Painful Stimuli Evoke Potentials Recorded From the Parasylvian Cortex in Humans


Departments of Neurosurgery and Neurology, Johns Hopkins Hospital, Baltimore, Maryland 21287-7713

INTRODUCTION

Substantial indirect evidence suggests that cortex of the parasylvian operculum and insula are involved in pain-signaling pathways in humans. Positron emission tomographic (PET) studies demonstrate pain-related blood flow activation of contralateral primary somatosensory (SI) cortex, bilateral parasylvian operculum (including secondary somatosensory cortex, SII), and insula (Casey et al. 1994; Coghill et al. 1994; Talbot et al. 1991). Human lesion studies demonstrate that lesions of the parasylvian operculum and insula cortex modify the sensation of experimental pain (Biemond 1956; Davison and Schick 1935; Greenspan et al. 1997; Obrador et al. 1957). Although this indirect evidence suggests that parasylvian structures mediate pain sensations, there is no direct evidence of nociceptive inputs to these structures in man.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Human studies demonstrate the presence of scalp potentials evoked by cutaneous stimulation with a CO₂ laser (LEPs) (Beydoun et al. 1993; Kunde and Treede 1993; Miyazaki et al. 1994; Tarkka and Treede 1993; Treede et al. 1988), which produces pain by activation of Aδ and C nociceptors (Bromm and Treede 1984; Carmon et al. 1978). The generators of these potentials are uncertain because the location of potentials recorded at the scalp depends on the complicated configuration of the generator and of the surrounding brain, cerebrospinal fluid, dura, bone, and scalp (Scherg and Picton 1991). These potentials may be explained, in part, by models that include generators in the parasylvian cortex bilaterally (Chen and Bromm 1995; Kitamura et al. 1995; Tarkka and Treede 1993). We now describe LEPs recorded from subdural electrodes over the parasylvian cortex in three awake patients evoked by mechanical or heat sensations never was reported spontaneously or in response to direct questioning (Bromm and Treede 1984; Carmon et al. 1978). To avoid sensitization, the laser

METHODS

Subdural electrodes were implanted over the left fronto-temporal areas (see Fig. 3) in three patients (2 men, 1 woman, ages 26–38 yr) with medically intractable seizures of temporal lobe origin. The implanted left hemisphere was dominant for language in all three, as established by intracarotid amobarbital injection (Lesser et al. 1994). Therefore potential differences between results recorded from the dominant and nondominant hemispheres cannot be assessed from these results (Coghill et al. 1997). Scalp LEPs were studied in four other patients (1 man, 3 women, ages 33–43 yr) during seizure monitoring. All patients had normal magnetic resonance imaging (MRI) scans and normal somatosensory testing (Lenz et al. 1993b), and none had had previous intracranial surgery. This and the lack of neurological abnormalities apart from epilepsy in patients with temporal lobe epilepsy (Adams and Victor 1984) argues that the present results may apply to normal subjects.

All studies were carried out at the Johns Hopkins Hospital. The protocol was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins University, and all patients signed an informed consent for these studies.

Patients wore protective glasses during testing and reclined, quietly wakeful. Both hands and both sides of the face were stimulated in separate trials of stimulation. Cutaneous heat stimulation was delivered by a portable CO₂ laser stimulator (LX-20i, Luxar, Bothell, WA; wavelength 10.6 μm) with a stimulus duration of 20 ms across a beam diameter of 6 mm. The stimulus intensity was adjusted to elicit a sensation of pain with a visual analogue scale of intensity reading of 3–4/10 (10 = 13 W/mm²). At these values, a component of mechanical or heat sensation never was reported spontaneously or in response to direct questioning (Bromm and Treede 1984; Carmon et al. 1978). To avoid sensitization, the laser...
beam was moved at random to a slightly different position for each stimulus. The stimulus was applied to the dorsum of each hand and over the V2/V3 distribution on each side of the face, at random intervals of between 5 and 7 s. During the entire recording session, continuous white noise was delivered to each ear through earphones (click-tone module, Grass Instruments, Quincy, MA).

