# SQUIDS IN NEURO- AND CARDIOMAGNETISM

**Olli V. Lounasmaa**, Low Temperature Laboratory, Helsinki University of Technology, 02015 HUT, Finland

**Heikki Seppä**, Measurement Technology, VTT Automation, 02015 VTT, Finland

**Keywords:** Brain, Cardiomagnetism, Current dipole, Flux transformer, Functional magnetic resonance imaging, Heart, Imaging techniques, Josephson junction, Magnetic field, Magnetic resonance imaging, Magnetic shielding, Magnetocardiography, Magnetoencephalography, Magnetometer, Multichannel instruments, Neuromagnetism, Pick-up coil, SQUID, superconductors

**Contents**

## Glossary

**Action potential:** The duration of an action potential (AP) in the heart is 300…400 ms, and the APs spread electrically from cell to cell in a synchronized manner.
**Arrhythmia:** A disturbance in the normal heart rhythm. Tachyarrhythmia is a disturbance where the heart rate rises up to 200…300 beats per minute, while in a bradyarrhythmia the heart rate is slowed.
**Brain rhythm:** The best known spontaneous oscillation of the brain is the 10-Hz α-rhythm, known for 50 years at least. It is generated in the occipital region of the brain. Its purpose is not known for sure. Another spontaneous oscillation is the 10- and 20-Hz μ-rhythm, whose generators are near the Rolandic fissure.
**Biomagnetic Technologies Inc:** Pacific Heights Boulevard, San Diego, CA 92121.
**CAT:** Computer assisted tomography. A revolving X-ray tube and a bank of counters are used to create a picture by analyzing the recorded X-ray intensities by means of a computer.
**CTF Systems Inc:** Port Coquitlam, Canada V3C 1M9.
**Current dipole:** A pointlike current element, with a position and direction, is a current dipole. Thousands of parallel currents through neighboring neurons are needed to form a current dipole which is sufficiently strong to be detected by MEG.
**DC:** Direct current.
**ECG:** Electrocardiography. Electrodes are placed at suitable points on the subject's chest. See also the description for EEG.
**EEG:** Electroencephalography. Electrodes placed on the scalp measure the same neuronal currents as in MEG, in theory. But since the electric-potential distribution is distorted by the skull, the scalp and other tissues that have electrical conductivities that differ from those in the brain itself, EEG is better for detecting currents that originate deep inside the brain or are radially oriented.
**FET:** Field effect transistor, described in any modern textbook on electronics.
**Fissures:** The grooves in the cortical surface are called fissures. Since the current dipoles in the brain are perpendicular to the surface of the cortex, dipoles in the walls of the fissures are tangential to the surface of the head. Therefore, MEG primarily measures activity in the fissures. This is, however, not so serious because 2/3 of the cortical surface is in the fissures and because the most important regions (for instance the somatosensory, motor, auditory and visual cortices) are mainly in the fissures.
**Flux transformer:** A superconducting flux transformer is used for transmitting magnetic flux from the region where measurements are made to the SQUID. The flux transformer is based on the fact that the magnetic flux, which penetrates a surface surrounded by a superconductor, is constant.
**fMRI:** functional magnetic resonance imaging. See MRI.
**HUCH**: Helsinki University Central Hospital, 00029 HUCH, Finland
**HUT:** Helsinki University of Technology, 02015 Espoo, Finland.
**IBM:** International Business Machines Inc.
**Intercellular current:** The current between cells.
**Inverse problem:** By measuring the magnetic field outside the head one can, in principle, use a computer to calculate the sources in the brain which have generated the field. Unfortunately, however, there is an infinite number of solutions to this so called inverse problem, as was shown by Hermann von Helmholtz 150 years ago. This is a mathematical fact, the problem is "ill posed". In order to get a definite solution, special conditions must be assumed. Usually it is postulated that the source within the spherical brain is a current dipole or several such dipoles. Then the locations, directions and strengths of the dipoles can be calculated uniquely.
**Josephson junction:** A weak link between two superconducting electrodes.
**LTL:** Low Temperature Laboratory at HUT.
**Magnetometers and gradiometers:** A single superconducting loop measures the magnetic flux threading it. A first order gradiometer measures the first derivative of the magnetic flux with two oppositely would superconducting coils (figure-of-eight configurations: 8, ∞). A second order gra-

diometer has four coils and it measures the second derivative of the magnetic flux. Gradiometers attenuate noise sigals from distant sources.
**MCG:** Magnetocardiography. Secondary subject of this article.
**MEG:** Magnetoencephalography. Main subject of this article.
**MRI:** Magnetic resonance imaging. The subject is exposed to a high static magnetic field and a small alternating radiofrequency field. Magnetic resonance signals produced by hydrogen nuclei in different tissues are measured, either to create an image of proton density in the anatomical structures (conventional MRI) or to monitor changes related to brain metabolism and blood flow (functional MRI).
**MSI:** magnetic source imaging; another name for MEG.
**Mu-metal:** Mu-metal is an alloy of iron and nickel and small amounts of other metals, which has a high magnetic permeability, considerably higher than soft iron. It is used for magnetic shielding of the closed volume where MEG measurements are made. Magnetic field lines are "trapped" in the mu-metal instead of the free space inside.
**PET:** Positron emission tomography. Radioactive markers are injected into the subject's bloodstream to monitor changes in brain metabolism, blood flow, or the distribution of receptors for different chemical transmitters. The short-lived radioactive substances emit positrons that hit electrons after travelling very short distances. Each collision causes annihilation of the positron and electron, which produces two γ-rays that fly in the opposite directions. They are detected by a large number of γ-coincidence counters placed around the subject's head or chest.
**PTB:** Physikalische-Technische Bundesanstalt (10587 Berlin, Germany).
**RF:** Radio frequency, 1 MHz … 1 GHz.
**QRS complex:** The tri-phasic main waveform in an ECG or MCG recording, caused by depolarization of the ventricular muscle cells.
**Source modelling:** When experimental data are mathematically analysed, it is necessary to assume the basis on which the formulae were derived. In MEG, it is usually assumed that the source is a current dipole in a spherical volume conductor.
**SQUID:** Superconducting QUantum Interference Device.
**Tachycardia:** Abnormally fast heartbeat.
**Tangential dipole:** It is a mathematical fact that dipoles radial to the nearest surface of the brain do not produce a magnetic field outside. Tangential dipoles, on the other hand, produce a field outside.
**VTT:** Technical Research Centre of Finland (02015 VTT, Finland).

## Summary

In this paper, an adequate account of the theory and practice of SQUIDs and of magnetoencephalography (MEG) and magnetocardiography (MCG) is given. MEG and MCG are two completely non-invasive imaging techniques, suitable for basic and clinical studies of human subjects. Large SQUID arrays, operating at liquid helium temperatures, are employed for detecting and localizing the magnetically active regions, modelled by current dipoles, in the working brain or heart. The measurements are usually performed in magnetically shielded rooms. Time resolution of both methods is better than 1 ms and spatial uncertainty 5 ... 6 mm. The evoked brain signals are as small as 40 fT, one billionth of the earths geomagnetic field. The dc SQUID is discussed with a detailed description of the ideas behind and construction of the modern VTT superconducting sensor. A shorted account is given on the PTB SQUID. Commercial multi-SQUID instruments, briefly described, are now available from three manufacturers. Seven examples of brain studies, including two clinical applications, are discussed. Cardiomagnetic instrumentation is described and the use of MCG in detecting heart abnormalities is presented with three examples. The advantages and drawbacks of modern imaging techniques, including MEG, MCG, MRI, fMRI, and PET, are compared and the future of MEG and MCG is discussed. Eventually, when it becomes feasible to use high-$T_c$ SQUIDs in MEG and MCG, the high cost of magnetic measurements can be reduced.

## 1. General comments

Activity of the brain and heart involves small electrical currents which flow in the biological tissue. These currents, in turn, produce tiny magnetic fields which can be measured outside the body, using ultra-low-noise Superconducting QUantum Interference Devices (SQUIDs). Two related techniques, magnetoencephalography (MEG) and magnetocardiography (MCG) have emerged to enable non-invasive utilization of the magnetic data. Clinical applications of both methods have evolved and further developments are in progress. MEG is sometimes called magnetic source imaging (MSI).

Exploration of the human brain is of utmost intellectual interest: The whole humanity depends on our minds. The human brain is the most complex "instrument" known in the universe. There are about $10^{11}$ neurons in the cerebral cortex. These nerve cells are the active units in a complex network, consisting of about $10^{14}$ interconnections or synapses. This is more than in the world's entire telephone system.

A great deal has been learned already about the cerebral anatomy and physiology, but the fundamental question of how the brain stores, retrieves, and processes information is still largely unknown. Neural computers are the future tools of designing and decision making. Recent developments in this new field of computing are one important source of inspiration to study the functional principles of the human brain, in addition to many interesting questions of basic and clinical neuroscience. For the first time it is now possible to investigate information processing in the living human brain, without philosophical speculations.

The heart in conceptually a much simpler device than the brain but, nevertheless, cardiology is a very important field of medical research. Heart deseases are the number-one cause of deaths in developed countries.

