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The Use of Squids in the Study of Biomagnetic Fields

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THE USE OF SQUIDS IN THE STUDY OF BIOMAGNETIC FIELDS

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1. INTRODUCTION

The investigation of biomagnetic fields, i.e. fields associated with bioelectrical activity in the human body, has marked impressive progress in the last few years and is proving to be a unique tool to achieve functional imaging of fundamental mechanisms in the heart and in the brain. In particular, the neuromagnetic approach to the study of cerebral functions provided definitive evidence on specific organizations of neural networks located in primary areas, i.e., those devoted to the first analysis of input signals from peripheral sensory systems. Last, but not least, some important pathologies of the heart and of the brain are being investigated by many groups in the world, and the results so far achieved have raised the enthusiasm of exponents from the clinical side. As a unique example we mention the identification of epileptic foci, in cases of partial (focal) epilepsy. The importance of this possibility is well focused if we remember that this disease affects an impressively large percentage of inhabitants in highly industrialized countries.

Several motivations stand behind such impressive and rapid progress in biomagnetic research: the strongest of them, however, is the rapid development of SQUID-based instrumentation that has permitted the achievement of unrivaled performance in magnetic field sensitivity, as well as in reduction of unwanted signals, currently defined as magnetic noise. It is probably worth remembering that approximately a dozen years ago the state of the art of biomagnetic instrumentation was reviewed during another NATO Advanced Study Institute on superconductivity. The performances of

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biomagnetic detectors have since improved by much more than one order of magnitude, and the miniaturization of sensing units, which may even include the detection coil(s) in a single chip, has permitted several research groups to start projects to develop large multichannel instrumentation for real-time functional brain imaging.

In this article we will describe the most studied biomagnetic fields and the primary sources of magnetic "noise". Then a simple outline of the problem of modeling biomagnetic sources will serve as an introduction to the instrumentation chapter, in which we will dwell on different designs for detecting circuitry, disregarding any mention of SQUIDs proper, as they are described in detail elsewhere in this volume. A glimpse at the state of the art of multichannel systems will precede a brief overview of some of the most recent and important findings which have significantly contributed to the understanding of cerebral functions.

2. FIELDS AND SOURCES

In 1963 Baule and McFee[1] succeeded in measuring magnetic fields associated with bioelectric activity in the human heart, namely a *magnetocardiogram*. The technological state of the art of the mid 1960's did not permit using a superconducting magnetometer. It was only a few years later that a SQUID sensor, located inside a magnetically shielded room, produced a magnetocardiogram[2], thus creating a new application of superconducting devices based on the Josephson effect. The first measurements of cerebral magnetic signals were reported a little later, and involved both spontaneous brain activity[3] and evoked fields[4].

The following period was devoted to a broad investigation of fields related to various bioelectric activities in the human body - see next section- while the number of research groups getting involved with the new technique rapidly increased. At the beginning of the 1980's the time was ripe for a new, fundamental step forward, i.e., the use of a relatively simple model of a bioelectric source to confront the inverse problem and achieve *source localization*. This feature, as described in a section below, undoubtedly represents the major advantage of the biomagnetic approach to the investigation of the brain and the heart. A localization procedure in use since the early 1980's has produced important results, such as the experimental demonstration of the tonotopic organization of the human auditory cortex[5], and the identification of epileptic foci in partial epilepsies[6-9]. The progress achieved in the source identification procedure during the last few years has marked impressive results, which will be partially described in the last section of this article. Before that, we must establish a comprehensive view of the phenomena under study and a brief description of the modeling problem.

2.1 Biomagnetic fields and noise sources

Figure 1 provides a comprehensive representation of the most extensively studied biomagnetic signals. The field amplitudes are expressed in femtotesla, 1 fT = 10^{-15} T, and should be compared with the intensity of the earth magnetic field, which is approximately $5x10^{-5}$ T. Other unwanted ambient magnetic fields, which are commonly defined as magnetic noise, are generated by micropulsations of the earth's field and by pumps, fans, elevators and other instruments located in proximity to the experimental area. The effect of these fields can be characterized in terms of a frequency spectrum. Considering that the experimental bandwidth required for all biomagnetic measurements - similar to what happens with any bioelectric phenomenon - is limited to the range from about 10^{-1} to 10^{3} Hz, the micropulsations of the earth's field affect the lower part of this spectral range, featuring an approximately 1/f behavior with circadian variations peaked in intensity during daytime. The other sources of *urban* noise are mainly characterized by specific components usually below 10^{2} Hz, and to a typical contribution at the line frequency and its harmonics which may extend well above the upper limit of the recording bandwidth and seriously affect the measurement.

Not all the fields reported in Fig.1 have the same bioelectric origin. Indeed, strong signals may be produced by magnetic particles contaminating the lung of specific workers, such as asbestos miners or arc welders.

