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A study was conducted to evaluate the feasibility of obtaining concurrent measures of event-related potentials (ERPs), and event-related magnetic fields (ERFs). Subjects participated in an oddball task while simultaneous ERPs and ERFs were recorded. Isocontour field maps generated for the P300 component are consistent with the suggestion that the P300 may be generated in, or near, the hippocampal formation.

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REPORT OF AFOSR P300 STUDY

Remarks

This progress report describes a project designed to test the feasibility of an active collaboration between two programs supported by AFOSR. One program located at NYU, with Lloyd Kaufman and Sam Williamson as Principal Investigators, and the other program located at the Cognitive Psychophysiology Laboratory (CPL), University of Illinois, with E. Donchin as Principal Investigator. The NYU project focuses on the study of evoked magnetic fields while the CPL project focuses on the study of event-related brain potentials. The current project was predicated on the assumption that a joint effort will yield results of utility. For this purpose, supplementary funds were made available to both labs to undertake a pilot study during the summer of 1984. The results of the feasibility study are reported here.

Introduction

Okada, Kaufman, and Williamson (1983) described a magnetic counterpart to the electrical P300, which was measured while the subject was counting infrequently presented visual stimuli. These stimuli were gratings having a spatial frequency other than that of a frequently presented grating, as in a typical "oddball" experiment. The neuromagnetic field associated with the P300 complex emerged from one side of the head and reentered the head in the occipital region. At the same time, the contralateral field emerged from the occipital region and reentered in the temporal region on the other side of the head. The depths and lateral positions of equivalent current dipole sources of these fields were computed using a method described by Williamson and Kaufman (1981). It was concluded that the observed field patterns could be accounted for by two equivalent current dipoles, with one in each hemisphere and located in or near hippocampal formation.

This result is consistent with recent data obtained by McCarthy, Wood, and Bentin (1985) in epileptics who had electrodes inserted in their brains for diagnostic purposes. However, these authors point out that their data are consistent not only with the presence of a source in or near the hippocampus, but also with a source in the frontal regions. This conclusion is tentative because of the limited amount of information obtainable from two electrode tracks, and where the precise depths of the active electrodes are not known.

At this point it should be emphasized that the concept of the equivalent current dipole is a convenient heuristic which allows us to account for observed patterns of neuromagnetic fields. The equivalent current dipole is considered to be the "source" of the measured field if the field could be produced by a current dipole in a particular position within the head. It is recognized by all workers in the area that a field which could be produced by a single equivalent current dipole may actually be produced by a number of active sources within the head. This follows from the fact that there is no unique solution to the inverse problem. Even so, if a very large amount of the variance in the P300 phenomenon can be accounted for by postulating an equivalent current dipole source, then it will be possible to test the hypothesis that the phenomenon is due to a unitary underlying process, which remains invariant under conditions that may affect the amplitude, latency or waveform of the observed P300.

The present research project focused on an issue that has raised a good deal of controversy in the ERP literature. In the past, investigators have applied the label "P300" to peaks of diverse latencies as long as their scalp distribution was similar and showed similar reactions to experimental manipulations. While this attribution is plausible, there is no direct evidence that all the peaks to which the label "P300" has been applied are manifestations of the activity of the same neural generator. The problem is compounded by the fact that there exists no conclusive way to identify an intracranial source based on scalp recordings, primarily due to the effects of anisotropies in conductivity in volume currents. Event-related magnetic fields, however, are relatively immune to such problems, allowing precise estimations of the intracranial source(s) of an ERP component (Kaufman and Williamson, 1982). The goal of this research was to attempt to identify the intracranial source(s) of the P300 component of the event related brain potential, and, equally important, to determine if the source(s) changed when the P300 shifted in latency.

The experimental paradigm used in this research was derived from McCarthy and Donchin (1981) and Magliero, Bashore, Coles, and Donchin (1984). McCarthy and Donchin manipulated two factors; stimulus discriminability and stimulus-response compatibility, which affect different stages of processing. The manipulation of stimulus discriminability influences the encoding stage of processing, while the manipulation of stimulus-response compatibility affects the response selection and execution stages of processing. Subjects were presented with matrices which contained either the word "LEFT" or the word "RIGHT". On half of the trials the remaining elements in the matrix were "#" symbols, providing an easy discrimination condition. On the other half of the trials the remaining elements in the matrix were random letters of the alphabet, providing a difficult discrimination condition. Two conditions of stimulus-response compatibility were included in the experiment. In the compatible condition subjects pressed the left button if the word "LEFT" was presented in the matrix, and pressed the right button if the word "RIGHT" was presented in the matrix. In the incompatible condition subjects responded with their left hand if the word "RIGHT" was presented in the matrix, and pressed the right button if the word "LEFT" was presented. Reaction time increased both with increases in difficulty of discrimination and compatibility. Further, the two effects were additive, confirming the assertion that the manipulations of discriminability and compatibility affect different stages of processing (see Sternberg, 1969). P300 latency increased as a function of discrimination difficulty, but was not affected by the manipulation of stimulus-response compatibility. Thus, the results imply that P300 latency is sensitive to some of the processes which influence reaction time, namely the processes of encoding and evaluation of the stimulus, but is insensitive to the subset of response related processes which influence reaction time.

