IEEE/CSC & ESAS SUPERCONDUCTIVITY NEWS FORUM (global edition), No. 27, January 2014;
Plenary presentation 2PL02 at EUCAS 2013

ITAB

IMPACT OF SUPERCONDUCTING DEVICES ON IMAGING IN NEUROSCIENCE

Gian Luca Romani

Institute for Advanced Biomedical Technologies (ITAB), and
Department of Neuroscience and Imaging
University “G. D’Annunzio” of Chieti

“EUCAS 2013”

Genova, September 15-19, 2013

Outline

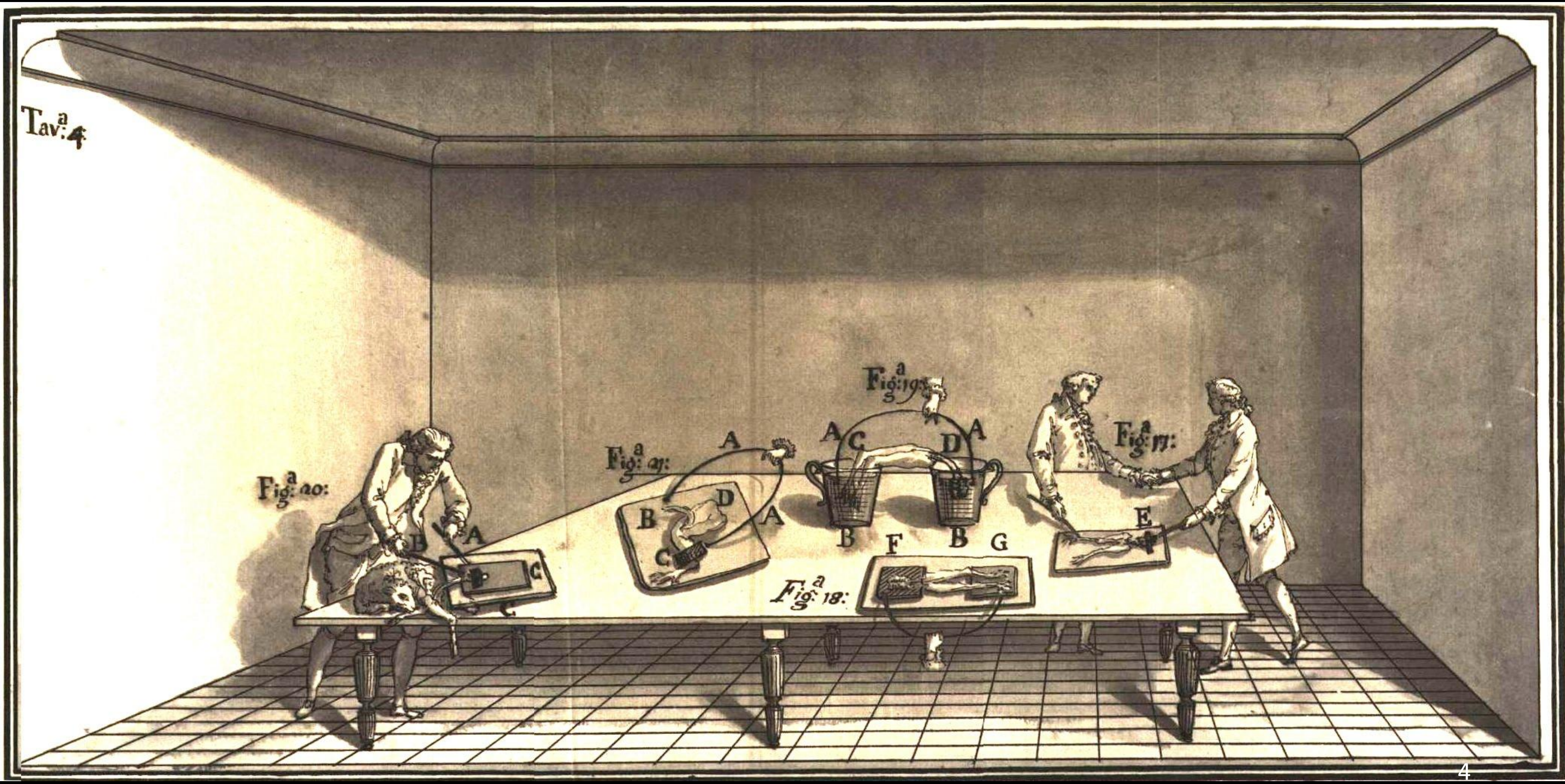
- Forty years of magnetoencephalography
  - the origins
  - early years
- MEG as a functional imaging technique
  - physiological basis
  - modelling
- Basics of instrumentation
  - detectors
  - large scale systems
  - hybrid systems
- Multimodal integration with fMRI
  - respective advantages and limitations
- MEG contribution to basic and clinical neuroscience
  - source identification
  - hierarchic organization (picture naming)
- Functional connectivity

Outline

- Forty years of magnetoencephalography
  - the origins
  - early years
- MEG as a functional imaging technique
  - physiological basis
  - modelling
- Basics of instrumentation
  - detectors
  - large scale systems
  - hybrid systems
- Multimodal integration with fMRI
  - respective advantages and limitations
- MEG contribution to basic and clinical neuroscience
  - source identification
  - hierarchic organization (picture naming)
- Functional connectivity

Late XVIII century

Luigi Galvani and his experiments on "animal electricity"…….



The origins

- As a consequence of Galvani experiments on animal electricity, also the existence of an *animal magnetism* was hypothesised by F. A. Mesmer, who tried to associate "mysterious" magnetic fields with a deep influence on human behaviour
- Mesmer theories were examined by a committee of scientists - including Benjamin Franklin - nominated by King Louis XVI, and were declared totally absurd. Nevertheless, mesmerism continued to widespread across Europe and to be practiced in the so-called Mesmer "saloons" for at least other 50 years
- Only when the deep connections existing between electric currents and magnetic fields were fully understood mesmerism definitively disappeared

The origins (II)

At the beginning of the XX century electric signals associated with cardiac and cerebral activity were recorded for the first time:

- electrocardiogram (ECG) - (Einthoven, 1903)
- electroencephalogram (EEG) - (Berger, 1929)

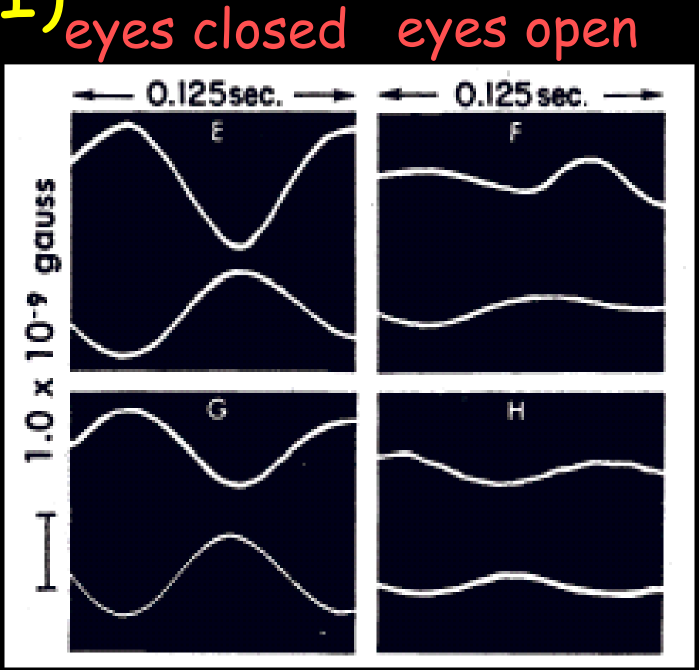
However, it was only at the beginning of the sixties that the magnetic signals associated with cardiac currents were first detected, namely
the magnetocardiogram (MCG)
(resistive coils, Baule&McFee, 1963)

Finally, a MCG was measured for the first time using the rfSQUID developed by Jim Zimmerman by Edelsack, Cohen, and Zimmerman at MIT (Cohen et al., Science 1970)

The origins (III)

The magnetic field due to electric currents flowing inside the brain was first recorded in 1968 by David Cohen using resistive coils

Cohen, Science 1968



In 1971 David Cohen measured the spontaneous alpha rhythm using a SQUID, and the expression magnetoencephalography (MEG) was introduced

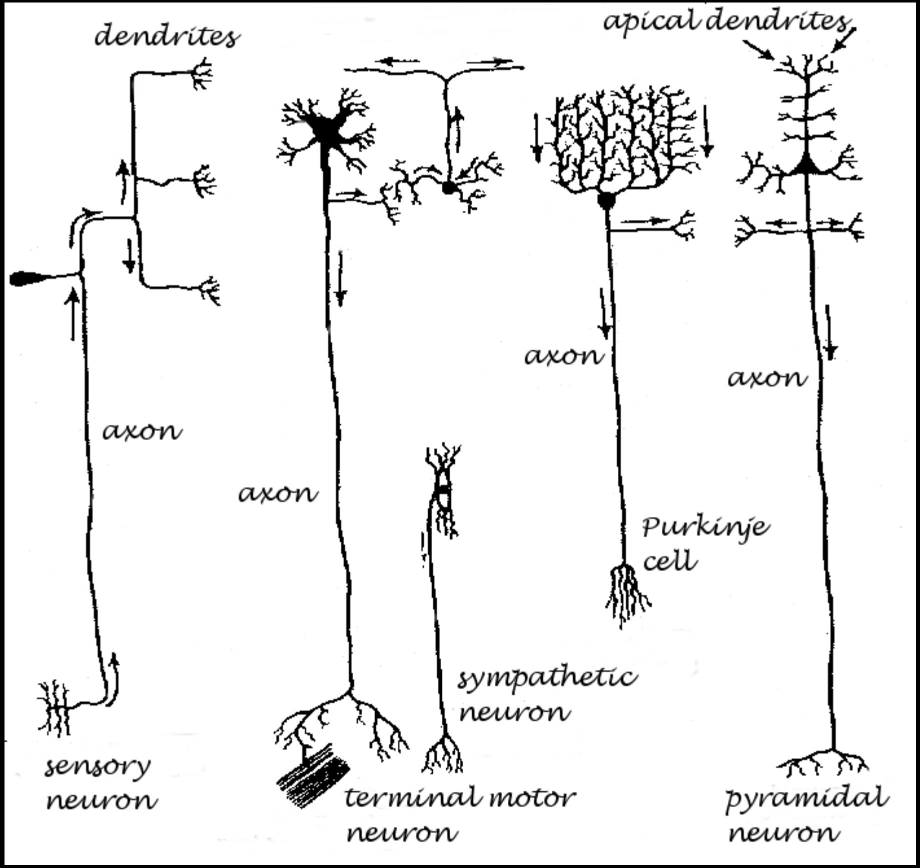
Cohen, Science 1972

Outline

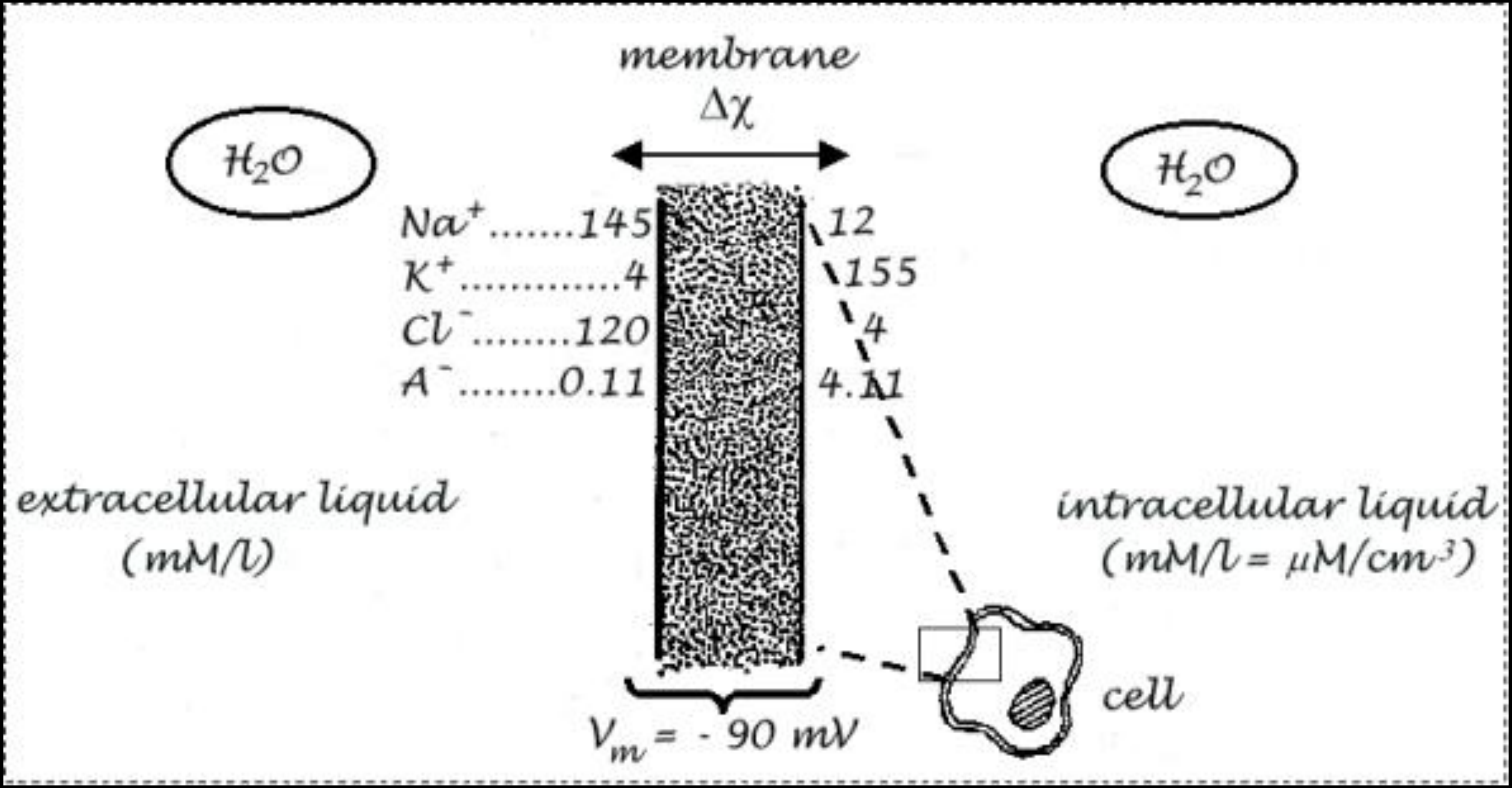
- Forty years of magnetoencephalography
  - the origins
  - early years
- MEG as a functional imaging technique
  - physiological basis
  - modelling
- Basics of instrumentation
  - detectors
  - large scale systems
  - hybrid systems
- Multimodal integration with fMRI
  - respective advantages and limitations
- MEG contribution to basic and clinical neuroscience
  - source identification
  - hierarchic organization (picture naming)
- Functional connectivity