This paper deals mainly with SQUIDs and their use in MEG studies. We naturally emphasize the MEG- and instrumentation work carried out under Riitta Hari and Olli Lounasmaa in the Low Temperature Laboratory of HUT, and the development of SQUIDs done under Heikki Seppä in VTT. A brief section towards the end describes the experimental arrangement and some results of MCG studies of the heart, emphasizing work carried out under Toivo Katila in the Laboratory of Biomedical Engineering of HUT and in the BioMag Laboratory jointly owned by HUCH and HUT.

## 2. Magnetoencephalography and magnetocardiography

### 2.1. Introduction

The intracellular currents that flow through the brain's individual nerve cells (neurons) produce magnetic fields which are too small to be detected outside the head. However, when thousands of nearby cells act synchronously, the current is large enough so that the field it generates can be measured non-invasively by a SQUID magnetometer, placed outside the skull. Neuromagnetic fields are 50 … 500 fT (femtotesla = $10^{-15}$ T) in strength, *i.e.*, one part in $10^9$ or $10^8$ of the earth's geomagnetic field. Cardiac fields are about two orders of magnitude stronger.

From the measured field distribution it is possible, by making suitable assumptions, to calculate backwards the brain area which was activated by a sensory stimulus, such as a sound, a picture, or a touch. Spontaneous brain rhythms, like the 10-Hz $\alpha$-activity, can be investigated as well. Figure 1 shows a typical experimental situation during MEG recordings.

Figure 1 about here

Magnetoencephalography and magnetocardiography are fully based on the SQUID which is a superconducting ring interrupted by one or two Josephson junctions. Phase coherence of charge carriers in a superconductor gives rise to flux quantization in the SQUID ring. Owing to the smallness of the flux quantum, about 2.07 fWb, the SQUID can be made into a very sensitive parametric amplifier.

Pioneers in the MEG field are James Zimmerman, the inventor of the practical SQUID in 1970, David Cohen who, with Zimmerman, first detected magnetic brain signals, and Samuel Williamson whose group did much of the earlier work. At present, about 100 laboratories worldwide are engaged in magnetoencephalographic studies of the human brain; some of the interdisciplinary teams consist of a dozen or more researchers, including physiologists, physicists, psychologists, linguists, and information scientists. Comprehensive reviews of the MEG technique and of experimental data are available (see Bibliography). The state-of-the-art in biomagnetism is reflected in the proceedings of the biennial International Conferences on Biomagnetism.

## 2.2. The human brain

In MEG, one is usually concerned with the uppermost layer of the brain, the cerebral cortex, which is a 2 ... 4 mm thick sheet of gray tissue, consisting of complexly interwoven neuronal networks. Both hemispheres of the brain, the left and the right, are subdivided by deep fissures into four lobes: frontal, parietal, temporal, and occipital (see Figure 2).

Figure 2 about here

Most regions of the cerebral cortex have been mapped functionally in animals and also in man during brain surgery. The area just in front of the nearly vertical Rolandic (= central) fissure, in the frontal lobe, is the motor cortex, concerned with control and integration of muscular activity. Behind this fissure, in the parietal lobe, the primary somatic sensory cortex is located. This structure is involved with the reception and analysis of information from the skin, joints, and muscles. The left and right auditory cortices, in the temporal lobes, are largely buried within the Sylvian fissures. The primary visual cortex is in the occipital lobe at the back of the head. Wernicke's and Broca's areas, which are important for the analysis and production of speech, are also indicated in Figure 2. Most of the remaining cortical regions are known as association areas where inputs from several sensory modalities are integrated.

Signals in the brain are processed by neurons, which communicate with each other via weak electrical impulses. The neurons are able to generate so-called action potentials, which are voltage pulses of about 100 mV that last for about 1 ms. Action potentials travel along axons, the long branches of individual neurons. When the pulse reaches a synapse where two neurons meet, it causes the release of chemical neurotransmitters that trigger a postsynaptic current in the next neuron. This allows transmission of interneuronal currents to continue through the brain.

Five parameters are employed to characterize the current dipole that is used to explain MEG data: three for the dipole's position in 3-D space, one for its orientation, and one for its strength. Just one parameter is needed to characterize the orientation, because only currents that are tangential to the nearest point on the surface of the brain produce external magnetic fields. Contributions from all other currents cancel each other out because the brain is approximately spherically symmetric. This means that MEG signals arise mainly from the walls of the fissures in the cortex, where the neurons are aligned in such a way that currents through them are parallel to the nearest surface of the head. Typical dipole moments (current x length of the dipole) encountered after sound stimuli, for example, are on the order of 5 … 50 nAm. Since the effective current only flows over a distance of about 1 mm in the cortex, these dipole stregths are associated with currents of about 10 μA.

## 2.3. Analysis of MEG and MCG measurements

Owing to spontaneous brain activity and incoherent "noise", individual signals resulting from 20 to 500 successive sensory stimuli are usually averaged. In this way the evoked response, for example after "beeps" of sound, emerges from the background. To collect enough data for calculating the magnetic field distribution, measurements must be made at many, typically at 50 to 100 different locations. In earlier MEG experiments this was done sequentially, over one or a few sites at a time. This was a slow procedure which also endangered the reliability of the data: The subject could not be expected to remain in the same state of vigilance throughout a long measurement session. Now this "human" problem has been overcome by the use of neuromagnetometers covering simultaneously the whole head (see Chapter 4).

Figure 3 shows, at left, a typical magnetic signal evoked in the auditory cortex by 50-ms tones presented to the subject's left ear. The field gradient, in fT/cm, is plotted as a function of time. By combining such signals from many locations, a computer can calculate the magnetic field distribution shown at right. The active region in the brain, underneath the center of the red arrow, may be determined from this type of data. The field pattern varies with time because the activated region in the cortex changes.

Figure 3 about here

In interpreting MEG data, one is dealing with the electromagnetic inverse problem, *i.e.*, with the calculation of the source currents responsible for the externally measured magnetic field. The inverse problem has no unique solution. One must, therefore, use a suitable source model to interpret the data. When the neural currents are confined to a small region in the cortex one may assume that, looking from the outside, the source is a current dipole. The magnitude, direction, and position of the active brain area can then be deduced unambiguously with a least-squares fit of the experimental data as shown on the right side of Figure 3. The dipole lies in the middle of the two field extrema, at a 90° angle to the line joining them.

## 2.4. Magnetic shielding

Since biomagnetic signals are small, rejection of all external disturbances is of extreme importance. Other body parts also generate signals. For example, the heart's magnetic field on the chest is two to three orders of magnitude larger than the brain signals just outside the head. The vulnerability of the system to external magnetic noise can be reduced greatly by a gradiometric design of the superconducting flux transformer which gathers the magnetic signal and transmits it to the SQUID. Two configurations are in common use (see Section 3.4): a flat figure-of-eight geometry and two axial but oppositely wound coils in series. Both loop systems are insensitive to spatially uniform background fields but respond to changes in an inhomogeneous field as generated by the nearby brain.

In addition, MEG experiments are usually carried out inside a magnetically shielded room, which in the LTL at HUT employs for noise reduction two layers of aluminum, that attenuate very effectively the high frequency band of the external magnetic disturbances, and two layers of mu-metal for rejection of noise at low frequencies. In addition, the magnetic field entering the outer mu-metal shield is detected by demagnetization coils. A controller and Helmholtz-type feedback coils outside the room are employed to compensate for low frequency magnetic fields. There is also a special feedback circuit to cancel the 50 Hz magnetic field.

## 3. SQUIDs

Since the late 1960's, SQUIDs have been familiar devices in most low temperature laboratories. Multi-SQUID applications, however, have materialized only after 1980, owing to the slow progress in fabrication technology and small demand. Today, reliable and stable thin-film Josephson circuits

can be manufactured in large quantities. The cost of one complete sensor unit, including the dc SQUID and the pick-up loop, is about $ 150, but the price will be reduced to $ 50 if production is markedly increased.

### 3.1. Properties of superconductors

Phase coherence of charge carriers in a superconductor gives rise to quantization in the SQUID ring: the total magnetic flux threading the loop must be an integral multiple of the so-called flux quantum, $\Phi_0 = h/2e = 2.07$ fWb. Owing to the smallness of $\Phi_0$, the SQUID can be made into a very sensitive device for measuring magnetic fields. A flux noise below $10^{-5}\Phi_0$ $Hz^{-1/2}$ in the frequency band of interest is necessary for a dc SQUID to be used in a state-of-the-art neuromagnetometer. Moreover, a flat noise spectrum down to well below 1 Hz, *i.e.*, a low $1/f$ noise, is required for recordings of brain signals.

If two superconducting electrodes are put within tunneling distance from each other, separated by an insulating layer, a supercurrent can flow through the barrier without voltage generation. The Josephson junction is characterized by a critical current $I_c$, which is the highest current that does not produce a voltage drop across the junction. Brian Josephson showed in 1962 that the current through a weak junction is a periodic function of the phase shift between the quantum mechanical wave functions on both sides of the barrier. By interrupting a superconducting loop with one or two such junctions, the quantum phase shift and thus the maximum voltageless current can be controlled by the magnetic field threading the loop.

There are several ways to accomplish a flux detector based on Josephson junctions, but only the rf and dc SQUIDs will be discussed here.