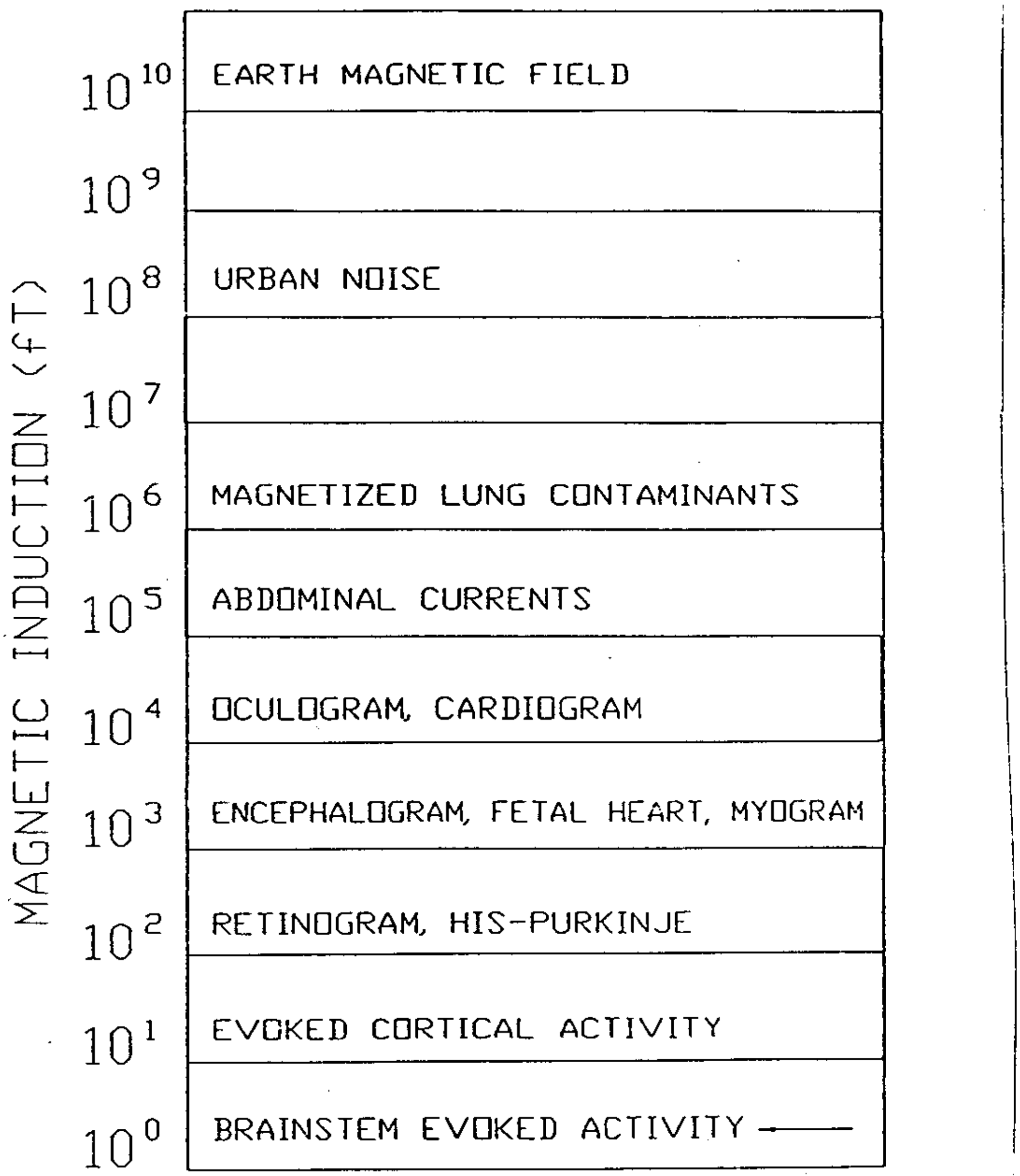

Fig.1 Typical values of the amplitude of the most commonly studied biomagnetic fields, as compared with those of the earth's field and of the environmental field noise in working areas. The intensity of the magnetic induction is expressed in femtoteslas (1 fT = 10^{-15} T). The sensitivity of the best SQUID systems is at the level indicated by the arrow.

Similarly, accumulation of iron compounds (like, for instance, hemoferritine) in the liver, spleen and myocardial tissue of patients affected by specific endemic diseases (thalassemia major, hemocromatosis, etc.) may result in a net paramagnetic signal measurable over the involved portion of the body. Also in these areas the application of the biomagnetic method has provided, or is in the process of providing, important results, and the interested reader is directed to appropriate references[10-13]. Spatial constraints force us to limit this discourse to fields associated with bioelectric activity and generated in the human brain. We infer from the figure that we are dealing with the weakest signals of the entire range. These signals originate from deep cerebral sources, like the brain stem, and are only a few femtoteslas in amplitude. Nevertheless, the SQUID has the necessary sensitivity to investigate all the mentioned phenomena, and the problem of reducing the ambient noise to levels comparable with, or possibly smaller than, the amplitude of signals to be measured is now solvable with the use of a gradiometric design for the detection coils- see Section 3 - and, possibly, with the additional help of a radiofrequency and magnetically shielded room. Indeed, it is an accepted procedure[14] to screen the experimental area by alternating layers of materials with high permeability and high conductivity, in order to get an attenuation of ambient fields about 100 below 1 Hz, and an attenuation increasing with frequency above that threshold, with an effective depletion of line frequency noise larger than 90 dB[15]. Equally important, the available space in these rooms for experimental measurements can be as large as about 30 m^3, more than adequate for any clinical study.

2.2 Modeling of neural activity

The challenge experimentalists must cope with to achieve source localization is commonly defined as the *inverse problem*, that is, the identification of a specific source configuration from a measured distribution of magnetic fields and electric potentials at the body surface. The inverse problem does not have a unique solution, as an infinite number of equivalent source distributions may account for the measured patterns. Thus, the most convenient procedure involves calculating the theoretical field and potential patterns as generated by a suitable model source, i.e., a source physiologically meaningful but yet mathematically tractable. Successively, the theoretical and experimental distributions are compared in a fit, and eventually the location of the source(s) may be identified.

Two events occur in the nervous system, and specifically at its higher level, the cerebral cortex: i) action potentials, and ii) post-synaptic currents. Both are related to ionic flows inside, across and outside the neural membrane - see Fig.2a. There is no space here to dwell on the physiology of these phenomena and on the generation of magnetic fields and electric potentials by these currents. The interested reader is directed to a recent article on the theory of neuroelectric and neuromagnetic fields[16].

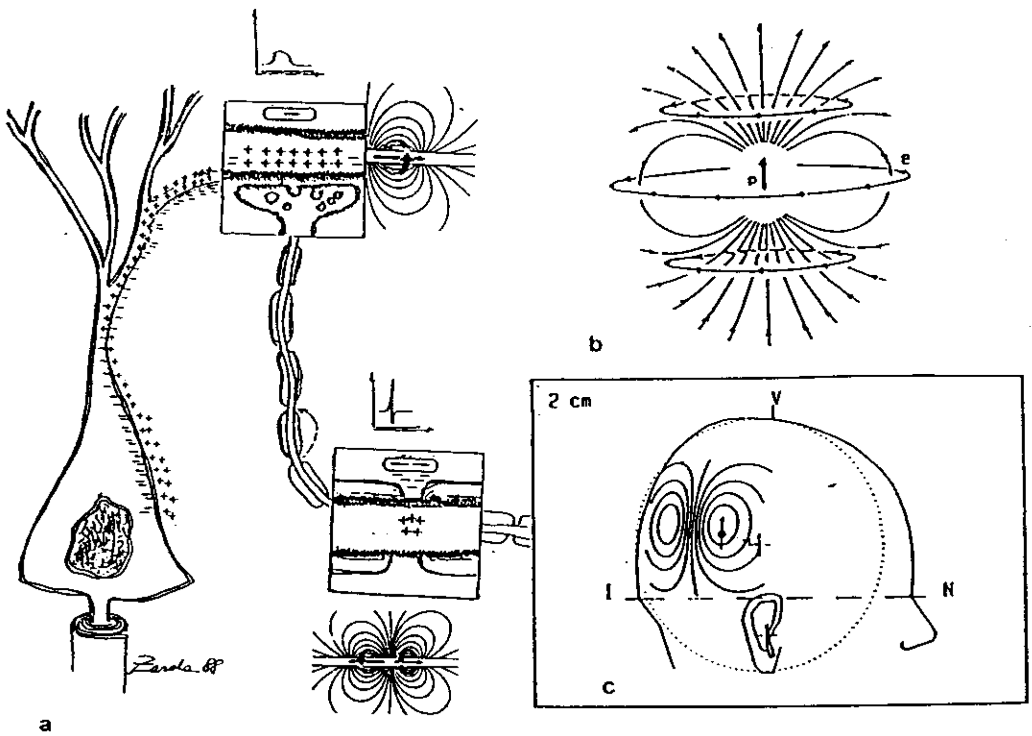

Fig.2 a) Schematic modeling of neural activity in terms of current dipoles (postsynaptic activity), and of oppositely directed dipoles (action potentials). The latter might also be considered as a magnetic quadrupole. b) A current dipole immersed in an infinite medium with homogeneous conductivity. The thin lines around the dipole are the volume currents, whereas the transverse circumferences are the magnetic field lines. c) Scalp distribution of the normal component of the magnetic field generated by a current dipole (immersed in a homogeneously conducting sphere).

We recall here only that the overall pattern of the current flow may reasonably be accounted for by that of a short element of current I, of length L and neglegible cross-section, namely a *current dipole*, with a "moment" Q = IL, when it is immersed in an infinite medium with homogeneous conductivity. It has been shown[16] that one current dipole may represent the pattern of post-synaptic currents, whereas two oppositely directed dipoles, traveling along the neural axon, may account for an action potential. It should be remarked that the majority of magnetic fields which are measured outside the head are associated with the relatively slow (10-100 ms) post-synaptic currents flowing in the cerebral cortex, at the level of the apical dendrites of pyramidal neurons and, consequently, may be accounted for by simple current dipoles or combinations of current dipoles - see Fig.2a.

