortex. This frontal subcomponent of the MMN might be associated with the involuntary orienting of attention following the automatic stimulus-change de-

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tection mechanism indexed by the auditory cortex sub-component of the MMN (Giard et al. 1990; Näätänen 1992). However, it has been difficult to disentangle the relative contributions of frontal and auditory cortex to MMN generation because of temporal and distributional overlap (Giard et al. 1990). While the frontal subcomponent would be expected to have an amplitude maximum at frontal scalp sites, the auditory cortex subcomponent of the MMN might also be largest at frontal sites because of generator orientation (Scherg et al. 1989; Tiihinen et al. 1993).

One frontal structure that might be involved in MMN generation is the dorsolateral prefrontal cortex (DPFCx) which is known to have an important role in the control of attention (Knight et al. 1981; Woods and Knight 1986; Fuster 1989; Knight 1991). The aim of the present study was to evaluate the role of this cortical area in MMN generation by comparing MMNs in patients with unilateral DPFCx lesions and in healthy control subjects.

Methods

Subjects

ERPs were recorded in 10 patients (males, 60–75 years) with unilateral DPFCx lesions (7 left-sided, mean lesion volume 41.0 ml; Fig. 1) due to infarctions of the precentral branch of the middle cerebral artery. Patient data were compared with data from 13 healthy, age-matched control subjects (9 males, 4 females, 54–80 years). The hearing thresholds of all subjects were tested before the experiment. All subjects had a normal corrected visual acuity and no history of alcoholism, drug abuse or psychiatric problems. All subjects were paid volunteers who participated after giving informed consent according to institutional guidelines.

Before the experiment, each subject underwent audiometric testing at 125, 250, 500, 1000, 1500, 2000, 4000, and 8000 Hz. At the highest frequencies (2000 Hz or higher), most control subjects showed age-related elevations of thresholds. However, at frequencies below 2000 Hz, their thresholds were always lower than 25 dB SPL. The patients showed somewhat greater hearing losses than the controls. At 1000 Hz, the thresholds of patients varied between 15 and 45 dB SPL (5 patients had thresholds higher than 25 dB SPL). At 1500 Hz, the thresholds varied between 10 and 55 Hz SPL (6 patients had thresholds higher than 25 dB SPL). In the patients, the mean hearing thresholds for 1000 Hz in the ear contralateral and ipsilateral to the lesioned hemisphere were 28 and 25 dB SPL, respectively. For 1500 Hz, these thresholds were 33 and 29 dB SPL, respectively. Although the patients had, on the average, higher thresholds than the control subjects, the 1000 Hz and 1500 Hz tones of 82 dB SPL used in the present ERP experiment were well above the hearing thresholds for all patients. Furthermore, an analysis of variance including Frequency (1000 Hz and 1500 Hz) and Ear (contralateral vs. ipsilateral to the lesion) as factors showed no significant differences in the thresholds of patients between the two frequencies or two ears.
**Stimuli and procedure**

Auditory and visual stimuli were presented in a random order in blocks of 440 stimuli. Interstimulus intervals (ISIs) varied randomly between 200 and 400 msec in 20 msec increments. Auditory stimuli were pure tones with a duration of 50 msec (5 msec rise and fall times) and intensities of 82 dB SPL. They were presented monaurally through TDH-39 headphones over a continuous binaural broadband masking noise (60 dB SPL). Standard tones of 1000 Hz occurred with a probability of 85% and deviant tones of 1300 Hz with a probability of 10%. In half of the stimulus blocks, the tones were delivered to the left ear and in the other half to the right ear.

In addition to auditory stimuli, 5% of stimuli were visual targets (occurring with a mean inter-target interval of 6 sec). Visual targets were white vertical gratings on a black background (spatial frequency 2 c/deg; luminance 6 fL; contrast 0.99; size 3.9° × 3.9°; duration 50 msec). They appeared in the center of a video monitor subtending 11.2° × 15.4° of visual angle and positioned 1.5 m in front of the subject.