### 3.2. The rf SQUID

The first practical rf SQUID magnetometer, consisting of one Josephson junction, was introduced in the late 1960's by James Zimmerman. The dc SQUID is a superconducting ring interrupted by two Josephson junctions. For operation, the sensors are kept at 4.2 K, the boiling point of liquid helium. SQUIDs made of high-$T_c$ materials work at liquid nitrogen temperatures.

When a radio frequency flux is superimposed, via a tank circuit, on the low frequency flux threading the superconducting ring, dissipation in the system becomes proportional to the signal flux. This is because the phase of the sinusoidal pump signal, at the moment when the Josephson junction is switched to its resistive state, depends on the low frequency flux. By monitoring the amplitude of the rf signal across the tank circuit, the applied flux can be measured. Since the change in the voltage amplitude of the tank circuit is reasonably high, several hundres of microvolts per flux quantum, this so called hysteretic rf SQUID became the first practical SQUID magnetometer. Owing to its complicated readout electronics the rf SQUID is no longer used in commercial neuromagnetometers.

### 3.3. The dc SQUID

Two Josephson junctions set in parallel via a small superconducting ring double the critical current $I_c$. An external magnetic flux generates a phase shift in the macroscopic wave function in the ring portion connecting the junctions. The total phase shift along the closed path around the ring has to be a multiple of $2\pi$, and thus the flux in the ring modifies the phase shift across the two junctions and the critical currents accordingly. If a current bias is set just above $2I_c$, the voltage across the junctions is close to zero in a fluxless ring, but an increasing flux decreases the effective critical current and thus also the voltage. By imposing a small voltage across the junctions, the current trough the device varies from zero to $2I_c$ while the flux is increased.

The interference pattern in a ring with two junctions was first demonstrated in 1965. As an example, Figure 4a shows the current-voltage characteristics of a dc SQUID for three different applied fluxes. The current in a voltage biased SQUID, as a function of the external magnetic field, is illustrated in Figure 4b.

Figure 4 about here

Noise in a SQUID is related to the thermal noise from shunt resistors set in parallel with the Josephson junctions; the resistors are needed in order to stabilize the system. The optimization of the energy resolution and the intrinsic flux noise leads to an extremely low loop inductance. Therefore, in a practical low noise SQUID, the loop sizes range from 4 $\mu m^2$ to 25 $\mu m^2$. Such a tiny loop is too small for detecting weak magnetic fields and thus flux transformers must be used to pick-up the signal from a much larger area.

### 3.4. The pick-up loop and the flux transformer

Owing to quantization of the flux in a superconducting ring, a closed loop can be used to pick-up the magnetic field from a large area, close to signal sources, and to transfer it into the SQUID ring. A multiloop signal coil wound around the SQUID compresses the magnetic field into the SQUID ring. The supercurrent induced by the applied field is inversely proportional to the inductance of the flux transformer and thus the signal coil inductance, *i.e*, the number of turns, should be as small as possible. On the contrary, high mutual inductance between the signal coil and the SQUID ring maximizes the flux threading the SQUID ring and thus a compromise is necessary. A simple calculation shows that inductance matching between the pick-up loop and the signal coil maximizes the transfer efficiency to convert magnetic field to flux in the SQUID ring.

There is variety of ways to accomplish a pick-up loop. High inductance is realized by using a multiloop configuration but connecting the loops in parallel leads to low inductance. Since the SQUID inductance is very small, the signal coil is made of several turns in series, in order to secure a high signal coil inductance.

The pick-up coil can be a single loop sensing homogenous magnetic field or it may comprise of two or more loops in series but in opposite directions sensing thus only gradients of the field. Gradiometers are easier to operate in a noisy environment, because the rapid decay of the gradient field as a function of distance makes the sensor most sensitive to nearby source currents, provided that the gradiometers are balanced sufficiently well. Immunity to external noise sources can further be improved by using a pick-up unit comprising of three separate coils. This arrangement leads to a second order gradiometer which is insensitive not only to the homogenous field but also to its gradient. Higher order gradiometers are employed in biomagnetic studies which are performed in unshielded environments. Magnetometers, on the other hand, are good for extracting information about deep sources but they unavoidably respond to distant noise sources, too.

Several possibilities of arranging magnetometers and first order gradiometers are shown in Figure 5. The tangential and planar gradiometers can be integrated on a silicon chip but the axial configuration requires a flexible board or it can be made of a superconducting wire.

Figure 5 about here

### 3.5. Manufacturing technology

Earlier, most SQUIDs were manufactured from pure Nb and Pb alloys, isolated by a layer of niobium pentoxide $Nb_2O_5$, except for the window defining the junction area. Nowadays, both electrodes are made from Nb and they are separated by artificial tunnel barriers such as $Al_2O_3$ or MgO which are

superior to niobium pentoxide layers. For example, an all-refractory Nb/Al-$Al_2O_3$/Nb fabrication process was developed by the IBM, resulting in SQUIDs with flux noise less than $2.5 \times 10^{-6}\Phi_0$ $Hz^{-1/2}$ at 0.1 Hz and a white noise of $0.5 \times 10^{-6}\Phi_0$ $Hz^{-1/2}$. Later, the company made dc SQUIDs, based on edge junctions and characterized by a small junction area (about 1 $\mu m^2$) and capacitance. Consequently, very low flux noise was observed.

### 3.6. A modern SQUID

#### 3.6.1. General design features

To avoid the problems of wire-wound flux transformers, which are expensive to manufacture and have only a modest balance, planar integrated sensors offer an elegant solution. The main advantages of flat thin-film gradiometers are their compact structure and excellent dimensional precision, providing a good intrinsic balance. Figure 6 depicts a SQUID-system designed and fabricated by the Technical Research Centre of Finland (VTT). The sensor is specially optimized for the frequency range between 0.1 and 1000 Hz, which is important for biomagnetic measurements. The white flux noise corresponds to an intrinsic energy resolution of $5h$, where $h$ is Planck's constant, the theoretical limit. The VTT SQUID, which is one of the best, will be described in some detail below.

Figure 6 about here

The sensor optimization for neuromagnetism is rather complex because many parts make up the complete system: the SQUID with the signal coil, the pickup coil, the inductance matching circuitry, the high frequency damping circuitry, the output transforming circuits, and the readout amplifier. The sensor should have sufficiently low magnetic field noise at the frequency band of interest and it must be sensitive to the field components that carry information about the source currents in the subject's brain or heart. The system should also have enough tolerance against environmental disturbances, and be robust and easy to manufacture. The chosen strategy on one of the parts unavoidably restricts choices available in designing the other parts. Furthermore, most of the design parameters influence each other. Due to these facts, it is best to optimize the sensor as a whole rather than divide it into subsystems optimized separately.

#### 3.6.2. Description of the VTT SQUID

The sensor described here consists of a 28 x 28 $mm^2$ silicon chip for three orthogonal pick-up coils, two 3 x 3 $mm^2$ chips for SQUIDs, and three directly coupled room-temperature amplifiers with flux feedback circuits. The SQUID chips are manufactured with a niobium based 2-μm linewidth superconducting thin-film process with ten mask layers. The coil chips are made with a more robust 8-mm feature size, six-layer process, and the chips are attached to each other with superconducting bond wires. This approach allows large volume manufacture of the area consuming pick-up coils with a quick and cheap process. Furthermore, the chips can be tested separately before assembly of the complete sensor.

The pick-up loops collect magnetic field over a large area and feed it to the small SQUID loop. The larger the area, the smaller is the effective magnetic field noise. The 28-mm chip size, even when including gradiometers, allows noise levels to be comparable to the parasitic noise sources in the vicinity of the sensor, such as the thermal radiation shields of the dewar. Owing to these noise sources, enlarging the coil size further would not increase sensitivity but rather limit the highest field that can be tolerated owing to the non-linearity of the SQUID. The loop size is small enough to be implemented economically on a silicon chip. The vacuum gap of the dewar and the patient's skullbone separate the sensors and the source currents in the brain by about 35 mm. Therefore, the sensors can be assembled close enough to each other to permit sufficient spatial sampling of the magnetic field.

### 3.6.3. The pick-up loops

On each pick-up chip there are two loops responding to the two field gradients $\partial B_z/\partial x$ and $\partial B_z/\partial y$, as well as one loop for the field $B_z$ itself. Even though these quantities are measured at one point they are independent terms of the multipole field expansion and thus give non-redundant information about the source currents. The thin-film technology, with its intrinsic dimensional accuracy, helps to attain the required balance for a gradiometer and the noise immunity needed for practical devices used in magnetoencephalography.

The SQUID loop with its three Josephson junctions resides on the SQUID chip, and on top of it is a 16-turn signal coil which forms the first stage of the inductance-matching transformer. The inductance of the SQUID loop is chosen to be 8 pH, as small as can be manufactured without degrading its coupling to the signal coil too much. This low inductance needs to be matched to the 10000 times larger pick-up inductances. A single stage transformer would need a very large number of turns, which would create a lot of parasitic capacitance across the loop. Thus a two-stage transformer is used. The second transformer stage occupies most of the SQUID chip area.

### 3.6.4. Design considerations

The energy resolution of the SQUID in the white noise region is proportional to the product of the loop inductance $L$ and the junction capacitance $C$. The magnetic field noise referred to the pick-up coil, on the other hand, is independent of $L$ because the flux transfer coefficient decreases at the same rate as the energy resolution increases with diminishing loop inductance. However, a small $L$ is desirable because it reduces the $1/f$ noise caused by critical current fluctuations in the junctions. The second benefit of a small $L$ is an increase in the dynamic range, which is particularly advantageous when magnetometer-type pick-up coils are operated in a noisy environment.

