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Neuromagnetic Evidence of Spatially Distributed Sources Underlying Epileptiform Spikes in the Human Brain

Abstract. *Neuromagnetic measurements were performed on 17 subjects with focal seizure disorders. In all of the subjects, the interictal spike in the scalp electroencephalogram was associated with an orderly extracranial magnetic field pattern. In eight of these subjects, multiple current sources underlay the magnetic spike complex. The multiple sources within a given subject displayed a fixed chronological sequence of discharge, demonstrating a high degree of spatial and temporal organization within the interictal focus.*

Human epilepsy is a disorder characterized by an uncontrolled discharge of brain neurons that produces seizures. In focal epilepsy, the source of the seizure is confined to limited regions of the brain. In the interictal period between seizures, isolated electrical spikes may often be recorded both from the scalp and from electrodes implanted within the brain (*1*). Interictal spikes have aroused clinical interest because of the possible role that they may play in diagnosis and in identifying the epileptic focus for surgical resection. Interictal spikes are also of neurophysiological interest in that they represent the spontaneous activity of epileptogenetic cortex in which the normal regulatory mechanisms have been disrupted.

Examination of the precise timing of the interictal spike recorded simultaneously from a number of scalp locations in the electroencephalogram (EEG) indicates that these spikes frequently differ in wave shape and latency at different sites; thus, the recorded discharge often appears to be composed of separately firing generators within the epileptic zone (*2*). The impression of multiple generators is confirmed by recordings obtained from indwelling electrodes (*3*). Furthermore, when spike complexes recorded from such depth electrodes are averaged, evidence of a systematic temporal order of discharge in adjacent cortical regions is often observed (*4*). Such data suggest the presence of preferred pathways of epileptiform discharge within the region of the interictal focus, but are insufficient to provide a complete mapping of the discharge zone.

Interictal spikes recorded in the EEG also produce extracranial magnetic fields that may be recorded in the magnetoencephalogram (MEG) (*5*, *6*). We demonstrated earlier that neuromagnetic mapping may identify the three-dimensional location of single sources of interictal spiking in the human brain with greater accuracy than the EEG (*6*), presumably because magnetic fields are not distorted or attenuated by the highly resistive skull (*7*). We now report that complex patterns of multifocal interictal discharges may be mapped directly from measurements of extracranial magnetic fields to provide a clear visualization of the contributing generators. These patterns exhibit a high degree of temporal and spatial organization of discharges within the epileptic zone.

Subjects were drawn from an ongoing neuromagnetic study of the interictal spike complex and consisted of 17 patients with focal (partial) seizure disorders. All subjects displayed orderly magnetic fields associated with interictal spiking. In nine subjects, the interictal spike appeared to originate from a single source. However, in the other eight subjects, distinct spatiotemporal discharge patterns suggested multiple intracranial generators. Two of these subjects showed particularly evident separation in the timing and location of sources producing the discharge sequence. Both had frequent interictal EEG spikes localized in the right temporal region.

The normal component of the extracranial magnetic field produced by spontaneous interictal spikes was measured and mapped with previously developed procedures (*6*, *8*). Visually identified interictal spikes in the scalp EEG recorded from a bitemporal bipolar montage (*9*) were used as time markers to generate digital averages of the magnetic signal over at least 20 spikes for each MEG probe position in a rectangular recording matrix covering the interictal focus. Sequential magnetic field maps were computed at 4-msec intervals during the averaged magnetic spike complex. From these, distinct temporal components of the magnetic spike were identified. The three-dimensional locations of putative sources were calculated for the identified magnetic field maxima of each component (*10*). These field distributions were plotted on the photographic image of each subject's head. Finally, computerized tomographic scans (CT) were obtained at levels indicated by the surface MEG localization to determine the position and depth of underlying cortical structures.

