rat cerebellum, particularly the external germinal layer. Enkephalin immunoreactivity is especially intense in germinative neural cells but can also be detected in other neuronal and glial cell types at early postnatal ages. Furthermore, the enkephalins have a specific subcellular location and are associated with the cortical cytoplasm but not the cell nucleus. Finally, the presence of enkephalin-like material in the cerebellum is age-dependent; the highest activity is detected during the periods of most rapid cerebellar development.

Our finding that enkephalin-like substances are present in the rat cerebellum only during development is consistent with earlier reports in which the greatest concentrations of β-endorphin and enkephalin were found during the first two postnatal weeks (*5, 6*). The endorphins are known to interact with specific brain receptors (*1*). In the cerebellum the highest levels of tritiated naloxone and tritiated Met-enkephalin binding also occur during the first 2 weeks (*5*). We have found that the major location of enkephalin-like activity in the cerebellum of postnatal rats is the external germinal layer. This proliferative cell matrix generates microneurons over the first 3 postnatal weeks, with a crescendo of activity occurring at 6 to 10 days. On the basis of previous in vivo and in vitro studies on the action of endogenous and exogenous opioids and growing cells and organisms (*2, 3, 9, 14, 15*), it appears that the endorphins interact with opiate receptors on developing cells in such a way as to inhibit cell proliferation; their effect on cell migration and differentiation is unclear (*2, 3, 15*). The presence of enkephalin immunoreactivity in developing but not adult nervous tissues indicates that endogenous opioids are involved in specific aspects of nervous system development.

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References and Notes

1. A. Beaumont and J. Hughes, *Annu. Rev. Pharmacol. Toxicol.* **19**, 245 (1979); H. Akil *et al.*, *Annu. Rev. Neurosci.* **7**, 223 (1984).
2. I. S. Zagon and P. J. McLaughlin, *Science* **221**, 1179 (1983); *Life Sci.* **33**, 2449 (1983); in *Physiological and Pharmacological Control of Nervous System Development*, F. Caciaglia, Ed. (Elsevier, Amsterdam, in press).
3. ———, *Life Sci.* **35**, 2057 (1984).
4. W. Krommer and H. J. Teschemacher, *ibid.* **25**, 835 (1979); A. Bayon *et al.*, *Brain Res.* **179**, 93 (1979).
5. D. Tsang, S. C. Ng, K. P. Ho, W. K. K. Ho, *Dev. Brain Res.* **5**, 257 (1979).
6. C. Maseda, E. G. Aguade, M. A. Mena, J. G. de Yebenes, *Neurosci. Lett. Suppl.* **14**, S237 (1983).
7. J. T. Coyle and C. B. Pert, *Neuropharmacology* **15**, 555 (1976).
8. J. Marzullo and A. Friedhoff, in *Endogenous and Exogenous Opiate Agonists and Antagonists*, E. L. Way, Ed. (Pergamon, Elmsford, N.Y., 1980), pp. 47–50.
9. I. S. Zagon and P. J. McLaughlin, *Pharmacol. Biochem. Behav.*, in press.
10. J. H. Neale, J. L. Barker, G. R. Uhl, S. H. Snyder, *Science* **201**, 467 (1978); E. L. Knodel and E. Richelson, *Brain Res.* **197**, 565 (1980); J. L. Kent, C. B. Pert, M. Herkenham, *Dev. Brain Res.* **2**, 487 (1982).
11. I. S. Zagon and P. J. McLaughlin, *Brain Res.* **170**, 443 (1979).
12. In subsequent experiments it was found that antigen concentrations of 10^{-4}, 10^{-5}, and $10^{-6}M$ could also be used for incubation.
13. M. Herkenham and C. B. Pert, *J. Neurosci.* **2**, 1179 (1982).
14. A. A. Smith, F. W. Hui, M. J. Crofford, *Eur. J. Pharmacol.* **43**, 307 (1977); E. R. Simon, in *Narcotic Drugs: Biochemical Pharmacology*, D. H. Clouet, Ed. (Plenum, New York, 1971), pp. 310–341.
15. I. S. Zagon and P. J. McLaughlin, *Natl. Inst. Drug Abuse Res. Monogr.* **49**, 344 (1984).
16. Supported in part by NIH grants NS-20500 and NS-20623.