The experiment consisted of 12–16 stimulus blocks. The left- and right-ear blocks were delivered in an alternating order. During each stimulus block, the subject was instructed to ignore the tones, to focus on a small fixation star in the center of the television screen, and to respond with a button press of the right-hand thumb to each visual stimulus. The subjects were instructed to be as fast as possible in their responses. Fixation was assured in the beginning of each stimulus block and eye position was continuously monitored with vertical and horizontal EOG (see below) and through a closed-circuit video camera.

Performance in the visual detection task was scored by computer. Responses occurring from 80 to 1000 msec after target onset were defined as hits and responses given outside this window were defined as false alarms.

After the main experiment, subjects participated in a supplementary auditory discrimination task without ERP recording. In this task, auditory stimuli were similar to those used in the main experiment, but the subjects’ task was to press the response button, as fast and accurately as possible, after each 1300 Hz deviant tone occurring among standard tones (1000 Hz). Responses given within 80–1000 msec from a deviant-tone onset were defined as hits and other responses were defined as false alarms. Two left-ear stimulus blocks and 2 right-ear blocks were presented. The order of the blocks was counterbalanced between subjects.

**EEG recording and averaging**

The EEG (bandpass 0.1–100 Hz) was continuously sampled (256 Hz/channel) from 27 scalp electrodes: Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, PA1 (left preauricular point), T1 (between F7 and T3), T3, C3, Cz, C4, T4, T2 (between F8 and T4), PA2 (right preauricular point), M1 (left mastoid), T5, P3, Pz, P4, T6, M2 (right mastoid), O1, Oz, and O2. Additional electrodes were attached below the left eye (BE) and lateral to the left eye (LE) to monitor EOG artifacts. All electrodes were referenced to interconnected, ECG-balanced electrodes at the base of the neck (Woods and Clayworth 1985).

EEG epochs starting 200 msec before stimulus onset were averaged off-line by computer. Trials contaminated by vertical or horizontal eye movements (peak-to-peak amplitude at Fpz, BE, or LE exceeding 80 μV), amplifier clipping, bursts of EMG activity, or other artifacts were automatically excluded from the averages. The first stimulus was omitted from the average in each stimulus block. Only hit trials were included in the ERPs to visual target stimuli. To avoid contamination of auditory ERPs at posterior scalp sites by ERPs to preceding visual stimuli (Alho et al. 1992), ERPs to auditory stimuli occurring within 600 msec of a visual stimulus were excluded from the average.

**Data analysis**

After averaging, ERPs were digitally filtered to eliminate frequencies above 40 Hz. Difference waves were obtained by subtracting standard-tone ERPs from deviant-tone ERPs separately for each ear of stimulation. ERP peak amplitudes and latencies were measured in relation to stimulus onset and ERP mean voltages were measured over consecutive 20 msec intervals between 10 and 510 msec (10–30 msec, 30–50 msec, 50–70 msec, etc.) in reference to a 200 msec prestimulus baseline. 2

The results were statistically evaluated with analyses of variance for repeated measures. Significance levels were adjusted with the Greenhouse-Geisser correction when appropriate. However, the original degrees of freedom are reported for each analysis.

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2 Due to the short ISIs (random 200–400 msec) used in the present experiment, ERPs may have been contaminated by overlapping time-smeared ERPs to preceding and subsequent stimuli. Although a contamination of auditory ERPs by the large P3 deflection elicited by visual target stimuli (see Fig. 6) was avoided by discarding ERPs to tones immediately following visual targets (see Methods), ERPs to tones were overlapped and affected by time-smeared ERPs to preceding and subsequent auditory stimuli, as well as by subsequent visual stimuli (for a further discussion, see Woldorff 1993). However, this response overlap would affect similarly the ERPs to deviant and standard tones delivered in a random order. Therefore, overlapping activity would not affect the mismatch negativity (MMN), the main topic of the present study, which was determined as a difference between the ERPs to deviant and standard tones. In these difference waves, the effects of overlapping responses are canceled by subtraction.
In the analysis of performance, the percentages of hits and false alarms/delayed responses, and mean reaction times (RTs) were calculated for the visual task of the main experiment and for the supplementary auditory discrimination task. Analyses of variance were used to compare RTs and performance in the patients and controls.

