THE USE OF EQUIVALENT SOURCE MODELS IN EP RESEARCH AND DIFFERENTIAL DIAGNOSIS

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Abstract

The dipole localization method (DLM) is a technique for finding an equivalent source of scalp-recorded evoked potentials. It is based on the principles of potential theory as applied to a layered spherical medium that simulates the head. The purpose of the method is to organize EP data, identify normative potential patterns and identify cases of dysfunction.

We report applications of DLM to the responses to median nerve stimulation and photic flash, in normal subjects and those suffering from documented neurological disorders. DLM is also applied to the scalp-recorded potentials generated by known current sources. In most cases, the position and direction of the equivalent sources are comparable to the locus and orientation of the presumed or known physiological generators.

Several possible uses of DLM in clinical applications will also be discussed.

Introduction

Investigators in electrocardiography and electroencephalography have developed methods for finding the equivalent sources of empirical voltages observed on the torso or scalp. These techniques are generally applications of electric field theory for finding theoretical sources of surface potentials in a medium that more or less simulates the physical medium containing the actual bioelectric generators. Since the head is architecturally and functionally complex and these methods involve rather few physical assumptions and parsimonious arguments (in order to lead to tractable mathematical models), one might be justifiably critical in attempts to overinterpret theoretical sources as actual physiological generators.

However, one of these mathematical models has provided useful results to the problem of localizing the neural generators of potentials evoked by sensory stimuli. In this particular method, the dipole localization method (DLM), the current dipole source for scalp-recorded EP components is constructed in a layered conducting sphere that simulates the head. Since this approach is noninvasive and results are easily (and inexpensively) obtained, it is desirable to establish those situations in which the theoretical results are anatomically reasonable and clinically useful. This is not to suggest that we should seek a literal interpretation of the virtual source produced by DLM. A current dipole source can be modeled by two point charges of equal magnitude but opposite polarity separated by a small distance. We are interested in assessing how closely the instantaneous potential fields observed at a distance (on the scalp) appear to be generated from such a theoretical source, rather than arguing that such a source actually resides in the brain. The purpose of assuming such a source is to make the inverse problem of finding the generators of surface potentials well-posed.

Thus, the equivalent sources produced by DLM cannot represent individual neuronal units, although they do represent the superposition of such units. One question that arises is whether or not the position and direction of an equivalent source correspond reasonably well to the locus and orientation of the actual generators. One might argue that the simplifications of the model probably preclude accurate and reliable source localization which generalizes across subjects. A second question concerns the possibility of the transmission, via volume conduction, of a recordable signal from deep structures to the scalp. With the possible exception of so-called far-field brain stem auditory and somatosensory evoked potentials [1,2] clinical EEG is largely based on the assumption that the scalp-recorded potentials are generated by sources very close to the recording electrodes on the scalp (e.g., [3]).

The purpose of this paper is to give partial answers to these questions. We shall present several empirical cases in which the equivalent sources calculated by DLM have agreed rather well in position and direction with the locus and orientation of the presumed generators of scalp-recorded data, with results that generalize across subjects. We shall also try to establish how closely the results of potential theory, as employed in the DLM model, apply to the electrical properties of the head. This will be demonstrated by applying DLM to the scalp-recorded potentials generated by a known current source. Since these results are encouraging, we shall also suggest some promising areas of future research.

The Dipole Localization Method (DLM)

If, as a first step, the head is modeled by a homogeneous sphere of radius R and conductivity S, then the potential V(A,D) that would be produced by a current dipole D at a surface electrode A is given in closed form by a formula in [4]. Then the equivalent dipole source for surface data (generally averaged evoked potentials) recorded t ms poststimulus is found by minimizing

$$\mathrm{RHO}(D) = \sum_{i=1}^{n} (V(A_i,D) - V(A_i,t))^2 \Big/ \sum_{i=1}^{n} V^2(A_i,t)$$

where $V(A_i,t)$ is the empirical AEP at electrode A_i at latency t ms. In most of our work, linked ears have been used as the reference. This minimizing dipole will be denoted by D_1 to emphasize that it has been derived from the one-layer model of the head. Its six parameters minimize the least squares difference between theoretical and empirical potentials.