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Electrical Sources in Human Somatosensory Cortex: Identification by Combined Magnetic and Potential Recordings

Abstract. *Magnetic fields and electrical potentials produced by neuronal activity have different properties that can be used for the identification of electrical sources in the human brain. Fields and potentials occurring 20 to 30 milliseconds after median nerve stimulation in human subjects were compared in order to investigate the sources of evoked potential components that have been attributed by different investigators to the thalamus or thalamocortical afferents, to separate radial sources in somatosensory cortex and motor cortex, or to a tangential source in somatosensory cortex. The magnetic and potential wave forms were highly similar in morphology, and their spatial distributions were centered over sensorimotor cortex, were dipolar in shape, and differed in orientation by approximately 90 degrees; distances between the minimum and maximum of the magnetic distributions were about 60 percent of those of the potential distributions. These results cannot be accounted for by thalamic sources or radial cortical sources alone, but are consistent with a tangential source in somatosensory cortex, with an additional smaller contribution from radial sources.*

Stimulation of the human median nerve at the wrist elicits a series of evoked potentials (EP's) that can be recorded noninvasively from the head and neck and are widely used to assess neurological abnormalities in the somatosensory pathway. The anatomical sources for some of these potentials are established but there is disagreement about others (*1*). We have used the different properties of magnetic and potential recordings to test alternative hypotheses for the sources of EP's at 20 and 30 msec, the origins of which are controversial.

The 20- and 30-msec EP's are seen at scalp locations contralateral to the nerve stimulated (*2, 3*). Evoked potentials at parietal locations are negative to positive (N20-P30), whereas those at frontal locations have peaks at similar latencies but opposite polarities (P20-N30). Evoked potentials with similar wave forms and larger amplitudes are seen in cortical surface recordings, with N20-P30 maximal in the hand representation area of somatosensory cortex and P20-N30 maximal in the hand area of motor cortex (*4, 5*). These distributions and recordings in patients with thalamic or cortical damage have led to three hypotheses concerning sources for N20 and P20 (*6*): (i) thalamus or thalamocortical afferents (*7, 8*); (ii) a pair of radially oriented sources in somatosensory cortex and the motor cortex (*3, 9*); and (iii) a single tangentially oriented source in area 3b of somatosensory cortex (*4, 5, 10*).

Magnetic recordings of brain activity can be made with devices capable of detecting the extremely small magnetic fields produced by neuronal currents (*11*). Theory indicates that surface magnetic and potential distributions have different properties that can be used for source identification (*11–13*): (i) Whereas potential recordings are sensitive to both tangential and radial current sources, magnetic recordings are sensitive only to that portion of the source having a tangential orientation to the scalp. (ii) For tangential dipoles, the surface magnetic distribution is oriented at right angles to the potential distribution. (iii) Unlike potential recordings, magnetic recordings are uninfluenced by the skull and scalp, and this results in magnetic distributions with a smaller spatial extent. Because of these different properties, the three source hypotheses lead to different predictions about the magnetic and potential distributions for the 20- to 30-msec potentials (*6*). We report direct comparisons of magnetic and potential record-

ings that strongly support the existence of a tangentially oriented source in somatosensory cortex.

Magnetic and potential recordings after right median nerve stimulation were obtained by conventional techniques (*14*) from 50 to 103 locations over the left hemisphere in two subjects (S1 and S2).