Magnetoencephalography: Physiological basis

MEG measures magnetic fields generated by the bioelectric activity of excitable cells in the brain (neurons)



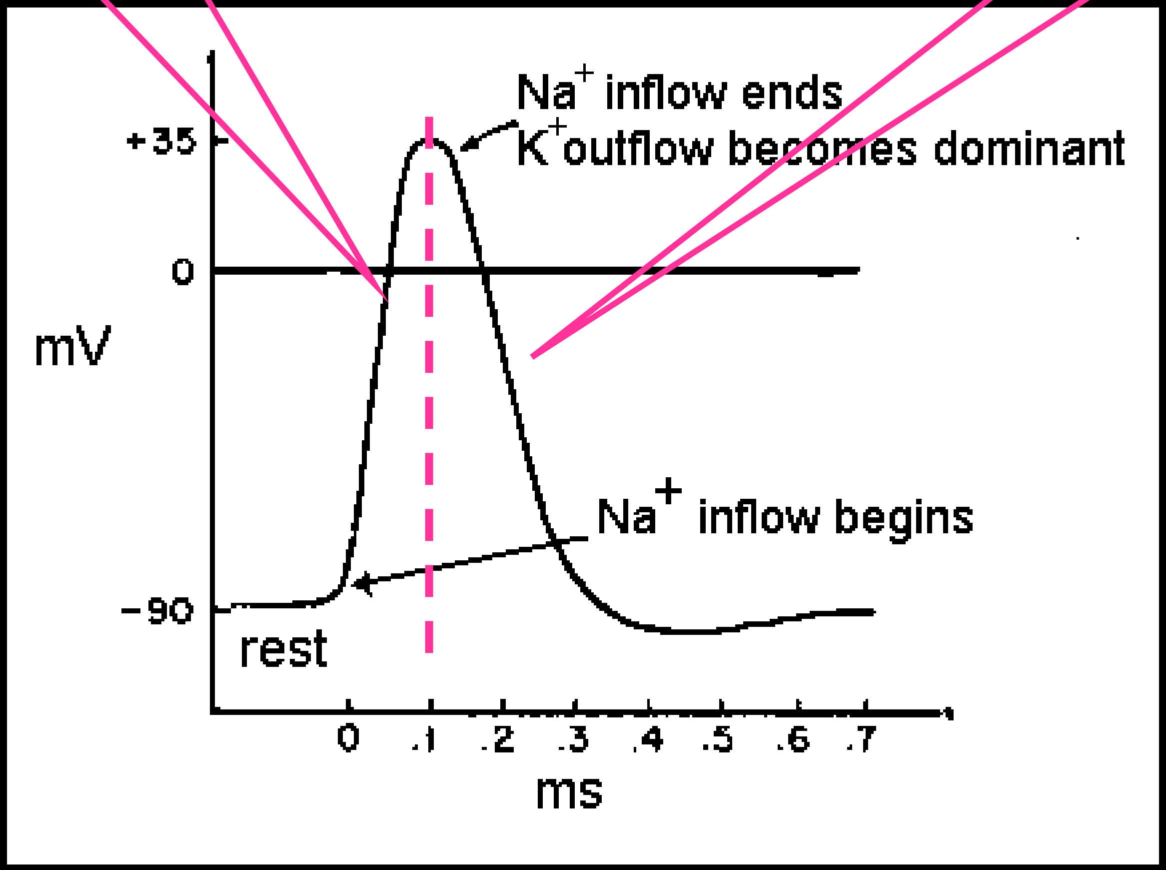
The neuron membrane



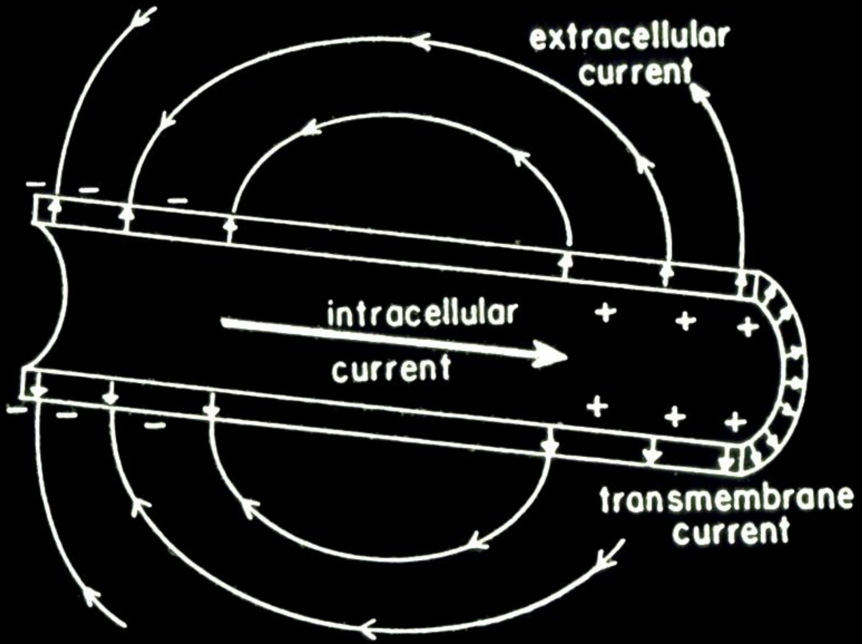
Action potential

membrane
depolarisation

membrane
ripolarisation

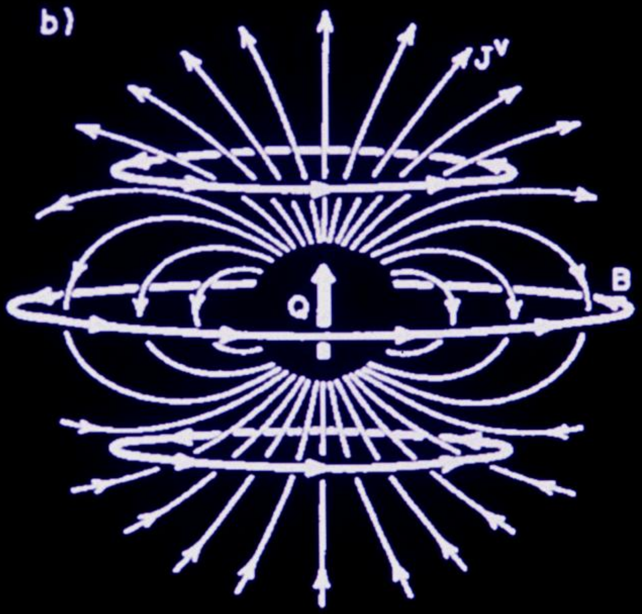


Schematic of the current pattern associated with membrane depolarisation



- The synaptic activity induces an intra-cellular current toward the nucleus of the neuron
- At the same time a return current flows in the extra-cellular space (charge conservation)

The simplest model: the current dipole



$Q = iL$

Units: Am (ampère meter)

To complete the modeling we need to put the current dipole inside a conducting medium with appropriate geometry

Field of a single neuron

- In an an infinite, homogeneously conducting medium

$$\mathbf{B}_{\infty}(\mathbf{r}) = \frac{\mu_0}{4\pi}\,\mathbf{Q}\,\frac{(\mathbf{r}-\mathbf{r}_0)}{|\mathbf{r}-\mathbf{r}_0|^3} \qquad \text{(Biot-Savart law)}$$

- Typical value for an apical dendrite of a pyramidal cell:
- $Q \sim 2 \times 10^{-13}$ A.m

(Murakami and Okada, J Physiol 2006)

- In the most favorable position $B = \mu_0 Q / 4\pi R^2$ where R is the distance from the dipole, with $Q = 2 \times 10^{-13}$ A.m and

  $R = 4$ cm, a typical sensor distance, $B \sim 1 \times 10^{-17}$ T = 0.01 fT
- In comparison the typical amplitude of evoked magnetic fields is about 200-400 fT

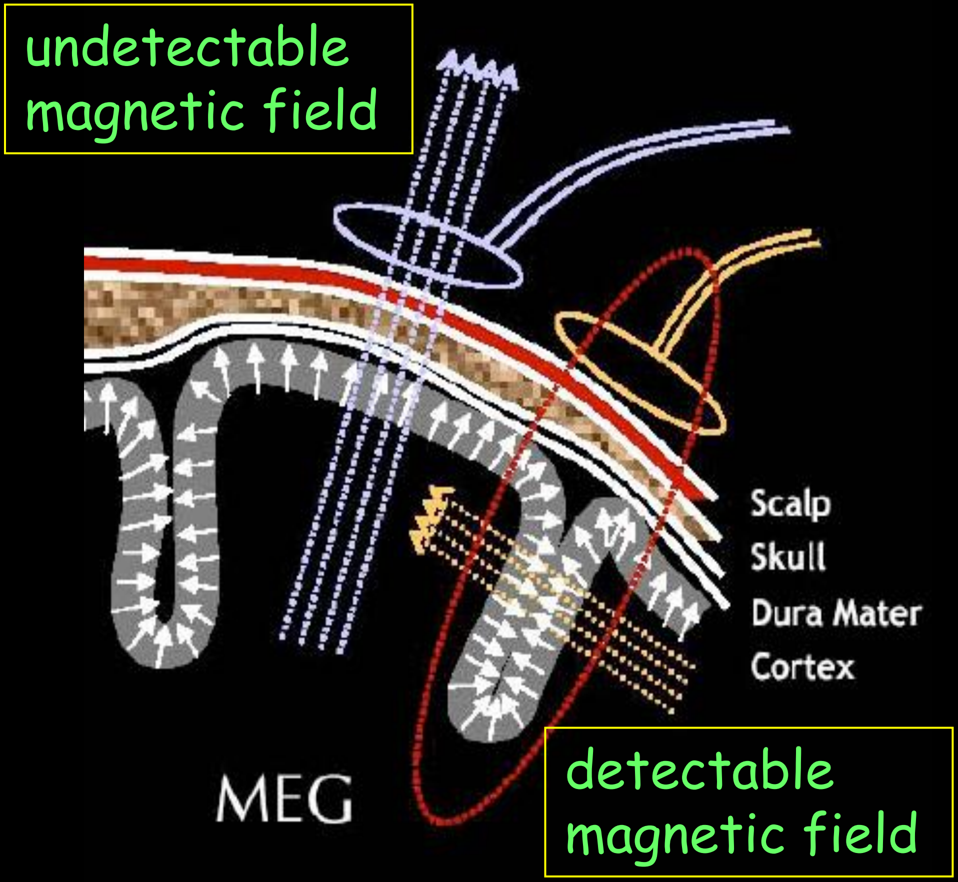
MEG monitors the coherent activity of a large population of neurons (about 50,000) and this is possible since the apical dendrites of pyramidal neurons are mostly aligned parallel to the cerebral cortex and often feature a synchronous activation. In this sense we speak of an Equivalent Current Dipole (ECD) that accounts for the measured magnetic field distribution

Current dipole in a homogeneously conducting sphere

- The simplest and most convenient approach

but

- tends to oversimplify the problem in some regions of the head
- a dipole radially oriented with respect to the sphere produces no measurable field
- distributed current models associated with a linear inverse estimation inside a realistic head model provide more accurate results