Intracranial LEPs were recorded from subdural grid electrodes. The grids consisted of platinum-iridium circular electrodes (2.3 mm diam) embedded in a transparent silastic sheet in 2 × 8 and 6 × 8 arrays, with electrodes evenly spaced at 1 cm center to center intervals (Ad-Tech, Racine, WI). Their position was determined by intraoperative observation, photographs, and postoperative radiological studies including superimposition of three-dimensional computed tomogram (CT) and three-dimensional MRI data sets, as in previous studies (Boatman et al. 1997). Laser-evoked potentials were recorded from 30 to 40 subdural electrodes, referenced to a frontal subdural electrode (Fig. 2, R), which was distant from the LEP maximum and from areas of ictal and interictal epileptiform activity on the electroencephalogram (EEG).

For the scalp recordings, disk electrodes were placed according to the International 10–20 system with linked ears reference (Jasper 1958). Recordings referenced to linked ears were obtained for electrode positions Cz, which was located over the vertex (Cz), and C3/C4 at points 40% of the distance from the vertex to the preauricular point on left (C3) and the right (C4). In each patient studied, results were recorded from two hemispheres (referential recordings from C3 and C4) in response to contralateral stimulation, or from the vertex (Cz) in response to stimulation of either side of the body. EEG recordings were obtained with standard amplifiers (Grass Model 12, band-pass: 0.1–100 Hz, amplifier gain: 5,000). Electrode impedances were maintained at <20 kΩ for subdural electrodes and <5 kΩ for scalp electrodes.

For each laser stimulus, the prestimulus (200 ms) and poststimulus (1,000 ms) segments were digitized by a computer at a sampling rate of 256 Hz. Responses to individual stimuli were stored for off-line evaluation. Individual responses were reviewed for artifacts before averaging. Each average consisted of 20–35 samples, repeated at least once to establish reproducibility of the potentials (Fig. 1, —— and ——). Peak latencies and amplitudes of each component were measured from the maximum potential (Fig. 2). Peak amplitudes were measured from an averaged baseline (0–50 ms) to peak. Peak latencies were measured from the peak amplitude for each component. In describing LEPs in the present results and in the literature (Beydoun et al. 1993; Chen and Bromm 1995; Kitamura et al. 1995; Kunde and Treede 1993; Tarkka and Treede 1993), we will refer to the largest negative wave as N2 and to the largest positive wave as P2.

Cortical stimulation was performed in the patients with subdural electrodes to localize sensory, motor, and language areas, as described elsewhere (Lesser et al. 1994). Briefly, pulses of duration 0.3 ms and alternating polarity at 50 pulses/s were applied across pairs of adjacent electrodes in trains of 2- to 5-s duration. This technique produced excitation beneath both of the stimulated electrodes in a pair (Ranck 1975).

RESULTS

Subdural electrode recordings

Waveforms from subdural recordings in patient H after bilateral facial and hand stimulation are shown in Fig. 1. Reproducible biphasic potentials were recorded from many subdural electrodes. The LEPs consisted of a prominent negative (N2) potential followed by a positive (P2) potential. The most reproducible potentials occurred after contralateral and ipsilateral facial stimulation. Maximal subdural LEPs (Fig. 1B) from facial stimulation had a mean peak N2 latency of 156 ms for contralateral and 164 ms for ipsilateral stimulation; the P2 had peak latency of 312 ms for contralateral and ipsilateral stimulation.

The mean peak latencies and peak amplitudes for the subdural LEP maximum recorded from one hemisphere in three patients are shown in Table 1 (left half). In patient H, potentials were measured in the hand representation of SI (top electrode in the posterior column of the 5 × 6 grid in Fig. 2 or in patient H of Figs. 3–5), labeled posterior

