IMPACT OF SUPERCONDUCTING DEVICES ON IMAGING IN NEUROSCIENCE

Stefania Della Penna\textsuperscript{1,2}, Vittorio Pizzella\textsuperscript{1,2} and Gian Luca Romani\textsuperscript{1,2}

1 Department of Neuroscience and Imaging, University of Chieti, Italy
2 Institute of Advanced Biomedical Technologies, University of Chieti, Italy
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Abstract

This paper provides an overview on the basic principle and applications of magnetoencephalography, which requires the use of many SQUID channels and thus represents one of the more important application of superconducting electronic devices. This paper is divided into 8 sections. Section 1 is an overview of the MEG technique. Section 2 provides a short historical background on the method. Section 3 explains how the magnetic fields measured by MEG are generated and which are the mathematical models for such sources. Section 4 rapidly explains which are the requirements of a MEG system. Section 5 presents and discusses the new trend in superconducting instrumentation for imaging, that is the Ultra Low Field Nuclear Magnetic Resonance/ Magnetic Resonance Imaging (ULF NMR/MRI); of note, this technique can be integrated with MEG to improve overall usefulness of magnetoencephalography. Section 6 provides some examples of standard MEG measurements and discusses MEG integration with fMRI. Section 7 presents some recent results on new applications of MEG, increasing the value of this method. Section 8 is a critical summary of the method state of the art and its perspectives.

1. Introduction

This review paper celebrates the impact of superconducting devices on imaging in neuroscience. The dream of using a device to capture someone else’s thoughts is as old as mankind. Today, this is of course not even imaginable, but superconducting devices, namely SQUIDs, with their exceptional magnetic field sensitivity made possible at least a first look at the inner brain functions in a very non-invasive way through the use of magnetoencephalography (MEG).

The MEG method aims at studying the electrophysiological activity of the brain from the measurement of the magnetic field generated by such activity [1,2]. The existence of a neuromagnetic field was already conjectured after the first measurement of the brain electric activity by Hans Berger in 1929. However, neuromagnetic fields are so tiny (≈1÷100 fT) that only low temperature SQUIDs actually provide the required sensitivity. Moreover, to properly characterize the neuromagnetic field and, more important, to infer the neuronal activity that generates this field, it is essential to know the magnetic field spatial distribution in all the space surrounding the brain. Because of this, all presently operating MEG systems feature hundreds of SQUIDs evenly spaced around the head. Indeed, today MEG devices are the most common and successfully commercial use of SQUIDs.
The following sections cover a short introduction to the physiological basis of MEG and its use as a functional imaging technique; a description of the state of the art of the MEG method, including an overview of MEG technology; a recent promising MEG instrumental development, i.e. the integration with magnetic resonance imaging technique; a few example of applications of MEG to basic and clinical neuroscience, including the hottest topic for MEG, the study of brain functional connectivity.

2. Forty years of magnetoencephalography

The beginnings

In the sixties, resistive coils measured the first magnetocardiogram (MCG) [3] and magnetoencephalogram [4]. Although technically possible, the measurement of the magnetic field generated by heart and brain by conventional inductive coils was of no practical use. After some years, the radiofrequency biased SQUID [5] was successfully tested and its application to the study of the tiny magnetic fields generated by heart [6] and brain activity [7] was made possible inside a magnetically shielded room. These pilot results raised the interest of several scientists and an increasing number of laboratories started studying the brain with the new technique. The SQUID immediately demonstrated an unrivaled sensitivity and a wide operation bandwidth extending down towards the low frequencies and thus permitting a satisfactory detection of the slow magnetic signals associated with cerebral activity, the frequency bandwidth of which typically spans between 0.1 and 100 Hz.

Early years

In the eighties, the possibility of three-dimensionally localizing sources of cerebral activity was demonstrated and the first clinical application of the neuromagnetic method, namely the study of focal epilepsy was reported on [8,9]. In that period, all the studies were performed using a single channel SQUID instrument. Medium scale systems were implemented in the early 1990s, comprising about 20 to 40 channels, such as the 28-channel hybrid system in Rome [10], the 37-channel “Magnes” from Bti [11], the 24 channel in Helsinki [12]. The measurement surface was enlarged allowing a greater feasibility and a larger number of applications of the method. Additionally, these systems were placed in medium quality shielded rooms, made of one to two layers of high magnetic permeability materials and one layer of aluminum. In the following years, the number of MEG systems in the world increased thanks to their stable and reliable performances. The first whole helmet MEG systems, Neuromag 122 [13] and the 64-channel CTF
system [14], were produced in the mid-nineties. They represented the first step towards the large scale systems operating nowadays. With these systems featuring few hundreds of channels a single shot measurement of the brain magnetic field over the whole scalp is possible, as well as following the evolution of the magnetic field distribution in time, with 1 ms temporal resolution.