Results

Performance

The mean RT to visual targets was 405 msec and 346 msec for the patients and controls, respectively (F(1, 21) = 7.58, P < 0.02). Hit rates did not differ significantly (controls, 94% vs. patients, 88.4%; F(1, 21) = 1.59, NS), nor were significant differences found between patients and controls in the percentages of false alarms/delayed responses.

In the supplementary auditory discrimination test, the patients detected fewer deviant tones (77.4%) than the controls (95.9%; F(1, 21) = 6.92, P < 0.02), and had longer RTs (439 msec vs. 375 msec, F(1, 21) = 7.40, P < 0.02). In the patients, 15.6% of the responses were false alarms, while in the controls, this percentage was 13.7%. In the patients, discrimination performance tended to be less accurate for deviant tones delivered to the ear ipsilateral to the lesioned hemisphere, but ear effects on RT and detection performance did not reach significance.

Auditory ERPs

Grand-average ERPs to standard tones in the DPFCx patients and control subjects are shown in Fig. 2. In both groups, standard tones elicited N1 and P2 deflections with maximal amplitudes at central and frontal scalp sites. Table I shows mean peak amplitudes and latencies at Cz for the N1 and P2 deflections elicited by standard tones. The N1 and P2 deflections had similar peak amplitudes for the patients and controls. Although the N1 peak latencies tended to be shorter, and the P2 peak latencies longer in the patients than in the controls, these latency differences failed to reach significance.

As seen in Fig. 2 (insert) the amplitude of the P1 deflection was relatively enhanced in the patients. An analysis of variance for P1 amplitudes (measured at Fz as mean voltages over 30–50 msec from stimulus onset) in the standard-tone and deviant-tone ERPs indicated a significant difference (on the average 0.4 µV) between the two groups (F(1, 21) = 4.95, P < 0.05). For the standard tones, the early portion of the N1 deflection (before the N1 peak) also tended to be enhanced in the patients in relation to the controls (see Fig. 2), but this effect, tested at 50–70 msec, 70–90 msec, and 90–110 msec was not statistically significant.

### Table I

Mean N1 and P2 peak amplitudes and latencies (S.E.M. in parentheses) in patients with frontoparietal lesions (N = 10) for standard tones delivered to the ear contralateral (right ear in 7 patients) or ipsilateral to the lesion, and in control subjects (N = 13) for standard tones delivered to the right or left ear.

<table>
<thead>
<tr>
<th>Ear</th>
<th>N1 and P2 amplitudes</th>
<th>Controls (N = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(µV) (msec)</td>
<td>(µV) (msec)</td>
</tr>
<tr>
<td>Frontals (N = 10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1 Contra/right</td>
<td>-1.2 (+0.2) 114 (+8)</td>
<td>-1.2 (+0.6) 127 (+7)</td>
</tr>
<tr>
<td>N1 Ipsi/left</td>
<td>-1.3 (+0.2) 107 (+9)</td>
<td>-1.2 (+0.7) 120 (+8)</td>
</tr>
<tr>
<td>P2 Contra/right</td>
<td>1.1 (+0.2) 223 (+6)</td>
<td>1.1 (+0.5) 219 (+7)</td>
</tr>
<tr>
<td>P2 Ipsi/left</td>
<td>1.2 (+0.1) 225 (+7)</td>
<td>1.2 (+0.5) 214 (+4)</td>
</tr>
</tbody>
</table>
At latencies longer than 100 msec, ERP negativity to deviant tones delivered to the ear ipsilateral to the lesion (left ear in 7 patients) was reduced in the patients in relation to controls (Fig. 3). A smaller reduction was seen for deviant tones delivered to the ear contralateral to the lesion. As discussed below, these effects appeared to be caused by smaller MMNs in the DPFCx patients.