\[
\text{LEPs recorded from scalp electrodes in response to stimulation of the right side of the face, referenced to linked ears. B: maximum subdural LEPs from stimulation of the ipsilateral and contralateral face (V2/V3 distribution). C: maximum subdural LEPs from stimulation of the dorsum of the hand. Subdural recordings (B and C) show the maximum from patient H (see Fig. 2) referenced to a subdural electrode (R in Fig. 2). Sweeps are of 500-ms duration. To establish reproducibility, 2 waveforms (—— and ——), representing an average of 15–25 trials, are shown for each potential. Negative, up.}
\]
superior grid in the table. Latencies and amplitudes were determined for LEPs recorded from the scalp at C3 and C4 in response to contralateral stimulation and Cz in response to stimulation of either side of the body (Table 1, right half). Scalp LEPs were recorded in four patients although not all patients had reproducible responses to stimulation of each part of the body so that averages in this part of the table include measurements from six to eight hemispheres. Subdural LEPs showed no significant difference in mean latencies (P < 0.05, t-tests) for the facial N2 LEP contralateral (162 ± 5 ms, mean ± SE) and ipsilateral (159 ± 10 ms).

Similarly, the facial P2 LEP had the same mean latency contralateral (340 ± 18 ms) and ipsilateral (333 ± 21 ms) to the side of stimulation. Subdural LEPs evoked by contralateral face stimulation were similar in morphology (Fig. 1) to those recorded from the scalp. Latencies of subdural LEPs evoked by face stimulation were significantly different statistically (P < 0.05, t-tests), but perhaps not physiologically, from those recorded at the scalp Cz (N2, 182 ± 7 ms; P2, 281 ± 14 ms; see Table 1) and C3/C4 potentials (N2, 184 ± 6 ms; P2, 281 ± 14 ms).

Subdural potentials evoked by hand stimulation in patient

**TABLE 1.** Scalp and subdural mean peak latencies and amplitudes of LEPs after stimulation of face (V2/V3 distribution) and dorsum of the hands

<table>
<thead>
<tr>
<th></th>
<th>Intracranial Grid</th>
<th>Scalp</th>
<th>C3/C4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maxima</td>
<td>Posterior superior grid</td>
<td>C</td>
</tr>
<tr>
<td><strong>Face</strong> Latency, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>162 ± 5.0 (3)</td>
<td>159 ± 9.6 (3)</td>
<td>180 (1)</td>
</tr>
<tr>
<td>P2</td>
<td>340 ± 18.4 (3)</td>
<td>333 ± 21.2 (3)</td>
<td>375 (1)</td>
</tr>
<tr>
<td><strong>Amplitude, μV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>50 ± 8 (3)</td>
<td>47 ± 10 (3)</td>
<td>17.2 (1)</td>
</tr>
<tr>
<td>P2</td>
<td>64 ± 8 (3)</td>
<td>67 ± 8 (3)</td>
<td>20.4 (1)</td>
</tr>
<tr>
<td><strong>Hand</strong> Latency, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>219–227 (2)</td>
<td>250–256 (2)</td>
<td>281 (1)</td>
</tr>
<tr>
<td>P2</td>
<td>354–398 (2)</td>
<td>427–453 (2)</td>
<td>445–480 (1)</td>
</tr>
<tr>
<td><strong>Amplitude, μV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>19–47 (2)</td>
<td>7–14 (2)</td>
<td>1.8 (1)</td>
</tr>
<tr>
<td>P2</td>
<td>50–57 (2)</td>
<td>49–72 (2)</td>
<td>21.7 (1)</td>
</tr>
</tbody>
</table>

Values are means ± SE; numbers in parentheses are numbers of hemispheres (grid and C3/C4) or sides of stimulation (Cz). C, contralateral stimuli; I, ipsilateral stimuli.
H are shown in Fig. 1C. Good reproducibility was shown in patient C but not in patient P. Therefore results from patients H and C were used for the data in Table 1 (bottom left quadrant) and Fig. 5. Biphasic potentials of similar morphology to those seen with facial stimulation were recorded in response to hand stimulation. Latencies for hand stimulation, however, were consistently longer for N2 contralaterally (219 and 227 ms) and ipsilaterally (250 and 256 ms) than for facial stimulation (contralateral, 162 ± 5 ms; ipsilateral, 159 ± 10 ms; see Table 1). P2 consistently had longer latency for hand stimulation contralaterally (354 and 398 ms) and ipsilaterally (427 and 453 ms) than for facial stimulation (contralateral, 340 ± 18 ms; ipsilateral, 333 ± 21 ms). Peak amplitude of the contralateral N2 for stimulation of the hand was 40% of that for facial stimulation; there was also a decrease in amplitude for P2. Potentials after ipsilateral hand stimulation showed longer peak latencies and reduced peak amplitudes for both N2 and P2.