Several investigators have used this method of analysis to find the equivalent sources of potentials evoked by median nerve stimulation [5], tibial nerve stimulation [6], light flash [7,8], pattern-reversal stimulation [9,10], and auditory click [6]. In addition, it is being used in neuropsychological investigations to recognize the brain response in the central masking paradigm [11] and to identify the laterality of brain response during verbal processing [12] and under stress conditions [13]. M. Schneider [14] was one of the first investigators to use DLM when he attempted to "localize" the origin of petit mal discharges.

One can account for the presence of the skull, a layer whose resistivity is approximately 80 times that of the brain and scalp, by simulating the head by three concentric layers. V(A,D) no longer has a closed form, but D_3, the equivalent source in this layered medium, can be obtained from D_1 by the arguments in [15]. In effect, D_3 is farther from the center of the medium than is D_1 and has greater strength (larger moments).

When applying DLM to EP data, we have usually first identified those epochs during which the quantity

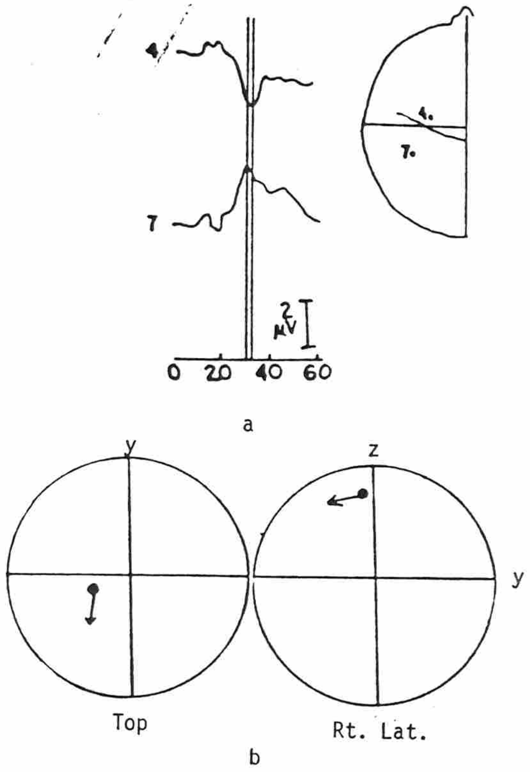
$$p(t) = \left(\sum_{i=1}^{n} V^2(A_i,t)\right)^{\frac{1}{2}} \text{ achieves a relative maximum.}$$

This quantity is a measure of strength or spatial "power" and the maxima apparently occur at those times of maximum underlying synchronous activity [16,17]. Before ascribing a physical meaning to DLM results, we have insisted that RHO remain small during an epoch in question (a dipole fits the data well), and that the dipole source remain stable or, if changing, move in a manner consistent with the apparent motion of potentials along sensory pathways. These constraints are necessary, but, as we shall see, not sufficient for the equivalent source to be anatomically reasonable.

DLM Applied to the Response to Median Nerve Stimulation

Several investigations have provided evidence for the neural origins of the P20-N30 sequence of potentials evoked by median nerve stimulation [18,19]. In particular, the feature or component appearing at approximately 30 ms poststimulus (denoted P30-N30) appears to be generated in the contralateral hemisphere by a single contiguous source layer in Brodmann's area 3b, that is, in the posterior bank of the central fissure. Topographical potential maps constructed at time points during the epoch containing this component exhibit anterior and posterior extrema that are thought to arise from a dipole-like source oriented tangentially to the cortical surface. In fact, the source-link nature of these scalp potential distributions led us to validate DLM with these data [5].