The Josephson junctions are chosen to be fairly big, 6 μm in diameter. Even though such large junctions degrade the white noise performance, low frequency noise is attenuated. The optimization procedure is aimed for the lowest possible noise at 1 Hz, which is in the middle of a typical frequency band in biomagnetic measurements. In most SQUID designs the junctions are located at the outer edge of the SQUID washer, but in the VTT sensor they are planted in the middle. In this construction the line formed by the washer slit appears in parallel with the loop inductance rather than in series, which reduces the inductance seen by the junctions and alleviates resonance problems. The junctions are fabricated with the standard trilayer process, in which a 2 nm thick $Al_2O_3$ tunnel barrier is sandwiched between Nb layers and the junction area is then defined by anodization.

SQUID sensors can, in principle, detect flux changes at arbitarily low frequencies, down to the μHz range and below. The internal SQUID dynamics includes oscillations typically in the 10 … 20 GHz frequency range, with harmonics up to 100 GHz. In contrast to theoretical models, the SQUID loop impedance seldom remains purely inductive over such a wide frequency range, especially when effects due to the impedance-matching transformer and the pick-up loop are taken into account. The impedance seen by the junctions must be non-capacitive at all frequencies, otherwise a resonance leading to multiple-valued dynamics appears, and increased noise caused by thermally activated hopping is observed. The VTT flux transformer circuitry is carefully designed using transmission lines with controlled impedance levels and proper resistive terminations. This keeps the junction load inductive or resistive from signal frequencies up to microwave frequencies while guaranteeing proper dc flux transfer to the SQUID loop.

The resistive terminations of the transmission lines created by the signal coil and by the pick-up loop circuitry produce noise which must be taken into account in sensor optimization. The improvement in the magnetic field noise, when the pick-up loop area is increased, is partially offset by this noise: longer transmission lines are then necessary and a lower line impedance is needed in order to avoid

stray inductances. The required lower termination resistance gives rise to higher noise currents, impairing the field sensitivity.

### 3.6.5. The readout system

Simplicity in the SQUID readout circuitry is a clear benefit when a large number of sensor channels must be employed in a single instrument. In a simple direct-readout scheme there is, however, the risk that the noise of the room-temperature amplifier dominates the system noise, since the SQUID output signal is rather weak and its output impedance is too small for a low noise room temperature amplifier. A small SQUID loop inductance helps since it increases the output signal.

If a circuit composed of an additive feedback coil and a cooled FET, acting as a tunable resistor, is set across the voltage biased SQUID, the so called "noise cancellation electronics" is obtained (see Figure 7). The circuit converts the noise voltage originating from the preamplifier into a flux and, furthermore, the SQUID converts it into a current. Finally, the voltage biased SQUID output current is converted to a voltage at the output of the preamplifier by a feedback resistor. The noise voltage at the input of the preamplifier conributes at the output directly and indirectly via the SQUID. The signals have an opposite sign, therefore, and by tuning the channel resistance of the FET, the contribution of the input noise voltage at the ouput of the SQUID can be made negligibly small.

Figure 7 about here

Tanks to the noise cancellation electronics, the readout system is very simple and thus suitable for mutichannel devices. Unfortunately, lack of bias modulation prevents elimination of the $1/f$ noise, which originates from critical current fluctuations. This is why very large Josephson junctions placed close to the SQUID washer were used.

The VTT SQUID sensor described above has proven to be quite succesful. With several thousand sensors in operation around the world right now, it may be the most used SQUID device ever made.

### 3.7. Other SQUID designs

Since the SQUID itself, the pick-up coil, and the accompanying electronics can be realized in many different ways, there are plenty of possibilities to construct a magnetometer or a gradiometer. Nowadays the fabrication technology and the design know-how, at least for low-$T_c$ devices, are so well established that a noise level on the order of 5 fT $Hz^{-1/2}$ at 1 Hz is easily realizable. At this level the total noise becomes dominated by the magnetic noise from the dewar or from other nearby external sources, rather than the intrinsic noise of the SQUID. Therefore, the dynamic range, sensitivity to external sources, easy operation, and price are the most important issues when the different types of magnetic field sensors are evaluated.

### 3.7.1. The PTB design

As mentioned before optimization of the flux or energy resolution of the SQUID favors a low loop inductance, but this its not the case when the SQUID is used as a field gauge. By enlarging the SQUID size, the total flux threading the ring in a magnetic field increases as well. If $k_B T$ , the thermal energy, remains much less than the magnetic energy corresponding to one flux quantum in the ring, $(\Phi_0^2/2L)$, the field resolution is nearly independent of the SQUID inductance. For higher values of $L$, the flux quantization in a superconducting ring is no longer complete and the periodic SQUID response collapses.

Since a sufficiently high loop inductance can be accepted, it is possible to construct a magnetometer without using a separate pick-up loop or flux-transforming circuits. At the Physikalische-Technische-

Bundesanstalt (PTB) in Berlin, a magnetometer has been developed in which the SQUID loop is split into several sub-loops set in parallel. The effective inductance of the SQUID is only $L_p/n^2$, where $L_p$ is the inductance of a loop covering the same area and $n$ is the number of sub-loops. This approach enables the construction of a SQUID with a large pick-up loop, while keeping the SQUID inductance low, at least low enough not to disturb flux quantization in the SQUID ring. The PTB SQUID comprises twelve sub-loops and looks like a cartwheel as shown in Figure 8. The chip size is about 7 x 7 $mm^2$ leading to a SQUID inductance which is less than 500 pH. The field-to-flux sensistivity is about $\Phi_0/nT$ and the field resolution is better than 5 fT $Hz^{-1/2}$.

Figure 8 about here

The main advantage of the PTB magnetometer is its simple construction; only one chip is needed to accomplish the complete magnetometer. Owing to the high SQUID inductance, the flux-to-current conversion efficiency is lower than that of a low inductance SQUID. Consequently, monitoring the weak output signal with room temperature electronics becomes more difficult. In addition, the flux noise of the high inductance SQUID is higher, which reduces the available dynamic range.

To amplify a weak output signal without adding noise, the feedback technique was adopted. An additive feedback coil converting the output voltage into a flux via an external resistor was integrated into the SQUID chip. Owing to direct external feedback the second slope of the periodic flux-to-voltage response becomes steeper increasing the efficiency. Since an integrated non-tunable resistor was used in the PTB design to convert the output voltage to a current, the positive feedback was controlled by the current bias.

The PTB device thus replaces the pick-loop, the flux trasforming circuits, and the SQUID with a simple multi-loop SQUID and increases the gain of the SQUID via positive feedback with integrated circuitry. The PTB system forms an elegant and compact magnetometer.

### 3.8. High-$T_c$ SQUIDs

The discovery of superconducting ceramic compounds more than ten years ago, with critical temperatures above 77 K, raised hopes for practical low noise magnetometers in clinical applications. A commercial 16 channel cardiomagnetometer, operating at liquid-nitrogen temperature, has been demonstrated by Sumitomo Electric Industries Ltd in Tokyo. Although the best single-channel high-$T_c$ SQUIDs are not much more noisier than existing 4-K magnetometers, a 77-K system is too expensive and, because of flux trapping problems, too difficult to use at the present time.

## 4. Multichannel instrumentation for MEG

Three types of whole-head covering instruments are now commercially available, constructed by Neuromag Ltd in Helsinki, by CTF Systems Inc. in Vancouver, and by Biomagnetic Technologies Inc. in San Diego. From the beginning of 2000, Biomagnetic Technologies Inc. and Neuromag Ltd have merged to a joint company 4-D Neuroimaging Inc. Manufacture of the Magnes$^R$ and Vectorview™ lines of neuromagnetometers will continue. Whole-head neuromagnetometers not only speed up the measurements but give more reliable data as well. Experiments that require simultaneous recordings over a large area, such as studies of spontaneous brain activity, benefit the most. Whole head neuromagnetometers, including the shielded room, cost approximately US$ 2.5 million.

### 4.1. The Neuromag system

Magnetoencephalographic measurements were first made with one-SQUID systems, and the number of sensors increased only slowly. In the Low Temperature Laboratory at HUT, a pioneer in the field of multi-SQUID instrument construction, the sequence of development was $1 \rightarrow 4 \rightarrow 7 \rightarrow 24 \rightarrow 122 \rightarrow 306$ channels. The 122- and 306-SQUID devices (see Figures 1 and 9) record the entire magnetic field pattern at once. At the beginning of the new millennium, 25 whole-head covering instruments had been sold by Neuromag Ltd.

Figure 9 about here

In the new 306-channel Vectorview™, the 28 x 28 $mm^2$ sensor element comprises of two orthogonal planar gradiometers, as in the 122-channel instrument, and one magnetometer coil, each connected to a multi-SQUID chip attached to the middle of the sensor element (see Figure 6). Every unit thus provides three independent and orthogonal measurements of the magnetic signal. The gradiometers best measure cortical current sources, whereas the magnetometer is sensitive to deep sources as well. The detector array of the Vectorview system includes 102 identical sensor units, feeding to 306 SQUIDs. As an option, 64 EEG channels can be included. The software arsenal is very extensive and fits practically every need of the user.