The Biot-Savart law permits calculation of the magnetic field associated with a current dipole when it is immersed in an infinite medium with homogeneous conductivity. The magnetic field has an axial symmetry with respect to the direction of the current dipole, as shown in Fig.2b. The current lines flowing in the medium outside the dipole are called *volume currents*, and represent the extracellular ionic flows around the neuron. One significant feature of this configuration is that the magnetic field at a point P at a certain distance from the dipole, depends only on the primary (i.e., intracellular) current, whereas the potential at the same point depends both on the primary and volume currents. Thus, the axial symmetry of the field provides a unique tool to obtain information directly on the actual sources of cerebral activity, independently of the smearing and spreading effect due to the outside medium. This fortunate situation is partially maintained also in more realistic cases, where a "boundary" is present to constrain the conducting medium. In particular, we consider a half space with homogeneous conductivity, a sphere with homogeneous conductivity, and a set of concentric spheres with homogeneous conductivity within each shell. In all these cases, the independence of volume currents is saved for the component of the field perpendicular to the bounding surface. For this reason all biomagnetic measurements of fields associated with bioelectric phenomena are performed almost invariably by sensing the normal component of the field.

We should remark that there is a magnetically "silent" situation, where the dipole is oriented normal to the surface. This statement can easily be verified by applying Ampere's law, and the reader is again directed to the cited reference[16]. An important consequence is that the magnetic measurement is somewhat blind to part of the cerebral activity, in that it cannot detect fields produced by current flows oriented perpendicularly to the scalp. Only flows with a tangentially-oriented component produce measurable fields outside the head. We will soon see that this "disadvantage" may become a real advantage in actual measurements. The pattern of the normal component of the field from a current dipole over the bounding surface, as shown in Fig.2c, features two regions of maximum field with opposite polarity, symmetrically shaped over the dipole. This distribution, referring to the case of a tangential dipole, shows only a decrease in relative amplitude when the dipole is tilted toward a normal orientation. A relatively simple relationship links the pattern shape to the three-dimensional location of the source in the medium below the surface. It is, therefore, clear that a simple fit can be performed between the measured distribution and the theoretical one, any time that the experiment provides a "dipolar" shape, such as the one depicted in the figure.

It is worth dwelling on a last point. We have considered, in a first approximation, the medium around the model source as a sphere. The real case is not exactly so, since the geometry of real human heads varies significantly from this ideal shape. Nevertheless, it has been demonstrated repeatedly[16-18] that even in the real case, the contribution from volume currents to the normal field is of minor importance, being limited to a few percent. Scalp potentials always depend on volume currents and are inevitably dependent on different conductivities of various layers interposed between the source and the electrodes. Indeed, we should consider that the skull conductivity is about 80 times lower than that of the scalp and of the cerebral fluid. As a consequence the potential distribution over the scalp is typically more widespread and smeared, and a localization procedure is much more complex, yielding poor results. The mentioned blindness to normally oriented current flows, typical of the magnetic measurement, may even be an advantage, in the sense that a "simplified" situation is presented to the experimenter, making it easier to distinguish specific cerebral events. We should finally consider that in the five millimeters of grey matter constituting the cerebral cortex, at least one population of neurons, the pyramidal cells, are preferentially aligned perpendicularly to the cortex surface. This means that we should expect to be most sensitive to activities occurring in the fissures rather than in convolutions. Fortunately, most of the primary cortical areas are located inside brain fissures, and indeed, the most significant results achieved by means of the magnetic approach regard these areas.

3. INSTRUMENTATION

As mentioned in the previous section, the amplitude of biomagnetic fields spans several orders of magnitude, so it is not necessary for a SQUID to be used in all applications. Non-superconducting induction coils have been used in several occasions to detect magnetic heart signals, even in a vectorial form[19]. The actual limitation for this kind of sensor is due to Nyquist noise associated with the resistance of the windings. This problem can be only removed partially by cooling the coils to liquid nitrogen temperature[11]. Again, only limited applications have been found for fluxgate magnetometers[11], the performance of which is limited by Barkausen noise in the ferrite core. In practice, fluxgates have been used to set up a lung scanner for the evaluation of lung contamination in workers exposed to occupational pollution. An extensive clinical investigation has been performed with this kind of instrument and has produced excellent results[20].

Also mentioned earlier is the fact that the SQUID has sufficient sensitivity to investigate all the other biomagnetic fields, especially those associated with brain activity. Rf biased SQUIDs have been used first, due to the higher reliability these devices showed for many years (relative to dc SQUIDs). Nevertheless, over the last few years a new generation of microfabricated ultra-low noise dcSQUIDs has demonstrated greater reliability and sensitivity. Thus, these devices are slowly replacing rfSQUIDs as the detector of choice. SQUIDs have been extensively described in another chapter of this volume, therefore we shall turn our attention directly to different geometries for the detection coil to be coupled to the SQUID in order to achieve the best reduction of ambient noise and improve *spatial discrimination*. Indeed, SQUIDs alone are not likely to be used directly for magnetic field sensing, as their field sensitivity is not particularly high. It therefore is most fruitful to couple the SQUID to an external detection coil, the shape of which can be adjusted to suit the experimental requirements and to increase field sensitivity. It is worth stressing that the operation of coupling a detection coil to the input coil of the SQUID, i.e., the construction of a *flux transformer or transporter*, should be handled carefully in order to achieve the best signal energy transfer from the primary to the secondary element of the flux transformer, and at the same time to provide acceptable noise reduction.

3.1 Detecting circuitry

It has been shown elsewhere in this volume that a flux transformer is "matched" when the inductance of the detection coil L_d is made equal to that of the SQUID input coil L_i. Under this condition the ratio between the flux measured by the SQUID and the external flux, namely the flux transformer ratio, is proportional to the number of turns of the detection coil and to the mutual indutance M_i between the input coil and the SQUID, which is generally a fixed parameter. Then, in the simplest case of a detection coil with just a few turns N_d of wire spaced fairly close together, enclosing an area A_d, the minimum detectable external field B_n is

$$B_n = \Phi_n(L_d + L_i)/A_d N_d M_i \qquad (1)$$

where Φ_n is the SQUID flux noise, and $L_d = L_i$ for optimal matching. As the area of the detection coil cannot be made larger than a few square centimeters - typical detection coil diameters span from 1 to 2 cm - the unique parameter to be handled is N_d. Furthermore, it is desirable to separate the individual turns of the detection coil so to reduce their mutual inductance. By using a spacing between adjacent coils of 1 mm or more; it is possible to make L_d about proportional to N_d rather than to N_d^2, and consequently, to achieve the inductance match with a larger value of N_d.

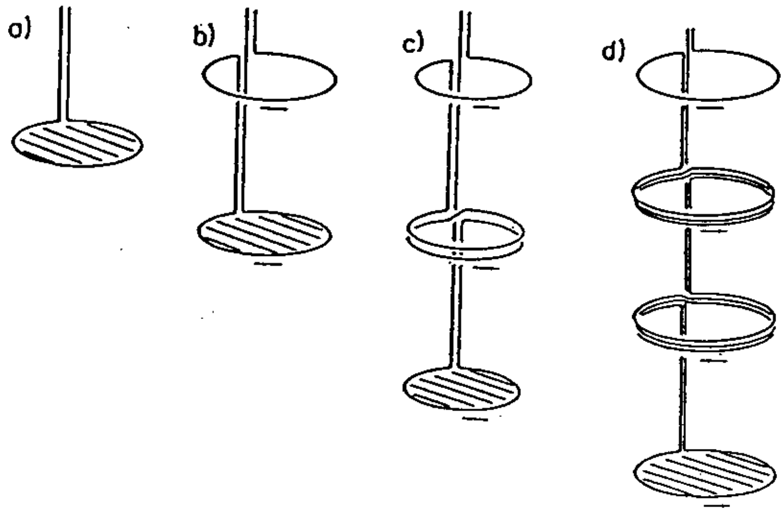

Fig.3 Most commonly used geometries for the detection coil to be coupled to a SQUID for biomagnetic measurements: a) magnetometer, b) first-order gradiometer, c) second-order gradiometers, and d) third-order gradiometer.