Figure 1A displays an outline of the right side of the first subject's head, with both the MEG recording matrix (dots) and scalp EEG electrode locations marked. The routine scalp EEG obtained with bipolar recording (Fig. 1E) showed a focal right anterior–midtemporal spike (electrodes F8–T4) which was used as a time marker for averaging ten channels of referential EEG (Fig. 1F) (*11*). The EEG spike from different regions of the right hemisphere occurred with a slight variation in latency.

Averaged magnetic spikes measured from each point in the MEG recording matrix are shown in Fig. 1G. Two distinct spike morphologies may be observed in areas of the matrix labeled a and b. Each of these spike morphologies appears in opposite polarity within a complementary region of the matrix (labeled â and b̂). Superimposed traces of the complementary pairs (solid and dotted lines in Fig. 1B) indicate that they are nearly mirror images, reflecting scalp locations where the magnetic flux simultaneously emerge from (upward deflection) and reenter (downward deflection) the cranium. Such a magnetic field pattern is expected if the underlying source for each of the pairs is modeled as a current dipole oriented tangentially to the scalp (*12*). The measured fields therefore provide evidence of two dipoles or sources (a and b) that differ in both location and orientation.

The discharge sequence between the two sources is composed of four components. The magnetic fields associated with each component (Fig. 1, H to K) display well-defined maxima where the normal components of the magnetic flux emerge from (plus) and reenter (minus) the cranium. From the field maxima of components 1 and 4, the location of source a (arrows in Fig. 1, H and K) was determined to be within the inferior portion of the right anterior temporal lobe. The magnetic field patterns associated with components 2 and 3 of source b indicate a location in the inferior temporal lobe posterior to source a (arrows in Fig. 1, I and J).

The depth of both sources a and b, calculated by the method of Williamson and Kaufman (*10*) from the angle subtended by the two field maxima of each component with respect to the center of a sphere modeling the cranium, was approximately 3 cm. The locations of both