### 4.2. The CTF Systems neuromagnetometer

CTF Systems Inc. of Vancouver now makes the Omega$^R$-system, which has 150 MEG sensors and up to 64 simultaneous EEG channels. Planar niobium dc SQUIDs, together with 5-cm baseline first order gradiometric pick-up coils, combine to give a sensing system optimized for a high signal-to-noise ratio. If optimum performance is not needed, Omega can be operated without a magnetically shielded room. Subjects may be examined at any angle between sitting upright and completely supine. Patient support is also fully adjustable. Analysis and display features include data editing, plotting, mapping, epoch averaging, and equivalent current dipole modelling. Figure 10 is a photograph of Omega$^R$, with the subject in the supine position.

Figure 10 about here

### 4.3. The neuromagnetometer of Biomagnetic Technologies

Figure 11 shows the Magnes$^R$ 2500 whole head neuromagnetometer in use. The instrument employs an array of 148 axial gradiometers. Measurements can be made in any position between vertical and horizontal to accommodate both seated and supine patient positions. The next instrument version of BTI, Magnes$^R$ 3600 WH, will contain 248 MEG channels and 98 EEG channels. The helium boil-off is less than 12 leters/day in the vertical position. The intrinsic system noise is 10 fT $Hz^{-1/2}$ down to 0.5 Hz, of which the SQUID noise is 2 fT $Hz^{-1/2}$.

Figure 11 about here

## 5. Examples of MEG studies

We will next describe briefly seven recent MEG experiments. The technique has been used mainly to study the way the brain processes signals, such as those arising from our senses of hearing, touch, smell and pain, as well as those associated with voluntary movements of the body. MEG has also been employed to examine the neural basis of more complex brain functions, such as attention, sensory memory and language. Magnetoencephalography is at its best for measuring signals from the cerebral cortex but, by assuming the source locations in advance, clear responses from the cerebellum, thalamus and hippocampus have been recorded by Claudia Tesche of the LTL at HUT.

### 5.1. Somatosensory responses to finger stimuli

Figure 12 shows responses which resulted from electric stimuli of the subject's left thumb. One can clearly see how the active brain region changes with time in the sequence A → B → C. The hand area of the right primary somatosensory cortex (A) responds first, with deflections at 35 and 65 ms after the stimulus onset, followed by signals generated in the secondary somatosensory cortices at right (B, 103 ms) and at left (C, 113 ms). An additional late response arises in the posterior parietal cortex (D, 101 ms). Separation of signals generated in these four brain regions allows easy monitoring of activity changes in the cortex. One can clearly see which regions become activated by the stimulus *and in which order* while the brain analyses the sensory input.

Figure 12 about here

### 5.2. Dynamic brain activation during picture naming

By naming objects humans try to bring order into their environment. This important process necessarily involves several regions of the brain, including those specific to speech analysis. In the LTL of HUT, picture naming was investigated in six subjects. The experimental procedure was as follows: Line drawings of common items were presented, once every 5 s, on a computer screen, seen through a hole in the wall of the magnetically shielded room. The subjects were instructed to pronounce, as soon as possible, the names of the objects shown.

Figure 13 illustrates how the dominant active area in the brain changed with time in one subject. The early visual response (Source 1) at the back of the head was followed by more lateral posterior signals in the left and right hemispheres (Sources 2 and 3), suggesting a contribution from Wernicke's area (see Figure 2), which is important for understanding a language, and its right-sided counterpart. Within the same time window (gray area in the magnetic field *versus* time plots), a left frontal site (4) close to the cortical face representation area showed activation, as in preparation for mouth movements.

Figure 13 about here

About 500 ms after the picture had been shown, signals emerged from a site anterior to the face representation region in the motor cortex, reflecting activation of Broca's area (5), which is known to be involved in vocalized word production, and its counterpart in the right hemisphere (6). These signals were immediately followed by activity at the top of the brain (7), probably generated in the supplementary motor cortex which programs complex tasks such as articulation. Information processing by the brain during picture naming is beautifully demonstrated by the experimental sequence in Figure 13. Only the MEG technique has sufficient resolution to reveal the order of events.

### 5.3. Face-sensitive areas in the human brain

Eric Halgren and his coworkers have recently investigated the cognitive profile of face-specific regions in the human brain. The lower part in Figure 14 illustrates the eleven different types of stimuli used. For evoked responses, the main comparison was made between normal human faces and randomized faces. The latter evoked more prominent responses over the occipital midline at 120 … 150 ms, while normal faces elicited clearly stronger responses over the temporo-occipital fusiform regions bilaterally at about 150 …185 ms (see insert in Figure 14). Responses between color and grayscale normal faces did not differ; colorness did not affect responses to randomized faces either. The results showed bilateral processing of faces, with a trend towards right-hemisphere dominance and a clear face-specificity in the fusiform area.

Figure 14 about here

### 5.4. Action viewing

The functional state of the motor cortex can be monitored by measuring changes in the 20-Hz μ-rhythm detected in this area. For example, Riitta Hari and her coworkers at the LTL in HUT have used magnetoencephalography to show that the μ-rhythm is significantly suppressed if subjects move their fingers, thereby activating the motor cortex. Interestingly, a similar but smaller suppression occurs when the subject merely *imagines* making such movements. More surprisingly still, a suppression, which again indicates motor-cortex activation, occurs when the subject just views someone else moving their fingers.

In other words, when we see someone performing a particular action, it triggers neuronal activity in the same areas of our own brain that we would use to perform that action ourselves. These "mirror neurons" are believed to form the basis of non-verbal communication between social animals, including humans, who spend much of their waking time in trying to predict the intentions and feelings of other members in their social group. MEG studies have suggested (see Figure 15) that Broca's region, which is a speech producing area in the left hemisphere of the human brain, plays a central role in this system.

Figure 15 about here

### 5.5. Increase of cortical representation with use

When playing music, the second to the fifth digits in the left hand of violin players are continuously fingering the strings. This task involves considerable manual dexterity and increased sensory stimulation. The right hand, which manipulates the bow, participates in a task involving much less individual finger movement. Therefore, in string players, inputs to the right and left somatosensory cortices differ considerably.

Thomas Elbert and his colleagues, while at the University of Münster in 1995, used MEG to study stringed-instrument players who had started their musical training at an early age. The group found that the evoked fields produced in response to tactile stimuli, applied to the fingers on the left hand, were much stronger in musicians than in non-musicians. They also observed that the strength of the response depended on the age at which the subjects had started playing the violin or cello. The result suggests that the cortical territory, occupied by the representation of the left hand digits, had increased in string players as compared with that of controls.

### 5.6. Clinical applications

Clinical uses of the MEG method are emerging rapidly. Up to now, the most important applications are in the study of patients suffering from epilepsy and brain tumors.

#### 5.6.1. Epilepsy

People who suffer from epilepsy can usually be helped with drugs, but if medication does not work, neurosurgery is an option. However, before the operation takes place it is vital for the surgeon to know more about the epileptic "discharges" that manifest themselves in such patients. These discharges are sudden "electrical storms" that occur in the brain. In many patients, epileptic activity arises in a small local area, from which it rapidly spreads throughout the cortex. The discharges are much stronger, up to 1 pT, than evoked responses. Therefore, they can be detected directly without signal averaging.

MEG has been used to study these electrical storms, and it can help the surgeon to ascertain whether the spikes arise from restricted areas of the brain and, if so, how many areas are involved and how

closely in time they fire. MEG can also give information about how near these areas are to such parts of the brain that should be left intact during an operation, for example the regions that control movements and speech. It is also important to determine how stable the distribution of the electrical discharges is with time.

The patient of Figure 16 obviously has two epileptogenic areas in the right hemisphere of his brain, one in the parieto-occipital lobe and another in the temporal lobe. In both locations the generators of epileptic discharges are distributed over fairly large areas. In this patient, the part of the parieto-occipital lobe that showed atrophy in MRI was operated on, which resulted in over 80% reduction in epileptic seizures.

Figure 16 about here

### 5.6.2. Localization of functionally important cortical areas

Combination of brain's structural data from MRI and functional information from MEG is today routinely used in some hospitals for preoperative examination of patients before surgical intervention. Figure 17 shows, as an example, MEG localization of the somatomotor cortex in a patient with a brain tumor. Somatosensory stimulations of foot, hand and lip and contraction of the forearm muscles was used to determine the course of the central sulcus. The noninvasive functional localization and the display of cortical blood vessels on the MRI reconstruction help the neurosurgeon in selecting suitable patients, in planning the operation and in navigation during actual surgery. The LTL of HUT and the HUCH have collaborated to combine anatomical and functional information in preoperative evaluation of over sixty patients with very encouraging results.

Figure 17 about here

## 6. Cardiomagnetic studies

### 6.1 The human heart

The rhythmic sequence of the human heart (see Figure 18) is controlled by the sino-atrial (S-A) node, which initiates the electric pulse that subsequently triggers the ionic currents causing muscle contractions. The activation propagates through the atria to the atrio-ventricular (A-V) node, which slows down the entry of the pulse to the ventricular muscles so that the atria are emptied of blood before the filled ventricles contract. The sinus node acts as the heart's pacemaker; its firing rate is regulated by input from the autonomous nervous system.