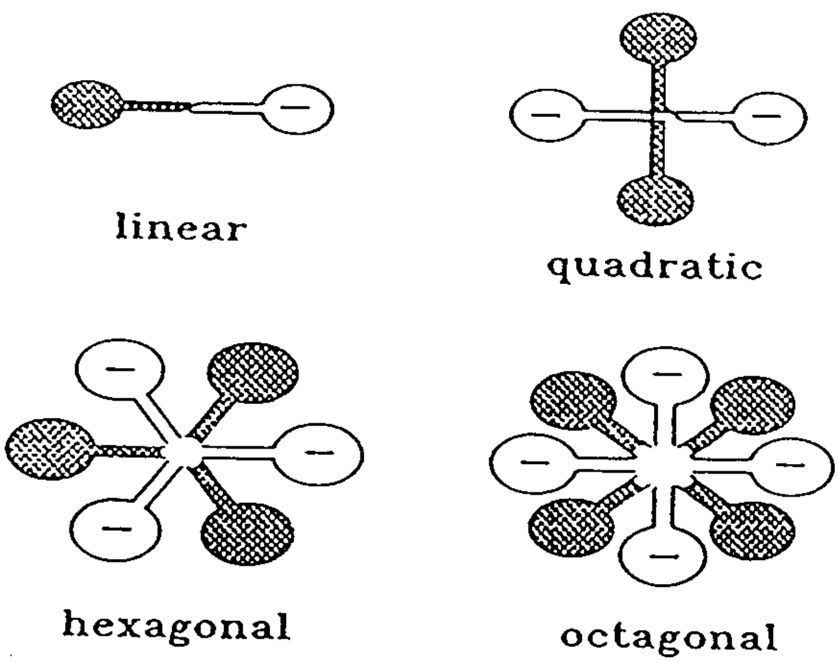

Fig.4 Possible configurations for planar gradiometers, to be directly integrated in the SQUID loop (not shown in the figure).

A detection coil consisting of a single coil, referred to as a *magnetometer coil*, responds to the applied field regardless of the distance of the source. However, the detection coil geometry can be altered, as illustrated in Fig.3, in order to achieve greater insensitivity to far sources. A *first-order gradiometer* is insensitive to fields uniform in space, whereas a *second-order gradiometer* is insensitive to both spatially uniform fields and gradients. The basic advantage in using these geometries is that a "noise" field produced by a far source, relative to the distance between the subcoils, or *baseline* of the gradiometer, can be substantially cancelled**, whereas a high sensitivity is maintained for sources close enough to one of the extreme subcoils of the gradiometer. Hence, the need for helium cryostat is needed with a "tail" providing a small distance- about 1 cm - from the inside to the outside of the dewar***. The penalty we have to pay in return for ambient noise reduction is a reduction in the overall sensitivity, as the signal energy is shared among the subcoils of the gradiometer. This effect[11] limits the performance of systems for unshielded environments to a sensitivity which is about a factor of 3 worse than that obtainable in heavily shielded rooms, where magnetometers can be used straightforwardly. It should be noted that for many years systems based on second-order gradiometers have been routinely used in many laboratories around the world. Nevertheless, the relatively low cost of a new generation of shielded rooms, and the greater complexity in balancing multi-gradiometric systems are convincing experimentalists to combine the rejection effect of gradiometers with the shielding effect of rooms.

The gradiometric geometries so far used for biomagnetic measurements have

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** The balance of the gradiometer versus constant fields and gradients is in practice limited by the mechanical accuracy during construction. Therefore, additional balancing procedures - by means of superconducting trim tabs, and fine baseline adjustements[11] - are usually required to achieve satisfactory insensitivity to ambient fields.

***The technological state of the art for cryogenic dewars is more than satisfactory. Continuous operation for about a week is guaranteed not only for single-channel sensors, but also for larger systems providing a "concave" tail for a few adjacent channels to ensure perpendicularity with respect to the head. Looking forward to imaging systems with 100 channels or so, further improvements are still to be made, particularly with regard to helium boil-off rate and magnetic noise associated with the thermal shielding in the tail.

the common feature of a vertical symmetry axis****. A different approach consists in using a *planar* configuration and integrating the gradiometer directly in the same chip that contains a planar SQUID. The motivation for this choice relates to the obvious difficulty that integration of a large number of magnetic sensors in a complex multichannel system (see below) presents, particularly with respect to accurate balancing for each channel. Figure 4 shows some examples of planar geometries for the detection coil which can be obtained with standard photolitographic techniques. Each configuration should be regarded as directly connected to a microfabricated SQUID, or inductively coupled to the SQUID input coil via a flux transformer also integrated in the same chip[21]. This feature is important in that it permits elimination of superconducting connections between each gradiometer and the respective SQUID. The increasing number of loops provides higher and higher spatial discrimination, and at the same time, the overall sensitivity is reduced as expected. Early attempts to build experimental devices trace back to the end of the 1970's and to the beginning of the 1980's[22-24], whereas none of these geometries has been used yet for practical measurements. Several computer simulations performed by many authors[25-28] have pointed out various advantages of these devices with respect to vertical ones, among which are a higher discriminating

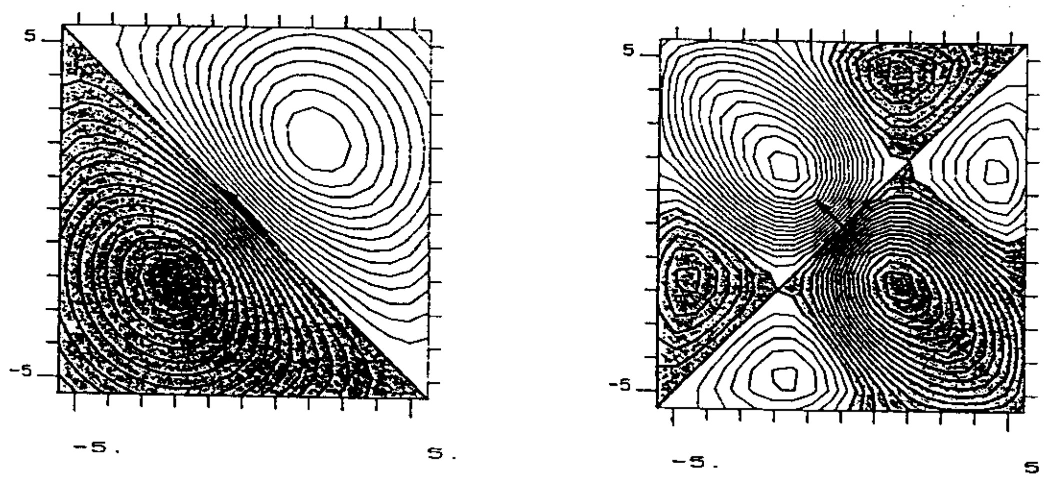


Fig.5 Simulated iso-contour maps illustrating the distribution of the field generated by a current dipole immersed in a homogeneously conducting half space at a depth of 4 cm, as measured (left) by an array of vertical gradiometers, 1.5 cm diameter detection coil, 5 cm baseline, and (right) by an array of planar (quadratic) gradiometers, .5 cm loop diameter, 1.5 cm baseline. The spacing in both directions of the sensors is 3 cm. Units are expressed in centimeters.