undetectable magnetic field

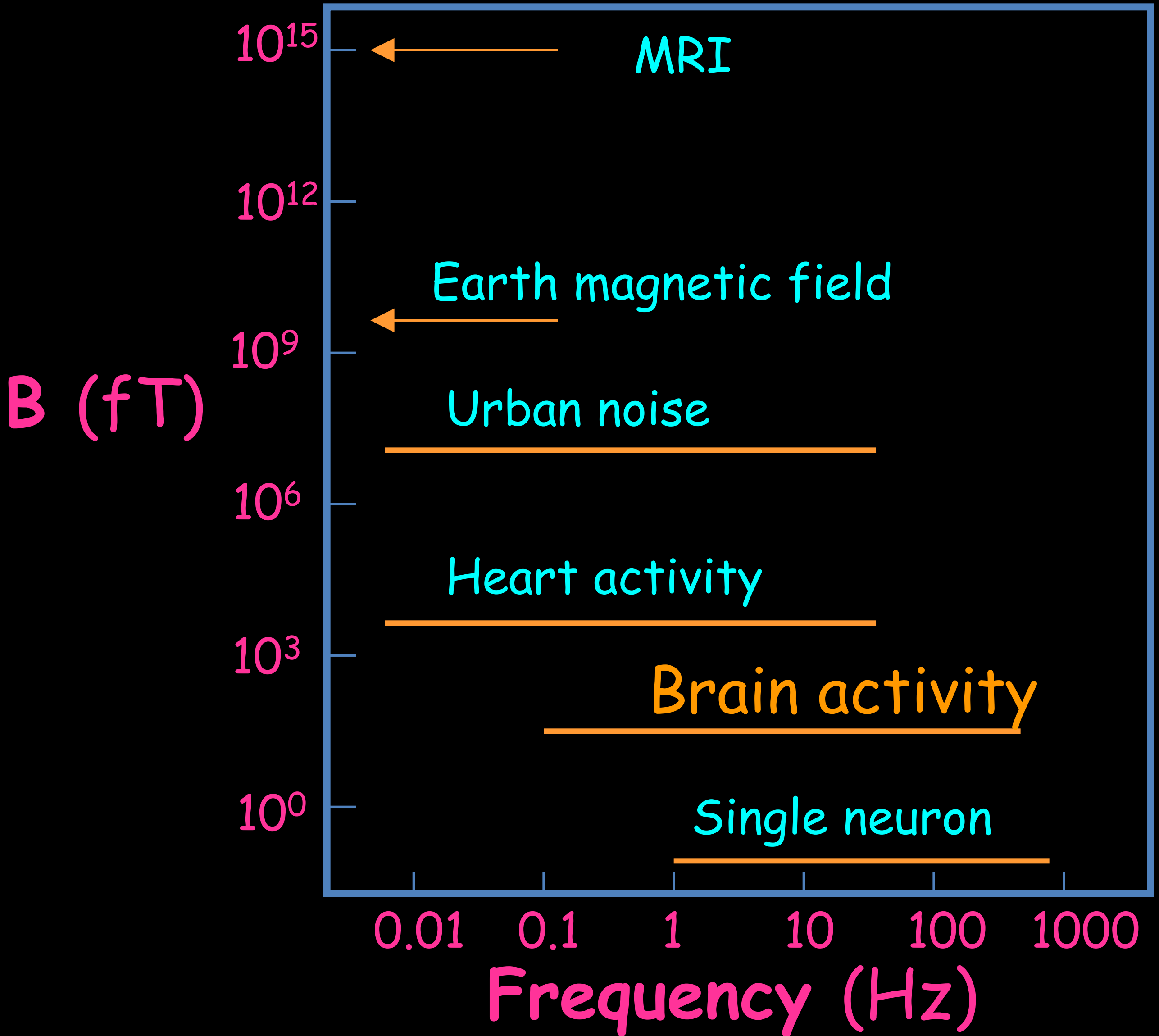
detectable magnetic field

Outline

- Forty years of magnetoencephalography
  - the origins
  - early years
- MEG as a functional imaging technique
  - physiological basis
  - modelling
- Basics of instrumentation
  - detectors
  - large scale systems
  - hybrid systems
- Multimodal integration with fMRI
  - respective advantages and limitations
- MEG contribution to basic and clinical neuroscience
  - source identification
  - hierarchic organization (picture naming)
- Functional connectivity

IEEE/CSC & ESAS SUPERCONDUCTIVITY NEWS FORUM (global edition), No. 27, January 2014;
Plenary presentation 2PL02 at EUCAS 2013

Intensity of biomagnetic fields

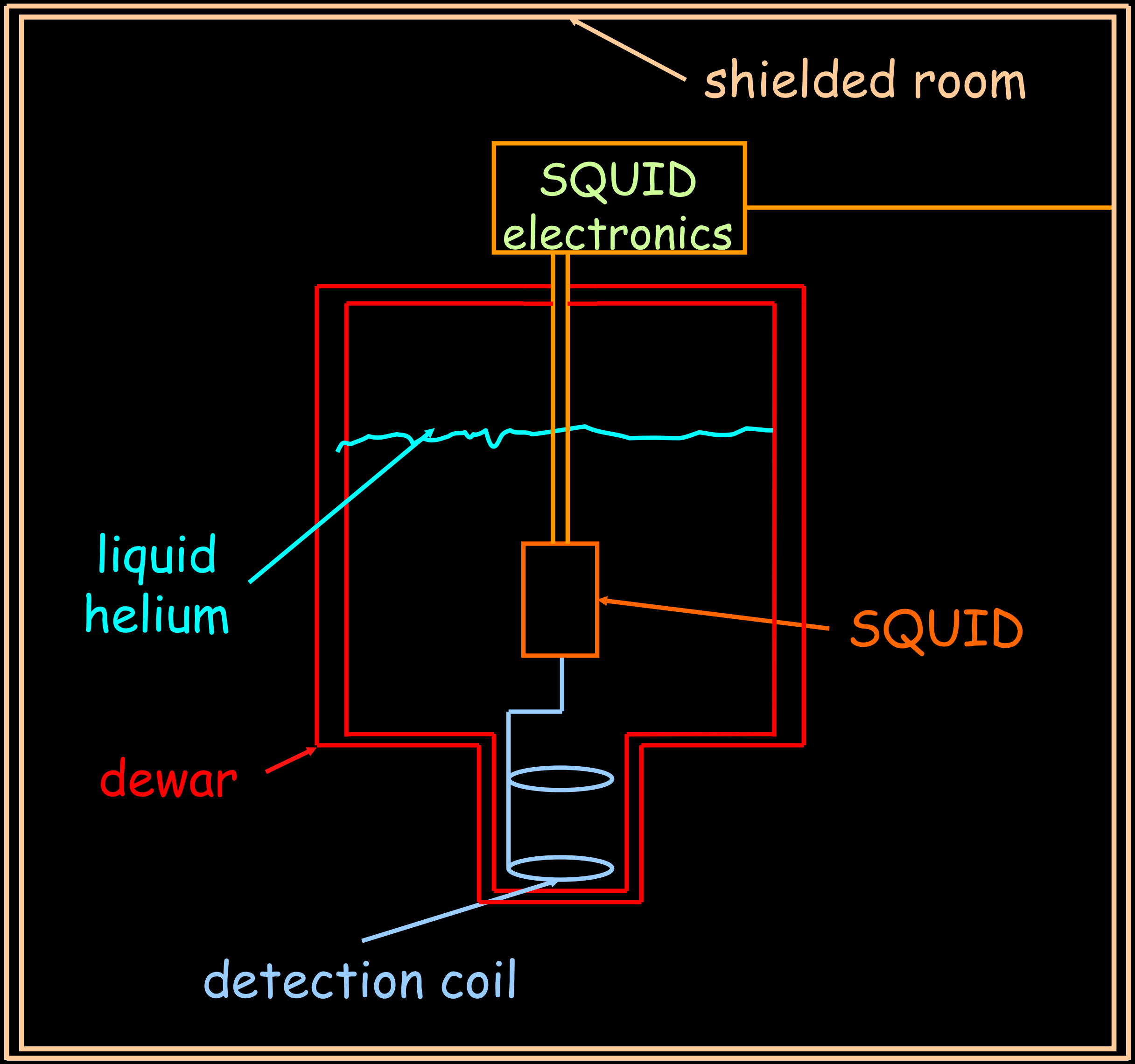


Instrumentation challenges

Very weak signals in a noisy background

- Extremely sensitive detectors: Superconducting Quantum Interference Devices (SQUIDs) – operated at 4.2 K - to be integrated in multichannel systems
  - sensitivity of about 10^{-15} T/√Hz
    - Thermal noise of the subject ~ 10^{-16} T/√Hz
    - Brain noise ~ 10^{-14} T/√Hz (DC-1000 Hz)
  - Low crosstalk ~ 1%
- Cryogenics
  - Cryostat noise ~ 10^{-15} T/√Hz
- Noise reduction techniques (hardware and software gradiometers, magnetically shielded rooms)
  - It must be able to operate in unfriendly environments (hospital).

A simple instrument for MEG measurements



Dewars for biomagnetism

The dewar used in biomagnetic instruments must satisfy severe requirements:

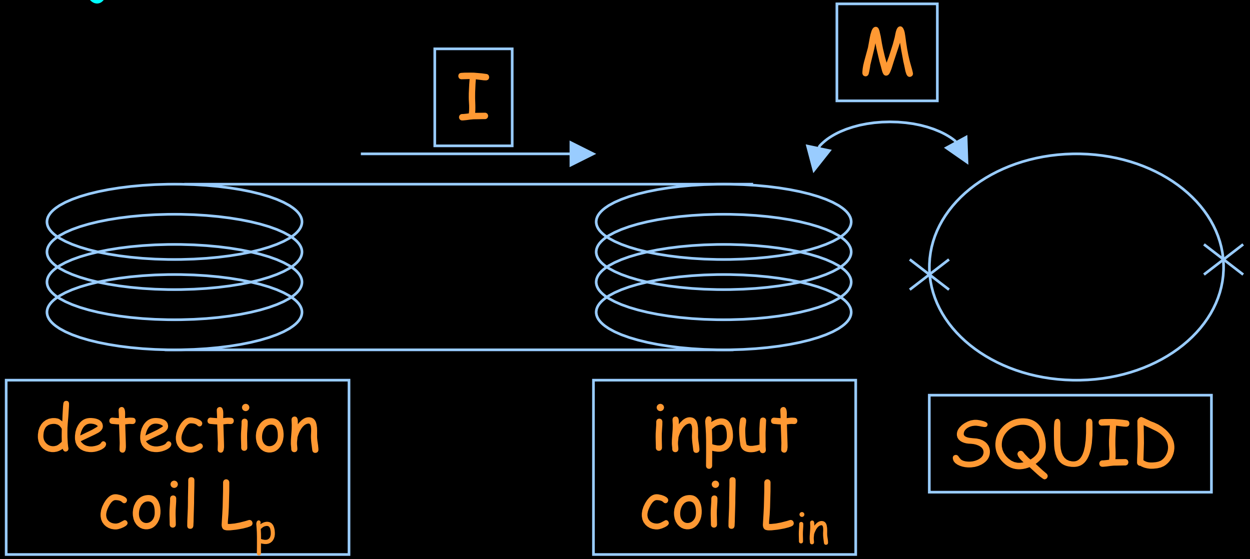
- the distance of the detection coil from the head should be as small as possible (less than 20 mm)
- the noise of the dewar should be smaller than the noise of the sensors (less than 1 fT/Hz$^{\frac{1}{2}}$)
- liquid helium reservoir should last as long as possible

Usually fiberglass is used to build the dewar. Fiberglass has excellent magnetic properties but does not provide any shield against radiation, therefore radiation shielding and 50-100 layers of mylar are added. The total helium capacity is typically 50-80 liters.

Mechanical cryocoolers are cheap, safe, and require moderate maintenance, but the magnetic noise is still too high

Detection coils

Since the SQUID inductance should be as small as possible, the SQUID loop cannot be used to detect the biomagnetic field. Additional use of an external coil of suitable shape is useful to reject environmental noise.

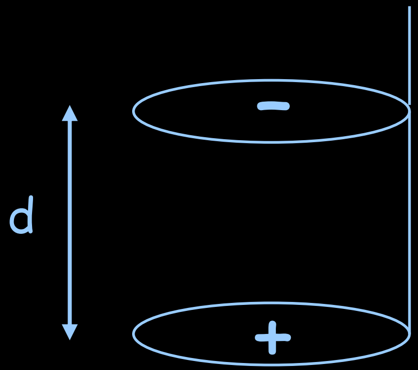


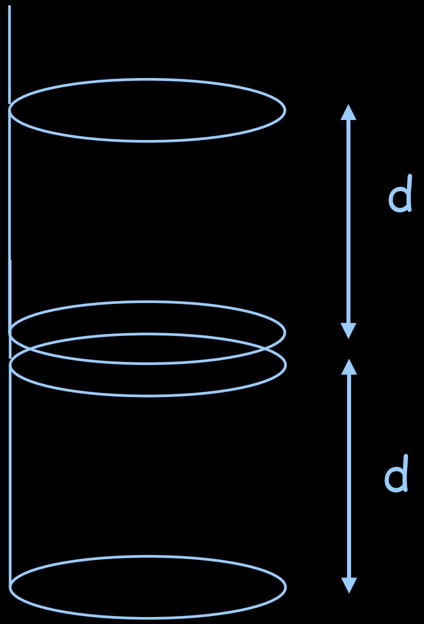
The flux transformer is a superconducting loop and "transfers" the flux to the SQUID loop.
To maximize flux transfer (once the SQUID parameters are fixed) L_p must satisfy the matching condition: $L_p \approx L_{in}$

Gradiometers

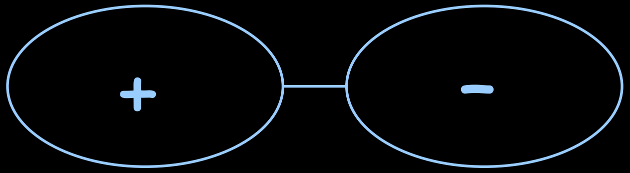
The use of an external coil of suitable shape is useful to reject environmental noise. In first order gradiometers the difference between the field at the two coils is measured.