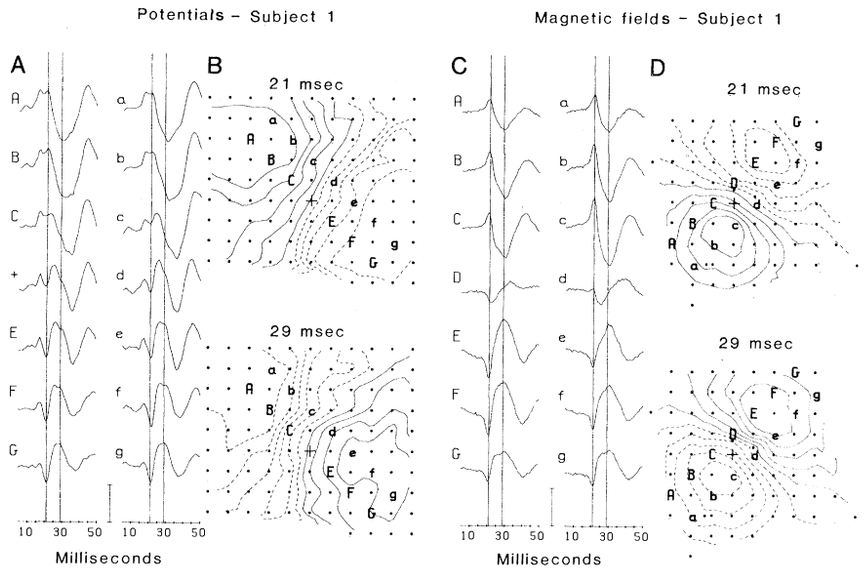

Fig. 1. Comparison of potential (A and B) and magnetic (C and D) recordings from the left hemisphere of subject 1. (A) Potential wave forms recorded from two parallel arrays of electrodes along the major axis of the potential distributions. Positive voltage relative to linked-ear reference is upward; calibration, 5 μV. (B) Isopotential contour maps plotted at the latencies of the 20-msec (top) and 30-msec (bottom) peaks in the EP wave forms shown in A (indicated by the vertical lines at 21 and 29 msec). Solid and dotted contours indicate positive and negative voltage; each contour represents 10 percent of the difference between maximum and minimum at the indicated latencies. Recording sites are indicated by dots and letters. The left side of the map is toward the nose and the bottom toward the left ear; scalp location C_3 (approximately over the sensorimotor hand area) is indicated by a cross. (C) Magnetic wave forms recorded from two parallel arrays along the major axis of the magnetic distributions. Vertical lines are plotted at the same latencies as are shown in A and B. Magnetic flux out of the head is upward; calibration, 1 pT. (D) Isofield contour maps plotted at the latencies indicated by the vertical lines in C, on the same scale as the potential maps in B. Solid and dotted contours indicate magnetic flux flowing out of and into the head. Map orientation and other details are as in B.

The EP wave forms and spatial distributions for S1 (Fig. 1, A and B) confirm those described previously (*2, 3*). At anteromedial locations (locations A to C and a to c) the EP wave forms were positive to negative with major peaks at about 21 and 29 msec, whereas at posterolateral locations (locations E to G and e to g), the major peaks were similar in latency but opposite in polarity. The potential distributions at both latencies were centered over sensorimotor cortex about 1.5 cm posteromedial to C_3.

Corresponding magnetic field data for S1 are shown in Fig. 1, C and D (*15*). The magnetic wave forms were similar in morphology to the EP's, with major peaks at the same latencies. The magnetic distributions were centered over the same region posteromedial to C_3 but differed from the potential distributions both in orientation and extent. These results are confirmed by the data for S2 (Fig. 2). Averaged over both subjects and both peaks, the magnetic and potential distributions differed in orientation by 89°, and the distances between their extrema were 6.2 and 9.8 cm.

To summarize, the magnetic and potential distributions were centered over the same region, near the sensorimotor hand representation, and differed in orientation by about 90° and in extent by about 60 percent. The ability of the three hypotheses concerning sources to account for these results was explored with a four-shell volume conduction model of the head and either one or two dipole sources (*16*).