3. MEG as a functional imaging technique

Physiological basis

Electric currents in the brain are driven by neural activity and flow in a large conductive medium (the head tissues). This medium may be considered for simplicity to have homogeneous and isotropic conductivity. The current carriers are, on one hand, ions driven by neural activity in the intracellular space, or across the cell membrane (i.e. “heavy” ions, mainly Na+ and K+ moving within the neurons), and, on the other hand, free ions moving in the extracellular space (i.e. the surrounding medium) in response to the electric field due to the intracellular currents. We view the first type of ion flow (impressed current) as an active current, directly related to neural functioning. This current is usually called the impressed current (see Figure 1). The other type of ion flow is a passive current flowing in the whole extracellular medium (volume current), generated by the electric field resulting from charge distribution over the cell membrane and determined by Ohm’s law.

![Figure 1](image-url)  
Figure 1: Left: A current dipole with volume currents $J_i$ stands for impressed current (in red) and $J_v$ for volume current (in black). The magnetic field lines are in green. Right: A current dipole modeling a postsynaptic potential. The current dipole is in gray inside the dendrite, volume currents are in violet.

In the simplest case, the impressed current is caused by a a post-synaptic potential (PSP, fig. 1), i.e. the electric potential taking place at the synapse after neurotransmitters intake inducing the membrane depolarization (or hyperpolarization). The PSP activity may be modelled as a small
current element called a current dipole and may be represented by a vector, namely the current dipole moment, with units units Am, and its current density in space may be represented as:

\[ J^i = \mathbf{Q} \cdot \delta(r_0) = I \mathbf{L} \delta(r_0) \]

where \( \delta(r_0) \) is the Dirac delta function and \( r_0 \) identifies current dipole position in space. The volume currents may be easily computed using the Ohm’s law:

\[ J^i = \sigma \mathbf{E} \]

where \( \sigma \) is the electric conductivity of the medium and \( \mathbf{E} \) is the electric field due to the impressed current. Overall, the total current related to a single current dipole is the sum of the impressed current and the related volume current, i.e.:

\[ J = \mathbf{Q} \cdot \delta(r_0) + \sigma \mathbf{E} \quad (1) \]

The current dipole may be used also to model a traveling signal along the axon of a neuron, i.e. the long output connection of a neuron to a distant site such as another neuron or a motor fiber (action potential –AP). In order for a signal to travel in one direction only without dampening, the depolarization wave flowing along the axon of a neuron is followed by a repolarization wave restoring the resting state transmembrane potential. The two waves are associated with intracellular currents of opposite directions. The AP (see Figure 2) may be modelled as a current quadrupole. The overall magnetic field generated during signal traveling is one order of magnitude smaller than the isolated current dipole due to PSP, since partial cancellation of the fields generated by the two oppositely directed current dipoles takes place. Although it is possible to detect the magnetic field of an AP from a single exposed axon in an animal model, as well as of APs from nerve fibers in the human noninvasively (e.g. over the arm), magnetic fields of APs from cortico-cortical or cortico-spinal connections have never been observed, likely due to weakness of the signals, and lack of synchronicity.
The frequency range of electrophysiological currents associated with brain activity extends from dc up to below 1kHz, therefore it has been shown that neuromagnetic phenomena can be described by the quasistatic approximation of Maxwell’s equations [15]:

\[ \nabla \cdot \mathbf{E} = \frac{\rho}{\varepsilon_0} \]
\[ \nabla \times \mathbf{E} = 0 \]  \hspace{1cm} (2)

\[ \nabla \cdot \mathbf{B} = 0 \]
\[ \nabla \times \mathbf{B} = \mu_0 \mathbf{J} \]

The magnetic field generated by a single current dipole embedded in a volume conductor is obtained by solving Maxwell’s equations:

\[ \mathbf{B}(r) = \frac{\mu_0}{4\pi} \frac{\mathbf{Q} \times (\mathbf{r} - \mathbf{r}_0)}{|\mathbf{r} - \mathbf{r}_0|^3} + \int \frac{\nabla \times \mathbf{E}(\mathbf{r}') d^3 \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} \]  \hspace{1cm} (3)

where the integral is calculated over the whole space.