The first figure is extracted from these results. Figure 1a shows the averaged response to right median nerve stimulation (RMN) at a precentral (#4) and postcentral electrode site (#7). Figure 1b shows the average equivalent dipole source for the interval 29.0-33.5 ms, the epoch containing the P30-N30 component. Sampling of data was performed at 0.5 ms intervals so that the equivalent source for this epoch is the average of ten dipoles. If the head is simulated by a unit sphere, then the x, y and z coordinates of this average source D_3 are -.32(.02), -.10(.02), 74(.01), where numbers in parentheses are standard deviations. In this and other analogous figures, the x-axis passes through the ears, the y-axis passes through the inion and nasion, and the z-axis passes through the vertex C_z.



a

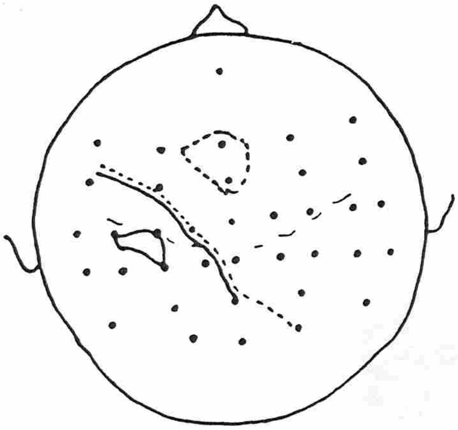
b

Figure 1

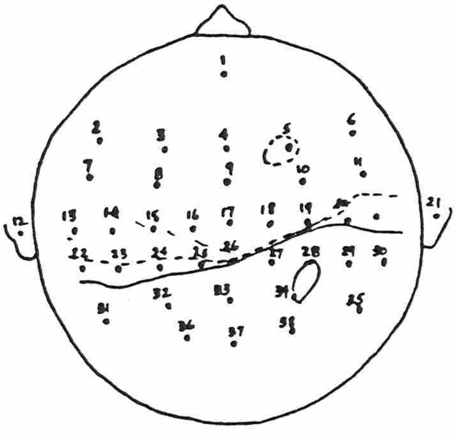
D. Papakostopoulos and H. J. Crow [20], noting a latency difference of 1-2 ms between the peaks of the precentral and postcentral waveforms (Fig. 1a), argued that two equivalent generators, lying in pre- and postcentral cortex, must be hypothesized to account for the difference T. Allison [21] showed that the dual source model cannot fit both the cortical surface and scalp topographies, but that the single source model can. We can also demonstrate that a single-current dipole <u>varying in time</u> can account for the observed latency difference. When the ten DLM-constructed dipoles D_1 (now uncorrected for the skull) are used in sequence via the formula in [4] to generate 4.5 ms of simulated data at electrodes #4 and #7, it can be shown that the waveform at #7 will have a positive peak at 31.0 ms, and the waveform at #4 will have a negative peak at 32.5 ms. A similar relationship holds at other pre- and postcentral recording sites.

Figures 2(a,b) are outlines of topographical potential maps, prepared by C. C. Wood, at certain latencies in the responses to left (LMN) and right median (RMN) in a patient with a left occipital tumor prior to surgery. The broken curves are negative equipotential curves and the solid curves have positive polarity. The closed contours enclose the positive and negative potential peaks at the latencies noted below each figure. These latencies are pre- precisely those at which p(t) is maximal. The approximate location of the central fissure, the presumed site of the generators of these data, has been sketched in these figures. The second pair of figures 3(a,b) show the average equivalent dipole sources D_3 for 4.5 ms epochs containing the appropriate latencies (ten time points).

The result for left median nerve stimulation can be considered "normal" in that the equivalent generator appears to be approximately perpendicular to the central fissure. The result for RMN is consistent with the physical displacement of sensory cortex by the tumor mass.