In patient H, recordings were obtained from an electrode at and posterior to the central sulcus, 3.5 cm above the sylvian fissure, the superior posterior electrode (top electrode, last column of the 5 × 6 grid in Fig. 2) and in Figs. 3–5, patient H) in the hand representation of SI (Penfield and Rasmussen 1955; Woolsey et al. 1979). At this site, N2 and P2 potentials evoked by stimulation of the hand and face were 10 and 50%, respectively, of the corresponding potentials recorded at the maximum, which was located inferiorly.

**Scalp electrode recordings**

Figure 1 shows that scalp LEPs from facial stimulation produced large potentials at Cz and C3/C4 both ipsilateral and contralateral to the side of stimulation. The N2 potential had a vertex maximum (Cz) and the scalp P2 had a maximum at electrode position Pz, located at 40% of the distance from the vertex to the inion (Jasper 1958). Compared with the subdural LEPs, scalp LEPs after facial stimulation showed longer latency N2 waves and shorter latency P2 waves (see preceding text). Scalp recordings were not made in the patients with grids because of the risk of infection if electrodes were applied to the scalp near the incision.

Subdural LEPs from stimulation of either hand showed N2 and P2 latencies (N2, 219 and 256 ms; P2, 354 and 453 ms) that were similar to those recorded at C3/C4 scalp LEPs (N2, 224 ± 5 ms; P2, 333 ± 5 ms). Subdural LEPs from stimulation of the hand were of reduced amplitude in comparison with face. For both facial and hand stimulation, contralateral stimuli usually elicited larger N2 potentials than did ipsilateral stimuli, although differences were not significant (P > 0.05, t-tests).

**Topography of subdural LEPs**

Figure 2 displays a set of subdural LEP waveforms in response to contralateral facial stimulation in patient H. Peak amplitudes for the N2 component are seen over the parietal operculum. A similar pattern was seen for patient C. In patient P, the distribution of LEPs was more anterior with the maximum over the central sulcus. In all patients, the largest N2 potential occurred over facial sensorimotor areas as identified by cortical stimulation mapping (indicated by shading of circles in Figs. 3–5).

Amplitude distributions of subdural LEPs after contralateral face stimulation are shown in Fig. 3. Each circle represents an electrode location; the size and the pattern of shading indicate, respectively, the size of the potential and the sensory and motor effect of cortical stimulation (see lists of symbols in Figs. 3–5). Stimulation-evoked sensations were always paresthesiae on the face. Pain was never evoked in this study and rarely is evoked in other studies of effects evoked by cortical stimulation (Penfield and Rasmussen 1955; Woolsey et al. 1979). The absence of pain evoked by cortical stimulation was consistent with the description of pain processing as a distributed cortical process (Casey et al. 1994; Coghill et al. 1994, 1997; Jones et al. 1991; Talbot et al. 1991), so that stimulation at any individual cortical site might not be expected to evoke pain. Alternatively, pain may not have been evoked because the location of cortex showing pain-related activity is deep in the sylvian fissure or interhemispheric fissure [PET studies and Lenz et al. (1998)] and thus inaccessible to stimulation from the surface (Penfield and Rasmussen 1955; Ranck 1975). Maximal amplitudes for the N2 potential from stimulation of the contralateral face occurred at precentral, postcentral, and parasyllvian areas, at or adjacent to the sites where facial sensory or motor effects were evoked by stimulation (Fig. 3). In patient H, the LEP distribution was located superior and anterior to a greater extent than was the case for patient P, whereas in patient C, the LEP distribution was located inferior to that for patient P. In general, maximal amplitudes occurred over face sensorimotor areas.