Axial gradiometer
$\partial B_z/\partial z$

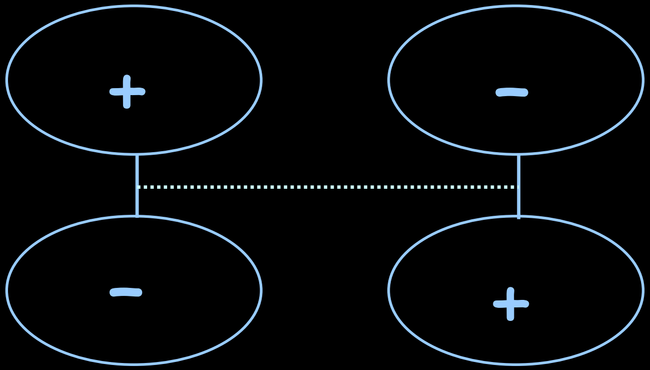




Axial gradiometer
$\partial^2 B_z/\partial z^2$



Planar gradiometer
$\partial B_z/\partial x$

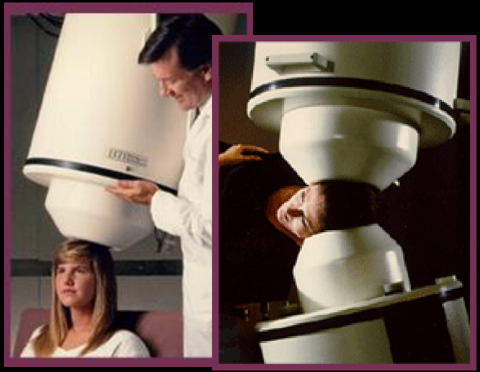


Planar gradiometer $\partial^2 B_z/\partial x \partial y$

Some history on MEG systems

In the eighties

- the single channel…

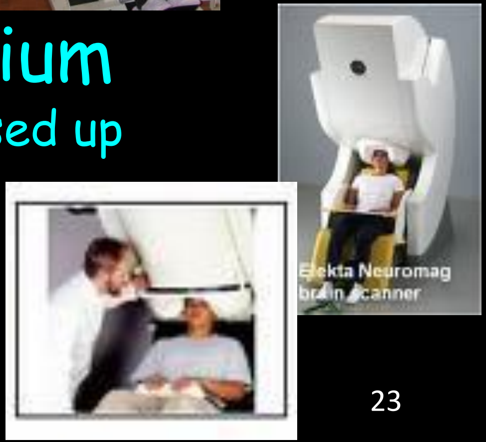


In the nineties

- from 37 to 150 channels…

In the current millennium

- the channel number is increased up to some hundreds



MEG systems

Presently there are almost 200 MEG systems installed worldwide. Several are operating inside clinical environments

- Whole head coverage
- 100÷300 detection points consisting of one to three channels
- Stable and reliable LTcS SQUIDs
- Easy and friendly operation
- Easy set-up and maintenance
- Cost-effective design
- Seated and/or supine measurement position

High Tc SQUID sensors

Advantages

- Simpler biomedical instrumentation
- Simpler cryostat
- Cost reduction

Challenges

- Robustness and reliability
- Performances homogeneity
- Feasibility for integration in large arrays
- Field noise (white and low frequency)
- Performances still insufficient for brain studies but adequate for cardiac studies

High-Tc superconducting quantum interference device recordings of spontaneous brain activity: Towards high-Tc magnetoencephalography.
F. Öisjöen1, J. F. Schneiderman2,3, G. A. Figueras1, M. L. Chukharkin1,4, A. Kalabukhov1,5, A. Hedström6, M. Elam2,3,6, and D. Winkler1
Appl. Phys. Lett. 100, 132601 (2012)

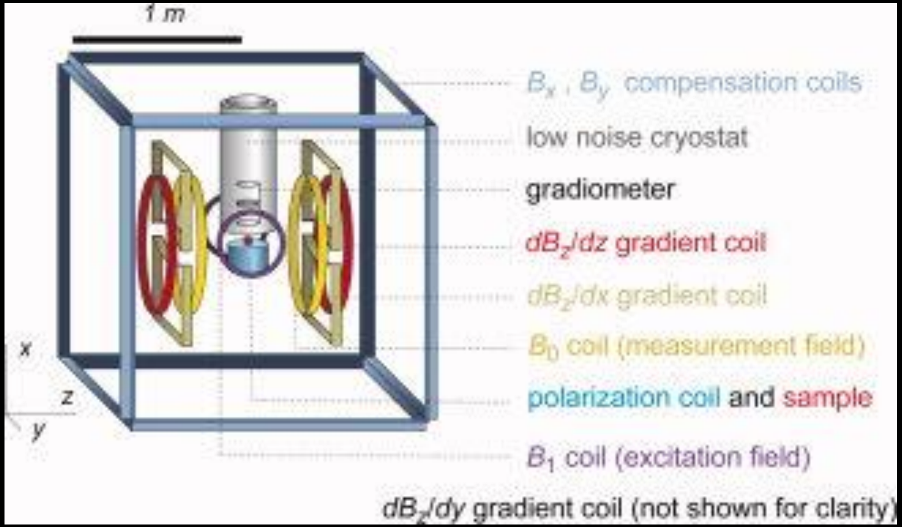
Other SQUID-based biomedical instrumentation for brain studies

- ultra-low field MRI
- hybrid systems

Ultra-low field MRI (J. Clarke)

- SQUID-based sensors measure the magnetic field directly, as opposed to its time derivative: then the signal-to-noise ratio (SNR) of the measurement for untuned sensors is independent of the Larmor frequency and thus the field strength after the prepolarization.
- MRI can be performed using a prepolarization pulse in the 10-100mT range, and an operating field B_0 in the 10-100 μT range.
- A significant advantage of such a low B_0 is that T_1 differentiates between normal and cancer tissues for $B_0 < 1$ mT (magnetic biopsy)

T1 maps to disentangle non healthy from healthy tissue

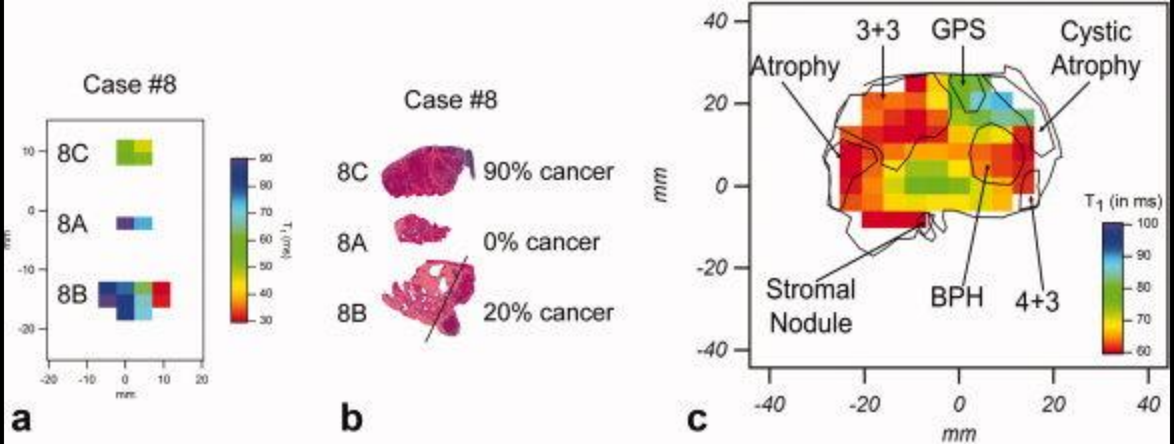


B_0=132 μT=B_{ev}
B_p=10 mT
Spin echo sequence
T= 4 °C

Histologic examination

ULF ex-vivo T_1 map (3-4 mm resolution)

Average T_1
54 ms
78 ms
70 ms



IEEE/CSC & ESAS SUPERCONDUCTIVITY NEWS FORUM (global edition), No. 27, January 2014;
Plenary presentation 2PL02 at EUCAS 2013

Busch et al., MRM 2012

Contents lists available at SciVerse ScienceDirect

Journal of Magnetic Resonance

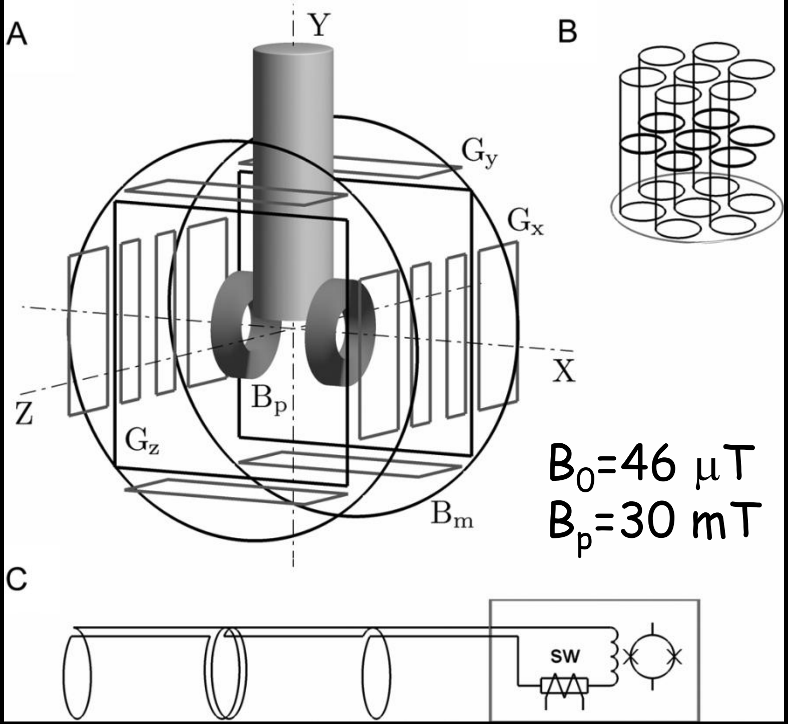
journal homepage: www.elsevier.com/locate/jmr

Perspectives in Magnetic Resonance

SQUID-detected ultra-low field MRI ☆

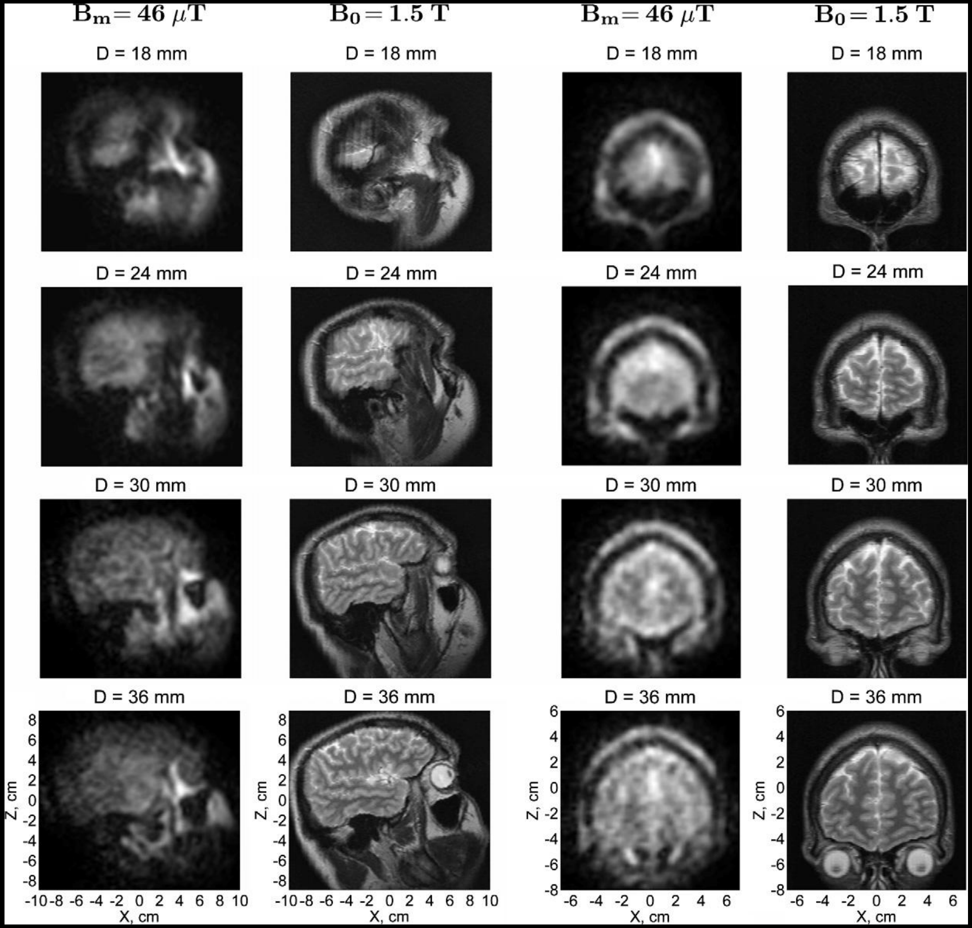
Michelle Espy *, Andrei Matlashov, Petr Volegov

Los Alamos National Laboratory, Los Alamos, NM 87545, United States



B_0=46 μT

B_p=30 mT



EU-FP7 MEGMRI Project (2009-2012)

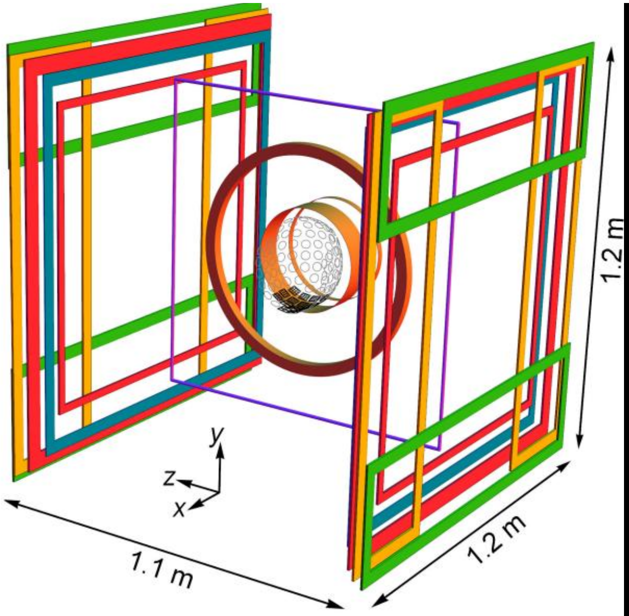
Mission of the project: development of a hybrid system for simultaneous ultra-low field MRI and MEG recordings in humans

1. Helsinki University of Technology - Finland (coordinator)
2. Valtion teknillinen tutkimuskeskus (VTT)- Finland
3. Hospital District of Helsinki and Uusimaa -Finland
4. Elekta AB - Finland
5. Aivon Oy - Finland
6. Commissariat à l'energie atomique - France
7. CEDRAT Technologies SA – France
8. Chalmers Tekniska Hoegskola Aktiebolag – Sweden
9. PTB – Germany
10. University of Parma – Italy
11. ITAB – Unversity of Chieti - Italy
12. Associazione Fatebenefratelli per la Ricerca (AFaR)- Italy
13. Imaging Technology Abruzzo – Italy

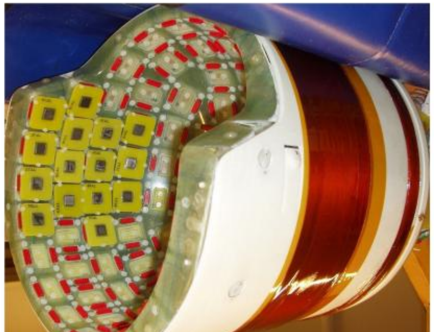
Hybrid Ultra-Low-Field MRI and Magnetoencephalography System Based on a Commercial Whole-Head Neuromagnetometer

Magnetic Resonance in Medicine 000:000–000 (2012)