Interestingly, when the current dipole is immersed in an infinite homogeneously conducting medium the dependence from electric conductivity vanishes and the above equation becomes

\[ \mathbf{B}(r) = \frac{\mu_0}{4\pi} \frac{\mathbf{Q} \times (\mathbf{r} - \mathbf{r}_0)}{|\mathbf{r} - \mathbf{r}_0|^3} \]  \hspace{1cm} (4)

Typical intensities for an apical dendrite of a pyramidal cell are about \(2 \times 10^{-17}\) Am [2]. According to the above formula, this current dipole generates a field of \(3 \times 10^{-17}\) T at about 4 cm distance (where the field sensors are located). Such a field intensity is much lower than the sensitivity of SQUID magnetometers. This indicates that when we record neuromagnetic fields we are actually receiving the signals from a large number (experimentally, about 50,000) of synapses simultaneously activated. In this case, the current dipole is usually called an equivalent current.
dipole (ECD) to emphasize that it is a macroscopic current dipole, equivalent, by the principle of superposition, to a large number of microscopic current dipoles.

**Practical models**

The neuroscientists/clinicians use MEG to estimate the brain activity (i.e. identify active brain areas or sources) at rest or during a specific tasks. In order to find the sources responsible of the measured field, an inverse problem must be solved. As usually, this is an ill-posed problem, and a model of the conductor containing the sources and of the source itself must be adopted to limit the possible solutions. The source model which is widely adopted is the current dipole model, while the simplest model that can be adopted for the conducting medium is the homogeneously conducting sphere. Under these conditions, equation (3) becomes:

\[
\mathbf{B}(r) = \frac{\mu_0}{4\pi} \left( \mathbf{F} \times \mathbf{r}_0 \cdot \mathbf{Q} \times \mathbf{r}_0 \cdot \mathbf{r} \text{ grad } \mathbf{F} \right)
\]

where \( F \) is a function only of \( r \) and \( r_0 \) (not of \( Q \)) and the medium conductivity \( \sigma \) is no longer involved in the magnetic field determination. This means that volume currents and radial sources do not contribute to the magnetic field external to the head (see Figure 3), which makes MEG an ideal technique to catch only neuronal functioning and that is not distorted by volume properties. The use of this model permits to solve the inverse problem, i.e. to estimate the source position and strength given the magnetic field distribution generated by the source itself. The homogenous spherical conductor is a simple model which is suitable, in a first order approximation, to represent the head. Nowadays, this approximation is less used, since tends to misestimate sources in some regions of the head, and a realistic head model obtained from the segmentation of MRIs of the subject’s head is fairly easy to obtain. When using a realistic geometry for the head, an analytical solution of the inverse problem is not possible and equation (3) must be solved numerically. Happily, the brain as a relatively homogeneous conductivity, and a single compartment homogeneous model, where the boundary is the brain surface, represents an excellent compromise between numerical accuracy and ease of computation. In this case the boundary element method can be used with excellent results [16].
Equation (5) describes the magnetic field generated by a single current dipole, or an ECD.

The ECD is a suitable model when only a small cortical area (few mm$^2$) is active at a specific time. However, this seldom occurs and often multiple brain areas must be considered active at the same time. If the number of active brain areas is small, a multiple ECD model may be adopted. This model simply replicates the single ECD model, with the total magnetic field calculated as the sum of the magnetic fields generated by the single ECDs. The inverse problem may be solved using the same approach used for the single ECD model, provided that the number of magnetic field sensors is larger than the ECD parameters to be estimated.