****measurements of the alpha activity with an off-diagonal, or 2-D gradiometer, were performed by Cohen in 1978[20] factor versus ambient noise, a larger sensitivity to higher spatial frequencies, and a calculatable quite satisfactory "intrinsic" balancing. It should be remarked, however, that a vertical gradiometer with a baseline longer than about 4 to 5 cm, essentially measures brain fields, rather than gradients. By contrast, a planar gradiometer, the baseline of which cannot be made larger than about 1-2 cm for practical reasons, always measures field differences. As a consequence, the detected patterns are complex-see Fig.5 - and do not show a symmetry for different orientations of the source. On balance, planar coil geometries are favored, particularly for integration into large multi-channel assemblies.

3.2 Multichannel systems

The goal toward which many groups around the world are moving is the achievement of neuromagnetic images through large systems with a number of channels of the order of 100. Later in this section we will see the basic requirements for these systems: the present state of the art is limited to instruments with a limited number of adjacent sensors[28-31]. A common feature for the systems which allow seven adjacent measuring sites is that they place six gradiometers equally spaced on a circle, and a seventh one in the center equidistant from the other six. It should be remarked that this configuration ensures maximum "packing" of sensors in dewars with a cylindrical tail and that, consequently, a sort of "magic numbers" sequence is established also for larger systems according to the progression $[1 + 3n(n + 1)]$, with n = an integer. On this basis the successive steps would be 19, 37, 61,... It should be pointed out that the spacing between adjacent channels is strictly related to the depth of the source under study[32], in that it determines the rate of spatial sampling of the field. Small spacing is useless, as the minimum distance of a cerebral source from the detection coil is typically larger than 3 cm. Large spacing is dangerous and may require replication of the measurement at shifted sites. A spacing of about 3 cm seems optimal given dewar constraints and the depth of the neuromagnetic sources.

The experimental procedure so far adopted to measure neuromagnetic fields and to obtain their spatial distribution over the scalp consists in accurately positioning the concave tail of the dewar over a specific scalp area and in recording activity related to underlying sources. The dewar positioning must be carefully checked with respect to anatomical reference points to ensure reliability. Since the present state of the art requires successive positioning over adjacent scalp areas, errors in this procedure may dramatically affect the validity of localization[32]. It is clear that this problem will gradually disappear when larger systems become available, and when magnetic activity related to a specific source is measurable in a single "shot".

Finally, the shape of the subject's head must be satisfactorily known before applying the localization algorithm. This can be achieved by direct craniometric measurements, by x-ray pictures or, better, by MRI images. This last method, currently under study, would permit identification of the internal structures of the subject's brain, matching the neuromagnetic localization with actual anatomy. The best "local" sphere, fitting the curvature of the head over the region of the measuring sites, should then be used to evaluate the theoretical distribution from the model source by fitting a least-squares algorithm to the experimental pattern. Statistical tests also may be used to determine the level of significance of the fit and 95% confidence intervals[32]. A further step, currently under development, consists in calculating the forward problem directly in the actual head of the subject, as reconstructed by a finite element method[17]. If successful, this procedure will definitely improve results, but at the cost of longer computing time.

4. OVERVIEW OF NEUROMAGNETIC RESULTS

We have seen at the beginning of this article that the most promising results of the biomagnetic method have been obtained in the study of cerebral functioning and pathology. This does not exclude that important results have been achieved in other areas. For example, we note that magnetic investigation of some heart pathologies, such as ventricular arrythmias and abnormal accessory excitation pathways, is proving to be a significant tool for preoperative studies. A recently identified application[33] probably will permit a follow-up of transplanted hearts and possibly predict rejection phenomena. More complete review articles are available[10,12,34,14,13,35].

4.1 Epilepsy

The analysis of epileptic activity by means of magnetoencephalographic (MEG) recordings represents one of the most promising applications of the neuromagnetic method in the clinical field. A systematic study of this disease was initiated in 1980 at the Istituto di Elettronica dello Stato Solido in Roma[36,7,9,37,38] and immediately pointed out the possibility of the new approach. An "historic" recording in Fig.6 shows a magnetic trace detected simultaneously with seven electrical traces. The measurement was of a patient with a calcification in the temporal lobe (as shown by the CT image), and the interesting finding was that a "paroxismal" activity - a sequence of sharp waves, namely *spikes* combined with a slow frequency modulation - was clearly identifiable in the MEG, with no electrical counterpart. The abnormal magnetic activity was quite evident also with respect to the "standard" activity detected over different regions of the scalp, and was most probably associated with an abortive seizure provoked

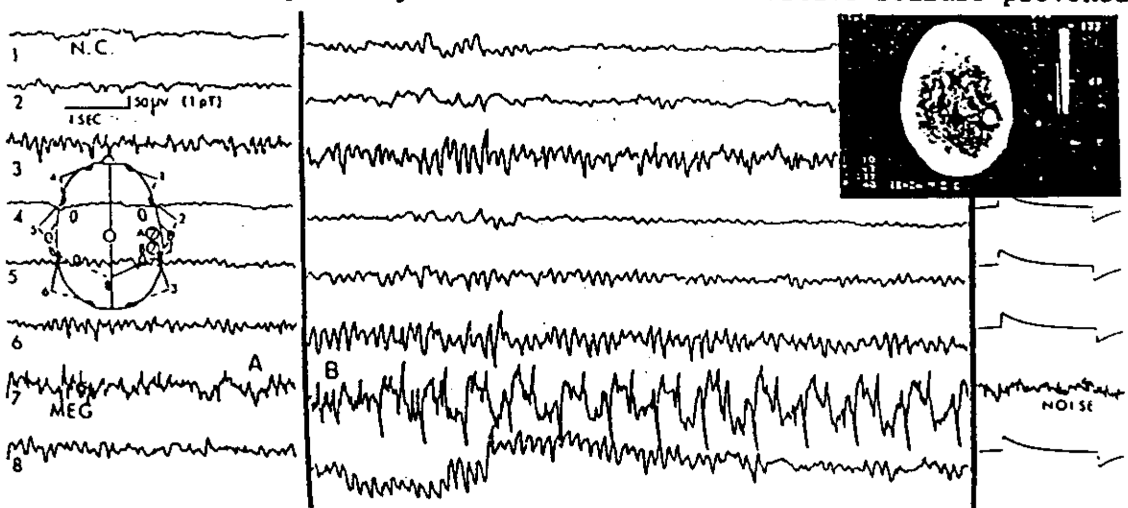


Fig.6 One of the first simultaneous EEGs and MEG (seventh trace) recording from a patient affected by focal epilepsy produced by the calcification revealed by the CT picture. The central magnetic tracing clearly shows pathological signals, probably related to an abortive seizure, not evident in the EEGs.