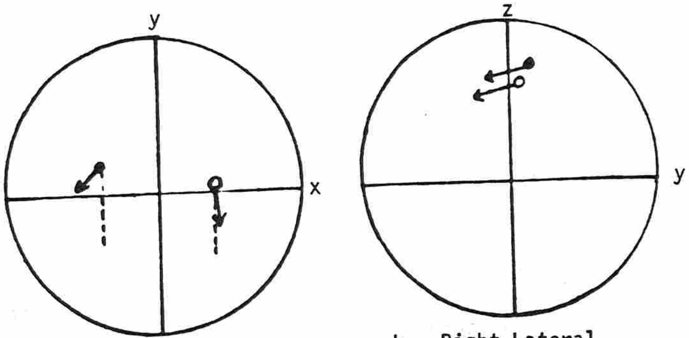


a. RMN at 34.5 ms



b. LMN at 32.5 ms

Figure 2



a. Top

b. Right Lateral

Equivalent Dipole Source
RMN = ●↗ LMN = ○↗

Figure 3

Another maximum of p(t) occurs, in each data set, at approximately 15 ms poststimulus. RHO is small, indicating a good dipole fit. In these cases, the equivalent generators for an epoch are not stationary but move vertically along the negative z-axis toward the center of the sphere. This suggests that we may be tracing the evolution of a brainstem response. This observation was not seen in two other cases in which only eight and 16 recording sites were used (including [5]). It appears that adequate spatial sampling of scalp potential fields is needed for DLM to recognize this brain stem response.

DLM Applied to the Response to Bilateral Light Flash

In an ongoing study, we have been using DLM to elucidate the processes that generate scalp-recorded EP components and distinguish abnormal responses. Our approach, at the outset, was to choose a stimulus that we might expect would produce a response which was symmetrical and would have similar components in subjects with no neurological dysfunction. Our expectation was that the dipole generators of such components would have their positions near the y-z plane, appearing to be near the midline when viewed from above, and be oriented toward the inion or nasion in this view. A significant divergence from the expected locus and direction might be consistent with impairment of the sensory pathways.

Visual-evoked responses to photic stimuli have been recorded from 40 normal subjects. A Grass PS22 stimulator was used with an intensity setting of four and with the strobe at a distance of 35 cm. The stimulus rate of 1.5 Hz was used, and all recordings were done with the subject relaxed and with eyes closed.

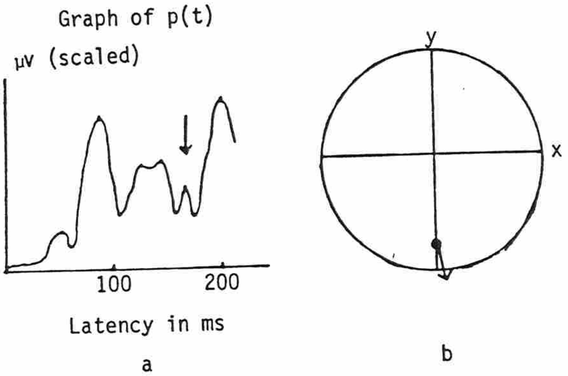
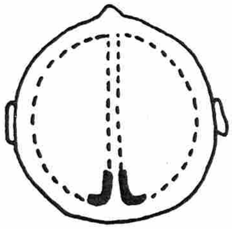


Figure 4. Normal

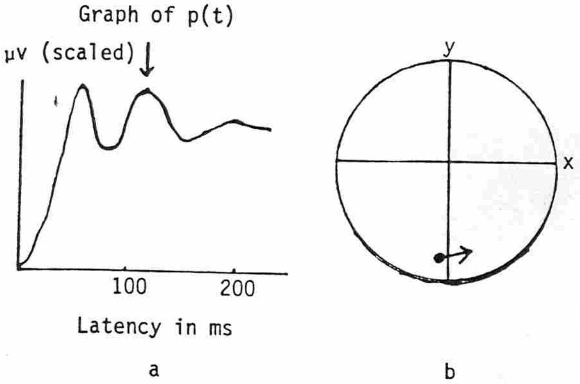
A typical result for one of these subjects is in Figure 4a. The power peak noted at approximately 160 ms has the equivalent generators depicted in Figure 4b. The significant observation is the orientation of the dipole toward the inion. The angle with the positive x-axis is approximately 90°. Based on the symmetry of the stimulated visual field, the symmetry of the activated visual cortex as viewed from above (in the x-y plane) and the cancellation of the intercalcarine contributions to the scalp-recorded potentials, this result would be anticipated in normal subjects [22,10,8]. In fact, such an occipitally localized power peak, with equivalent sources oriented toward the inion, was found in all 40 subjects.