While the pattern of results was rather clear and was well supported by subsequent work in the CPL (Magliero et al., 1984) and in other laboratories (Ford, Pfefferbaum, Tinklenberg, and Kopell, 1982), the pattern of the ERPs elicited in the difficult discriminability condition was quite different from the pattern of ERPs elicited in the easy discrimination condition. In the latter case the ERP contained a sharp peak positivity. When the noise was added to the matrix the waveform was characterized by a relatively slow wave with at least two peaks. McCarthy and Donchin interpreted the noise-elicited pattern as reflecting the shift in time of the P300. Analysis of the pattern of the scalp distributions, as well as the data reported by Magliero et al., (1984) are consistent with this interpretation. It would however, be very useful to determine in a more direct manner whether the P300s elicited in the easy and difficult discrimination conditions originated from the same set(s) of neural generators. The magnetic recordings provide a method for comparing components elicited across different experimental conditions. The purpose of this research was to replicate the findings reported by Okada et al., (1983) using a visual oddball paradigm with stimuli similar to Magliero et al., and then extend the results of McCarthy and Donchin, using the noise/no noise manipulation of Magliero et al., while concurrent electrical and neuromagnetic recordings are made from the same subject. These two sets of measurements allow us to determine how well the electrical P300 is correlated with the magnetic, and also to determine if the location of the equivalent current dipole source of the P300 of the EMF is the same under these two conditions.

Visual Oddball Experiment

The goal of this preliminary experiment was to determine if the stimuli used by McCarthy and Donchin can be used to obtain Event-Related Fields (ERFs) comparable to Event-Related Potentials (ERPs), including the deflections in the ERP waveform conventionally referred to as "P300." This cooperative effort was possible because of the availability of the PEARL system (Heffley, Foote, Mui, and Donchin, 1985), a portable data acquisition and experimental control system developed at the CPL in which the experimental paradigm described above was implemented. Since the neuromagnetic measurements require the facilities of a low temperature physics laboratory the most effective means for accomplishing this research was to transport PEARL to the neuromagnetism laboratory at New York University.

Methods

Three subjects were run in experiments at NYU. Two 25 year old right-handed female subjects participated in a visual oddball paradigm (see Donchin 1979, 1981) and one 26 year old right-handed male subject was run in a noise/no noise oddball paradigm (McCarthy and Donchin 1981; Magliero et al., 1984).

Two experimental paradigms were employed in the experiments. In the visual oddball the words LEFT and RIGHT were generated in a Bernoulli sequence with the presentation probability of .25 for the word LEFT. The words were displayed in the center of the screen with a visual angle which subtended approximately 2.5 degrees. In the noise/no noise experiment the stimuli were generated according to the rules described by McCarthy and Donchin (1981). Four matrices produced in this manner are presented in Figure 1.

Insert Figure 1 About Here

Each matrix contained the word LEFT or the word RIGHT. The matrices were composed of 4 rows and 6 columns of characters arranged as a rectangle which subtended a horizontal visual angle of approximately 2.5 degrees. The stimulus words RIGHT or LEFT were written horizontally from left to right and appeared with equal probability in each of the four rows. Both the row and starting column (columns 1, 2, or 3 for LEFT and 1 or 2 for RIGHT) were randomly chosen on each trial. Half of the trials are no-noise trials on which the background positions of the matrix were filled with the "#" symbol. The remaining trials were noise trials on which the background positions were filled with letters randomly chosen from the alphabet. The words LEFT and RIGHT were generated in a Bernoulli sequence with the presentation probability of .25 for the word LEFT.

Subjects were given practice in the experiment prior to the recording sessions. Subjects were instructed to count the word LEFT and report their total at the end of each experimental block. EEG and EOG electrodes were attached to the subject. The subject reclined on a table with the SQUID sensor positioned within 1 CM of the subject's head. When neuromagnetic recordings were taken from the right or left temporal areas the subject would lie on her side. When neuromagnetic recordings were taken from occipital areas the subject would lie on her stomach. The visual stimuli were displayed on a Panasonic monitor. When the subject was lying on her stomach she would look through a hole cut out of the table at a mirror which reflected the image of the monitor. During this condition the image presented on the monitor was inverted so as to look normal when seen through the mirror.