A different approach must be used when many (or all) brain areas are active at the same time. In this case the number of parameters to be estimated may easily be much larger than the available data. The most effective approach is to model each brain region, e.g. a brain voxel, as an ECD with fixed position, and to estimate only the ECD moments, so that the relationship between source and field is linear (current density methods, [17]). In this case the problem of source reconstruction is a linear problem, although it is the linear estimation of a heavily underdetermined system. Such a problem requires the application of a regularization procedure which de facto introduces constraints on the possible solutions. Since the number of parameters may easily exceed the number of magnetic field sensor by a factor 100, other constraints improve source estimation. One of the most promising approach makes use of the Bayesian inference, with priors gathered from other imaging techniques such as, for example, fMRI [18,19]. Different approaches based on spatial filters (e.g. beamformers) have also been introduced to obtain a whole head mapping of brain activity[20,21]. These filters estimate the contribution of a specific brain location to the overall signal, by filtering out the contribution of all other brain locations.
4. Basics of instrumentation

Detectors

Since brain magnetic fields range from few fT to some pT, LTS SQUID based detectors are nowadays used as standard detection units in MEG systems. Thin film fabrication technology is well assessed and allows to produce large numbers of LTS SQUID based detectors with comparable performances. From the 1990s up to now advances in thin film fabrication techniques allowed to produce magnetometers and planar gradiometers integrated on the same chip of the SQUID, suitable to be densely arranged over the measurement surface, as well as current sensors connected to superconducting detection coils (e.g. second order wire wound gradiometers). Innovative design of the detectors, such as the “Drung wheel” [22] or gradiometric input coils [23], have been introduced to improve sensitivity and to reduce channel crosstalk for densely packed sensor arrays. Overall, the sensitivity of these detectors has been improved over years, ranging from 2 to 5 fT/√Hz on average, with a small standard deviation even on a large number of channels. This noise figure is adequate with respect to the noise of about 10 fT/√Hz below 50 Hz generated by volume currents and non-locked activity in the brain.

Large scale systems

Current systems, featuring few hundreds of channels (100:300 sampling positions), allow a single shot measurement of the brain magnetic field over the whole scalp [24,25] (see Figure 4).

Figure 4 The Elekta Neuromag systems consisting of 306 channels arranged on 102 sampling positions on a helmet surface. Each measurement module consists of two orthogonal planar gradiometers and one co-planar magnetometer all integrated onto a single chip
The detection coils are placed as near as possible to the scalp, in practice at about 3-4 cm because of the cryogenic vessel containing the SQUIDs, since the magnetic field generated by an ECD decreases as $1/r^2$ with distance. Additionally alternate read-out schemes better suited for a large number of channels, such as direct read-out with applied positive feedback and voltage bias with noise cancellation, were adopted in place of the standard flux-modulation FLL. These schemes are simpler, with a smaller number of wires per channel fed through the cryostat plug and with a reduced crosstalk among channels. The read-out electronics is set remotely by a digital interface, integrated in a user-friendly acquisition system. The use of whole-head systems asked for new designs of the cryostats, which are larger to host all the sensing system placed at their bottom, as near as possible to the room temperature surface. In some cryostats the helmet is placed with its axis at 45° with the vessel axis, allowing to measure in supine or seated position by a 45° tilt of the cryostat. The systems are always installed in a magnetically shielded room. Shielded rooms are built by layers of materials providing eddy current shielding (aluminium), and by layers for magnetic shielding (high magnetic permeability materials). The typical shielding factor is ~ 60 dB at 1 Hz and 100 dB at 50 Hz. The overall shielding can be improved by using coils placed outside the room. The residual magnetic noise is further suppressed by using sensing channels with gradiometric geometry and/or a set of reference channels, placed far from subject and only sensitive to the background noise. The reference channel outputs are processed to digitally reject the field noise, during acquisition or off-line. With these systems, installed inside good quality shielded rooms, clinical studies are feasible due to their high level of engineering and their ease of operation.