Amplitude distributions of subdural LEPs after stimulation of the ipsilateral face in the same three patients are shown in Fig. 4. Maximal amplitudes for the N2 potential occurred over the central sulcus (patients P and H), at or adjacent to sites where cortical stimulation evoked facial movement or sensation. The maximum amplitude in patient C was over the superior temporal gyrus. The P2 potential was maximal at the same electrode as the N2 potential in patients P and H; these electrodes were located over the central sulcus. The P2 maximum was located over the central sulcus, superior and posterior to the N2 maximum, in patient C.

Amplitude distributions of subdural LEPs after contralateral hand stimulation in the two patients with reproducible potentials (C and H) are shown in Fig. 5. Potentials were not reproducible in patient P and consequently were not studied further. Maximal amplitudes for the N2 potential occurred postcentrally, just above the sylvian fissure, at sites where cortical stimulation evoked facial motor or sensory effects. In patient H, the topographic distribution of responses surrounding the maximum was located superior to the sylvian fissure, whereas in patient C, the distribution was located inferior. In both patients, the LEP maximum evoked by hand stimulation was located over the inferior aspect of the central sulcus, facial sensorimotor areas as identified by cortical stimulation (indicated by shading of circles in Figs. 3–5).

In patient H, the N2 maximum was found at the same electrode in response to laser stimulation of both the contra- and ipsilateral face. This electrode was superior and adjacent to the maximum in response to stimulation of the contralateral hand. In patient C, the N2 maximum was
FIG. 3. Peak amplitude percent distribution of N2 and P2 components after contralateral facial laser stimulation in 3 patients with subdural electrodes over the left fronto-temporal areas. For each patient, the subdural electrode with the largest amplitude for each component (N2 and P2) was identified and selected as the maximum. Each circle represents electrode position over the lateral fronto-temporal cortex. Size of the circle indicates the size of the potential relative to the maximum, and shading within the circle indicates the sensory and motor effect of stimulation as listed in the figure. Pure sensory effects were not evoked by stimulation in this patient. CS, central sulcus; LS, lateral (sylvian) sulcus; STG, superior temporal gyrus.

found at the same electrode in response to laser stimulation of both the contralateral face and hand; the N2 maximum in response to stimulation of the ipsilateral face was found adjacent and inferior to the sylvian fissure. The P2 maximum evoked by stimulation of the contralateral hand was found adjacent and superior (patient H) or inferior
(patient C) to the electrode at which the P2 maximum was recorded in response to laser stimulation of the face both ipsi- and contralaterally. Thus maximal LEPs for hand stimulation could be located either inferior or superior to those for facial stimulation. Furthermore, LEPs from stimulation of the ipsilateral hand were recorded over parasympathetic cortex (Fig. 1). Therefore it is difficult to relate the location of maximal LEPs evoked by stimulation of the face and hand to that predicted by the accepted somatotopic organization of SI (Penfield and Rasmussen 1955; Woolsey et al. 1979), even given the variability of such maps (Uematsu et al. 1992).
**Discussion**

Laser-evoked potentials (LEPs) were recorded from the dominant, left, parasympathetic cortex in awake humans with implanted subdural electrodes. These potentials consisted of a negative (N2) wave followed by a positive (P2) wave, which occurred at longer latency after hand than after facial stimulation. The amplitude of subdural LEPs was maximal over the parietal operculum for ipsilateral stimulation of the face and contralateral stimulation of both the face and hand. The topographic distribution of LEPs in response to stimulation of the face and hand was not consistently organized in accordance with the accepted somatotopy of SI (Penfield and Rasmussen 1955; Woolsey et al. 1979; cf. Uematsu et al. 1992). Short-duration cutaneous stimulation with a CO₂ laser has been shown to evoke cerebral potentials due to activation of cutaneous nociceptors (Bromm and Treede 1984; Carmon et al. 1978). The cortical distributions of these subdural potentials suggest that their generators are located in the parietal operculum or in the insula, or in both, consistent with previous PET, magnetoencephalographic, and scalp LEP source analyses. Because interpretation of these previous studies incorporates multiple assumptions, the present results are the first demonstration of direct nociceptive inputs to human parasympathetic cortex.