Panu T. Vesanen,[1*] Jaakko O. Nieminen,[1] Koos C. J. Zevenhoven,[1] Juhani Dabek,[1] Lauri T. Parkkonen,[1,2] Andrey V. Zhdanov,[1,3] Juho Luomahaara,[4,5] Juha Hassel,[4] Jari Penttilä,[5] Juha Simola,[2] Antti I. Ahonen,[2] Jyrki P. Mäkelä,[3] and Risto J. Ilmoniemi[1]



C

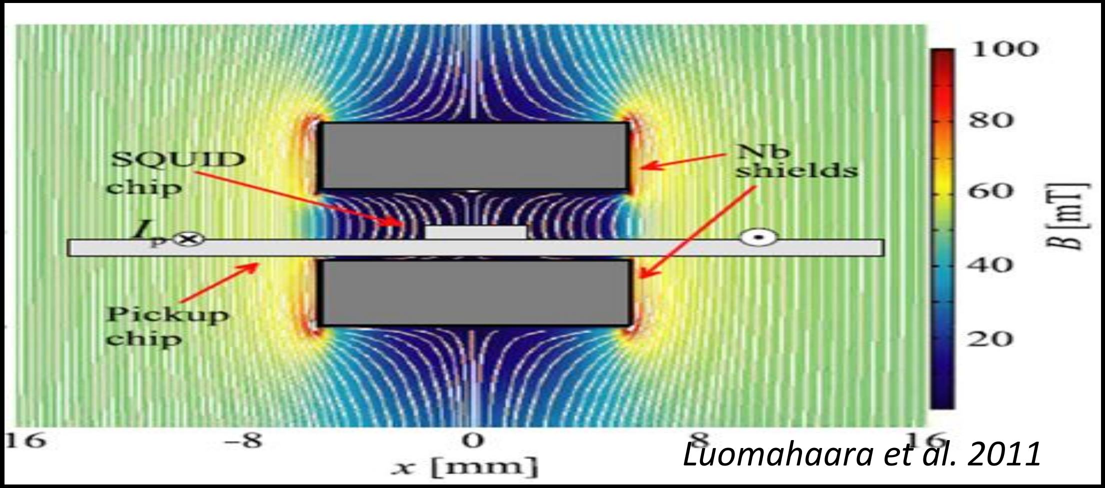


SQUID Sensors for MEG-MRI

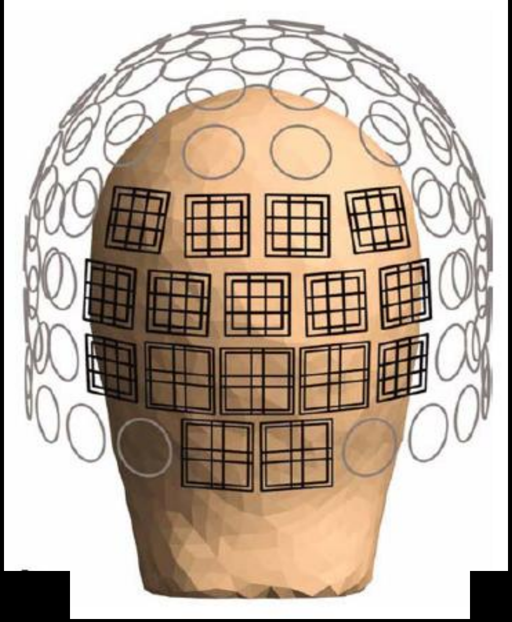
(courtesy of Risto Ilmoniemi, Aalto University)

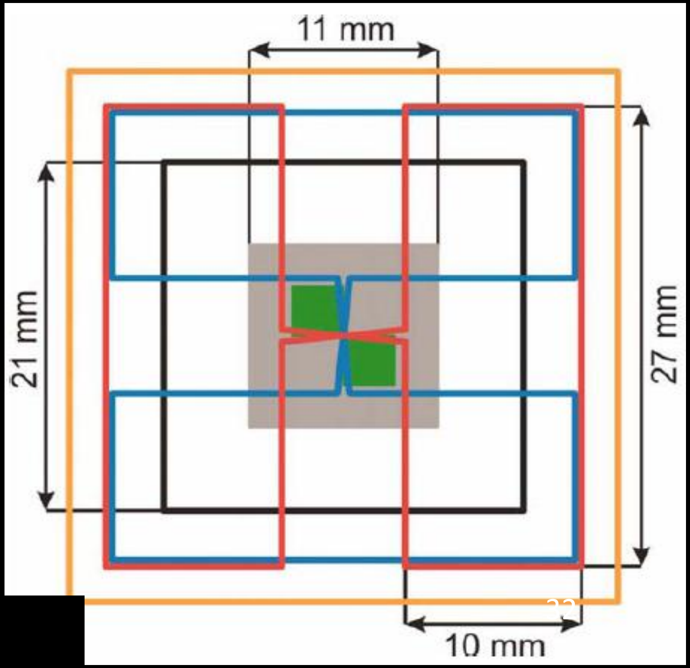
- Nb-shielded LTc SQUID with thin-film and Pb-wire pick-up loops (B_0=50μT)
- Flux dams (Josephson junctions) in series with the pick-up
- Recovery time ~15 ms from 22 mT
- Thin-film sensor noise
  4 fT/Hz$^{1/2}$; 3 fT/cm/Hz$^{1/2}$
- Pb sensor noise
  2 fT/Hz$^{1/2}$; 1 fT/cm/Hz$^{1/2}$
- Dewar noise
  3 fT/Hz$^{1/2}$; 2 fT/cm/Hz$^{1/2}$

@ 0.1–3 kHz



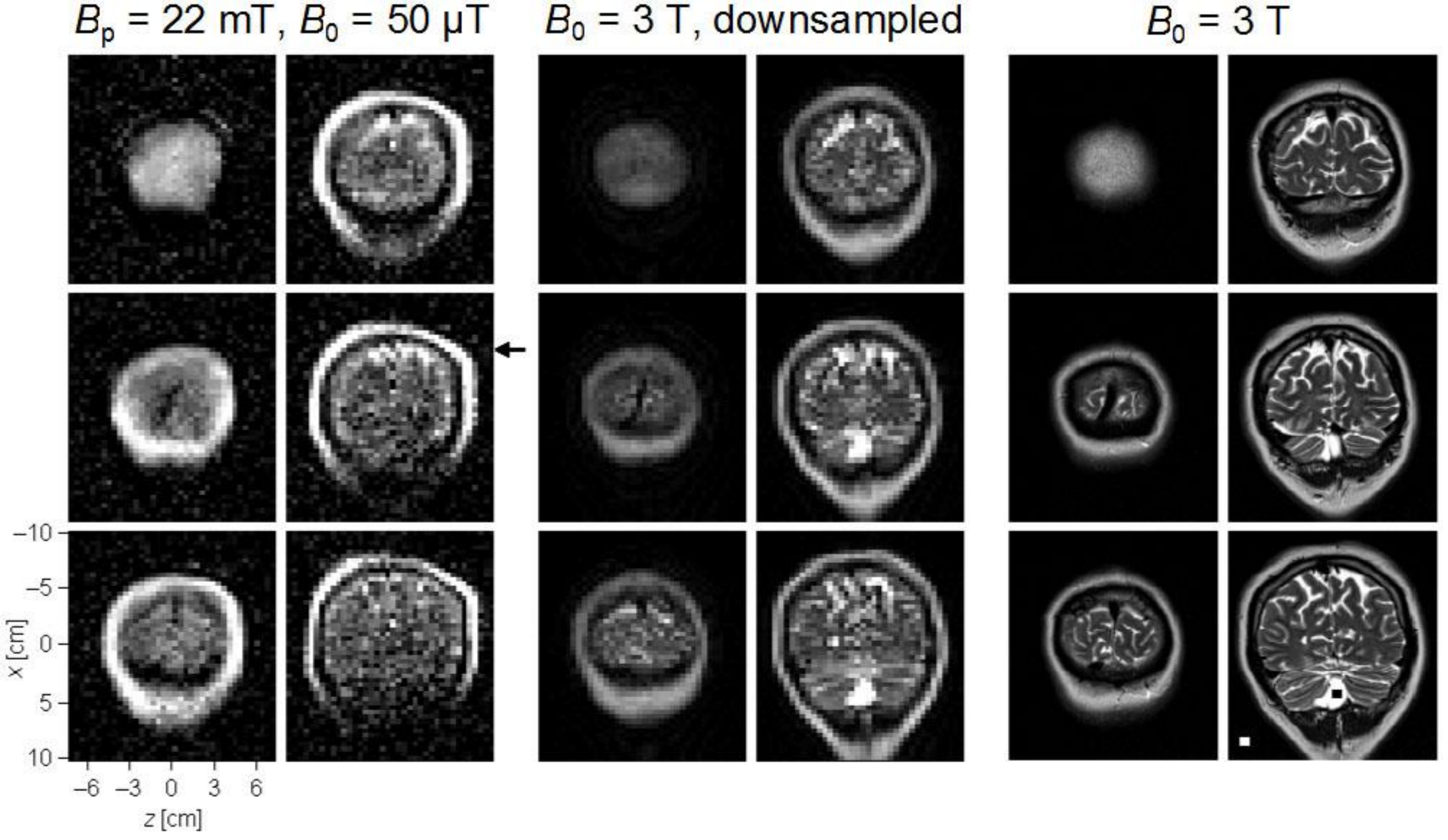
Luomahaara et al. 2011





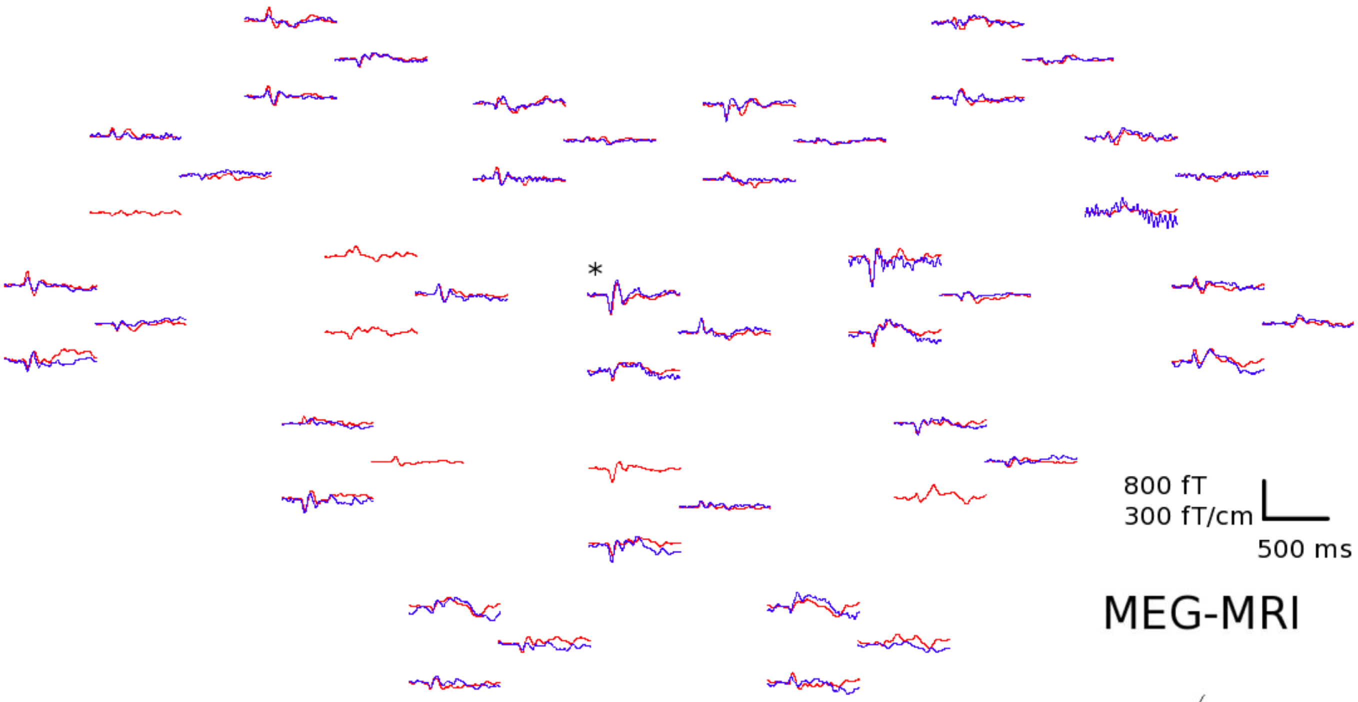
MRI Prototype vs. Commercial 3-tesla System

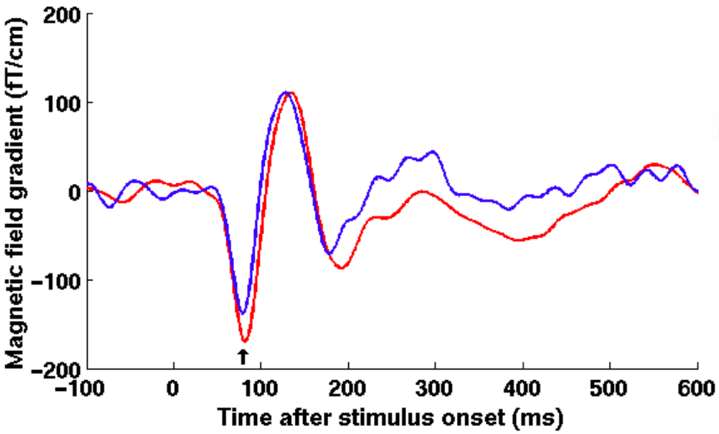
(courtesy of Risto Ilmoniemi, Aalto University)