5. ULF NMR/MRI

Introduction on ULF NMR/MRI

Magnetic Resonance Imaging (MRI) is a well-known technique to obtain tomographic images of body sections. It relies on the nuclear magnetic resonance of nuclei, once these are placed in an applied magnetic field $B_0$ [26]. When studying human body, H protons are investigated. An additional magnetic field varying at a frequency $\nu=(\gamma/2\pi)B_0$, with $\gamma/2\pi = 42.58$ MHz/T, changes the alignment of the magnetization of the protons and the following relaxation signal (that decays according to two basic time constants $T_1$ and $T_2$) is usually detected by an induction room temperature coil. The signal is dependent on $\nu^2$, and to increase the SNR actual systems are designed to operate at applied fields as high as possible ($B_0 = 1.5$T or 3.0T on standard clinical devices). However, an opposite trend towards Ultra Low Fields (50÷200 $\mu$T) can be deduced from the recent literature [27,28]. To increase SNR, ULF NMR/MRI is usually performed using SQUID based systems and pulsed (prepolarization) techniques [29], ranging from 10 mT to some hundreds
of mT. Advantages of ULF NMR/MRI are an increased frequency sensitivity[30], reduced sensitivity to field inhomogeneity and susceptibility artifacts[31], enhanced T1 contrast [32]. Last but not least, ULF NMR/MRI instruments are compatible with MEG systems[33,34], since both use the same or similar detectors. Integrated ULF MRI/MEG systems, to be described in the following, consist of deeply revised whole helmet MEG systems equipped with field-robust MEG sensors and additional coils for MR imaging. The advantages of such integrated systems are an increased spatial sensitivity of the MEG results thanks to the reduction of co-registration errors and the possibility of scanning also patients that are normally discarded since they cannot undergo HF MRI (children, pregnant women, patients with internal magnetic staples from surgery). Recently, the possibility of direct neural imaging through ULF NMR systems has also been proposed[35].

**ULF NMR/MRI and MRI/MEG systems**

The general design of these systems is based on the use of one or more detection channels each consisting of a gradiometric superconducting detection coil using Q-spoilers or superconducting switches, coupled to a dc SQUID. The geometry of the coil and the use of current dampers prevent the SQUID from damage that may occur even if it is switched off when the pulsed field is on. The robustness of the SQUID based detector is a main issue driving the design of all the existing systems, and the possibility of using more robust sensors, such as mixed sensors[36], is under investigation[37, 38]. The majority of existing systems are prototypes and no commercial systems are on the market up to now. However, a considerable number of patents on systems, channel design and procedures have been registered. One of the first ULF NRM/MRI system has been developed at Berkeley, by Clarke’s group [39]. The system consists of a single channel, based on a low noise dc SQUID (~1fT/√Hz ) coupled to a second order gradiometer equipped with Q-spoilers, installed in a ultra-low noise cryostat. Images of a human forearm, [40] of food inside a can [41] and of vegetables have been presented as first results. This system has been recently used to obtain an ex-vivo T1 map of prostate tissue affected by cancer[32]. The system is operated in a measurement field of 132 µT and a prepolarizing field of 150 mT.

Different system designs have been introduced by other research groups, with the aim at integrating ULF MRI and MEG with the same set-up. The Los Alamos group has implemented ULF MRI/MEG small scale systems. The first one was designed as a proof of concept [42] and was based on a single channel consisting of a planar gradiometer coupled to a LTS SQUID, a measurement field of 6.4 µT and a prepolarizing field of 5 mT, both orthogonal to the gradiometer axis. Somatosensory MEG responses and NMR signals were simultaneously recorded and then separated by different filters. Since the noise introduced by the NMR sequence was too large to
record NMR and MEG simultaneously, this system evolved towards a design allowing subsequent MEG and MRI recordings. Thus, a multichannel system comprising 7 channels each consisting of a second order axial gradiometer (with a diameter of 37 mm and a baseline of 60 mm) coupled to a dc SQUID, was implemented [43]. The system uses an applied field of 46 µT and a prepolarizing field of 30 mT, to increase the SNR. SQUID safety relays on the use of superconducting switches making the detection coil resistive during prepolarizing field switching. In vivo images of the occipital part of the human brain were obtained with a voxel of \(3 \times 3 \times 6 \text{ mm}^3\), using a recording time of 1.5 hours[33]. These images were associated with auditory evoked fields recorded by the same instrument (see Figure 5)[44]. One drawback of this system is that the same channels are used for both detections. Indeed, a channel geometry which might be optimal for MEG (diameter of detection coils \(\sim 1 \text{ cm}\)) is sub-optimal for NMR (diameter of coil \(\sim \text{some cm}\)). Thus, a design of a whole helmet system for integrated MEG/MRI has been reported [45]. This system includes different channels for MEG and MRI, with suitable geometries. The number of MRI channels is smaller than the one of MEG channels which are arranged over the whole helmet surface to allow good quality MEG measurements. The system is equipped with external coils generating the measurement field, the prepolarizing field and the gradients for imaging.