As seen in comparisons of Figs. 2 and 3, the N1 deflection was larger in amplitude and longer in duration to deviant than standard tones. The early part of the negativity to deviant stimuli may have received some contribution from enhanced N1 components which may have been less refractory for the infrequently occurring deviant tones (see, e.g., Scherg et al. 1989; Lang et al. 1990; Woods 1994), while the later portion appeared to reflect mainly the addition of an MMN. The MMN was more readily seen in difference waves obtained by subtracting the ERPs to standard tones from the ERPs to deviant tones for DPFCx patients in comparison with control subjects (Fig. 4): significant Group effects were observed at Fz at 130–150 msec (controls = -2.2 µV, patients = -1.3 µV; F (1, 21) = 6.99, P < 0.015) and at 150–170 msec (controls = -2.0 µV, patients = -1.0 µV; F (1, 21) = 5.79, P < 0.025). Similar Group effects were observed in analyses of variance of ERP amplitudes at the frontal Fi and Fe electrodes located over the lesioned and
intact hemispheres, respectively (Fig. 4; 130–150 msec, $F(1, 21) = 7.88, P < 0.010$; 150–170 msec, $F(1, 21) = 7.33, P < 0.015$).

Analyses of MMN amplitudes at Fi and Fc electrodes showed significant Group $\times$ Ear $\times$ Hemisphere interactions at 170–190 msec ($F(1, 21) = 6.84, P < 0.015$) and 190–210 msec ($F(1, 21) = 5.50, P < 0.03$, with a trend at 150–170 msec ($F(1, 21) = 3.57, P < 0.07$). This was due to the fact that MMN amplitudes were more reduced over lesioned than intact hemispheres for tones delivered to the ear ipsilateral to the lesion than for contralateral tones (Fig. 4). For example, at 170–190 msec, mean MMN amplitudes in the patients for stimuli delivered ipsilaterally to the lesion (left ear in 7 patients) were $-0.2 \mu V$ and $-0.6 \mu V$ at Fi and Fc, respectively, whereas in the controls, corresponding MMN amplitudes were $-1.5 \mu V$ and $-1.3 \mu V$, respectively.

Fig. 5 shows the MMN scalp distributions in the patient and control groups. In the controls, the MMNs to left- and right-ear deviant tones had frontal distributions that were symmetrical over the two hemispheres. In the DPFCx patients, the MMN to deviant tones delivered to the ear ipsilateral to the lesion had a frontal distribution and was reduced over the lesioned hemisphere (Fig. 5, see statistical analysis above). The MMN to deviant tones delivered to the ear contralateral to the lesion showed a tendency toward a similar ipsilesional reduction (at 130–170 msec; see Fig. 5) which failed to reach significance.

It is important to note that the reduced MMN in DPFCx patients retained its frontal scalp distribution.

| TABLE II |
| Mean MMN amplitudes in control subjects ($N = 13$) and in patients with frontal lesions ($N = 10$). Mean voltage measures from difference waves for standard tones delivered to the ear contralateral (right ear in 7 patients) or ipsilateral to the lesion, and to standard tones delivered to the right or left ear in controls. |

<table>
<thead>
<tr>
<th>MMN amplitude (deviant − standard) over 150–170 msec</th>
<th>Contra ear (right)</th>
<th>Ipsilateral ear (left)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>Frontals</td>
<td>Controls</td>
</tr>
<tr>
<td>FpI</td>
<td>$-1.8$</td>
<td>$-1.2$</td>
</tr>
<tr>
<td>Fpz</td>
<td>$-1.7$</td>
<td>$-1.2$</td>
</tr>
<tr>
<td>Fpc</td>
<td>$-1.7$</td>
<td>$-1.1$</td>
</tr>
<tr>
<td>Fi</td>
<td>$-1.9$</td>
<td>$-1.4$</td>
</tr>
<tr>
<td>Fz</td>
<td>$-1.9$</td>
<td>$-1.2$</td>
</tr>
<tr>
<td>Fc</td>
<td>$-1.7$</td>
<td>$-1.2$</td>
</tr>
<tr>
<td>C1</td>
<td>$-1.2$</td>
<td>$-1.0$</td>
</tr>
<tr>
<td>Cz</td>
<td>$-1.2$</td>
<td>$-1.1$</td>
</tr>
<tr>
<td>Cc</td>
<td>$-1.0$</td>
<td>$-1.2$</td>
</tr>
<tr>
<td>P1</td>
<td>$+0.1$</td>
<td>$-0.5$</td>
</tr>
<tr>
<td>Pz</td>
<td>$-0.2$</td>
<td>$-0.4$</td>
</tr>
<tr>
<td>Fc</td>
<td>$-0.2$</td>
<td>$-0.4$</td>
</tr>
<tr>
<td>Oc</td>
<td>$+0.4$</td>
<td>$-0.2$</td>
</tr>
<tr>
<td>Oz</td>
<td>$+0.3$</td>
<td>$-0.1$</td>
</tr>
<tr>
<td>Oc</td>
<td>$+0.4$</td>
<td>$-0.3$</td>
</tr>
</tbody>
</table>