The neuromagnetic recording system consisted of a 5 channel SQUID sensor a series of Rockland band pass filters and a series of comb filters. The output of the neuromagnetic system was passed to a PEARL computer which controlled the experiment and collected data. EEG activity was recorded from Fz, Cz, and Pz (Int 10-20 system, Jasper 1958) using a GRASS EEG amplifier. EOG activity was corrected off-line (Gratton Coles and Donchin 1983). The electrical and neuromagnetic data were recorded concurrently and the single trial data were written to magnetic tape for subsequent analyses. This led to the computation of five different average ERFs at the same time as we recorded the average ERPs associated with the rare and frequent events. The field measurements were replicated numerous times so that we could generate field maps that would allow us to compute the location of the source of the P300 (see below). These measurements were made with a five-sensor neuromagnetometer ("Freddy") described by Pelizzone, Williamson, Kaufman, and Schafer (1985). The sensing coils of Freddy were superconducting second order gradiometers with a baseline of 4.0 cm and a coil diameter of 1.5 cm. The gradiometers associated with the SQUIDs were immersed in a bath of liquid helium contained within a fiberglass cryogenic Dewar. The gradiometer pick-up coils were located at the four corners of a square, with the 5th coil in the center of the square. The distance between the centers of adjacent pickup coils was 2 cm, and the gradiometers were canted outward by 10 degrees relative to the central gradiometer. Since all five sensing elements were contained within a single cryogenic Dewar, the pickup coils were effectively tangential to the surface of a spherical with a radius of curvature of 10 cm. (The outer surface of the tail section of the Dewar had a radius of curvature of 9 cm, and the bottom of the tail section was 1 cm thick). The entire Dewar could be moved in its gimbaled holder (SCANNER) so that the bottom of its tail section could be moved along a spherical surface having a 9cm radius of curvature. With the head centered on a 9 cm radius spherical volume, it is possible to move the Dewar so that the pick-up coils measure the field at many different positions on the sphere that best fits the head. This permits the use of a sphere model in computing the locations of equivalent current dipole sources associated with the measured fields (Williamson and Kaufman, 1981). In the present experiment the field was measured at 45 positions over the right temporal region, 80 positions over the occipital region, and 90 positions over the left temporal region. Since most of these positions were non-overlapping, the field was measured at approximately 215 distinct locations for subject SG. The coordinate system used for placing the sensor was referred to the ear canal or to the inion. When measuring the field in the temporal region the horizontal axis was the line joining the ear canal to the outer canthus of the eye. When measuring the field over the occipital region the horizontal axis passed through the inion and was parallel to the horizontal axis for the temporal region, with the midline as the vertical axis. The ear canals were 12.5 cm anterior and 2.5 cm below the inion in subject SG.

In addition to the five gradiometers and associated dc SQUIDs used to detect the fields of interest, the ambient magnetic noise was detected by each of four different "noise" channels. These were composed of rf SQUID magnetometers that measured the ambient field in the X, Y, and Z directions, and a first order gradiometer that measured the field gradient or first spatial derivative of the field along the Z axis. The outputs of these noise channels were given different weights and then subtracted from each of the signal channels. The weightings given these outputs before subtraction from each channel were chosen so that the channel outputs would be at a minimum when they were in the presence of a uniform field. The fields for balancing the channels so that they would be insensitive to them were generated by large square (10 ft. per side) Helmoltz coils. The outputs of the signal and noise channels were bandpass filtered between 0.3 and 45 Hz before signal averaging. For the present experiment, the output of the Pz channel was collected both with and without Rockland filtering. This permitted assessment of any distortions which were introduced by filtering. Whenever noise levels exceeded a value that resulted in signal saturation, the epoch in which the event occurred was eliminated from subsequent analyses.

In the first studies using the Freddy system we encountered difficulties associated with using the Rockland filters. These filters distort the waveforms of the responses so that the "P300" deflection is shifted and distorted in the filtered response. The distortion could be attributed to two problems. First, the Rockland filters introduced a non-linear delay for different frequencies. For example, a 1 Hz sine wave was delayed by 280 msec, while a 5 Hz sine wave was delayed by 100 msec. This had the unfortunate consequence of differentially shifting components of the ERP. A second distortion added by the Rockland filters was created when the input to the Rockland filters was overloaded, causing the filters to "ring". This ringing introduced additional changes in the waveform morphology making it difficult to identify any ERP components.

Results

The electrical activity recorded at the parietal electrode was filtered in two different ways before averaging. The electrical activity was filtered with an 8 sec time constant and a high frequency cutoff of 35 Hz, with roll-offs of 3 dB per octave. This resulted in minimum distortion of the average waveform. The same activity was also averaged after being processed by the Rockland filters (bandwidth of 0.3 - 45 Hz and roll-offs of 48 dB per octave). Figure 2 illustrates the effects of the Rockland filters on the ERP waveform.