There is only one medium scale MEG/MRI system operating up to now (see Figure 5), which can be expanded to a whole head system [34]. It has been developed in the frame of a European FP7 project, the MEGMRI project [46], at Aalto University. Two different field robust SQUID designs have been tested on this hybrid system, based on channel modules with different geometries, which are differently tolerant to the applied pulsed field and are adopted to reduce flux trapping and increase recovery after switching off the pulsed field[47]. Both types include one magnetometer and two planar gradiometers with slightly different dimensions placed on the same chip, each coupled to a dc SQUID which is shielded by a Nb plate. The first type is based on Nb stripes fabricated on the module, whereas the second type uses Pb wire coils. The maximum pulsed field value which can be applied without damaging the modules is 50 mT. The noise levels are 4 fT/Hz\(^{1/2}\) and 2 (fT/cm)/Hz\(^{1/2}\) for the thin film modules and 2 fT/Hz\(^{1/2}\) and 1 (fT/cm)/Hz\(^{1/2}\) for the wire modules. A polarizing field of 22 mT is generated by a compact superconducting coil placed in the helium bath. Additional shielding coils are used to reduce the intensity of the prepolarizing field on the walls of the magnetically shielded room and that of the related secondary field[48]. The measurement field of 50 µT is generated by room temperature coils external to the dewar. T2-weighted images of the occipital part of the cortex together with Visual Evoked Fields have been successfully recorded.
Finally, the possibility of directly imaging neural currents has been proposed both with high field setups [49] and with low field ones[50,51]. The major limitation to this method is the SNR, which should be considerably higher than that featured by the existing systems. Recently, a three channel ULF NMR system using multiloop SQUID based modules [22] and operated in a very high quality magnetically shielded room, has detected the NMR signal associated with a phantom simulating brain activity[35]. An improvement of the SNR needed to image real brain activity seems to be achievable in the next future.

Figure 5 Left: The 7-channel Los Alamos system, including an array of 7 SQUID-based channels and a set-up of coils for NMR imaging; images of the right side of the brain together with the evoked auditory field are also shown (modified from [43,44]). Right: The Aalto system, installed in a whole helmet dewar for MEG and using a superconducting pre-polarizing coils; the system obtained images of the occipital part of the brain together with visual evoked fields (modified from [34]).

6. MEG contribution to basic and clinical neuroscience
First contributions of MEG Since its inception, magnetoencephalography has been acknowledged as a very important tool for basic and clinical neuroscience. The first findings accomplished using small MEG devices were related to sensory processing by the human brain. Very simple sensory stimulation, such as an electric pulse applied to the median nerve, can elicit neuronal pools to activate, thus generating a detectable neuromagnetic field (see Figure 6).

Figure 6 Activity of the first and second somatosensory cortex as obtained by MEG. Colored pins identify the four active brain regions, while the time course of each activation is represented by the corresponding trace at the corners.

One of the first achievements obtained with a very simple yet effective MEG device was the demonstration of the tonotopic organization of the human auditory cortex [52]. This result was presented in Science by Romani and colleagues, and it was the first evidence that the sources of the evoked field elicited by auditory stimulation by tones with increasing frequency are systematically - and logarithmically – located at increasing cortical depth (see Figure 7).

Figure 7 Estimated depth of auditory sources as a function of the sound frequency (modified from [52]).

Multimodal integration with fMRI

Magnetoencephalography strengths and weaknesses, as more extensively discussed in sections 3, are mainly related to the ability of directly capturing true neuronal activation and the poor spatial
resolution. Interestingly, functional Magnetic Resonance Imaging (fMRI) has complementary features. Indeed, fMRI may be used to identify active neuronal pools thanks to the Blood Oxygen Level Dependent (BOLD) contrast [53], i.e. the increase of hemoglobin oxygenation related to brain activation, that is found to be related to the increased oxygen demand of the activated neurons. The BOLD contrast is linked to hemodynamic response, that typically requires seconds to occur, thus heavily limiting the temporal resolution of the technique. On the other hand, MRI nicely exploits the spin resonance phenomena to select signal originating in small brain voxels, therefore allowing the detection of neuronal activation with a spatial resolution as high as 1 mm[54].