**Methodologic considerations**

There are latency differences for both N2 and P2 components between scalp and subdural recordings after facial stimulation. The N2 component on scalp recordings has a
The latencies of intracranial LEPs shown in Table 1 (Lenz et al. 1998) are consistent with the suggestion that the N2 is a cortical wave evoked by direct transmission of the laser-evoked afferent volley to cortex. The cutaneous laser stimulus evokes a pure pain sensation due to selective activation of cutaneous Aδ nociceptors (Bromm and Treede 1984; Cameron et al. 1978). Estimated latencies for the onset of the N2 (~50 ms before the peak) attributable to direct conduction from the hand (Fig. 1C) are in good agreement with measured latencies. Latency of N2 conduction from the hand can be estimated from 40-ms receptor activation time (Bromm and Treede 1984), 100-ms conduction delay in the peripheral nerve (Aδ fibers, 8–12 m/s) (Beydoun et al. 1997; Kakigi et al. 1991; Kenton et al. 1980), and 30-ms
conduction delay through the STT (8–10 m/s) (Kakigi and Shibasaki 1991). Thus the N2 of the LEP may represent the cortical response evoked by the afferent volley resulting from the laser stimulus.

The distribution of LEPs recorded in the region of the parietal operculum and insula is consistent with the suggestion that neural elements in the parietal operculum and insula signal pain. The LEPs resulting from laser stimulation of the ipsi- and contralateral face could be evoked in SI or SII or insula. The LEPs after stimulation of the ipsilateral hand (Fig. 1) can be explained by a generator in parietal operculum or insula. Maximum potentials recorded at the same or adjacent electrodes for stimulation of face and hand might be predicted if the generators are in SII or insula, given the compact somatotopy of these areas (Penfield and Rasmussen 1955; Robinson and Burton 1980a,b; Woolsey et al. 1979). LEP generators in the insula or parietal operculum are consistent with the failure of cortical stimulation to evoke pain (Erickson et al. 1952; Penfield and Rasmussen 1955; Woolsey et al. 1979). Stimulation of the surface of the hemisphere would not be expected to activate these deep structures (Penfield and Rasmussen 1955; Ranck 1975) even if electrical stimulation applied within these structures evokes pain (Price and Dubner 1977).

Studies in monkeys are also consistent with activation of SI, parietal operculum, and insula by painful stimuli. Simian SI (Kenshalo and Isensee 1983; Kenshalo et al. 1988), parietal operculum, and insula (Dong et al. 1978, 1989, 1994; Dostrovsky and Craig 1996a; Robinson and Burton 1980a) contain cells that respond to noxious inputs. Intracortical potentials evoked by tooth pulp stimulation (Chudler et al. 1985) are maximal over the parietal operculum just posterior to the central sulcus (see Fig. 3 in Chudler et al. 1986).

Finally, lesions of SI reduce the ability of monkeys to discriminate painful stimuli (Kenshalo et al. 1991).

Thalamic connectivity

Thalamic connectivity links parasyylvian areas to pain-signaling pathways. Cells responding to painful stimulation are recorded in human thalamic nucleusventralis caudalis (Vc) and in subnuclei of Vc parvocellularis (Vcpc) and Vc portae (Vcpor) (Lenz et al. 1993b, 1994b) and ventral medial posterior (VMpo) (Dostrovsky et al. 1996b). Studies of patients at autopsy after lesions of the STT show that the human STT terminates in Vc (Bowsher 1957; Mehler 1962, 1966; Mehler et al. 1960; Walker 1943), Vcpc (Mehler 1966), and Vcpor (Mehler 1966). A recent study shows that thalamic nucleus VMpo receives lamina I STT input in monkeys (Craig et al. 1994). In humans, this region displays a pattern of calcium binding protein staining similar to that found in the region of monkey thalamus where STT terminates and where many cells respond to noxious and cold stimuli (Craig et al. 1994). Stimulation in these nuclei can produce somatic pain (Dostrovsky et al. 1991, 1996b; Halliday and Logue 1972; Hassler and Reichert 1959; Lenz et al. 1993a, 1995), visceral pain (Davis et al. 1995; Lenz et al. 1994a) and memories of previously experienced pain (Davis et al. 1995; Lenz et al. 1994a, 1995). Cortical connections of Vc, Vcpor, and Vcpc have been studied using silver stain (degeneration) techniques at autopsy in patients with thalamic lesions (Van Buren and Borke 1972). This material indicates that Vc projects to SI and SII (Van Buren and Borke 1972), Vcpc projects to anterior insular cortex (Van Buren and Borke 1972), and Vcpor to the inferior parietal lobule, including the parietal operculum and SII (Van Buren and Borke 1972).