Generators of VER in striate cortex
(from [10,22])

Figure 5

In four additional cases, specific lateralized occipital-parietal lesions had destroyed part of the primary visual cortex. In these cases, there was no intercalcarine cancellation of the contribution to surface potentials generated from the intact lobe. The equivalent source was located near the occipital pole in the intact hemisphere and oriented toward the lesion. Figure 6 depicts one of these cases, with a right occipital-parietal tumor.



a b

Figure 6. Tumor

All of these subjects exhibited normal ongoing EEG's, with occasional slowing of alpha frequencies and normal or nonlocalizing photic-flash responses.

Five apparently normal subjects, for the reasons just mentioned, exhibited no occipitally localized power peaks. Medical records indicated that all of these subjects were suffering from presenile or senile dementias.

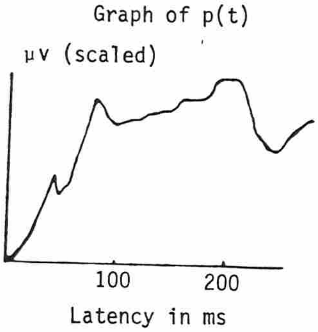


Figure 7. Power curve for case of Alzheimer's disease

We shall discuss these observations and possible interpretations of the equivalent sources of other power peaks later in this paper.

DLM Applied to the Scalp Potentials Generated from Known Current Sources

In the course of presurgical evaluation of several patients with medically intractable epilepsy, we have had the opportunity to record at both scalp sites and depth electrodes the potentials generated by known electrical current sources. One purpose of these studies was to show that the values of generated potentials measured at the depths and on the scalp and the attenuation of these potentials were qualitatively and quantitatively consistent with those values predicted by potential theory as applied to the layered volume conduction model of the head. The other aim was to compare the position and direction of the dipole generators of the scalp-recorded potentials with the position and orientation of the actual generators.

The patient discussed here had three electrode arrays, labeled I, III and V, implanted unilaterally in hippocampus, amygdala and the posterior mesial temporal region.

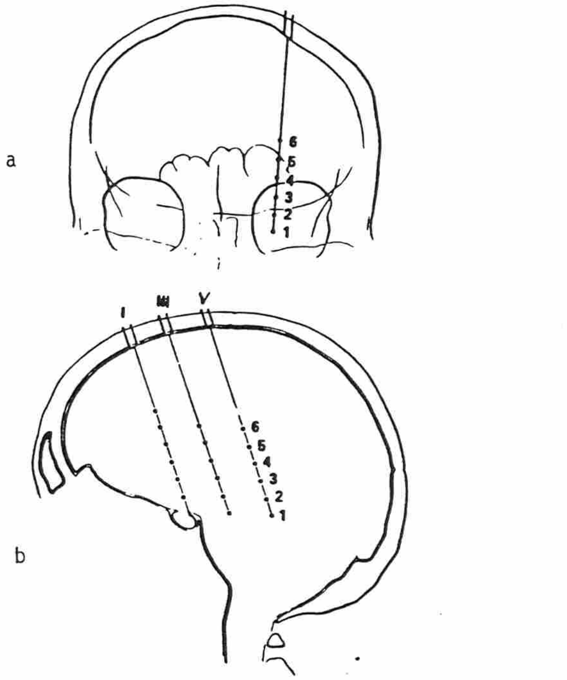


Figure 8

There were six contacts per electrode post spaced at one centimeter intervals. In addition, scalp recordings were taken from scalp electrodes in the standard international 10-20 array.