These complementary features speak for a combined use of MEG and fMRI to best characterize neuronal activation. Because of the conflicting requirements discussed in the previous section, it is today impossible to simultaneously detect MEG and fMRI BOLD contrast. However, the benefits of such a device have been already demonstrated using successive measurements. A first study performed by fMRI [55] proved the functional sub-division of somatosensory area II (SII). Successively, MEG was able to characterize the temporal and amplitude evolution of these two areas (see Figure 8), highlighting an anterior area with typical contralateral pathway (contralateral activation occurring earlier than the ipsilateral one) and a posterior area with bilateral pathway (both activation occurring at the same time) related to the painful sensation of the stimulus[56].

![Figure 8](image_url)

**Figure 8.** Left: Dipole positions in the anterior and posterior sub-regions after the fitting procedure. BOLD clusters observed in the antero-posterior axis in SII area during the fMRI study were used as constraints for the initial location of dipole sources modeling the MEG data. Right: time evolution of the ECDs shown on left panel. Modified from [56].

**An example of MEG contribution to basic and clinical neuroscience**

After the development of the first whole-head MEG systems in the nineties, MEG began to be used to address neuroscience issues.

Among the first achievements of MEG in basic neuroscience, there is the study of the dynamics of language. A remarkable study performed by Salmelin and coworkers [57] disclosed the dynamics of...
the cerebral representation of language. During picture naming, i.e. the naming by the subject of pictures of everyday objects, a cortical activation progressing bilaterally from the occipital visual cortex towards temporal and frontal lobe was observed. This observation was performed using a dipolar model for cortical activation. More recent analysis are able to estimate the current density within the brain following the same paradigm, as shown in figure 9. Here, the progression from occipital to frontal cortex is completed within about 200 ms from the display of the image. Afterwards, the cortical activation bounces back to the parietal cortex (Wernicke’s area) and again to the frontal lobe (Broca’s area). This interplay of several neuronal pools is important to ensure proper language ability.

![Figure 9 Dynamics of brain activity during picture naming](image)

Alteration of this timing, may result in cognitive disabilities such as dislexia ([58] and reference therein).

### 7. Functional connectivity

The study of functional connectivity in the healthy and pathological brain is the most promising application of MEG. Indeed, the old perspective viewing the peculiarity of the human brain relaying in its size or cell number - big mammals such as elephant and whale have larger brains with a
higher number of neurons – has been overreached by the relationship with the specificity and abundance with which neurons are connected.

Functional connections are studied by MEG estimating the synchronicity modulation of activities at two brain sites. The activity of a brain site is the convolution of neuronal oscillations at that site. A brief description of neuronal oscillations is in the following (for a review see [59]). Detailed biophysical studies revealed that even single neurons are endowed with complex dynamics, including their intrinsic abilities to resonate and oscillate at multiple frequencies [60], which suggests that precise timing of their activity within neuronal networks could represent information. Information must be moved from one place to another during processing in the brain. Fast oscillations are used for local processing whereas slower rhythms are related to the involvement of distant and widespread neuronal groups [61]. Oscillations are important because they provide an effective means to control the timing of neuronal firing. Thereby, they support spike-timing dependent plasticity and they can temporally coordinate the information transfer across brain regions. The study of maps of functional cerebral connections is therefore the basis for understanding how the brain works.

Recent advances on data analysis together with the use of good quality whole head MEG systems and the integration of results with data obtained by other modalities dramatically improved the quality and salience of MEG studies of connectivity in the scientific community. Various connectivity measures have been introduced[62] to account for the specific properties of MEG signal. The most common are the Pearson correlation and the coherence, in their stationary and non-stationary versions, together with measures linked to the phase lag between signals [63,64]. Each of these measures is able to elucidate specific properties of MEG functional connectivity.