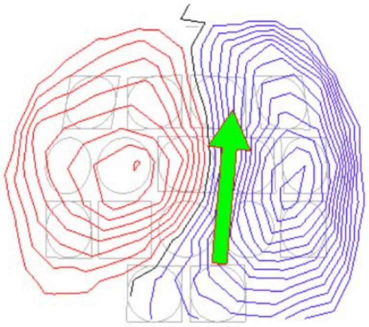
Vesanen et al. 2012

MEG signals obtained with the prototype

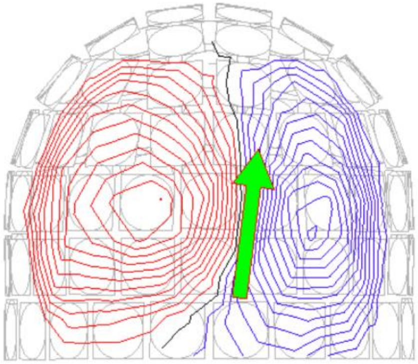




MEG-MRI

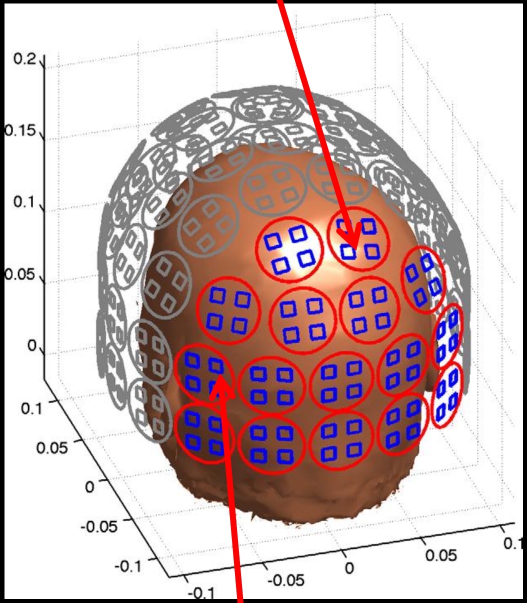


Commercial MEG

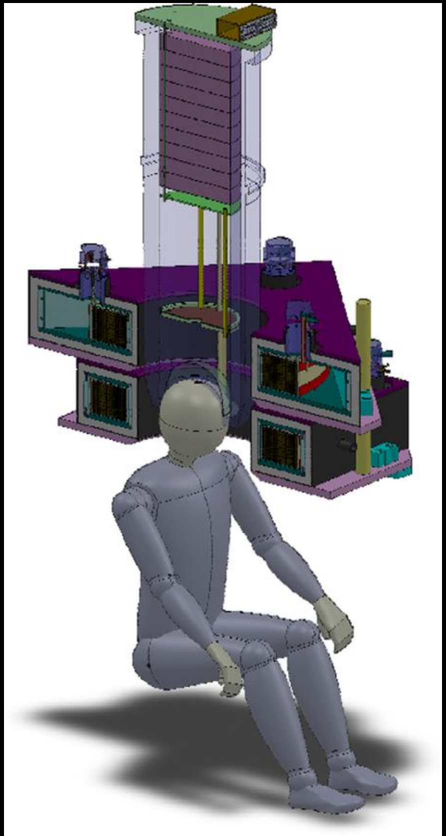


Design of MEG/ULF MRI system at LANL

MRI pick-up coils
(diameter~ 40 mm)



SQUID pick-up coils (side ~ 8 mm)



Other future developments in the field expected by the Korean Center of Excellence KRISS

IEEE/CSC & ESAS SUPERCONDUCTIVITY NEWS FORUM (global edition), No. 27, January 2014;
Plenary presentation 2PL02 at EUCAS 2013

Outline

- Forty years of magnetoencephalography
  - the origins
  - early years
- MEG as a functional imaging technique
  - physiological basis
  - modelling
- Basics of instrumentation
  - detectors
  - large scale systems
  - hybrid systems
- Multimodal integration with fMRI
  - respective advantages and limitations
- MEG contribution to basic and clinical neuroscience
  - source identification
  - hierarchic organization (picture naming)
- Functional connectivity

fMRI - MEG relationship

fMRI	MEG
Generated by increase in HB oxygenation with brain activation	Generated by post-synaptic currents in activated neurons
Functional images are directly related to structural images	Functional images are not directly related to structural images
No source model required	Imaging depends on source and head models - inverse problem
High spatial resolution (but depends on vascularization)	Low spatial resolution (related to source type)
Low time resolution (limited by hemodynamic response)	High time resolution (better than 1 ms)
Resolution independent of source depth (but for susceptibility artifacts in some areas)	Poor resolution for deep sources

Outline

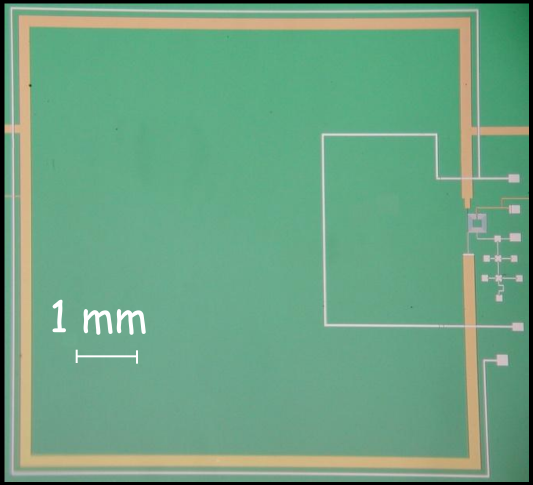
- Forty years of magnetoencephalography
  - the origins
  - early years
- MEG as a functional imaging technique
  - physiological basis
  - modelling
- Basics of instrumentation
  - detectors
  - large scale systems
  - hybrid systems
- Multimodal integration with fMRI
  - respective advantages and limitations
- MEG contribution to basic and clinical neuroscience
  - source identification
  - hierarchic organization (picture naming)
- Functional connectivity

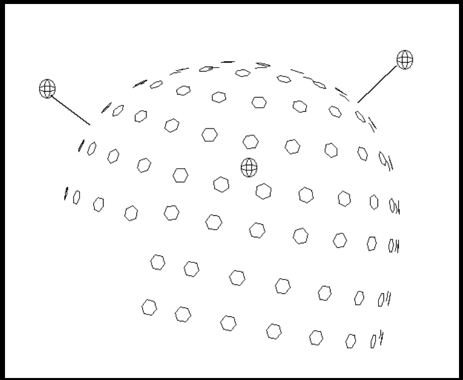
The 165-channel MEG system at ITAB

- 153 measurement channels spaced 3.2 cm on average
- 4 triplets of 3 orthogonal reference channels
- 32 EEG channels
- Somatosensory, visual, acoustic stimulation apparatus

Magnetometers with 8 mm side integrated on the same chip with the SQUID
Noise better than 2 fT/√Hz

System assembled in collaboration of ATB, Pescara
SQUIDs fabricated at Istituto di Cibernetica – CNR, Pozzuoli (NA)

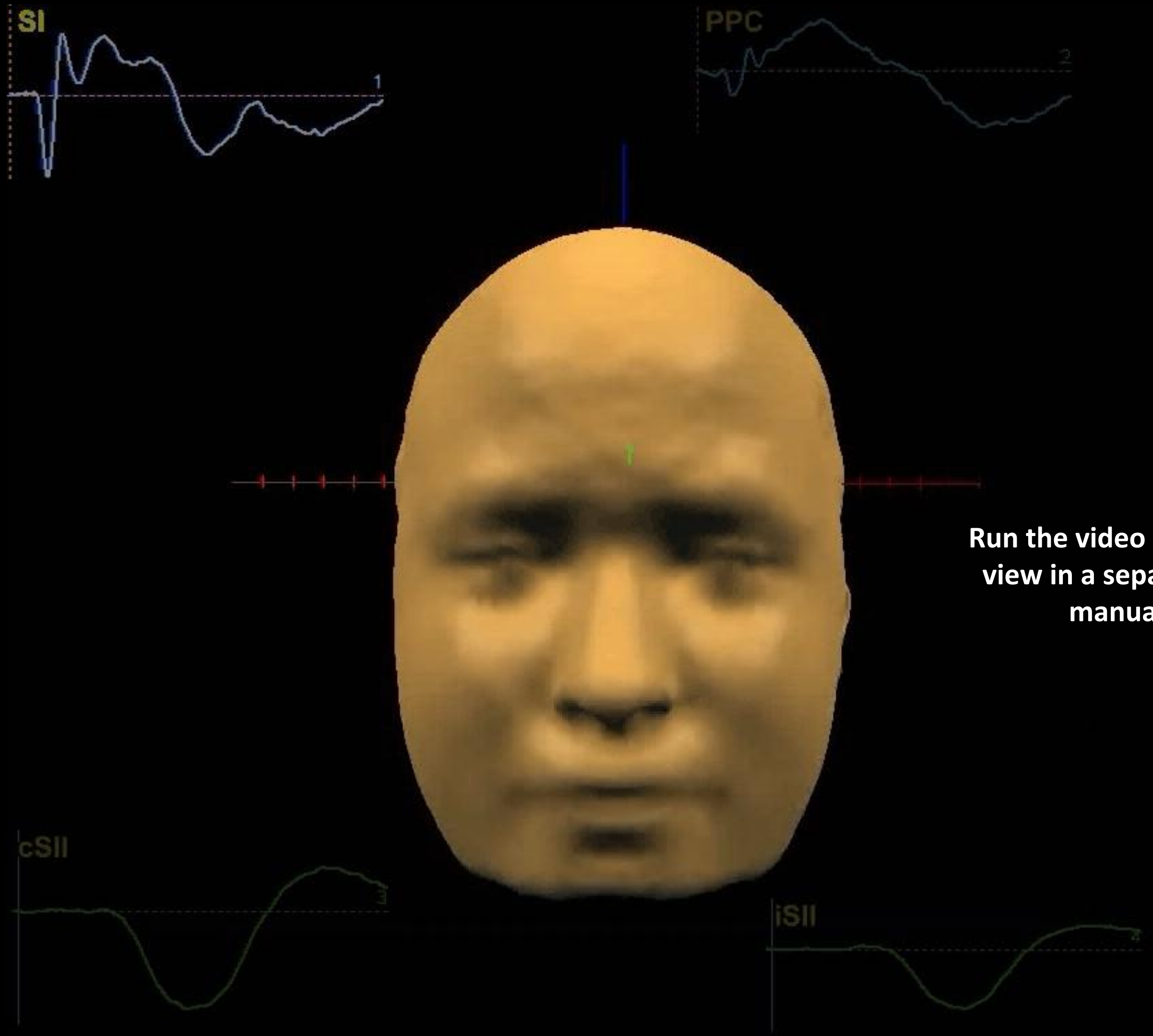




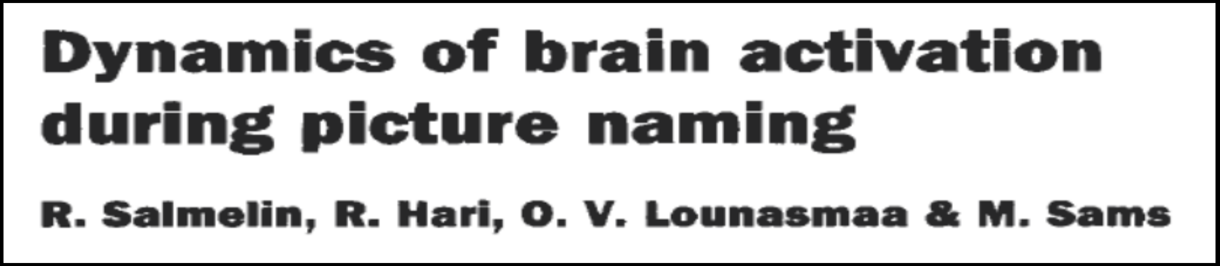
Granata et al., IEEE Trans. Appl. Super., 2001

MEG source localization

right median nerve stimulation



Run the video MEG_fMRI from here, view in a separate window, return manually to slide 41.