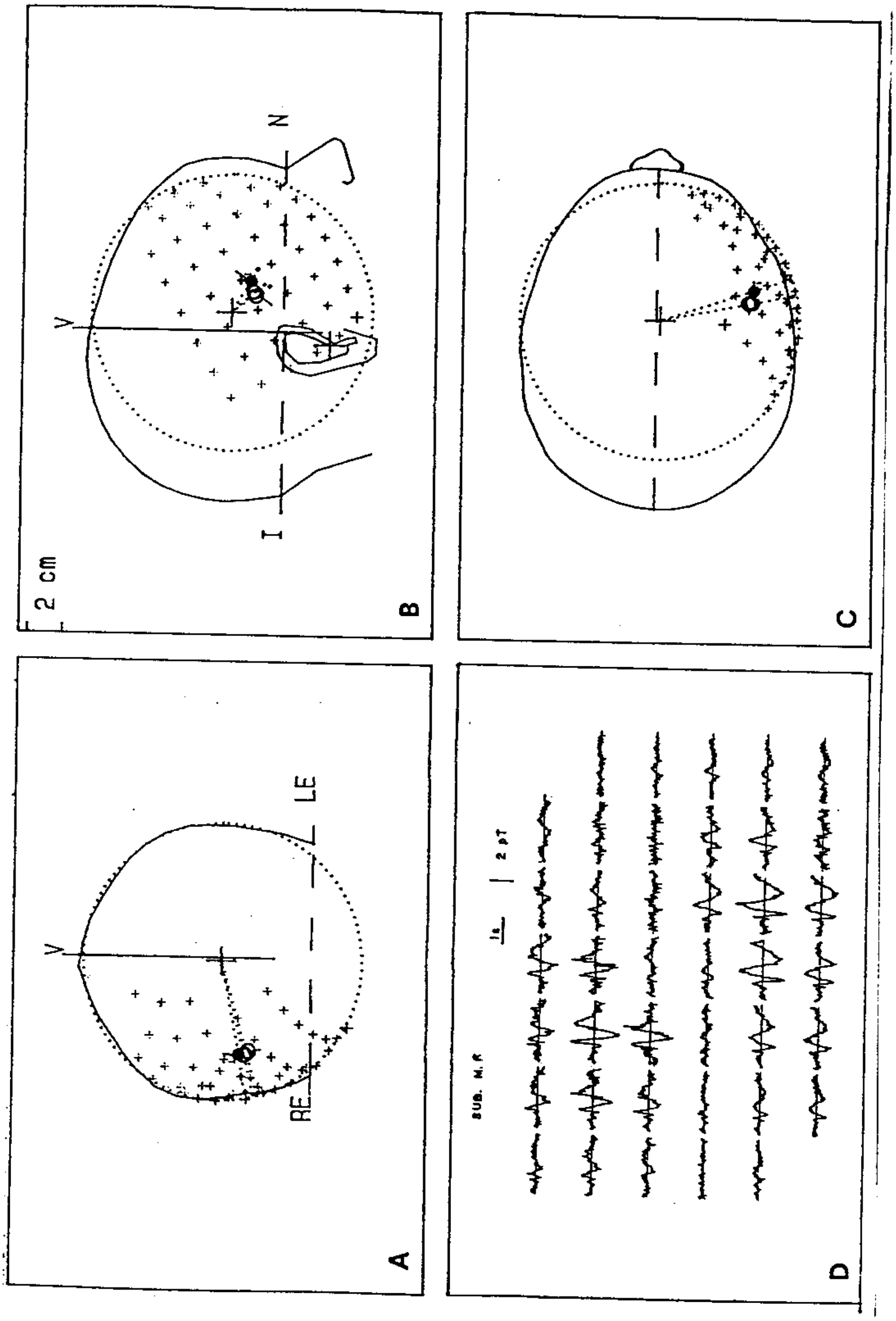


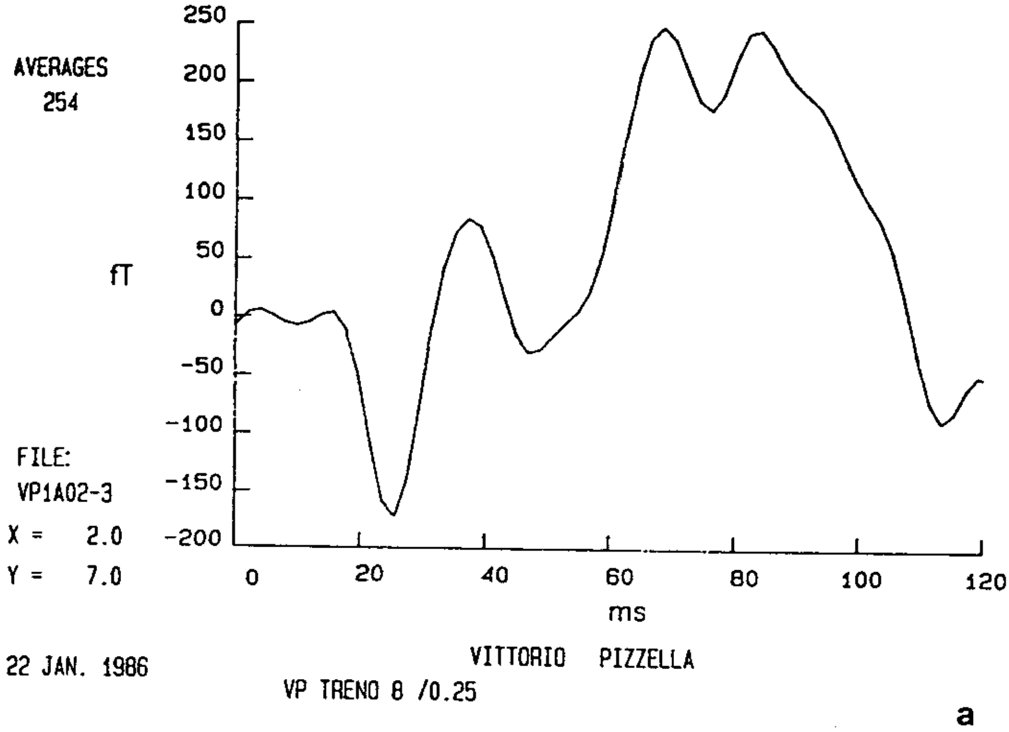
Fig.7 Map of pathological magnetic signals recorded over the right hemisphere (temporal lobe) of a patient affected by focal epilepsy. Each trace was recorded at the corresponding site identified by the cross in the three profiles of the patient's head. The neuromagnetic localization was carried out for different conponents of the pathological signals. The equivalent generators are identified by circles.

by compression of neural tissue by the intrusive mass.

In general, the study of "interictal" spikes, i.e., activity occurring between seizures, has shown that magnetic signals often display a dipolar distribution over the scalp[6,7,8]. The localization of the relatively concentrated neural tissue which is firing abnormally is, therefore, often simple. The same procedure based on measured electric potentials would be much more difficult, in fact, even impossible in many cases, due to the interference of extracellular currents and the smearing effect of different layers interposed between the source and the probe. In practice, the magnetic method permitted in many cases a three-dimensional localization of the epileptic focus that was confirmed by intra-operative findings[7,38,39]. One of these examples is illustrated in Fig.7, where the map of spike signals clearly shows polarity reversal. The neuromagnetic localization carried out for the different components of the abnormal signal is reported in the three profiles of the patient's head. This result was confirmed during surgery where the extension of the "active" area was found to involve approximately 7 cm^2 of cortex. Relatively extensive spreading of pathological tissue is typical of this kind of disease and may cause problems for possible non-invasive tissue destruction by means of radiographic techniques. An additional problem may be the insensitivity of the magnetic measurement to radially oriented current flows. A combined mapping of magnetic and electric signals is probably desirable for large-scale clinical use[39].