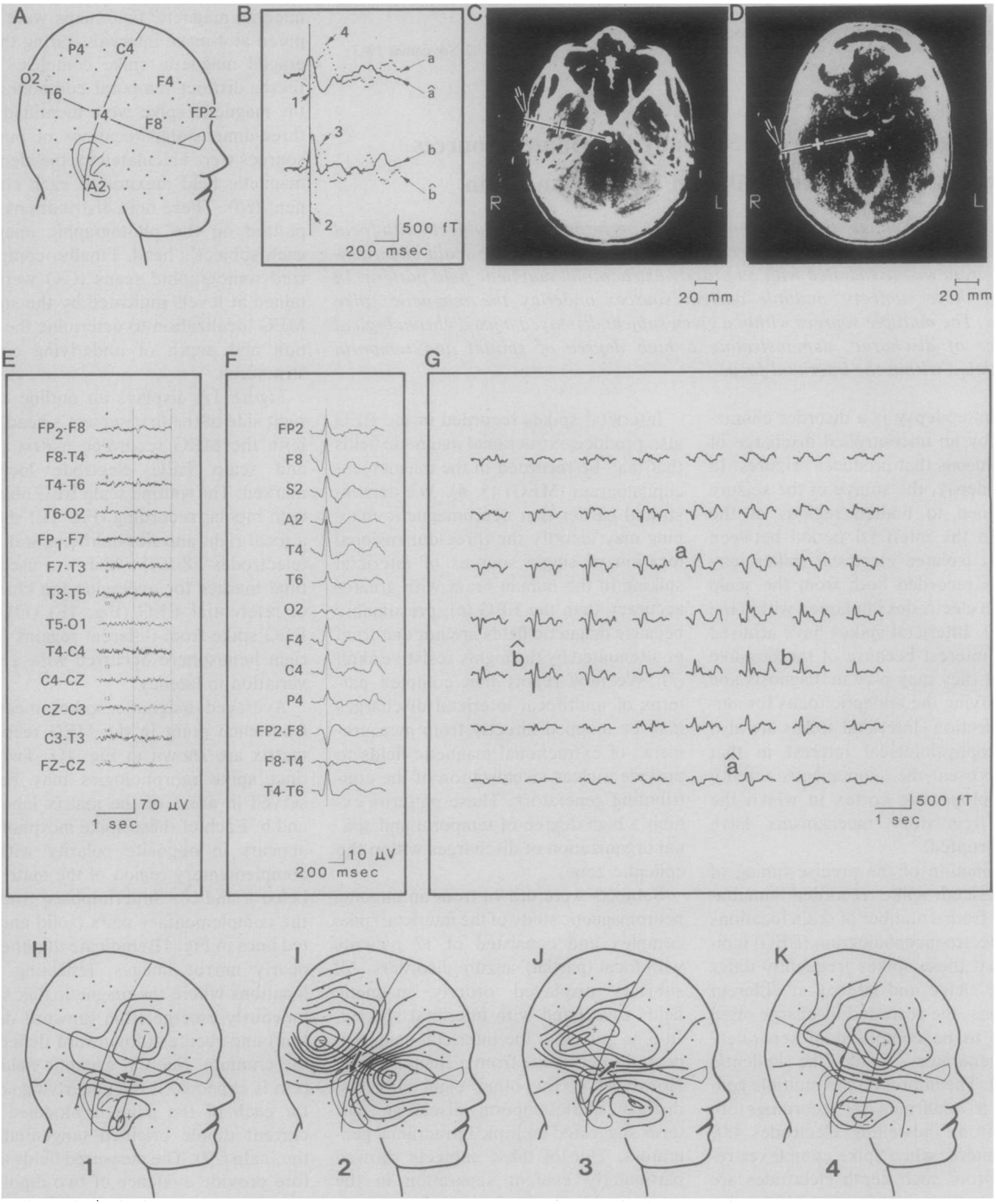

Fig. 1. (A) Rectangular MEG measurement matrix (2-cm spacing) oriented along the temporal axis of subject 1. All EEG electrodes are marked except the sphenoidal electrode (S2). (B) Enlargements of averaged magnetic spikes from separate complementary regions (*a* and *b*) of the scalp show four components; the opposing polarities reflect the magnetic field simultaneously emerging from (upward) and reentering (downward) the cranium. (C and D) Computerized tomography scan sections at the levels of sources *a* and *b*, respectively, show the depth of the source (cross) located along a line connecting the surface location of the source marked with a washer (arrow) to the center of the cranium. (E) Spike in the raw EEG recorded from both hemispheres. (F) Averaged EEG spike from three bipolar channels (lower three traces) and ten electrodes referenced to a noncephalic site (upper ten traces). (G) Averaged magnetic spikes recorded from the MEG matrix exhibit two distinct complementary regions of differing morphology marked *a* and *b* (fT, femtotesla). (H to K) Isocontour maps displaying the magnetic fields for each of the four temporal components of the magnetic spike complex (see text for details).

sources were plotted on CT sections along radii connecting the approximate center of the cranium with respective surface locations of the sources, which were marked with aluminum washers attached to the scalp. This showed that both sources lay between the mesial and lateral regions of the right temporal lobe, on its inferior surface.

The same analysis was undertaken for the second subject. As in subject 1, averaged spikes in the referential EEG showed a slight temporal dispersion across the scalp (Fig. 2F). The averaged magnetic spike complex was once again composed of two temporal components produced by two separate sources (Fig. 2, B and G). Sequential magnetic field maps demonstrated that components 1 and 3 were produced by a common source a in the anterior temporal lobe (Fig. 2, H and J). Components 2 and 4 were produced by source b, inferior and posterior to source a (Fig. 2, I and K). Computed depths for both sources were approximately 3 cm from the surface of the scalp, and CT sections showed both sources to be located on the edge of a large area of scar tissue in the right temporal lobe (Fig. 2, C and D).