Insert Figure 2 About Here

The upper left quadrant of Figure 2 presents the rare and frequent overplots of the parietal electrode filtered with the GRASS amplifier for subject SG during the first recording session. Two dominant components appear in the waveform. First, a large positivity occurring around 250 - 300 msec, maximal at Pz, is present in both the rare and frequent plots. This component is labeled P200. The second component is a larger positivity occurring around 450 msec, maximal at Pz, which is present only for rare stimuli. Based on scalp distribution, latency, and sensitivity to experimental manipulation, we label this component P300. It is important to note that the P300 is much larger for the rare stimulus that for the frequent stimulus, consistent with previous research (Duncan-Johnson and Donchin, 1977). The upper right hand portion of Figure 2 presents the same electrical data passed through the Rockland filters. Comparison of the upper left and right hand portions of Figure 2 suggests that is not altogether easy (though not impossible) to identify the P300 component with any degree of confidence after the data have been passed through the Rockland filters. The lower section of Figure 2 presents ERP waveforms collected during the final recording session of subject SG. The data are presented in the same manner as in the upper portion of the Figure. Comparison of the waveforms across sessions reveals that the amplitude of the P300 component decreases dramatically. This is what one might expect if the oddball task had become automated during the course of the recording session. Alternatively, the effect could be due to fatigue, boredom, or motivational changes. The inconsistency across recording sessions adds yet another caveat in the interpretation of the data.

The tracings depicted in Figure 3 were obtained when the five pick-up

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Insert Figure 3 About Here

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coils were located over the occipital region just to the right of the midline, and over the right temporal region. Similar results were obtained with the pick-up coils over the left temporal region (though of opposite polarity to those from over the right temporal region) and over the region slightly to the left of the midline at the occiput. In fact, the regions of strongest response were temporal and occipital, while intervening areas gave either weak responses or no detectable responses at all. These results are qualitatively quite similar to those reported by Okada et al. (1983) obtained using gratings as stimuli.

Despite the problems encountered with the Rockland filters, the data for one of the subjects (SG) in the visual oddball paradigm were analyzed and isofield contour maps generated. Isofield contours were plotted to show how the field measured when P300 was at its peak varied as a function of position about the scalp (Figure 4).

Insert Figure 4 About Here

The legend of Figure 4 explains the coordinate system used. The important point to note is that the field extrema in the occipital region are not well defined. This is likely to be due to overlap of fields of opposite directions. However, the location of the extremum to the right of the midline can estimated by interpolation. It lies between the two positive "apparent" extrema. These are probably produced by the overlapping negativity (inwardly directed field) associated with the source whose field emerges from the left temporal region and reenters in the occipital region. The emerging over the right temporal region is much more clearly defined.

Using the location of the estimated occipital extremum associated with the extremum over the right temporal region as reference points, we made use of the spherical model to estimate the location of the source giving rise to these two extrema. This estimation is shown in Figure 5. Despite the evident "noisiness" in these data, it is apparent that we are dealing with a very deep (subcortical) source. Also, the equivalent current dipole source appears to be located within 1 cm of the position of the source in the experiment using grating stimuli. This places the source in or near the hippocampal formation, as concluded previously. It should be stressed that this consistency in source location is present despite the fact that alpha numeric stimuli were employed in this experiment, while grating stimuli were employed in the earlier experiment.

It is worth noting that students of the limbic system are unclear about the precise boundaries of the so-called hippocampal formation. It is not a well-defined anatomical entity. Even so, our results are consistent with the previous results, at least within our experimental error, and as Halgren and his colleagues have pointed out, strongly implicate the limbic system.

The preceding experiment was conducted to determine if alpha numeric stimuli employed in the McCarthy and Donchin experiment can be used effectively to conduct magnetic P300 studies. An important criterion is whether or not the signal-to-noise ratio is adequate to permit distinctions among sources that differ in locations. It is clear that this is possible, if and only if, the sources are in widely separated places, as difficulties do exist. Some of these difficulties can be surmounted simply by choosing subjects who have large head diameters, as our experience has shown that the overlap of fields of opposite polarity in the occipital region is less when the head diameter is large. However, we now know that it is possible to locate an equivalent current dipole source by measuring the field near only one extremum.

A current dipole is defined by its strength (dipole moment), orientation, and its three spatial coordinates. Since only five parameters are needed to define a dipole, only five independent measurements are needed to determine its properties. These minimum requirements are satisfied by the five sensors when positioned so that one of them is at or near one extremum. However, the accuracy of the determination made in this way is inversely related to the amount of noise. This can be offset by taking multiple measurements at the same places, and also by increasing the spatial sampling near one extremum. We plan to do this in the major experiment, which is described below.

Visual Noise Experiment

Our main goal is still to replicate the McCarthy and Donchin experiment and determine if the change in P300 due to the addition of visual noise (letters that make it harder to detect the target words) is due to a change in the source of the response or if it is due instead to a modulation in activity of the same source of P300. Unfortunately, the PEARL system had to be moved from NYU, since we had run out of the time allocated for it. Moreover, the NYU group experienced a severe shortage in programming help and has not been successful in completing a program that will effectively emulate the properties of PEARL using its PDP 11/34. Assuming that this will be completed in the near future, it would be possible to complete an equivalent experiment without recourse to the PEARL system. The NYU group plans to devote a major amount of time to this particular effort, and will send the results to Dr. Donchin for validating analysis.