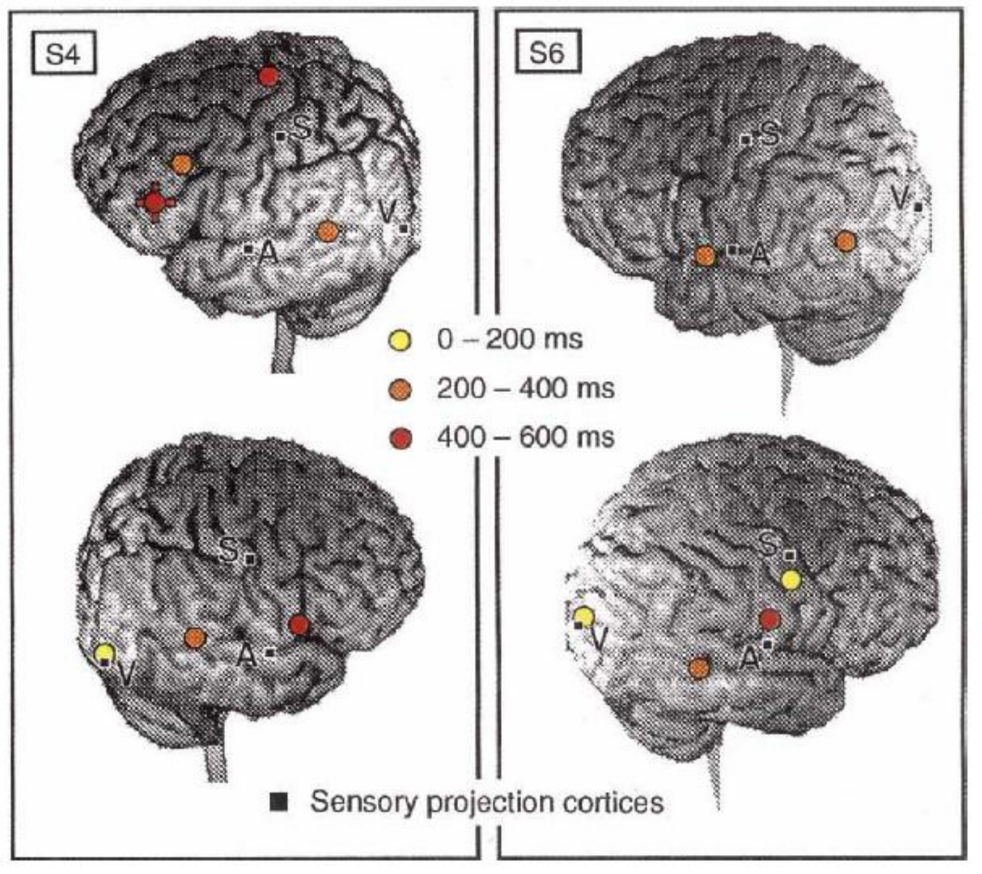


Dynamics of brain activation during picture naming

R. Salmelin, R. Hari, O. V. Lounasmaa & M. Sams

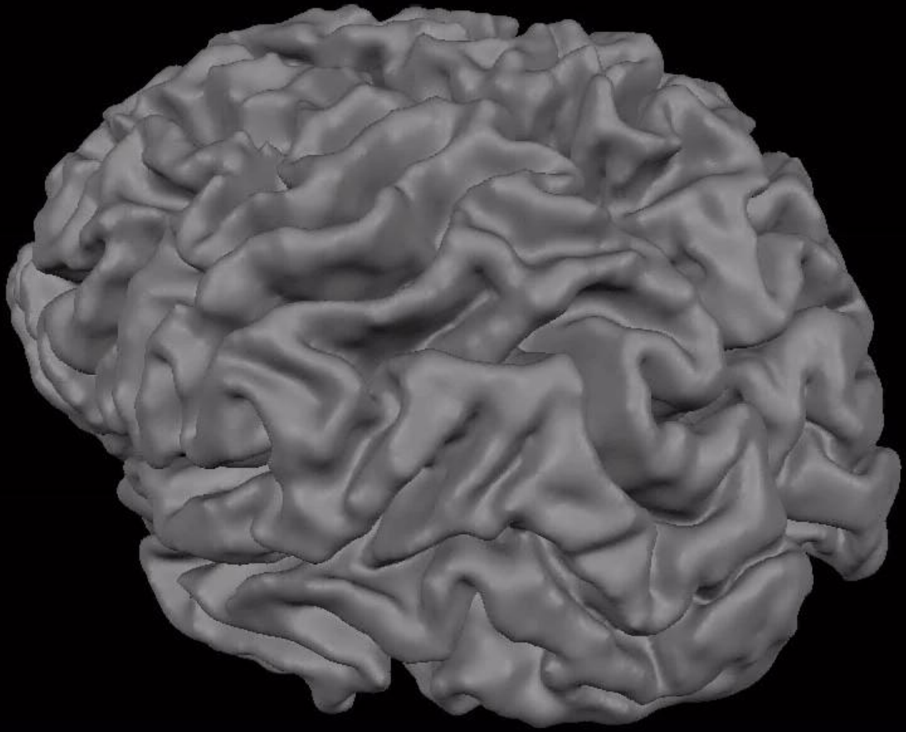
Nature, 1994

- First example of multiple source imaging followed in time: measurement performed by means of a whole-head MEG system
- Line drawings of everyday objects (vase, book, cat, etc.) were presented randomly for 100 ms every 5s; the subjects were asked either to ignore or to name the object seen

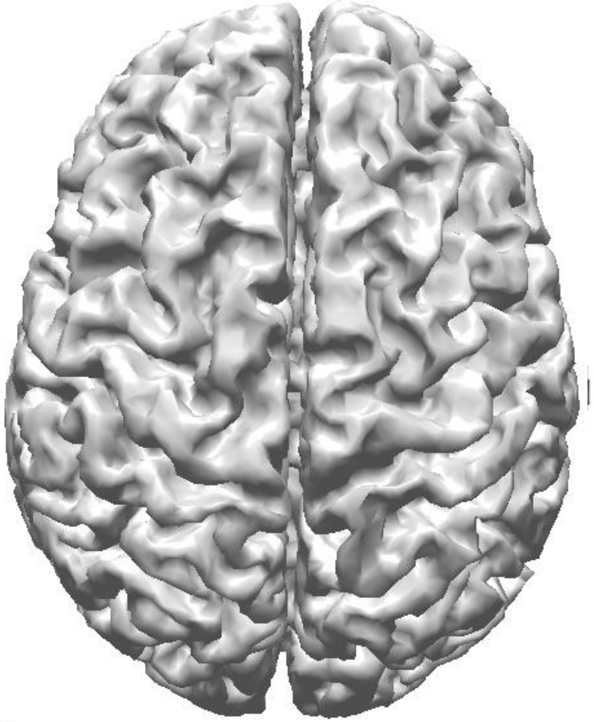


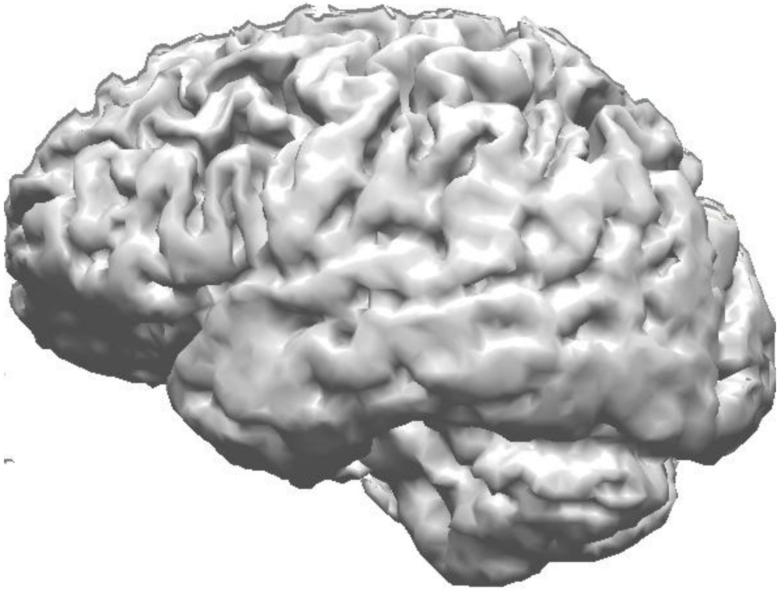
Word reading and naming (by fMRI)

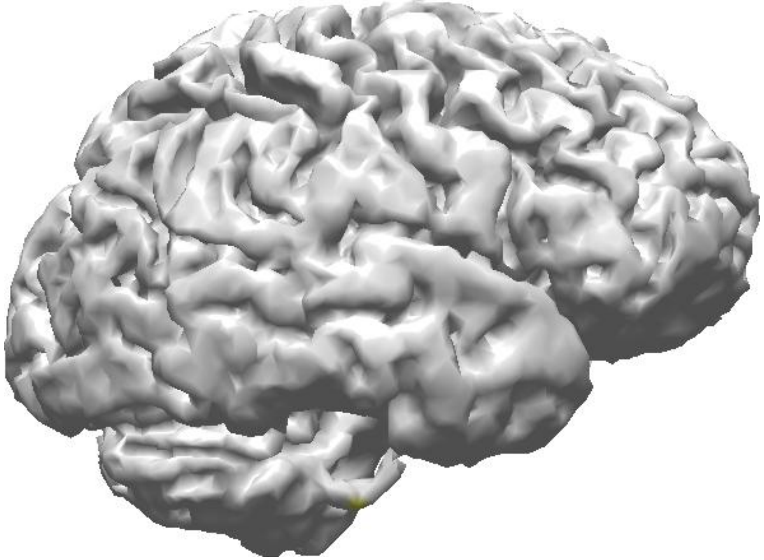
book



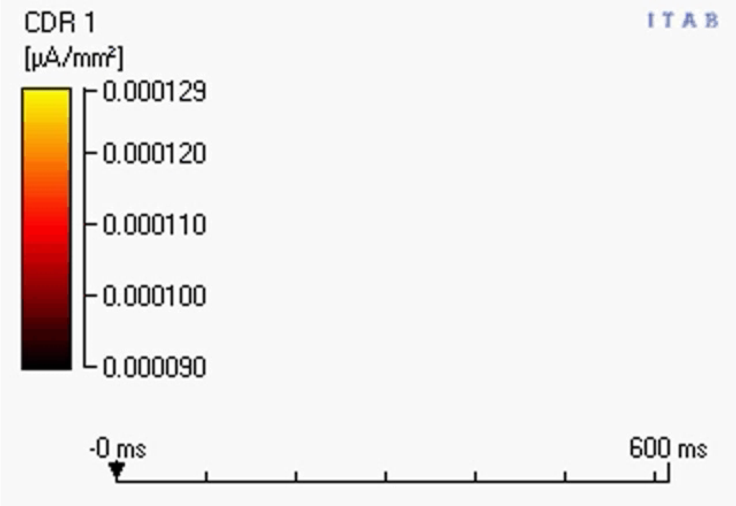
- fMRI activations for picture naming
- sub-cortical fibers

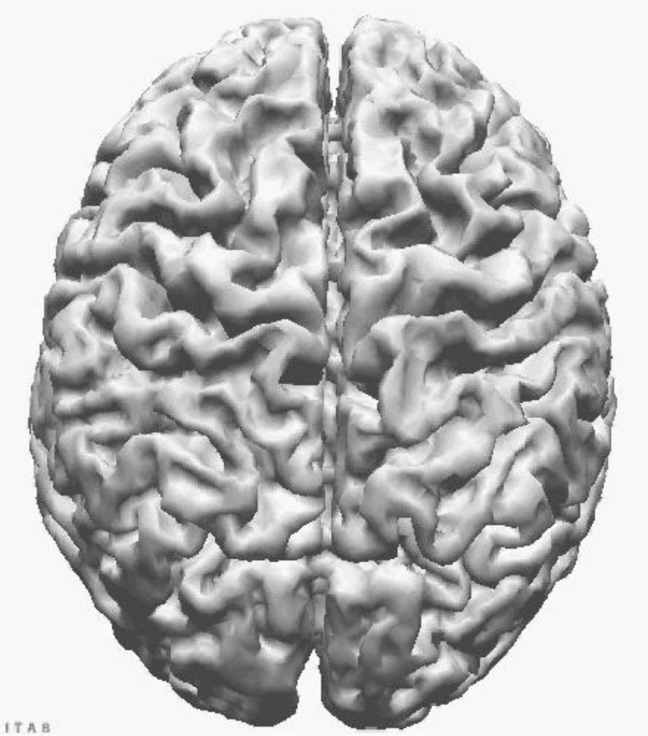


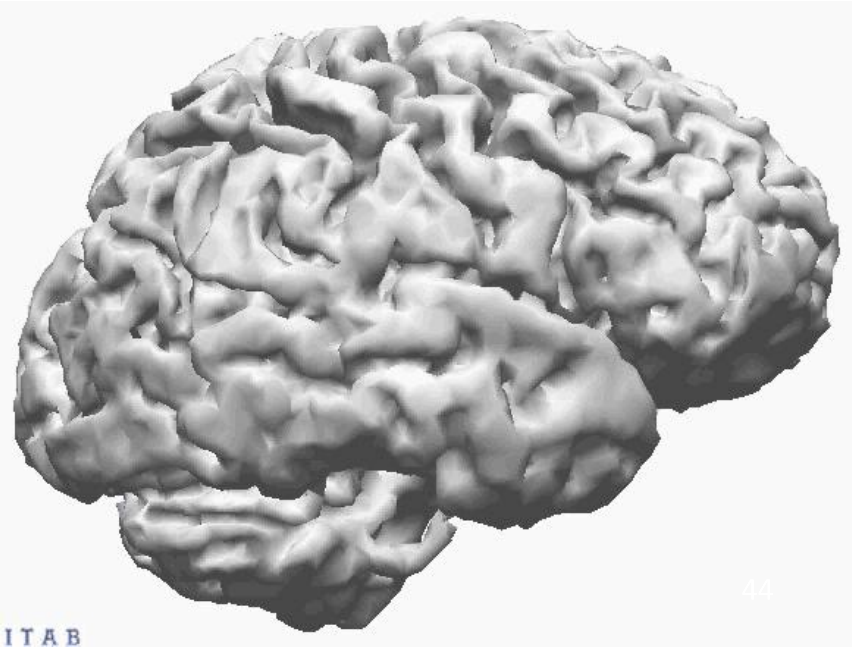




Picture naming - MEG



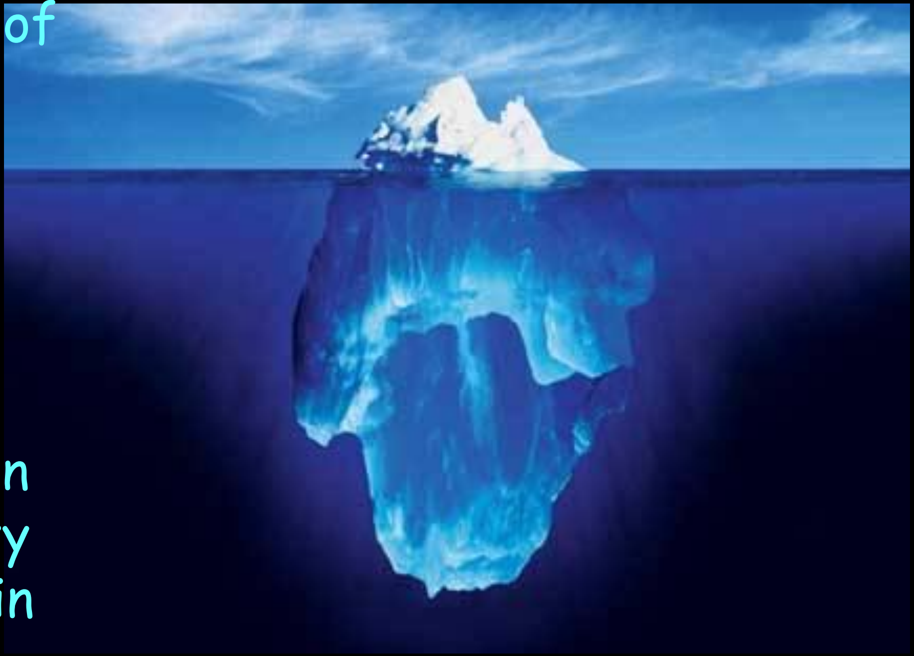




Outline

- Forty years of magnetoencephalography
  - the origins
  - early years
- MEG as a functional imaging technique
  - physiological basis
  - modelling
- Basics of instrumentation
  - detectors
  - large scale systems
  - hybrid systems
- Multimodal integration with fMRI
  - respective advantages and limitations
- MEG contribution to basic and clinical neuroscience
  - source identification
  - hierarchic organization (picture naming)
- Functional connectivity