Figure 18 about here

When an electrical impulse travels across the heart it causes a time-dependent action potential. Currents responsible for muscle contractions in the heart are partly transmitted to the surrounding tissue and some of the electrical activity reaches the body surface, where it can be measured as a potential difference between suitably placed electrodes. The output, voltage *versus* time, is called an electrocardiogram (ECG).

### 6.2. Methods and instrumentation in magnetocardiography

Magnetocardiography (MCG) is a non-invasive technique for studies of the working human heart. Similar experimental techniques as in MEG are employed, including the use of a shielded room and SQUIDs. However, the volume conductor geometry is more complicated in the thorax than in the head. This must be taken into account when dealing with the inverse problem. The cardiac fields, usually in the range of 1... 100 pT, are so large that signal averaging is not necessary in most cases.

The Laboratory of Biomedical Engineering at the Helsinki University of Technology has carried out a large number of MCG studies in close collaboration with cardiologists at the Helsinki University Central Hospital. Their joint venture, the BioMag Laboratory, has now been operating for five years near the clinics. For heart studies, the hospital unit is equipped with a state-of-the-art 67-SQUID cardiomagnetometer, specifically designed for patients (see Figure 19). The system allows studies of very weak signals, normally hidden under experimental noise. The 30-cm diameter coverage also offers a unique possibility to explore the spatiotemporal dynamic changes from one heartbeat to the next. The position of the dewar containing the SQUID-sensors, in respect of the patient's torso, is determined by measuring the magnetic field produced by small marker coils attached to the chest.

Figure 19 about here

### 6.3. Detection of heart abnormalities

Even though magnetocardiography is not yet a routine clinical tool, non-invasive MCG investigations have been reported on a number of clinically important cases. These include localization of arrhythmia-causing regions of the heart, assessment of the risk of life-threatening arrhythmias, and characterization and localization of myocardial ischemia. Recently many groups have investigated fetal MCG's which can indicate heart abnormalities in unborn children.

Figure 20 depicts a recording made in the BioMag Laboratory using the 67-channel cardiomagnetometer. After its installation in April 1995, the system has been used in over 800 patient studies. Typically, data are collected for 5 min, and the whole measurement procedure requires less than 30 min. The main focus in these investigations has been on various cardiac arrhythmias. The example shown exhibits a spontaneous abnormal but large beat following the regular cardiac cycle. Such additional contractions usually originate in the ventricles and can sometimes trigger life-threatening arrhythmias of over 250 heart beats per minute.

Figure 20 about here

The most promising application of magnetocardiography so far has been the localization of sites where cardiac arrhythmias are generated. Multichannel measurements allow feasible and quick patient studies. MR imaging provides the necessary link to relate the MCG localization results accurately to the anatomy of the heart. The clinical locating accuracy of the MCG method has been tested by numerous authors for localizing the site of the earliest abnormal ventricular activation in patients with the Wolff-Parkinson-White syndrome or other focal ventricular arrhythmias. When drug therapy does not cure the problem, the area causing abnormal activity must be invasively eliminated. In addition, MCG localization has been reported in patients suffering from atrial tachycardias. An example is presented in Figure 21; the result was in excellent agreement with the invasive localization obtained during catheter ablation.

Figure 21 about here

### 6.4. Estimation of life-threatening arrhythmia

Disparity and variability of ventricular repolarization is a good measure of sudden cardiac death. Figure 22 is an example of detection of abnormal repolarization by magnetocardiographic mapping in a 14 year-old young woman, suffering from an inherited cardiac desease called the long-QT syndrome. The normal and abnormal T-wave patterns are clearly different.

Figure 22 about here

Recently an MCG group in Berlin has made an interesting approach to estimate a patient's future risk of serious arrhythmia**.** Their method is based on spatial distribution of the high-frequency components in magnetocardiographic signals during the QRS complex. The data were recorded in a magnetically shielded room using 49 magnetogradiometer channels in a low noise SQUID system. A score *S* was defined as a measure of fragmentation in the bandpass-filtered QRS complex.

The *S*-score was examined to determine its sensitivity and specificity for discriminating between 34 healthy volunteers, 42 post-myocardial infarction patients, and 43 patients with coronary heart disease and with a history of malignant sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). The multichannel information was visualized by two-dimensional mapping of the *S*-scores in single channels (see Figure 23). By averaging the *S*-scores for the seven central channels and for all 49 channels, and by calculating the standard deviation for all channels, a higher sensitivity and specificity for identifying patients with VT or VF was reached than by an analysis of single channels. Combination of these parameters furnishes a sensitivity of 90% and a specificity of 70% for identifying patients prone to VT/VF.

Figure 23 about here

In addition, several groups have reported signal-processing methods in the time and frequency domains, resulting in satisfactory results for detecting patients with arrhythmia risk in symptom-free persons.

### 6.5. Discussion on MCG

Magnetocardiography has many advantages to become a routine clinical method. The technique is totally non-invasive, and it is not necessary to attach electrodes or other sensors in contact with the patient. With a multichannel cardiomagnetometer, a clinical study can be carried out in less than five minutes. The spatio-temporal resolution of MCG is much higher than that of conventional ECG.

Magnetocardiography has some disadvantages as well. Currently, MCG equipment is expensive and requires the use of liquid helium in a shielded room. Bed-side tests requiring catheter intervention are not possible. Since MCG systems are very sensitive to moving magnetic objects, certain patients are excluded from the studies. In a few years' time it may become possible to use high-$T_c$ SQUIDs in MCG instruments. This should lower the cost and make measurements more convenient.

## 7. Comparisons of MEG, MCG, EEG, ECG, PET, and fMRI

There are, nowadays, many methods to study the intact human brain and heart. Anatomical structures can be investigated precisely by means of computer assisted X-ray tomography, CAT, and by magnetic resonance imaging, MRI. Both these techniques provide high quality but *static* pictures of living organs. Information about the *working* brain or heart can be recorded by means of positron emission tomography, PET, and by functional magnetic resonance imaging, fMRI. For all these techniques the inverse problem has a unique solution, which makes the spatial localization quite reliable. These methods allow studies of the brain or heart without opening the skull or chest, but the techniques are weakly invasive because the subject is exposed to X-rays, to small time-varying and large static magnetic fields, or to radioactive marker substances. The temporal resolution of PET and fMRI, which depend on metabolic changes in cells, is 500 ms at best. This is *insufficient* to determine the *order* in which the different sites in the brain or heart become activated.

Electroencephalography, EEG, *i.e.*, the measurement of electric potentials on the scalp, the so-called "brain waves" in layman's language, is a widely applied clinical technique. EEG is closely related to MEG. In both methods, the recorded signals are generated by the same synchronized currents that flow in the neural network. The time resolution of these two techniques is better than a millisecond,

which exceeds that of PET and fMRI by several orders of magnitude. With MEG and EEG it is thus possible to follow rapid changes of cortical activity that reflect signal processing in the brain. A further very important advantage of these two techniques is their complete non-invasiveness. The subject is not exposed to radioactivity or to high magnetic fields. One only measures what comes out of the brain, spontaneously or as a result of natural stimuli. Electrocardiography, ECG, and magnetocardiography, MCG, have similar advantages as EEG and MEG.

In locating the active area of the brain from the field or potential distributions, MEG has better spatial resolution than EEG, 5 … 6 mm under favorable conditions. This is because electric potentials measured on the scalp are often badly affected by inhomogeneities in the head. It is then difficult to determine accurately the activated area since the detailed conductivity structure is not known. The magnetic field, in contrast, is mainly produced by currents in the relatively homogeneous brain tissue. Furthermore, the head is magnetically transparent. In EEG, accurate positioning of many electrodes on the scalp is a time-consuming procedure. In MEG, the subject's head just has to be brought inside the helmet.

In heart studies, likewise, magnetocardiography has to compete with electrocardiography; both methods have again their advantages and drawbacks. In MCG body contacts are not needed while in ECG the skin-electrode impedance may often disturb the data. In addition, the SQUID sensor locations in MCG can be defined with millimeter precision in respect to the heart, while it is much more difficult to determine the precise electrode locations in ECG. The main drawback of MCG is the high price of an installation, more than a factor of ten over a comparable ECG unit.

## 8. Conclusions

During the first decades of the new millennium, much progress will be made in all subfields of neural and cardiac studies. Magnetoencephalography and magnetocardiography should play important roles in this development. How the brain processes information is a problem which probably will be solved with the help of mathematicians and information scientists, but a large amount of data by neuroscientists will be needed to guide the various theorists. Clinical uses of MEG will increase. It is also likely that MCG research will give hints for the best cure in many heart diseases.

The first MEG measurements using a SQUID were published in 1970, at about the same time as the first PET experiments were carried out. The development of MEG was slow because too much time was spent with 1-SQUID devices and with studies of the unsolvable inverse problem. Whole scalp covering PET instruments became available in 1975; their construction was carried out briskly by nuclear physicists, who were used to multimillion dollar research grants. MEG was in the hands of solid state scientists who were not familiar with big money and, at first, did not seriously think about whole head covering devices, even though IBM had in its coffers plenty of high quality SQUIDs in the early 1980's. Another difficulty later arose because many scientists believed, MEG pioneer David Cohen among them, that the much cheaper EEG technique was just as good.