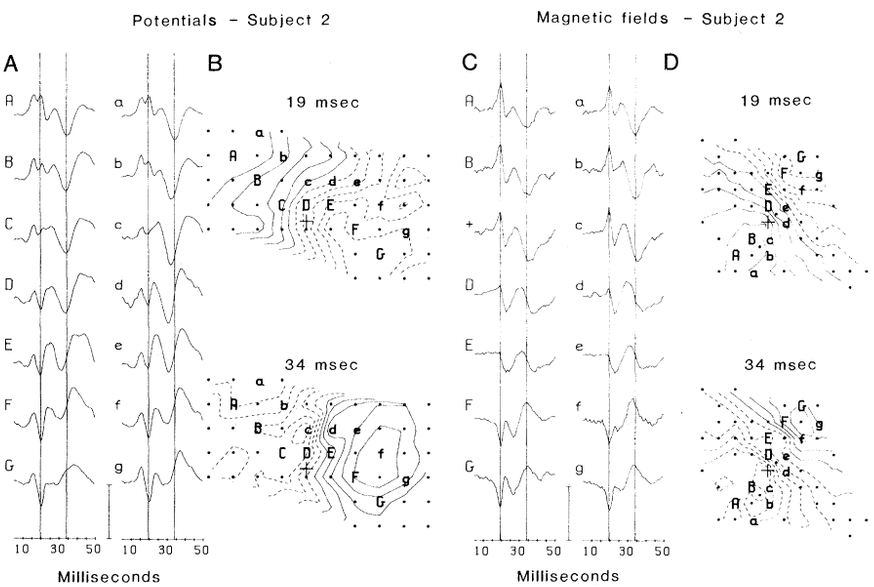

Fig. 2. Comparison of potential (A and B) and magnetic recordings (C and D) for subject 2. Contour maps are plotted at the peaks of the 20- and 30-msec peaks, which occur in this subject at 19 and 34 msec. Other details are as in Fig. 1.

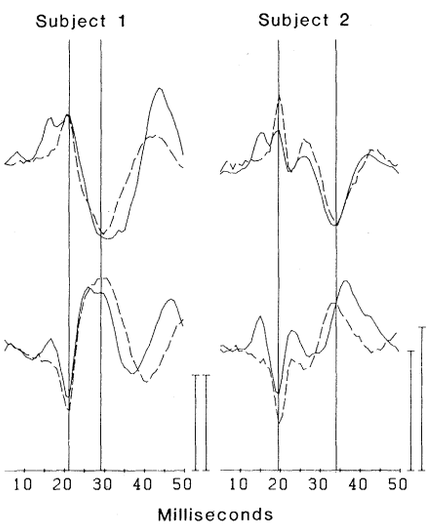

Fig. 3. Comparison of potential (solid) and magnetic (dotted) wave forms for subject 1 and subject 2 at locations near the extrema of the distributions shown in Figs. 1 and 2. Calibrations: potential wave forms (left), 5 μV; magnetic wave forms (right), 1 pT.

1) Sources deep enough to approximate the thalamus produce magnetic and potential extrema more than 70 percent farther apart than those obtained. Except for their superficial terminals near somatosensory cortex, thalamocortical afferents are also too deep to account for the obtained data (*17*).

2) Different pairs of nearly radial sources are capable of explaining the potential and magnetic data taken separately, but the same pair of sources cannot simultaneously explain both sets of data. Two radial dipoles located in the crowns of the precentral and postcentral gyri can account for the obtained magnetic data if they are tilted so as to produce a nonzero tangential component oriented frontomedially. However, such sources produce potential extrema separated by distances 50 to 60 percent smaller than those obtained; this is true even when the dipoles are tilted more than 80° from a purely radial orientation. Conversely, two nearly radial dipoles located far enough anterior and posterior to account for the obtained potential data produce magnetic distributions with multi-dipolar shapes that can be clearly discriminated from those obtained. In addition, such sources predict maximal cortical surface EP's far anterior and posterior to those obtained in somatosensory and motor cortex (*4, 5, 8, 18*).