4.2 Evoked fields

The procedure to study functions related to primary areas of the brain consists in stimulating a peripheral sensory system (visual, somatosensory, auditory) and in measuring the evoked response over the appropriate region of the scalp. The evoked field is generally quite small and, consequently, is by no means distinguishable from the background cerebral activity, which can be regarded as "noise". If the brain is considered as a "stationary"



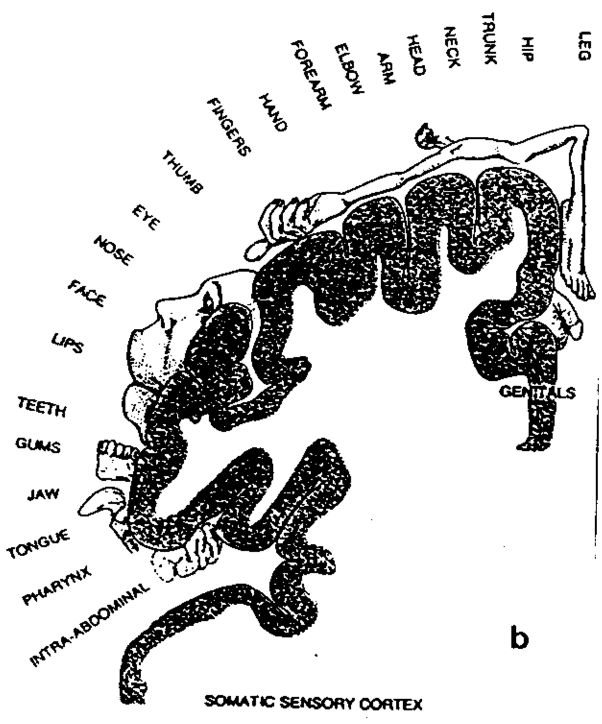


Fig.8 a) Evoked magnetic field under median nerve stimulation at the wrist, as recorded over the side of the scalp contralateral to the stimulated limb. b) Somatosensory homunculus, representing the one-to-one mapping of the peripheral somatosensory system onto the cortex.

system*****, each individual response is "time locked" to the stimulus and is identically repeated after each stimulation. The signal-to-noise ratio can then be increased by averaging many epochs, with a gain proportional to the square root of the number of trials. The result is an *evoked field* like the one reported in Fig.8a. In this case, the stimulation was delivered at the wrist of a normal subject, and consisted of a short electric pulse, 0.1 ms in duration, applied to the median nerve so as to produce an appreciable twisting of the thumb. The response recorded over a specific site of the scalp contralateral to the stimulated limb is structured in a sequence of "components" with different polarity, each one identified by a respective delay, or "latency", from the stimulus onset. By replicating the measurement, other responses can be obtained at many positions of the scalp, typically 40 to 50. From all these time traces it is then possible to obtain field maps corresponding to the latencies of different components. Finally, if the structure of the field distribution is dipolar, a source localization procedure can be applied to identify equivalent generators responsible for the recorded activity. This procedure, applied to the study of the somatosensory cortex, provides results that are in quite good agreement with the so-called somatosensory "homunculus", i.e., the projection of the soma onto the cortex - see Fig.8b - and that has been established many years ago in a highly invasive way during surgery[40]. Fig.9 shows the isofield contour maps obtained for the first component of the responses evoked by stimulation of the median nerve at the wrist and of the tibial nerve at the ankle, respectively. The two maps are both dipolar in shape and the results of the localization algorithm are illustrated in the three plots on the right, representing the three profiles of the subject's head. The equivalent generators, inserted with their respective 95% confidence interval, fit positions in the brain which agree well with the location of the hand and foot area in the homunculus.

A similar procedure can be used to investigate other cortical areas, such as the auditory one. For this case the stimulus usually consists of tone

*****the hypothesis of brain stationarity is very questionable, and indeed, has been criticized by many authors. Nevertheless, it has been commonly accepted in all clinical measurements of evoked potentials. Accurate selection of individual responses to each stimulus usually shows different cerebral responses, ranging from a maximum amplitude to even no response at all. We should consider the assumption only as a "working" hypothesis, to get a true "averaged" response.

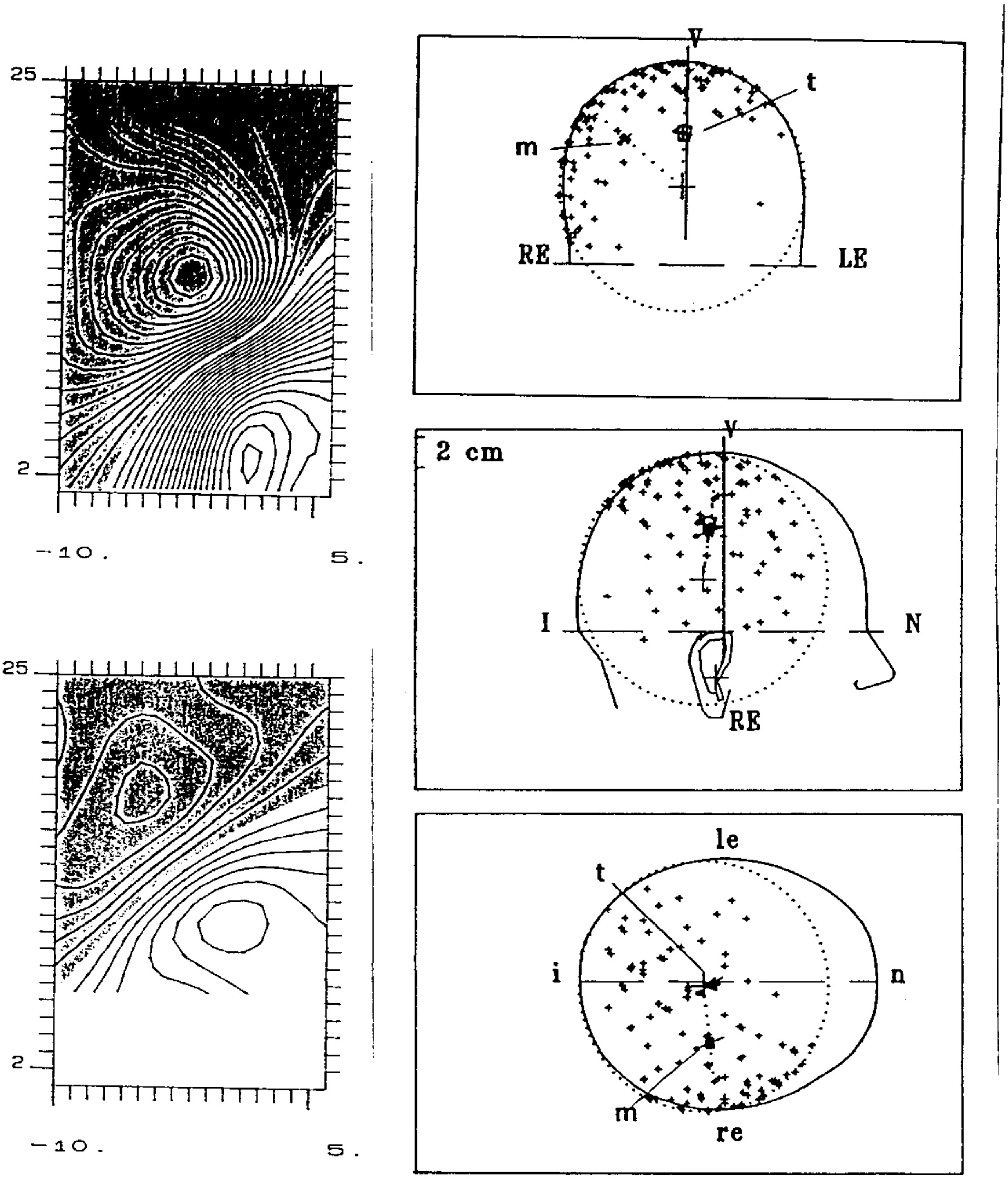


Fig.9 Left: The iso-field contour maps illustrating the scalp distribution of the magnetic field evoked by median nerve stimulation at the wrist (top, m) and by tibial nerve stimulation at the ankle (bottom, t). The iso-line step is 7 fT, and the shaded areas identify negative field polarity. Right: Three-dimensional localization in the actual profiles of the subject's head of the equivalent generators (m, t) accounting for the dipolar distributions reported on the left. The crosses identify the measuring sites and the 95% confidence intervals are also shown.