Research using MEG, not just developing the method, is finally coming up in force, many years behind PET and even fMRI. Since MEG is eminently suited for certain tasks, like functional mapping of cortical areas, diagnostic uses of the method are now emerging. Cognitive neuroscientists, likewise, have understood that MEG is a unique technique for investigating temporal aspects of signal processing and of other complex phenomena occurring in the human brain. MEG and EEG offer complementary information, but the two techniques have not been employed much in conjunction so far. Similarly, fMRI and PET data should be combined with MEG and EEG.

The use of MEG will expand, if more applications emerge in medical diagnostics, follow-up, and elsewhere; if not, the possibilities of MEG will not be utilized adequately, which would be a pity, both for basic brain research and for modern patient care. However, the price of MEG instruments

should become significantly lower first. There is still plenty of interdisciplinary work to be done by physicists and mathematicians, together with basic and cognitive neuroscientists and clinicians, to develop MEG still further.

MEG and EEG will remain, at least for the time being, the only fully non-invasive techniques for monitoring brain activity on a millisecond scale. The very rapid development of magnetic resonance imaging has provided an ideal medium for linking the functional MEG information to anatomical MRI data.

Multichannel instruments for MEG and MCG are the largest users of SQUIDs by far. Late in 1970's IBM had decided to develop a supercomputer based on Josephson junctions. However, in 1982 the project was abandoned and the Company let the LTL in Helsinki use some of their SQUIDs in non-commercial neuromagnetometers. Today many companies manufacture dc SQUIDs, but the volume of production is relatively small.

## 9. Acknowledgments

We thank Riitta Hari and Jukka Nenonen for valuable comments on the manuscript and Mark Mehtonen for skillful digital preparation of illustrations. We also like to thank Mikko Kiviranta for his contributions to Chapter 3.

## 10. Bibliography

Andrä W. and Nowak H., Editors (1998). *Magnetism in Medicine*. 511 pp. Berlin: Wiley-VCH. [Discusses all uses of magnetism in medical practice and research, including SQUIDs, MEG, MCG, MRI and fMRI]

Hämäläinen M., Hari R., Ilmoniemi R.J., Knuutila J. and Lounasmaa O.V. (1993). *Magnetoencephalography – Theory, Instrumentation and Applications to Noninvasive Studies of the Working Human Brain.* Reviews of Modern Physics **65**, 413-497. [A comprehensive treatment of MEG]

Hämäläinen M. and Nenonen J. (1999). *Magnetic Source Imaging*. Encyclopedia of Electrical Engineering **12**. Webster, J., Editor. 133-148 pp. New York: Wiley & Sons [A recent overview of source imaging techniques in MEG and MCG].

Hari R. and Salmelin R. (1997). *Human Cortical Oscillations: A Neuromagnetic View through the Skull*. Trends in Neuroscience **20**, 44-49. [ Review of MEG measurements on rhythmic oscillations generated in the human brain]

Lounasmaa O.V. (1996). *Medical Applications of SQUIDs in Neuro- and Cardiomagnetism*. Physica Scripta **T66**, 70-79; Lounasmaa O.V., Hämäläinen M., Hari R. and Salmelin, R. (1996). *Information Processing in the Human Brain: Magnetoencephalographic Approach*. Proceedings of the National Academy of Sciences of the USA **93**, 8809-8815; Hari R. and Lounasmaa O.V. (2000). *Neuromagnetism: Tracking the Dynamics of the Brain*. Physics World **13**, 33-38. [The present paper uses liberally material from these publications]

Nenonen J., Montonen, J. and Mäkijärvi M. (2000). *Principles of Magnetocardiographic Mapping*. *Cardiac Mapping*, Shenasa M., Borgreffe M. and Breithardt G., Editors. Mount Kisco, NY: Futura Publishing Co. [Short review of MCG mapping to be published in 2000]

Nicholls J.G., Martin A.R. and Wallace B.G. (1992). *From Neuron to Brain*. 805 pp. Sunderland: Sinauer Associates. [An excellent text on the human brain]

Ryhänen T., Seppä H., Ilmoniemi R. and Knuutila. J. (1989). *SQUID Magnetometers for Low Frequency Applications.* Journal of Low Temperature Physics **76**, 287-386. [Comprehensive review of SQUIDs describing their fabrication, electronics and operation, as well as the use of SQUIDs in several applications]

Williamson S.J., Romani G.-L., Kaufman L. and Modena I., Editors (1983). *Biomagnetism – An Interdisciplinary Approach*. 706 pp. New York: Plenum Press. [This book treats in detail all basic aspects of biomagnetism but is now partly outdated]

Yoshimoto, T., Kotani, M., Kuriki, S., Karibe, H. and Nakasato, N. (1999). *Recent Advances in Biomagnetism – Proceedings of the 11th International Conference in Biomagnetism.* 1161 pp. Sendai: Tohoku University Press. [Short papers on recent advances in MEG and MCG]

## Figure captions

**Figure 1.** The first whole-head MEG instrument, installed to the Low Temperature Laboratory at HUT. During actual measurements the double doors to the shielded room must be tightly closed. The concave, helmet shaped bottom of the helium dewar, with the flux transformer coils near its tip, is brought as close as possible to the subject's head. The 122 SQUIDs in this prototype instrument were manufactured by the IBM Company of Yorktown Heights, NY.

**Figure 2.** Illustration of the cerebral cortex from the left side.

**Figure 3.** *Left:* Typical magnetic response from the brain as a function of time; the N- and P-numbers refer to latencies in milliseconds after the stimulus was given. *Right:* Topographic map of the magnetic field gradient from which the active cortical area (center of the red arrow) can be determined. Gray indicates field out of the head and white into.

**Figure 4.** (a) Current-voltage characteristics of a dc SQUID for three different applied fluxes. The solid line represents the external flux value $\Phi_a = 0$; the dashed line, $\Phi_a = \Phi_o/4$; and the dash-dotted line, $\Phi_a = \Phi_o/2$. (b) SQUID's output current as a function of the external magnetic field for three different bias voltages. The solid line indicates the periodic response for the optimal point of operation ($U = 25$ μV). The dashed line represents the voltage value, $U = 50$ μV, and the dash-dotted line, $U =$ 100 μV. In this example, 1 nT corresponds to one flux quantum and thus the maximum sensitivity of the magnetometer is 200 μA/nT.

**Figure 5.** Different types of pick-up coils. (a) Simple multi-turn pick-up loop with high output inductance and sensitive to the homogenous magnetic field $B_z$. (b) Magnetometer with low output inductance composed of several sub-loops set in parallel. (c) Axial gradiometer which measures $\partial B_z / \partial z$. (d and e) Two tangential gradiometers that measure the vertical gradient of the magnetic field, $\partial B_y / \partial z$ and $\partial B_x / \partial z$, respectively. (f and g) Planar gradiometers responding to two gradients of the field, $\partial B_z / \partial y$ and $\partial B_z / \partial x$, respectively. In gradiometric sensing coils the distance between the loops (baseline) should be close to that from the source but is smaller in practice, at least in integrated gradiometers.

**Figure 6.** Magnetometer responding to two gradients of the field, $\partial B_z / \partial x$ and $\partial B_z / \partial y$ as well as to the field $B_z$ itself. Two microcircuits in the center of the pick-up chip consist of flux transforming circuits and SQUID sensors for the three independent channels. The device was designed and fabricated at the Technical Reseach Centre of Finland. Figure provided by Mikko Kiviranta of the Laboratory of Measurement Technology at VTT.

**Figure 7.** Block diagram of the direct readout scheme based on the noise cancellation method. The voltage noise of the amplifier is detected by the SQUID via an external feedback coil and a FET acting as a tunable resistor. The flux-to-voltage characteristics for different values of the FET gate voltage illustrate cancellation of the voltage noise in the amplifier. The noise of the preamplifier is artificially increased to emphasize the noise cancellation process. NC is the noise cancellation parameter.

**Figure 8.** Micrograph of the PTB integrated multiloop SQUID magnetometer. The chip size is 7 x 7 $mm^2$. Figure provided by Dietmar Drung of the PTB in Berlin.

**Figure 9.** Photograph of the 306-SQUID Vectorview™ instrument. Figure provided by Neuromag Ltd of Helsinki.

**Figure 10.** Photograph of the 150-SQUID Omega$^R$ instrument with the subject in the supine position. Figure provided by CTF Systems Inc. of Port Coquitlam, Canada.

**Figure 11.** Photograph of the 148-SQUID Magnes$^R$ 2500 instrument. Figure provided by Biomagnetic Technologies Inc. of San Diego, California.

**Figure 12.** *Left:* Somatosensory responses elicited by electric stimuli of the left thumb. The polar derivatives $\partial B_z/\partial y$ along longitudes (blue traces) and the azimuthal derivatives $\partial B_z/\partial x$ along latitudes (red traces) are plotted above each other at every measurement site. The head is "flattened" by using the zenithal equidistant projection. The subject's nose points up. *Right:* Magnetic field patterns on the head (A and B from the right side, C from the left, D from the top); the field emerges in the gray areas. The isocontours are separated by 40 fT. Centers of the red arrows indicate the activated regions. The elaborate software for the data analysis was written by Matti Hämäläinen and his coworkers. Figure modified from Forss *et al.*, Brain Res. **685**, 68 (1995).