3) A single tangential dipole located 2.5 to 3 cm below the outer shell accounts well for both the potential and magnetic data; its magnetic and potential distributions are oriented at 90° (the obtained value was 89°) with extrema separated by 5.9 to 6.8 and 8.8 to 11.2 cm (the obtained values were 6.2 and 9.8 cm). For the 20-msec activity, such an "equivalent dipole" (*6*) corresponds to a tangential current flow (posterior to anterior intracellularly, with an anterior-to-posterior extracellular return current), whereas for the 30-msec activity it corresponds to current at the same location and orientation but in the opposite direction. These patterns of current flow occur when pyramidal cells in area 3b of somatosensory cortex are activated by a thalamocortical afferent volley, producing intracellular current flow from cell bodies to apical dendrites and followed 5 to 10 msec later by intracellular current in the reverse direction (*19*).

If a tangential dipole source were the only one active, then the shapes of the magnetic and potential wave forms would be identical. Figure 3 shows that the obtained wave shapes were similar, but not identical, during the 20- to 30-msec interval; this suggests a smaller contribution of radial sources in somatosensory cortex or motor cortex, or both, in addition to the area 3b source (*20*).

These results demonstrate the value of combined potential and magnetic recordings for source identification. Potential recordings are sensitive to distant or radial sources and hence may permit the study of activity not evident in magnetic recordings. Magnetic recordings are differentially sensitive to superficial, tangential sources and hence may permit activity of such sources to be dissociated from other activity. Direct comparison of magnetic and potential recordings obtained from the same subjects and conditions permits stronger inferences concerning the number, location, and orientation of electrical sources in the human brain than are possible with either technique alone.