In particular, DPFCx lesions did not produce a focal frontal amplitude reduction: the MMN reduction in patients was similar (in percentage terms) at frontal, central and parietal electrodes over the lesioned hemisphere (Table II).

The MMN was followed by a smaller, frontally distributed late negative shift in deviant-tone ERPs (Fig. 4). Analyses of variance for the mean ERP amplitudes indicated a significant difference between ERPs to deviant and standard tones at 290–510 msec at frontal sites ($F(1, 21)$ ranged from 4.78 to 38.51, $P < 0.05$ in all cases). The late negativity tended to be reduced in the DPFCx patients over the lesioned hemisphere (see Fig. 4), but this effect failed to reach significance.

ERPs to visual target stimuli

ERPs to the infrequently occurring visual target stimuli are shown in Fig. 6. These stimuli elicited an occipito-parietal N1 preceded by a short-duration P1. No significant group differences were noted at P1 latency. Analyses of variance for N1 amplitude at O1, Oz, and O2 indicated that there was no significant difference in peak amplitude between the groups (patients $-4.0 \mu V$; controls $-5.4 \mu V$). However, N1 peak latencies were significantly shorter in patients than in controls (patients 129 msec vs. controls 148 msec; $F(1, 21) = 4.33, P < 0.05$).

Visual targets also elicited a P3 which was largest at Pz (peak amplitude: patients 11.7 $\mu V$; controls 13.3 $\mu V$; peak latency: patients 391 msec; controls 375 msec).
Differences in the P3 peak amplitude and latency between the two groups did not reach significance.

The P3 was preceded by an N2 wave peaking at about 250 msec from stimulus onset (Fig. 6). Visual N2 amplitudes were maximal over posterior temporal electrodes suggesting a visual cortex or visual association cortex generator. In control subjects, the N2 was also larger over the left hemisphere (see electrodes Fc and Cc in Fig. 6), i.e., the hemisphere contralateral to the hand used for responding consistent with a possible contribution from the time-smeared movement-related potentials (MRPs) preceding the button press.

The N2 was reduced in amplitude over the lesioned hemisphere in the frontal patients. For example, at 230–250 msec, the mean visual ERP amplitudes for the patients at F1 and Fc were 5.0 μV and 3.5 μV respectively, while in the control subjects F3 and F4 mean amplitudes were 0.2 μV and 2.0 μV, respectively. Analyses of variance (factors: Group, Hemisphere) for mean visual ERP amplitudes (measured over consecutive 20 msec periods) at F1 and Fc indicated significant Group × Hemisphere interactions at 210–290 msec from stimulus onset ($F(1,21) = 4.42–7.71, P < 0.05$ in all cases). Similar significant Group × Hemisphere interactions were also observed for the C1 and Cc amplitudes at 210–290 msec ($F(1,21) = 4.52–6.73, P < 0.05$ in all cases). A strong tendency toward N2 reductions was also seen at temporal, posterior temporal, and parietal electrodes over the lesioned hemisphere.