**Figure 13.** Information processing in the brain during picture naming. The locations of the primary visual (V), auditory (A), and somatosensory (S) cortices are marked by small squares. The cortical surfaces were generated from MRI scans of the subject. Magnetic signals recorded as a function of time from each site, during three different experimental paradigms, are shown as well. Figure modified from Salmelin *et al.*, Nature **368**, 463 (1994).

**Figure 14.** Face-specific detectors in the human brain. Columns illustrate source strengths in the fusiform cortex (white dots on both sides in the inserted MRI picture) at 165 ms after the stimulus (shown below each column) was presented. Description of stimuli: f = face, c = color, g = grayscale, b = black-and-white, s = scrambled, r = randomized, a = animal, wb = whole body, o = object. Figure modified by Tommi Raij from Halgren *et al.*, Cerebral Cortex **10**, 69 (2000).

**Figure 15.** Result of an experiment in which the subject was asked to look at another person pinching a manipulandum. *Above:* An example of the hand movements that the subject viewed. *Below left:* Areas of the brain's left hemisphere activated during viewing, according to MEG measurements. As expected, the visual cortex at the back of the head (violet dot) was responding first because the subject saw the moving hand. The next activation occurred in the left Broca's region (black dot), followed by the left motor cortex (red dot). *Below right:* The last area to be activated was the primary motor cortex (green dot) in the right hemisphere. Figure modified from Nishitani and Hari, Proc. Natl. Acad. Sci. USA **97**, 913 (2000).

**Figure 16.** Generator areas of epileptic spikes recorded from a patient who had suffered partial epilepsy for many years. An analysis of the MEG spikes showed two epileptogenic regions in the right hemisphere of his brain. Activation of sources in the two regions revealed no systematic time differences. Figure modified by Nina Forss from Lamusuo *et al.*, Epilepsia **40**, 921 (1999).

**Figure 17.** MR image of the brain's left side of a patient with a large tumor (oligoastrocytoma) in the vicinity of the central sulcus. The somatosensory cortex was traced by MEG responses generated by stimulating the right tibial nerve at the ankle (red dot), the right median nerve at the wrist (purple dot) and the right lip (yellow dot). The primary motor cortex (green dot) was identified during extension of the right wrist. The violet dot indicates the site of the auditory cortex. Large veins on the brain surface were made visible by injecting a small amount of gadolinium into the patient's bloodstream during MR imaging. Figure modified by Nina Forss from Mäkelä *et al.*, Human Brain Mapping (to be published in 2000).

**Figure 18.** Frontal view of a coronally cut human heart. Oxygen-rich blood from the lungs fills the left atrium (upper compartment at right) and oxygen-depleted blood from other body parts enters the right atrium (upper compartment at left). Both atria contract almost simultaneously and propel blood to the left and right ventricles (compartments below), respectively. Next, the valves between atria and ventricles close and the ventricles contract. Oxygen-depleted blood is thereby pumped to the lungs for

intake of fresh $O_2$ and for removal of $CO_2$, while oxygen-rich blood is forced to other parts of the body to supply them with $O_2$ and needed nutrients. The exit valves from the ventricles are then shut to prevent backflow of blood, and the cycle is repeated. Description of the cardiac conduction system: (1) sino-atrial (S-A) node, (2) atrio-ventricular (A-V) node, (3) bundle of His, (4 and 5) right and left bundle branch, (6) Purkinje network connected to the myocardial muscle. Figure from EKG – Perusteet ja tulkinta, edited by Juhani Heikkilä of the Division of Cardiology at HUCH.

**Figure 19.** Photograph of the 67-SQUID cardiomagnetometer in the BioMag Laboratory of the Helsinki University Central Hospital. The cylindrical dewar bottom has a diameter of 30 cm and a curvature of 79 cm. Figure provided by Neuromag Ltd of Helsinki.

**Figure 20.** Magnetic heart signal recorded by the 67-SQUID cardiomagnetoimeter of Figure 19 on a patient suffering from arrhythmia. The normal heartbeat is followed by a larger abnormal beat spontaneously initiated in the ventricles. Figure provided by Juha Montonen of the Laboratory of Biomedical Engineering at HUT.

**Figure 21.** An example of MCG localization of continuous atrial tachycardia in a 24-year old patient. *Left:* Spatial MCG distribution during the abnormal small-amplitude P-wave (marked by the vertical line). *Right:* Two independent MCG localizations of the P-wave, superimposed on a transaxial MR image of the heart. The results were in excellent agreement with invasive localization obtained during catheter ablation. Figure provided by Markku Mäkijärvi of the Division of Cardiology at HUCH; see reference by Nenonen *et al*. in Bibliography

**Figure 22.** Detection of abnormal repolarization by MCG mapping. (a) Time points displayed on the T-wave are at 340 ms, 400 ms, and 460 ms after the onset the main QRS-peak at left. (b) Normal magnetic field distribution during ventricular repolarization. (c) MCG recording on a symptomatic 14-year old girl with a long-QT syndrome. The magnetic field pattern during the T-wave is clearly abnormal and displays typical multipolar structure. Figure provided by Jukka Nenonen of the Laboratory of Biomedical Engineering at HUT.

**Figure 23.** Examples of spatial distributions of the QRS fragmentation score *S* in a healthy volunteer (a), in a patient with old myocardial infarction but without arrhythmias (b), and in a patient with coronary heart disease and vith VT/VF (c). The dots indicate the locations of the 49 SQUID sensors above the anterior chest of the subjec. Color code shows the fragmentation score in various locations. Figure modified from Müller *et al.*, Phys. Med. Biol. **44**, 105, 1999.

**Total number of words:** 13370

## Author information

# 1
Hierarchial number of contribution: 6.8.5.2.
Lounasmaa
Olli Viktor
Low Temperature Laboratory, Helsinki University of Technology, Box 2200, 02015 HUT, Finland
Telephone: +358-9-4512952 (office); +358-9-481541 (home)
Telefax: +358-9-4512969
E-mail: olli.lounasmaa@hut.fi
Y
Author Agreement No. EOLSSAA 001891

# 2
Hierarchial number of contribution: 6.8.5.2.
Seppä
Heikki Juhani
Measurement Technology, VTT Automation, Box 1304, FIN-02044 VTT, Finland
Telephone: +358-9-4566419 (office); +358-9-555414 (home)
Telefax: +358-9-4567029
E-mail: heikki.seppa@vtt.fi
N
Author agreement must be made with Heikki Seppä

## Author biographies

### Olli Lounasmaa

Olli Viktor Lounasmaa (OVL) obtained his D.Phil. degree at the University of Oxford in 1958. He then worked four years at the Argonne National Laboratory in the US. In 1965 he was appointed Professor of Technical Physics at the Helsinki University of Technology (HUT) where he founded the Low Temperature Laboratory (LTL). In 1970 he was appointed Professor of the Academy of Finland but continued his work at HUT until his retirement in January 1996. In the LTL, his research has been on superfluid $^3$He in the millikelvin region and on nuclear ordering in several metals at positive and negative temperatures in the nano- and picokelvin regions of temperature. SQUIDs were developed and used extensively in the LTL for thermometry at ultralow temperatures. Brain research, especially the development of multichannel instrumentation, has been OVL's secondary field of interest since 1980. In 1987, a 7-channel neuromagnetometer became ready for MEG measurements in the LTL. Studies of evoked responses to acoustic, somatosensory, and visual stimuli were then made under Academy Professor Riitta Hari, MD; later her work was extended to investigations of cognitive brain functions and clinical applications. OVL participated in some of this research. In 1982 the first neuromagnetometer covering the whole scalp became available with 122 SQUID sensors. In 1998, the Finnish company Neuromag Ltd. inaugurated its Vectorview™ instrument with 306 sensors, constructed in collaboratuion with the LTL. Twelve of these neuromagnetometers had been sold abroad by mid-2000. OVL is a Foreign Member of the Royal Swedish Academy of Sciences and of the National Academy of Sciences of the USA. He is also the recipient of the Kapitza Gold Medal of the Russian Academy of Sciences and of numeous domestic and international prizes. He has an Honorary Degree of Medicine from the University of Helsinki.

### Heikki Seppä

Heikki Seppä obtained his Ph.D. degree in technology from the Helsinki University of Technology (Espoo, Finland) in 1989. From 1976 to 1979, he was an assistant at HUT, working in the area of electrical metrology. He joined the Technical Research Centre of Finland (VTT) in 1979 and since 1989 he has been working there as a Research Professor. In 1994 he was appointed Head of the Measurement Technology Laboratory which is part of VTT Automation. During 1996 … 98 he was acting as the Director of VTT Automation. Besides his research work, Heikki Seppä has developed several measurement apparatuses and sensors for industry, *e.g.*, dc SQUIDs and readout electronics used by Neuromag Ltd in the Vectorview™ system. He is the recipient of several domestic prizes and has discovered numerous patented inventions. He has done research work on electrical metrology, in general, and on superconducting devices for measurement applications, in particular. Heikki Seppä has developed most of the standards used to realise and maintain electrical units in Finland. He is currently doing and directing research on dc SQUIDs, Josephson circuits, quantized Hall effect, and rf instruments. Recently, his work has been focused on mesoscopic systems and micromechanical devices.