In both of these subjects, the interictal magnetic spike complex was produced by a systematic patterned discharge between two sources in the temporal lobe. Although the requirement of over 1000 spikes for the completion of an averaged

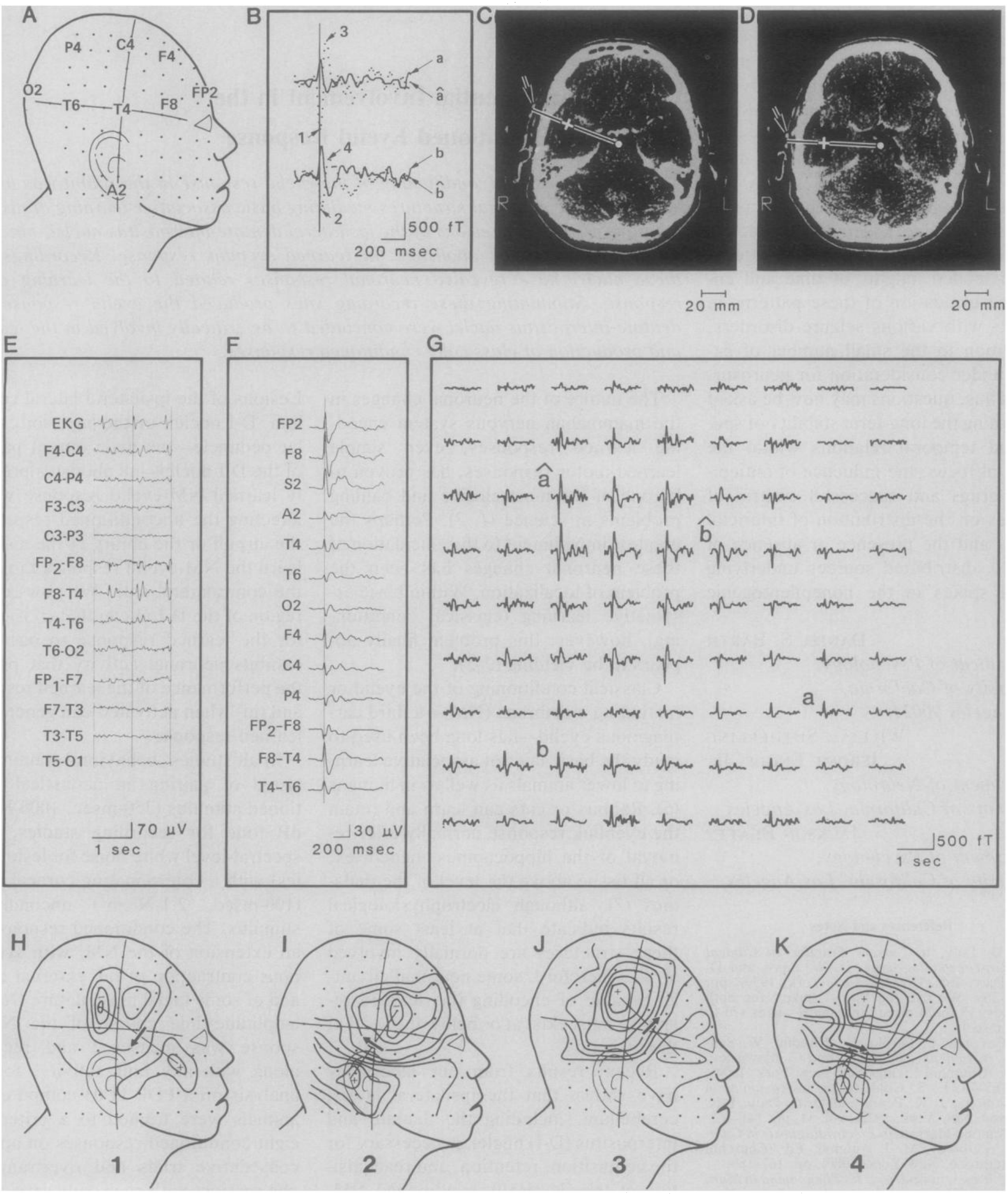

Fig. 2. Averaged electrical and magnetic spike activity measured from the right hemisphere of subject 2. See Fig. 1 for details.

magnetic field map necessarily obscures potentially interesting variations from one spike to the next, the resultant fields represent extremely stable components of the discharge pattern that were replicated precisely on successive days. Similar patterns have been seen in half of the subjects we have studied.