In each experimental session, a balanced square-wave stimulus of current amplitude 10 μamps was introduced either at the more superficial contact points III-6 and V-6 or at the centric pair of contact points III-1 and V-1. Depth recordings were made at the six electrode sites on post I. Stimulus duration was 40 ms followed by a 40 ms pause, which was followed by an equivalent current stimulus of the same duration but of opposite polarity. The stimulus was repeated at a frequency of 1.5 Hz, and 200 stimuli were averaged for each analysis using a 1 ms sampling rate. The current density was less than 10 μcoulombs/cm^2 per phase, so that loading was within recommended limits of safety in order to avoid tissue damage. No neuronal activation was seen, and stimulus intensity was significantly less than that used in subsequent stimulation sessions for the purpose of eliciting a clinical response and after discharges. Using DLM analysis, we hoped to show that voltages well within the physiologic range produced in deep structures could be recorded on the scalp and localized using surface data alone. Complete details of the procedure and results can be found in [23, 24].

Figure 9 shows averaged recordings from both depth and two scalp electrodes in the case in which current has been introduced between electrodes III-1 and V-1. The vertical scales represent ±12 μv for F_7 and T_5 and ±85 μv for the depth sites I-1 through I-6. The horizontal "latency" scale is marked at the times 45 ms and 120 ms, at which we applied DLM to the scalp data.

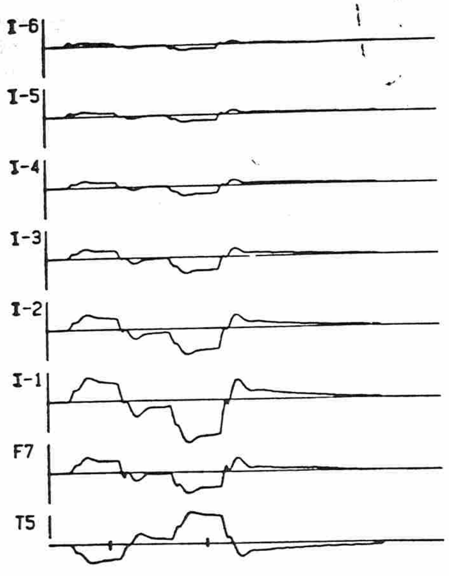
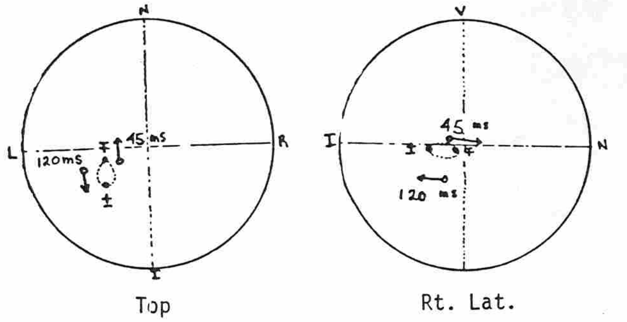
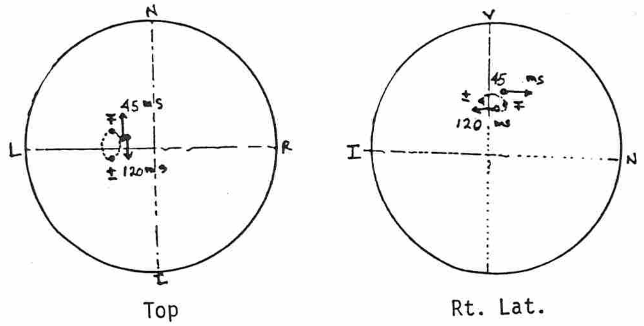


Figure 9



a. III-1 and V-1 active



b. III-6 and V-6 active

Figure 10

Figure 10 shows the DLM equivalent sources (D_3) for the two latencies. In each case, the direction of the theoretical source is almost precisely the direction of the line segment connecting the active contact points, and the locus is within 1.5 cm of the midpoint of the connecting line segment. The discrepancies are most likely due to the fact that the generated electric fields are not precisely dipolar in nature, since the active sites are separated by approximately 2 cm. In fact, when scalp data is simulated mathematically by allowing the contact points to approach one another, the theoretical dipole source of the simulated data can be shown to coincide with the "actual" generator.