Regional connectivity can be studied during task, and the MEG method allows to provide information on the latency of the interaction and the frequency driving it. The involvement of specific cerebral networks, instead of single regions independently analyzed, can be associated to the processing of specific stimulus categories, or to cerebral mechanisms adopted during processing. As an example, a visuospatial attention task has been demonstrated to induce frequency-specific modulations of the interregional synchronization between regions involved in the processing of the stimulus [65]. The frequency-specific modulation of interaction within and across auditory and language networks has been proposed as neural substrates for behavioural outcomes [66,67]. Additionally, synchronization between cerebral signals and other reference signals is an approach widely used in MEG connectivity studies. As an example, coherence between cortical areas and spinal cord activity (corticospinal coherence) has been indirectly measured using
electromyography signals as references [68]. Frequency specific (gamma band 40-70 Hz) corticospinal coherence has been proposed as an efficient mechanism of motor integration, as it has been demonstrated to correlate with subject’s motor readiness.

In the last years the traditional focus of attention of MEG studies, namely the study of task related activity and connectivity, has moved to the analysis of rest. Indeed it has been measured that the brain energy consumption during active tasks is only 5-10% higher than during rest [69,70]. We remind that brain oscillations are always on at rest and they account for about 80% of the brain metabolism (here comes the concept of the “dark brain energy”). The first suggestion on what this energy is used for came from fMRI, demonstrating that spontaneous BOLD fluctuations were correlated across distant brain areas, forming what have been named the Resting State Networks (RSN, [71]). These network involve regions which are commonly activated during specific tasks. Although a growing fMRI literature has been produced on these RSN, elucidating their functional role, only recently MEG studies were able to detect some of these networks. Indeed the information produced by MEG is fairly more complex than fMRI, since time, frequency and time scales (e.g. the fast raw signal and the slow Band Limited Power) are added to spatial information. MEG could demonstrate the neurophysiological correlates of some RSN (Figure 10, upper left) based on spontaneous fluctuations of the rhythmical power (BLP- [72-75]) and of the oscillations themselves (Figure 10, lower left) [76]. Of note, the main findings obtained by MEG are that i) RSN involve ultraslow fluctuations of BLP, with spectral contents resembling the fMRI ones; ii) the interaction within RSN is not stationary but changes over time, waxing and waning, and they involve and share different brain rhythms. Eventually, a mechanism for non-stationarity of RSN has been proposed from MEG investigations [77]. Indeed, one of these RSN, the Default Mode Network (DMN), has been demonstrated to play a central role (see Figure 10, upper right) in a specific frequency band (beta-13-25 Hz). This implies that when the DMN is internally connected, part of other RSN link to it in a mechanism of time-specific segregation(in the RSN specific band)/integration (in the beta band). The modulations of these RSN during natural vision of a movie with respect to rest has also evidenced frequency specific within network decreases and across network increases of interaction (see Figure 10 lower right), suggesting new interpretation of their functional role[78]. The impact of the above studies has pushed the MEG connectivity study as one of the methods adopted in the Human Connectome Project [79,80], a 5-year NIH funded project aiming at producing connectivity matrices obtained with different approaches.
8. Conclusions

In this paper we summarized the state of the art of the MEG method. Concerning the instrumentation development of innovative MEG systems, we can state that system technology had already reached its best design in the previous decade and only incremental improvements have been added to the existing system design. However, innovative designs of integrated MEG and ULF MRI systems have been introduced and might give birth to a new generation of systems with a considerably improved spatial resolution. The state of the art is actually at prototype level, however we expect to praise the first commercial MEG/MRI integrated systems in the next future. We have provided here a quick overview of the recent achievements, which should deserve a review themselves. Thus, although we might have unintentionally omitted the description of some systems, and we apologize for this, we aimed at providing the direction where the technological development is heading to. Thanks to the well established technology for standard MEG systems and to the novel methodological achievements obtained in the field of MEG data analysis, many new applications of MEG to the study of brain activity and to the clinical research and practice have been introduced.
Due to the tremendous amount of studies reported in the last decade, we had to make a selection which should be descriptive of the main recent advances. The main message here is that the importance of the MEG method has raised up in the last decade, as stated by the impact of the papers published in high IF journals. The information provided by MEG is extremely rich and only part of it is actually being analyzed, although extensive analysis methods are applied (analysis of evoked activity, rhythmical activity, large scale connectivity). As a consequence, new laboratories traditionally using other imaging methods are adopting MEG for studying brain activity. The new study protocols and analysis methods are being transferred to clinical studies of brain disease and aging. We thus expect a wider acceptance of the MEG method in the clinical community, with a consequent increase of the number of systems in the world.

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