Although the anatomical location of the measured sources is clear, the possibility remains that other sources may also be active either before or after the observed discharges, since the MEG apparatus we used measures only tangential sources (*13*) and is more sensitive to lateral than to mesial generators (*14*). Nevertheless, the multiple sources measured neuromagnetically in this study are similar in complexity to what would be expected from invasive recordings performed with electrodes implanted deep in the brain.

These noninvasive neuromagnetic measures provide a detailed characterization of interictal discharge patterns over extended lengths of time and enable the evaluation of these patterns in patients with various seizure disorders, in addition to the small number of patients under consideration for neurosurgery. Thus, questions may now be asked concerning the long-term stability of spatial and temporal relations within the interictal focus, the influence of antiepileptic drugs and successful control of seizures on the distribution of interictal spikes, and the presence or absence of spatially distributed sources underlying benign spikes in the nonepileptogenic brain.

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Cerebellum: Essential Involvement in the Classically Conditioned Eyelid Response

Abstract. *Classical conditioning of the eyelid response in the rabbit was used to investigate the neuronal structures mediating basic associative learning of discrete, adaptive responses. Lesions of the ipsilateral dentate-interpositus nuclei, but not of the cerebellar cortex, abolished the learned eyeblink response. Recordings from these nuclei have revealed neuronal responses related to the learning of the response. Stimulating these recording sites produced the eyelid response. The dentate-interpositus nuclei were concluded to be critically involved in the learning and production of classically conditioned responses.*

The nature of the neuronal changes in the mammalian nervous system encoding learned responses, even simple learned motor responses, has proven to be one of the most elusive and baffling problems in science (*1, 2*). Perhaps the greatest impediment to the elucidation of these neuronal changes has been the problem of localization. Within basic associative learning (classical conditioning), however, this problem finally appears to be yielding (*2–5*).

Classical conditioning of the eyelid or nictitating membrane (NM)—a third cartilaginous eyelid—has long been used to study the basic laws of associative learning in lower animals as well as in humans (*6*). Rabbits or cats can learn and retain the eyeblink response normally after removal of the hippocampus, neocortex, or all tissue above the level of the thalamus (*7*), although electrophysiological results indicate that at least some of these structures are normally involved (*8, 9*). Therefore, some neuronal circuitry capable of encoding this learned response must exist at or below the level of the thalamus.

Recent results from our laboratory have shown that the ipsilateral lateral cerebellum, including the dentate and interpositus (D-I) nuclei, is necessary for the acquisition, retention, and reacquisition of the classically conditioned NM-eyelid response in the rabbit (*3*), a finding that has been replicated by others (*4*). Lesions of the ipsilateral lateral cerebellum, D-I nuclei, or the superior cerebellar peduncle—the main output pathway of the D-I nuclei—all abolish a previously learned NM-eyelid response without affecting the unconditioned response to the airpuff or the ability of the animal to learn the NM-eyelid response rapidly on the contralateral side. We now report a region of the D-I nuclei that (i) is critical for the learned response to occur, (ii) exhibits neuronal activity that predicts the performance of the learned response, and (iii) when activated can generate the learned response.

In all studies, behavioral training consisted of pairing an acoustical conditioned stimulus (350-msec, 1000-Hz, 85-dB tone for recording studies, 36-dB spectral-level white noise for lesion studies) with a coterminating corneal airpuff (100-msec, 2.1-N/cm^2) unconditioned stimulus. The conditioned response was an extension of the NM, with synchronous contraction of the external eyelids and of some facial musculature (*10*). The amplitude-time course of the NM response was measured and recorded, along with any unit activity, for later analysis on a PDP 11/03 computer. The animals were trained to a criterion of eight conditioned responses on any nine consecutive trials and overtrained by one session, with each daily session consisting of 120 trials. For the recording studies, the manipulator base (short-