While our results are not scientifically conclusive, it should be emphasized that we accomplished the goals set for the feasibility study. We have demonstrated that it is indeed possible to conduct experiments in which the techniques of ERP and EMF are brought to bear jointly on an important problem. We have solved most of the logistical problems involved in the collaboration and, but for the Rockland filters which are easily replaced, we could get the necessary data. Both groups are quite eager to continue the collaboration. Proposals to this effect are being considered.

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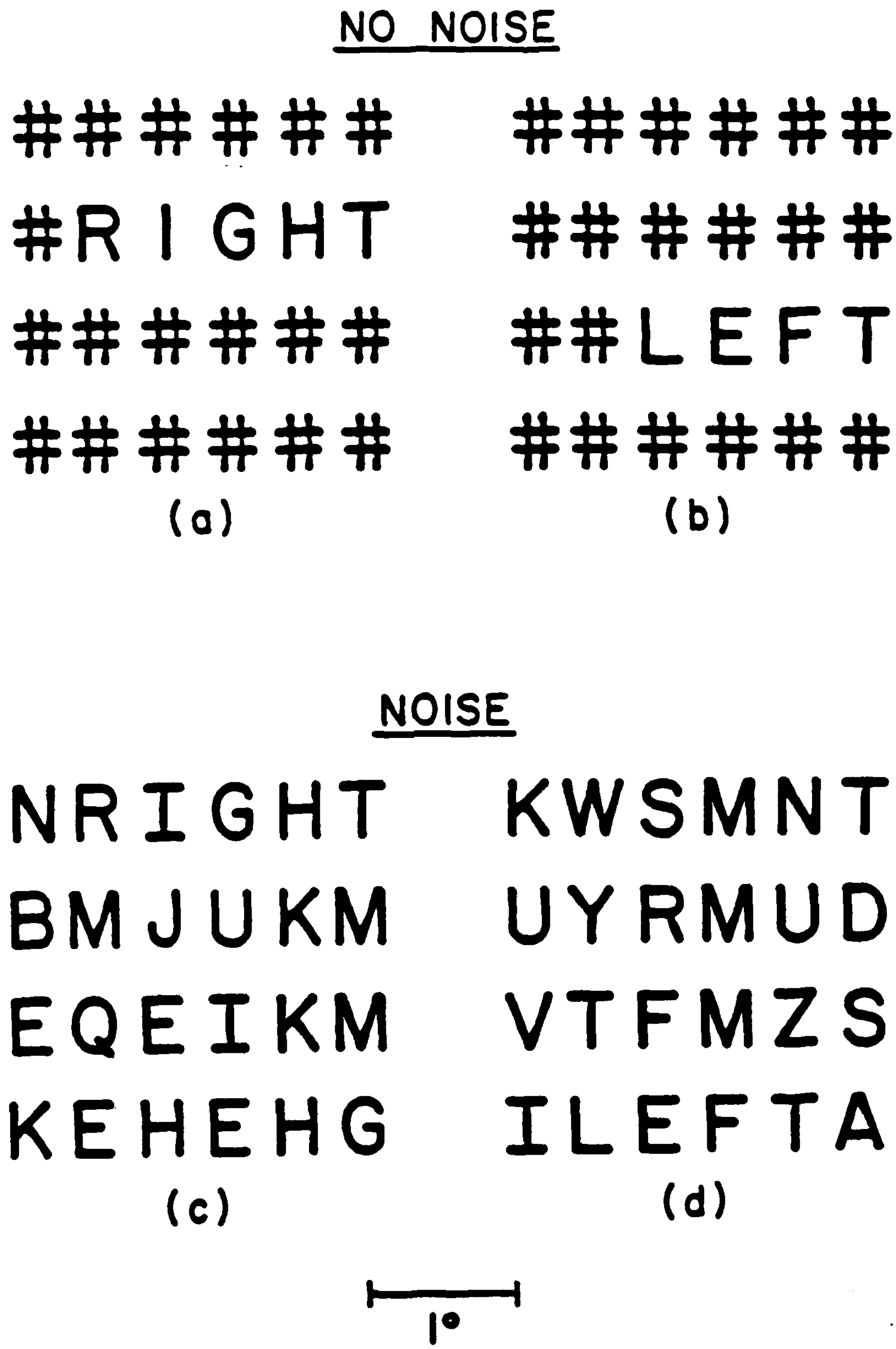

Figure 1. Stimulus used by McCarthy and Donchin (1981).