In summary, anatomic studies demonstrate connections between human parasyylvian cortical structures and thalamic nuclei that show pain-related activity.

Evidence of nociceptive inputs to parasyylvian cortex also comes from more recent studies of monkey thalamic nuclei VP, VPI, and pulvinar oralis, corresponding to human Vc, Vcpc, and Vcpor (Hirai and Jones 1989). Cells in VP, VPI, pulvinar oralis, and VMpo respond to noxious stimulation (Apkarian and Shi 1994; Bushnell and Duncan 1987; Bushnell et al. 1993; Casey 1966; Casey and Morrow 1983; Chung et al. 1986; Craig et al. 1994; Kenshalo et al. 1980; Morrow and Casey 1992; Perl and Whitlock 1961). VP projects to SI and SII cortex (Burton 1986; Jones 1985; Kenshalo and Willis 1991), whereas VPI projects to SI and insular dysgranular cortex (Burton and Jones 1976; Friedman and Murray 1986). The posterior nuclear group projects widely to parasyylvian structures (Burton 1986; Burton and Jones 1976). Medial and oral division of pulvinar, corresponding to human Vcpor (Hirai and Jones 1989), project to 7b (Burton 1986; Burton and Jones 1976). VMpo projects to anterior dorsal insula at the level of the central sulcus (Craig 1995). These monkey studies suggest that parasyylvian cortical structures are involved in pain-related activity through input from thalamic nuclei corresponding to human Vc, Vcpc, Vcpor, and VMpo.

Functional significance of parasyylvian LEPs

The functional significance of pain-related activity in the parietal operculum and insula is suggested by studies demonstrating that lesions of these structures (Biemond 1956; Davison and Schick 1935; Greenspan et al. 1997; Obrador et al. 1957), and specifically lesions of the parietal operculum (Greenspan et al. 1997), disable the discriminative aspect of pain. Lesions of the insula are associated with decreased unpleasantness of painful stimuli (Berthier et al. 1988) or decreased motivation to escape from painful stimuli (Greenspan et al. 1997). Stimulation of Vc, Vcpc, and Vcpor can reproduce pain associated with a strong emotional or affective dimension (Davis et al. 1995; Lenz et al. 1994a, 1995, 1997) in patients with prior experience of such pain (Lenz et al. 1997). Stimulation of parasyylvian cortex can reproduce sensory experience and the affective tone associated with the original experience (Penfield and Perot 1963). These results suggest that the coupling of pain and a strong affective component is conditioned by the prior experience of pain through corticolimbic connections (Mishkin 1979). The processing of nociceptive signals in the parietal operculum and insula shares many characteristics with the inferior temporal cortex, which is involved in visual memory through corticolimbic connections (see Lenz et al. 1997; Mishkin 1979). Therefore parietal operculum may be involved in the learned component or memory of the affective dimension of pain through corti-
colimic connections. The present results suggest that the involvement of human parasympathetic structures in the sensory and affective dimensions of pain occurs through a mechanism including direct nociceptive input to these structures.

We thank Drs. S. Breiter, N. Crone, and B. Gordon for assistance with radiological studies and D. Jackson for technical assistance. This work was supported by grants to F. A. Lenz from the Eli Lilly Corporation and National Institute of Neurological Disorders and Stroke Grants NS-28598, K08 NS-01384, and P01 NS-32386-Proj. 1. Address for reprint requests: F. A. Lenz, Dept. of Neurosurgery, Meyer Bldg. 7-113, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21287-7713.

Received 5 March 1998; accepted in final form 29 June 1998.

REFERENCES