Discussion

**Frontal lesions and sensory ERPs**

Auditory stimuli elicited sensory ERPs with a similar component structure in frontal patients and control subjects. P1 amplitudes were larger in the patients than in the controls, both to standard and deviant tones. An enhancement of middle latency auditory evoked potentials in patients with unilateral DPFCx lesions has been previously reported by Knight et al. (1989). They suggested that this early ERP enhancement was associated with reduced DPFCx mediated thalamic gating of sensory inputs to the auditory cortex (see also Skinner and Yingling 1977; Yamaguchi and Knight 1990; Knight 1991). In the present study, the occipital N1 deflection elicited by visual stimuli had shorter peak latencies in DPFCx patients than in controls, an effect that might also be caused by reduced thalamic gating of visual inputs.

**Frontal lesions and the mismatch negativity**

MMN amplitudes were attenuated in the DPFCx patients in comparison with the control subjects, consistent with the possible involvement of frontal cortex in the generation of MMN (Näätänen 1992). Previous studies have shown that DPFCx lesions also cause decreased N2-P3a responses elicited by unexpected, novel auditory stimuli (Knight 1984, 1990, 1991; Scabini et al. 1989).

The present MMN attenuation in the patients cannot be explained by elevated hearing thresholds. Tone intensities were well above the hearing thresholds of both ears in all patients. Moreover, thresholds were similar for ipsilesional and contralesional ears in the patients, even though MMN abnormalities were more marked for tones presented to the ipsilesional ear. Although the performance in the supplementary auditory discrimination task was not as good in the patients as in the control subjects, all patients were able to discriminate deviant from standard stimuli. Several studies have suggested a relationship between discrimination performance and MMN amplitude and/or latency (Sams et al. 1985b; Lang et al. 1990; Novak et al. 1992). Therefore it is possible that the less accurate discrimination of deviant tones and longer RTs to these tones in patients than in controls were partly caused by dysfunctioning of the stimulus change detection mechanism generating the MMN. However, visual RTs were also prolonged in the patients. This is consistent with the possibility that the prolongation in auditory RTs seen in the patients may have been partly caused by general problems in motor performance associated with DPFCx lesions (Singh and Knight 1990).

It might be argued that smaller MMNs to auditory deviants were elicited in patients because they found the visual task more difficult than the controls and so had less spare attentional capacity for processing irrelevant auditory stimuli (cf., Näätänen 1991; Woldorff et al. 1991). However, previous results indicate that the amount of attention demanded by a visual task has no effect on the MMN to deviant stimuli in unattended
auditory inputs (Alho et al. 1992). Moreover, attending to auditory stimuli does not enhance the MMN to large frequency changes such as those used in the present study (Alho et al. 1992). In any case, even differential between-group effects of attention on the MMN would not explain the group differences in MMN scalp distribution observed in the present study.

Previously, a contribution of a frontal source to the MMN was suggested by scalp current density maps in normal subjects (Giard et al. 1990). In the present study, the MMN was attenuated over the lesioned hemisphere, which might be regarded as evidence that the lesions damaged a frontal MMN generator. However, this interpretation is contradicted by the similarity in distribution over the lesioned and intact hemispheres; there was no alteration in the frontality of the MMN distribution. This result could be explained by a frontal MMN source in ventro-lateral frontal or basofrontal regions. Alternatively, a DPFCx source may have been spared because most of the patients had a frontal lesion in the left hemisphere while the generator of the frontal MMN component may preferentially involve the right DPFCx cortex (Giard et al. 1990). The small number of frontal patients with right-hemisphere lesions did not permit an adequate evaluation of a possible right DPFCx generator.

Another explanation for MMN attenuation is that the lesions resulted in an attenuation of MMN generation in ipsilesional auditory cortex. Models of MMN sources show that generators in left and right auditory cortices cause a frontally dominant MMN scalp distribution even in the absence of a frontal MMN subcomponent (Scherg et al. 1989). The persistence of neuronal sensory-memory traces necessary for the mismatch process might depend on sustaining fronto-temporal projections to auditory cortex. There is also evidence that the MMN may have at least two auditory cortex subcomponents (Paavilainen et al. 1991). Perhaps the generator of the later one of these subcomponents is triggered by frontal activation caused by a stimulus change, and is therefore attenuated by frontal lesions. Whichever is the explanation for the present MMN attenuation in the DPFCx patients, the lack of reduction in P1, N1, and P2 amplitudes in these patients suggests that any effect of frontal lesion on functioning of the auditory cortex would have specifically affected discrimination or memory functions (Baddeley and Wilson 1988; Wilson et al. 1993) rather than auditory analysis in general.