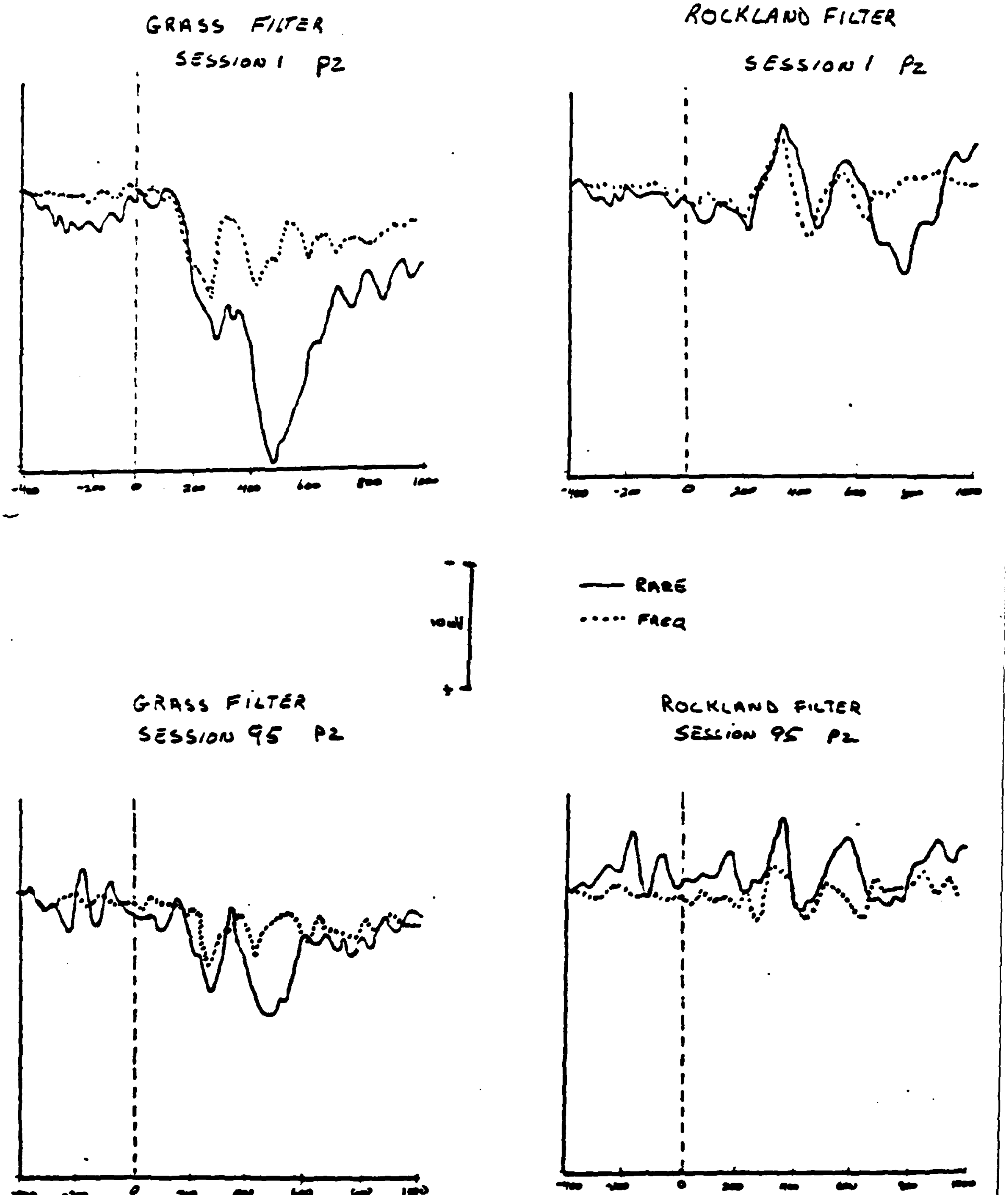

Figure 2. Event-related potentials recorded from Pz. Solid line represents rare stimulus, dotted line represents frequent stimulus. Left-hand figures were recorded with GRASS filters right-hand figures were recorded with Rockland filters. Top figures were recorded during Session 1. Bottom figures were recorded during Session 95.