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References and Notes

1. I. Bodis-Wollner, Ed. *Evoked Potentials* (New York Academy of Science, New York, 1982); J. Courjon *et al.*, Eds., *Clinical Applications of Evoked Potentials in Neurology* (Raven, New York, 1982); A. M. Halliday, Ed., *Evoked Potentials in Clinical Testing* (Churchill-Livingstone, Edinburgh, 1982); M. Stohr *et al.*, *Evozierte Potentiale* (Springer-Verlag, Berlin, 1982).
2. G. D. Goff *et al.*, *Electroencephalogr. Clin. Neurophysiol.* **42**, 57 (1977).
3. J. E. Desmedt and G. Cheron, *ibid.* **50**, 404 (1980).
4. T. Allison *et al.*, *Prog. Clin. Neurophysiol.* **7**, 51 (1980).
5. R. J. Broughton *et al.*, *Can. J. Psych.* **35**, 136 (1981); T. Allison, *Ann. N.Y. Acad. Sci.* **388**, 671 (1982); H. Lueders *et al.*, *J. Neurosurg.* **58**, 885 (1983).
6. Sources have been proposed mainly for N20 and P20, although the two cortical hypotheses apply to the 30-msec potentials as well. The thalamic hypothesis (*7, 8*) refers only to N20; P20 has not been explicitly considered. By "source" we mean a specified configuration of transmembrane currents in a particular brain region; under certain conditions such physiological sources can be adequately modeled by "equivalent dipoles" [C. C. Wood, *Ann. N.Y. Acad. Sci.* **388**, 139 (1982)].
7. T. Allison, *Electroencephalogr. Clin. Neurophysiol.* **14**, 331 (1962); T. Fukushima *et al.*, *ibid.* **40**, 481 (1976); K. Chiappa, *Evoked Potentials in Clinical Medicine* (Raven, New York, 1983).
8. G. G. Celesia, *Arch. Neurol. (Chicago)* **36**, 399 (1979).
9. R. Q. Cracco, *Prog. Clin. Neurophysiol.* **7**, 1 (1980); D. Papakostopoulos and H. J. Crow, *ibid.*, p. 15: P. J. Maccabee *et al.*, *Electroencephalogr. Clin. Neurophysiol.* **55**, 34 (1983).
10. This hypothesized source is tangential because area 3b of somatosensory cortex, which receives the heaviest thalamocortical input, is buried in the posterior bank of the central sulcus and its pyramidal cells are therefore oriented parallel instead of perpendicular to the scalp.
11. D. Cohen, *Science* **175**, 664 (1972); for review, see S. J. Williamson and L. Kaufman [*J. Magn. Magn. Mater.* **22**, 129 (1981)].
12. G. Baule and R. McFee, *J. Appl. Phys.* **36**, 2066 (1965); D. Cohen, *Phys. Today* **28**, 34 (1975); M. Reite and J. Zimmerman, *Annu. Rev. Biophys. Bioeng.* 7, 167 (1978); D. Cohen and B. N. Cuffin, *Electroencephalogr. Clin. Neurophysiol.* **56**, 38 (1983); L. Kaufman and S. J. Williamson, *Ann. N.Y. Acad. Sci.* **340**, 45 (1980). These theoretical relationships are based on dipole sources in spherical models of the head and are thought to apply to current sources in the brain.
13. B. N. Cuffin and D. Cohen, *Electroencephalogr. Clin. Neurophysiol.* **47**, 131 (1979).
14. Median nerve stimuli were 0.5 msec constant-current pulses (one per second) at an intensity eliciting a thumb twitch. Potential recordings were obtained from disk electrodes referred to a linked-ear reference. Magnetic recordings were made in the MIT magnetically shielded chamber using a SQUID (superconducting quantum interference device) with a 2.8-cm monopolar coil configuration 0.7 cm above the scalp. Signals were amplified, filtered using matched bandwidths (3 to 300 Hz), and digitized at 1300 Hz for signal averaging ($n > 100$; sampling epoch 197 msec; 64-msec prestimulus baseline). Contour maps were computed by linear interpolation; extrema were defined as the recording sites having the maximum and minimum values.
15. Magnetic distributions of similar orientation were reported by D. Brenner *et al.* [*Science* **199**, 81 (1978)] and L. Kaufman *et al.* [*Int. J. Neurosci.* **15**, 223 (1981)].
16. The model employed was that of B. N. Cuffin and D. Cohen (*13*), except for the use of shell radii of 10.0, 10.2, 10.9, and 11.5 cm, derived from J. Talairach and G. Szikla [*Atlas of Stereotaxic Anatomy of the Telencephalon* (Masson, Paris, 1967)]; T. W. Todd, *Anat. Rec.* **27**, 245 (1924); _____ and W. Kuenzel, *J. Anat.* **58**, 231 (1924).
17. Activity in even the most superficial region of thalamocortical afferents is unlikely to account for much of the obtained magnetic data since currents associated with action potentials would be expected to produce distributions appropriate for a pair of opposing dipoles rather than the single dipolar pattern obtained [see J. P. Wikswo, J. P. Barach, J. A. Freeman, *Science* **208**, 53 (1980)].
18. H. Jasper *et al.*, *J. Nerv. Ment. Dis.* **130**, 536 (1960); P. Stohr and S. Goldring, *J. Neurosurg.* **31**, 117 (1969).
19. For review, see C. C. Wood and T. Allison [*Can. J. Psychol.* **35**, 113 (1981)].
20. Differences between magnetic and potential wave forms are evident both before and during the 20- to 30-msec interval: (i) A diffuse positive peak at 13 to 16 msec is present in the potential wave forms but absent in the magnetic wave forms (Figs. 1A, 2A, and 3). This peak reflects subcortical activity (*1*) that contributes little to the magnetic recordings because of their insensitivity to deep sources. (ii) The magnetic and potential wave forms diverge over the 20- to 30-msec interval in a manner suggesting activity of radial sources. Although evident in wave forms at the extrema shown in Fig. 3, the divergence is more pronounced between extrema at locations immediately over sensorimotor cortex (compare the potential and magnetic wave forms at locations C to E and c to e in Figs. 1 and 2). Such a divergence could be due to radial sources in area 1 of somatosensory cortex (4) or motor cortex (*3, 9*) and F. Mauguière *et al.* [*Brain* **106**, 271 (1983)]. Differences between the magnetic and potential data suggesting radial sources are being assessed quantitatively by calculating the difference between the obtained potential distribution and that generated by the best-fitting dipole source for the obtained magnetic distribution (D. Cohen and B. N. Cuffin, in preparation).
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