The deteriorated performance of the DPFCx patients in the supplementary auditory discrimination task is consistent with dysfunctions of the change-detection mechanism associated with the MMN (Nääätänen 1992). However, the present lesions might have been expected to more markedly disrupt the processing of auditory stimuli in contralateral hemispace since unilateral lesions of frontal cortex usually result in contralateral deficits in orienting (Heilman and Valenstein 1972; Heilman and Watson 1977; De Renzi et al. 1989; Hugdahl et al. 1991). However, in some patients unilateral frontal lesion may be associated with inappropriate orienting, rather than neglect, to contralateral stimuli ("visual grasp"; Butter et al. 1988) and impaired orienting to stimuli in ipsilateral hemispace (Kwon and Heilman 1991). In the present study, we found evidence for ipsilateral auditory neglect: the MMN attenuation seen in the DPFCx patients was more marked for ipsilateral than contralateral tones and frequency discrimination in the patients tended to be less accurate for ipsilesional tones. The ear-specific reduction in the MMN suggests that it did not result simply from a non-specific decline in arousal and/or motivation. Rather, it suggests that separate cortical circuits are involved in processing auditory stimulus change in left and right auditory hemispace.

Another reason for the reduction in MMN following tones delivered ipsilaterally to the lesion may relate to circuity of MMN generation. Scalp current density maps (Giard et al. 1990) suggest that MMN sources in the left and right auditory cortices are more strongly activated by stimuli delivered to the contralateral ear than by stimuli delivered to the ipsilateral ear. Hence, projections from the ipsilateral frontal lobe may provide relatively more important inputs to the weaker MMN generator process activated by ipsilateral stimuli. For example, this might occur if the MMN generator in auditory cortex required convergent projections from both primary auditory cortex and the ipsilateral frontal lobe.

The MMN was followed by another negativity to deviant tones. A similar late negativity has been observed in previous studies (Nääätänen et al. 1982; Alho et al. 1992). Nääätänen et al. (1982) suggested that this negativity following the MMN might reflect "sensitization processes" after an occurrence of a stimulus change which elicits an MMN but fails to trigger any subsequent endogenous processes. Such "sensitization" might express automatic preparation for detecting possible subsequent stimulus changes. In the present study, no significant attenuation of the late negativity following the MMN was observed in the DPFCx patients suggesting different neural origins for the late negativity and the MMN.

Frontal lesions and ERPs to visual targets

ERPs to visual target stimuli showed reduced N2 amplitudes in the DPFCx patients. These effects were particularly pronounced over the left hemisphere suggesting a possible contribution from reduced movement-related cortical potentials (MRPs) that would have made time-smereared contributions in the stimulus-locked averages to targets (Singh and Knight 1990).
However, the tendency toward N2 reduction over temporal and parietal cortex ipsilateral to the DPFCx lesions suggests that fronto-parietal projections (Yeterian and Pandya 1985; Selemon and Goldman-Rakic 1988) may be necessary for the generation of a visual N2 of normal amplitude (Deacon et al. 1991).

Conclusions

The MMN attenuation in patients with DPFCx lesions suggests that the frontal cortex plays a role in the neural circuitry underlying the MMN. The present MMN attenuation in the DPFCx patients was not caused by a general reduction of auditory ERP amplitudes. On the contrary, P1 amplitudes were enhanced in the patients. This effect may have been caused by reduced frontal gating of sensory input from thalamus to the auditory cortex. Also, shorter visual N1 peak latencies in the patients may have indexed reduced thalamic gating of visual input.

DPFCx lesions also slowed visual target detection and reduced N2 amplitudes to the target stimuli. These effects might be caused in part by motor impairment and reduced movement-related negativities. Alternatively, they may reflect damage to a fronto-parietal network involved in target detection and discrimination.

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References