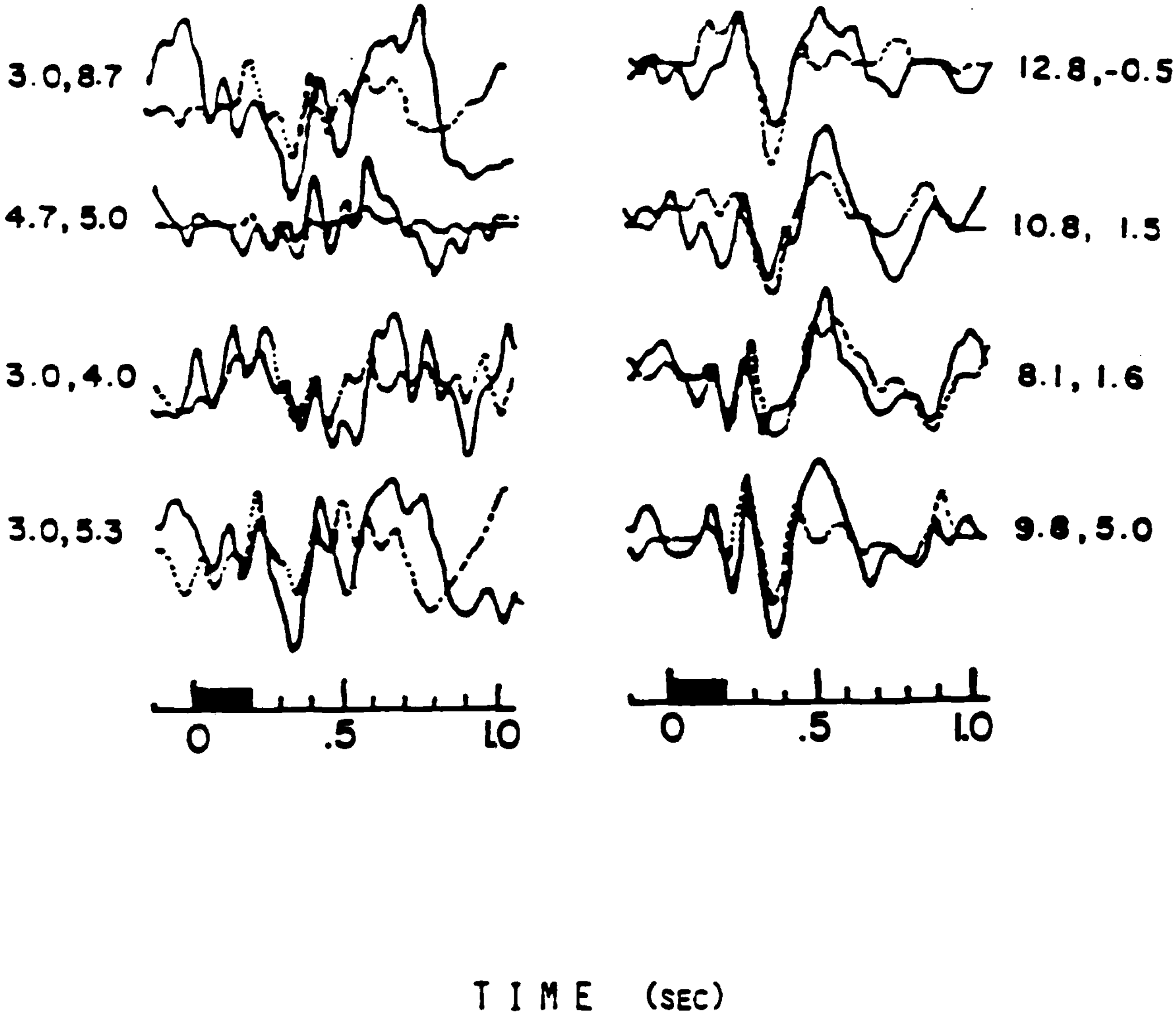

Fig. 3. Event-related magnetic field associated with an infrequent word (solid curves) and with a frequent word (dashed curves) over the right occipital area (left column) and over the right temporal area (right column) of subject S.G. The coordinates are relative to the inion: (3 - 4) = 3 cm to the right and 4 cm above the inion.