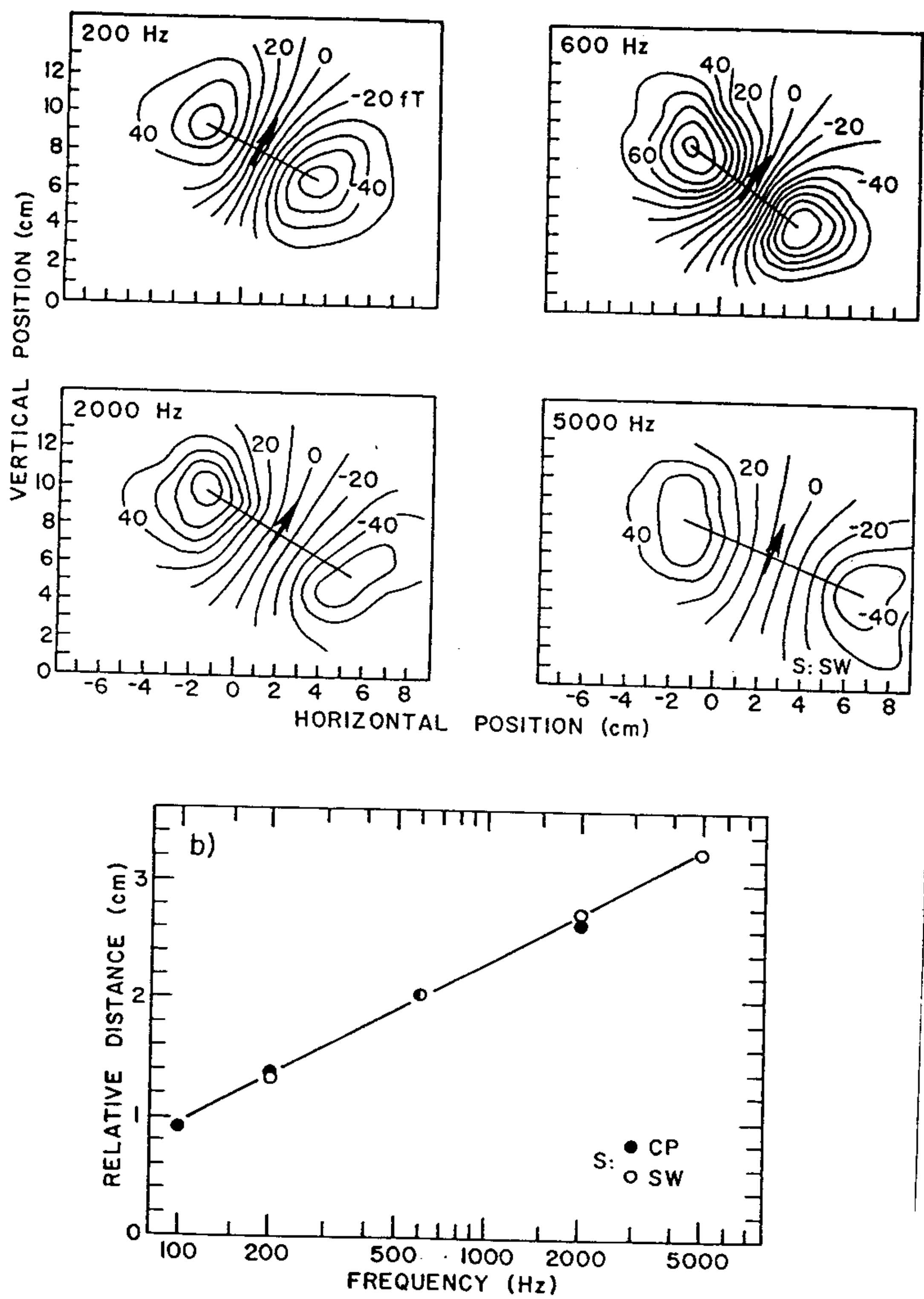


Fig.10 Top: Sequence of iso-field contour maps illustrating the distribution of the magnetic field over the temporal region of the scalp in response to stimulation of the auditory system by means of pure tones with increasing frequency. Bottom: The graph represents the relative straight-line distance between adjacent equivalent sources along the cortex, for two subjects, versus stimulus frequency.

bursts at a specific frequency, or clicks, or combinations of tones. Thus, it was possible to identify a "tonotopic" organization of the human auditory cortex by delivering the subject pure tones of increasing pitch, sinusoidally modulated at low frequency[5]. Fig.10 (top) shows the isofield maps obtained from one subject in response to tones with 200, 600, 2000, and 5000 Hz fundamental frequency. Beyond the clear dipolarity of all the maps, an increase of the distance between the two maxima with opposite polarity and a lateral translation of the midpoint were appreciable. The localization algorithm provided three-dimensional identification of the equivalent generators activated by different stimuli and permitted establishing that their location over the auditory cortex followed a clear logarithmic progression versus stimulation frequency - Fig.10, bottom. This was the first demonstration that in humans, as in animals, the auditory cortex is organized similarly to the cochlea, and that an equal number of neurons is devoted to each octave of sound.

The evoked field method seems particularly appropriate to study cortical organizations and functions, probably because it permits focusing investigation on a very specific phenomenon, and somewhat cancels all the other activity of the brain. Indeed, many results have been obtained in the last few years which definitively confirm this possibility[14,34,35]. The current state of the art permits the study of brain responses to different kinds of stimulation, including composite stimuli. The magnetic response can be analyzed in terms of isofield maps at steps of 1 ms, which seems appropriate to the speed of cerebral events. The localization algorithm can be sequentially carried out and provides the time-spatial evolution of the equivalent generators responsible for the studied activities. The lack of simultaneity still remains a problem, which will be overcome in the near future when large multichannel systems become available. Then experimentalists will have a unique tool to investigate, in almost real time, rapidly-occuring events in the brain, such as information processing.

5. CONCLUSIONS

The aim of this survey has been to provide at least a hint of current progress in SQUID-based biomagnetic research. Because of spatial limitations, no attempt has been made to be comprehensive. However, this is a rapidly growing area of interdisciplinary research, and biomagnetism embodies one of the most important application of SQUIDs. Still, some problems remain to be solved in order to achieve the goal of biomagnetic functional images. One such problem involves the need for liquid helium refilling. It should be noted that the cost of maintaining a class 100 system, i.e., a system with about 100 sensors, would be large enough to make the cost of helium a secondary contribution to the total cost. The development of closed cycle cryocoolers might also help to solve this problem. Finally, the impact of high T_c superconductors might dramatically modify the present situation. Even if the state of the art in this field is not yet adequately developed, it is conceivable that at least part of the superconducting circuitry may consist of high T_c materials, thus simplifying the cryogenic assembly and reducing the overall cost. How fast these improvements can be made is not easy to predict. The hope is that it will not take long.

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