DLM Applied to Auditory-evoked Potentials

In [6], DLM was applied to the N_1-P_2 sequence of auditory evoked potentials. The analysis produced a stable centrically localized equivalent generator of potentials that several investigators believe arise bilaterally in separated areas of auditory cortex. The lesson to be learned from this case is that one must be circumspect about interpreting an equivalent generator literally as a physiological source.

Discussion

The analysis of the potentials generated from known current sources demonstrates that, in some respects, the head behaves like a volume conductor. It also suggests the possibility that physiological generators in deep brain structures can be localized or at least identified from scalp data alone. We are investigating the possibility of employing DLM to localize the origin of certain generalized epileptiform discharges.

Schneider [14] attempted this unsuccessfully several years ago. One reason for the failure was that he applied the method to petit mal discharges, inappropriate data which were not generated by a localized synchronous source. In addition, he did not "average" the epileptiform discharges, and background activity undoubtedly contributed to the morphology of the waveforms. It is not technically difficult to superimpose similar discharges, thus eliminating background noise. Using this kind of averaging or superposition technique, it may be possible to localize the origins of these discharges without resorting to invasive techniques, such as depth recordings.

The results obtained for the flash-visual-evoked response are encouraging and indicate that DLM may be able to identify areas of dysfunction which cannot be well-localized by usual EEG and EP techniques. These studies have been limited to lesions in the parietal occipital head regions, and it would be important to determine whether more anterior lesions in the visual pathways can be identified and localized as accurately. Because of the large number of patients who would have some degree of field cut following temporal lobectomy for intractable epilepsy, it will be possible for us to test the model in the cases of more anterior lesions. The importance of being able to localize lesions in the temporal head regions, as well as the parietal occipital regions, is emphasized by the fact that the vast majority of cerebral vascular accidents occur in the distribution of the middle cerebral artery, and this involves the temporal lobe, with or without detectable visual field deficits on gross neurological examination. CT scans are frequently normal beyond 48 hours following an ischemic infarct, while the EEG may show poorly localized or even generalized dysfunction. If the model can recognize such dysfunction before the CT scan shows the anatomic disruption caused by the infarct, this would have great clinical advantage in diagnosis.

The auditory evoked potentials in these same patients who have had temporal lobectomies should also be valuable. Hearing is bilaterally represented, and even taking cerebral dominance into consideration, a significant asymmetry in the localization of the equivalent dipole should provide evidence of unilateral dysfunction.

As noted above, the DLM analysis was applied to the flash response of patients with early stage dementia of an apparently degenerative nature. These subjects had normal EEG's and normal or nonlocalizing flash EP's, but in whom it was virtually impossible to localize an occipital equivalent dipole source. It would be important to follow up these observations to see whether the ability to localize this component posteriorly deteriorates as a function of age, or whether it is more specifically affected by degenerative processes that affect the cortex.

It must again be emphasized that, while under best conditions, equivalent sources can be related to physiological generators, the main theme of DLM in a clinical setting is to establish normative results and identify and classify neurological disorders. The evoked response for the normal subject in Figure 4 exhibits five power peaks. The source of the first is frontal and oriented toward the nasion, consistent with the ocular origin of these potentials (e.g., [7]). The second peak has a centric equivalent source, possibly thalamic or thalmocortical in origin. The algorithm does not provide a good dipole fit for the third (broad) peak. The source for the fifth peak is localized near the occipital pole but is oriented toward the nasion, perhaps indicating the movement of potentials through association region toward deep midline structures. These observations, though suggestive of the movement of potentials along the visual pathways, are quite speculative. They must be clarified by comparing age-matched normal controls with patients suffering from specific disorders.

It would also be desirable to apply DLM to the responses to quarter-field and hemiretinal pattern-reversal stimulation, where the latencies and amplitudes of components are better controlled and somewhat more is known about the neural origins of these components (see bibliography in [10]).

Finally, the DLM model has been implemented on an Apple II, where the computation costs are low and calculations can be done interactively and almost on line. It is thus possible to do these analyses with a minimum of expense or disruption of routine.

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