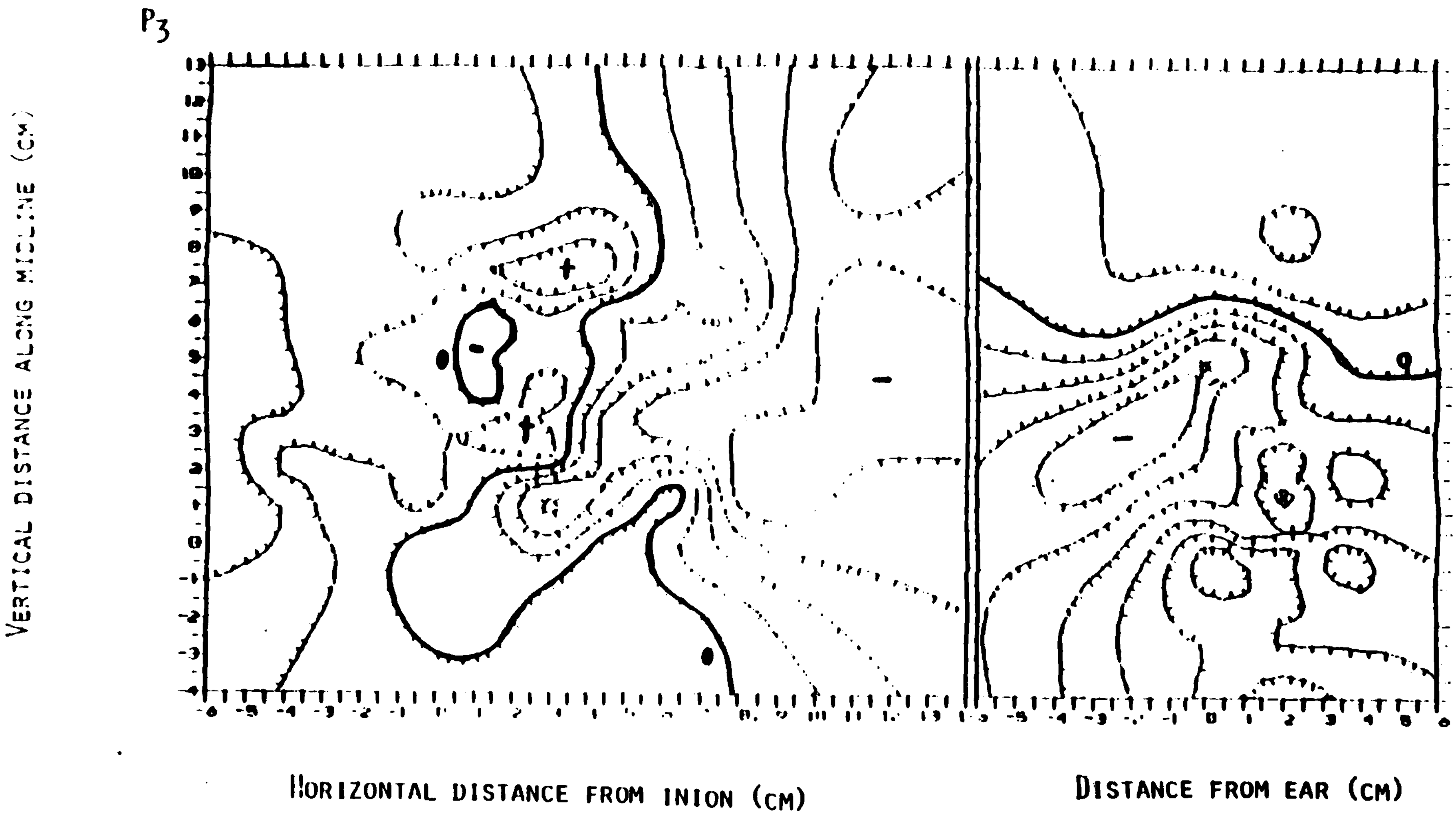

Fig.4. Isofield map of the magnetic field at the P3 latency. The map is based on peak amplitude within the time window of 465 ± 25 msc after stimulus onset. The left panal is for the right occipital region and the right is for the right temporal region. The emerging field is positive and reentering field is negative. The negative field extrema can be seen at (-2 - 3) over the temporal area and positive extrema at (3 - 7 - 5) and (3 - 3) over the occipital area.

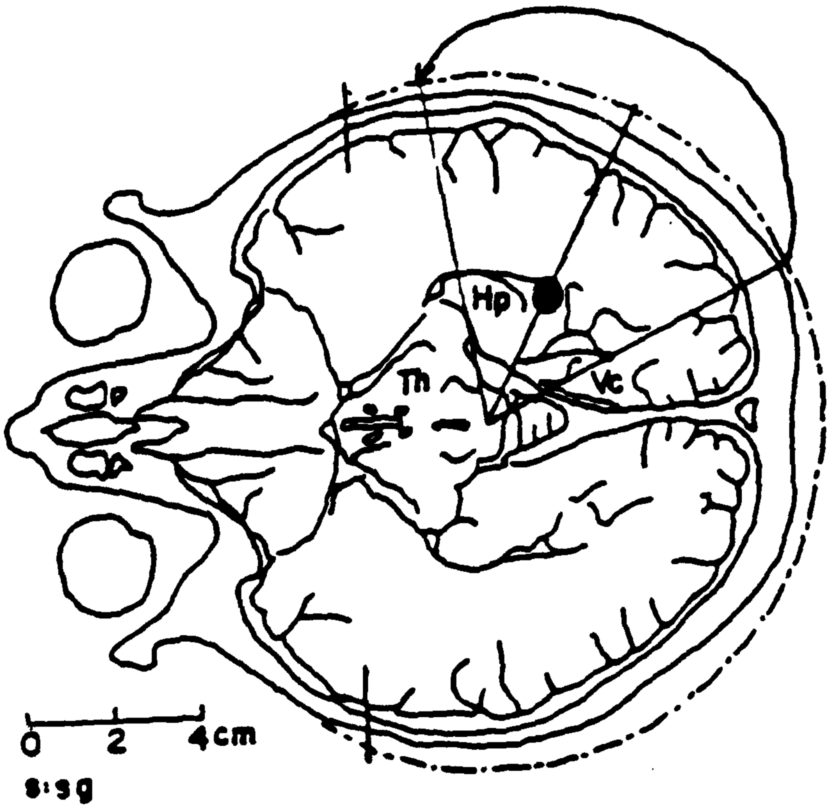

Fig. 5. The estimated location of the equivalent current dipole for the field shown in Fig. 3 assuming that the field extrema are at (-2 - 3) over the temporal area and (3 - 5) over the occipital area. The horizontal section was taken from an atlas (Delmas and Petuiset, 1959) and are 25 mm above Francfort's plane.