The brain "dark energy" and RST



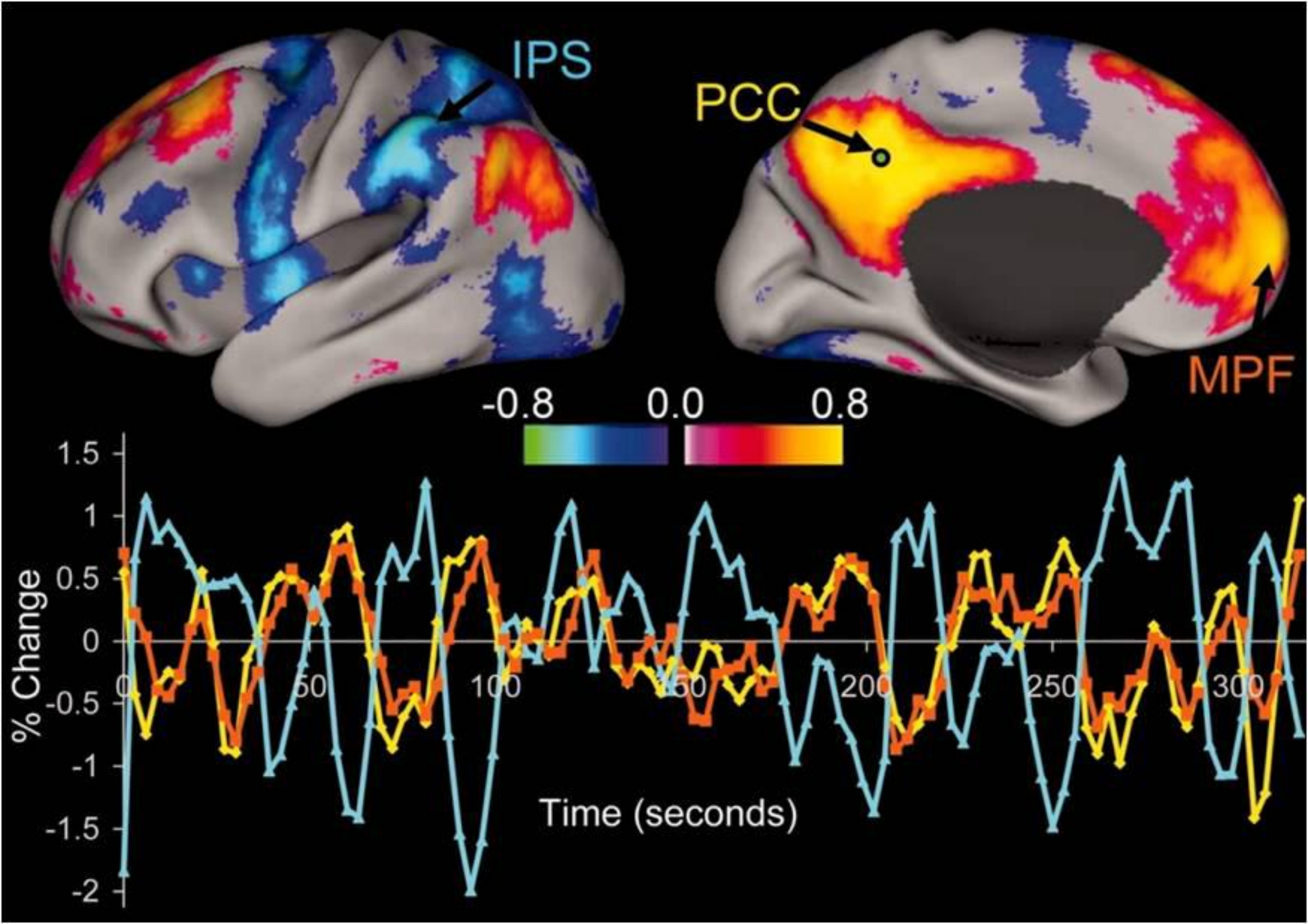
Indeed, task activation, the traditional focus of fMRI, MEG and PET research, is actually only the tip of the iceberg of brain activity. The brain energy consumption is only slightly higher during active tasks than during rest (Raichle & Gusnard 2002, Raichle & Mintun 2006). Task-evoked activity accounts for only an additional 5% to 10% of the brain's energy consumption above the spontaneous level of activity that accounts for 70% to 80% of brain metabolism (Raichle 2010b, Raichle & Mintun 2006) – namely, the α, β, δ, γ rhythms.

The ongoing energy that the brain continuously expends has been coined as the brain "dark energy" because the brain uses most of its energy for ongoing, spontaneous functions that currently are unaccounted for (Raichle 2010a).

Resting State Networks

- By analyzing fMRI data acquired during periods of rest it was observed that the time activity in some voxels was not random, rather seemed to be either positively or negatively correlated with activity in other voxels.
- The time scale of these fluctuations is of the order of several tens of seconds.
- Extending this analysis to the whole brain, this positive/negative correlation was found to involve several cerebral districts, in turn forming different "networks".
- They appeared to be associated to specific functions of the brain (vision, motion, audition, but also attention, memory, etc.).They were active during rest periods and therefore were defined as Resting State Networks"

Resting State Networks



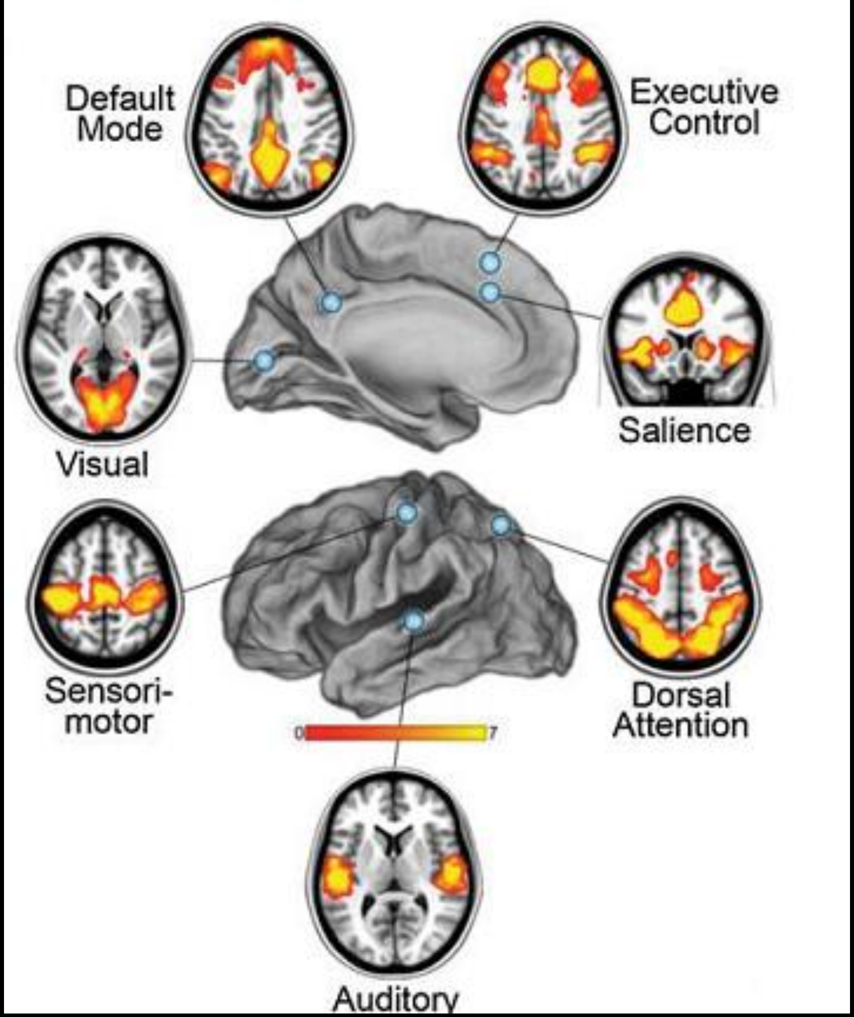
(Fox et al., PNAS 2005)

Brain anatomical and functional Networks

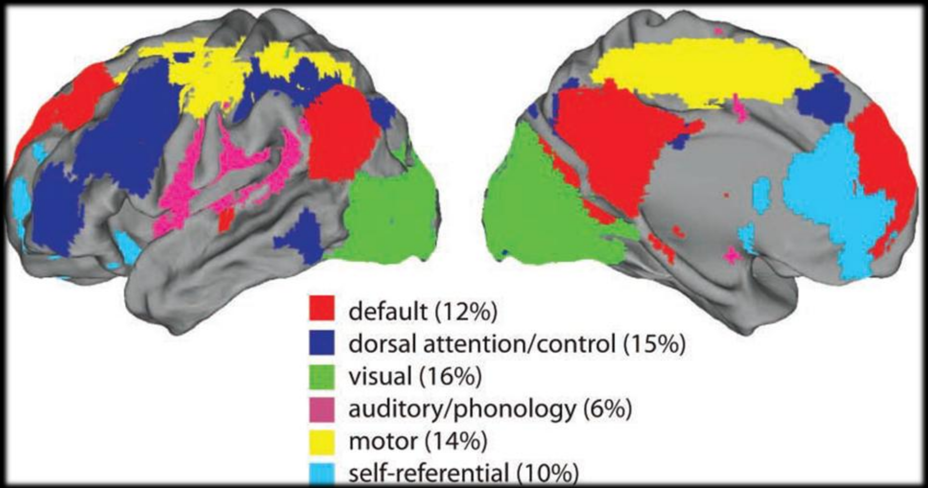
From structure to function

- Anatomical connectivity – underlying structural substrate
- Functional connectivity – modulated by experience and learning during life span

Resting State Networks



Several networks active during rest have been identified with fMRI



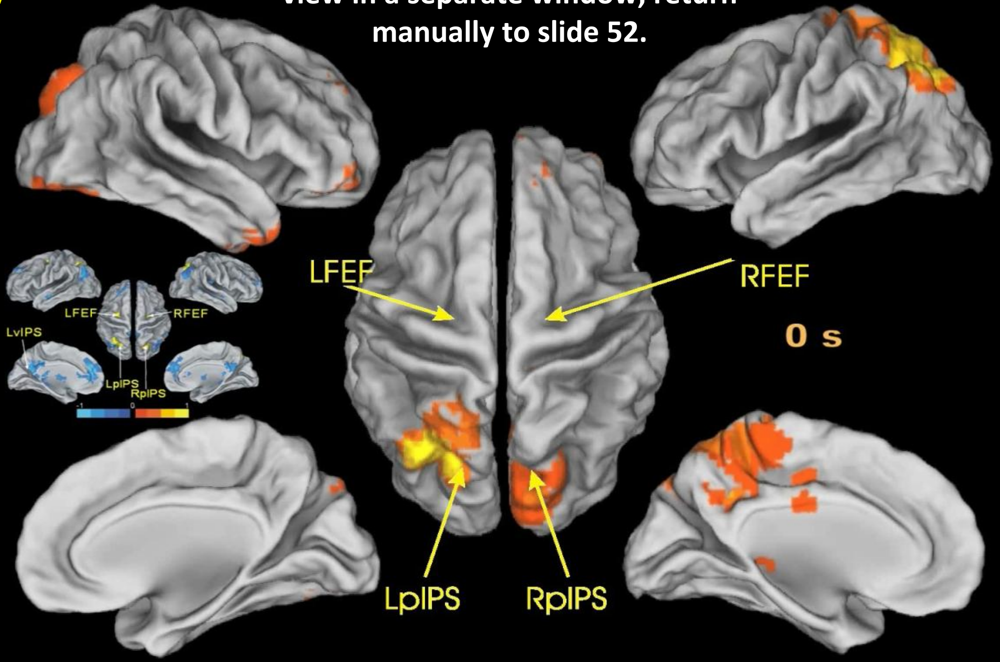
Raichle, Brain Connectivity 2011

Deco & Corbetta, Neuroscientist 2011

Dynamics of resting state networks activity revealed by MEG

Run the video MEG_RSN from here, view in a separate window, return manually to slide 52.

- Recently it has been demonstrated by MEG that RSNs are not "static", rather their correlated activity slowly fluctuates both within a single network and between different networks.
- Fluctuations may simultaneously involve and share different brain rhythms



de Pasquale et al., PNAS 2010, Neuron 2012
Betti et al., Neuron 2012
Marzetti et al., Neuroimage 2013

- This may be interpreted in terms of energy saving: the brain is always in a sort of "stand-by" mode and, when a stimulation occurs or a task is required, the response is provided, immediately increasing the activity of a network and depressing that of the others. RSNs are an efficient model (modulation of existing trained circuits)

The human connectome

On the basis of this findings NIH launched in 2010 the Human Connectome Project aimed at identifying the connectivity maps of 1200 normal subjects. The project uses anatomical, structural and functional MRI, together with MEG to establish a huge database open to any user for basic and clinical studies.
Particular interest is being given all around the world to studies investigating the degradation of the normal connectome in various kinds of brain diseases

Conclusions

- Low Tc SQUIDs are routinely used in large scale systems with excellent performances and reliability
- High Tc SQUIDs need further improvements for MEG applications (lower noise, integration in whole-head systems)
- MEG allows the recording of whole-head maps at millisecond time resolution
- MEG is commonly used in basic and clinical neuroscience
- Multimodal integration with fMRI provides a powerful tool for high temporal resolution and high spatial resolution functional imaging
- A novel generation of hybrid MEG-Ultra-low field MRI whole-head systems is likely to become available in the near future and might represent a real breakthrough for clinical applications
- MEG is a unique tool for studying the dynamics of brain connectivity!

Institute for Advanced Biomedical Technologies (ITAB) University of Chieti

Thanks to all my collaborators and to you for your attention!

www.itab.unich.it