HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

DZD
Deutsches Zentrum
für Diabetesforschung

Fetal Magnetoencephalography

Tübingen, 25.6.18

Hubert Preißl
Institute for Diabetes Research and Metabolic Diseases (IDM) of the
Helmholtz Center Munich at the University of Tübingen

EBERHARD KARLS
UNIVERSITÄT
TÜBINGEN

LUMINOUS
LUMINOUS H2020 FET PROJECT

UNIVERSITÄTS
KLINIKUM
TÜBINGEN

Questions addressed

What is magnetoencephalography?
How can we measure magnetic fields generated in the human body?
Why do we need to measure magnetic fields in the human fetus?
What are the requirements to measure magnetic fields in the human fetus?
How can we use fetal biomagnetic recordings in research?
Are there possible clinical applications?
What is the future?

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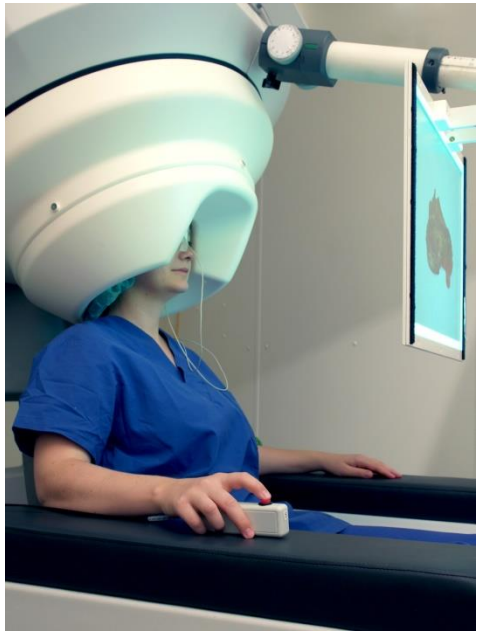
Magnetoencephalography (MEG)





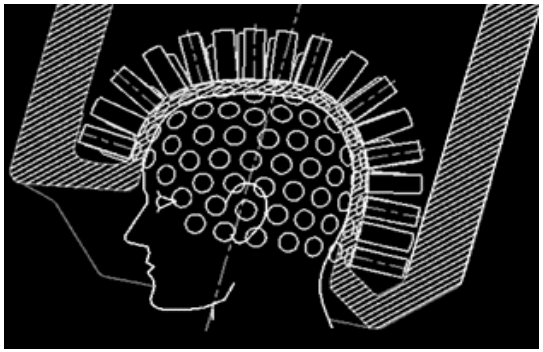
MagnetoEncephaloGraphy (MEG)



- Magnetoencephalography (MEG) is a non-invasive, imaging method to study brain functions
- Magnetoencephalography records neuronal electro-magnetic activity of the brain.
- Magnetoencephalography and Electroencephalography (EEG) can be recorded simultaneously.

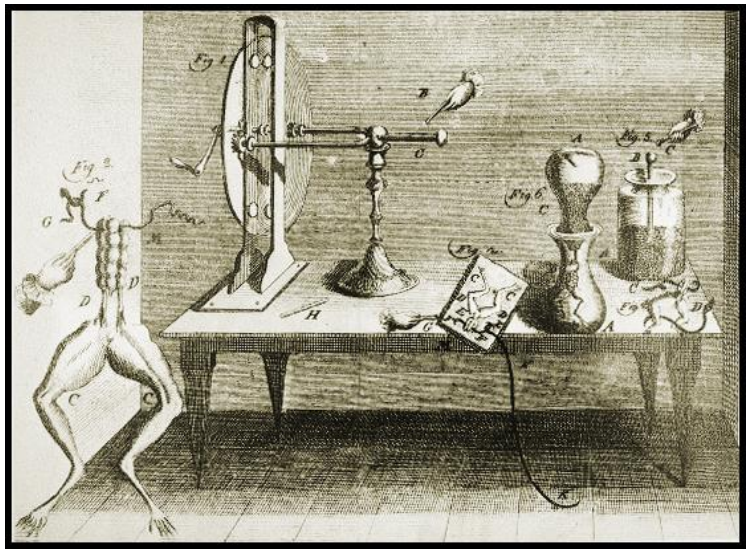






Luigi Galvani: “Animal Electricity“

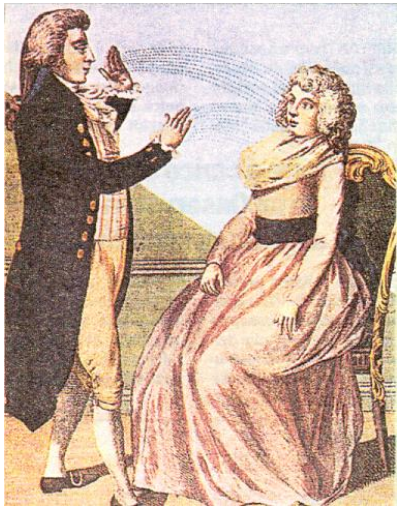
late 18th century





Luigi Galvani
1737 - 1798

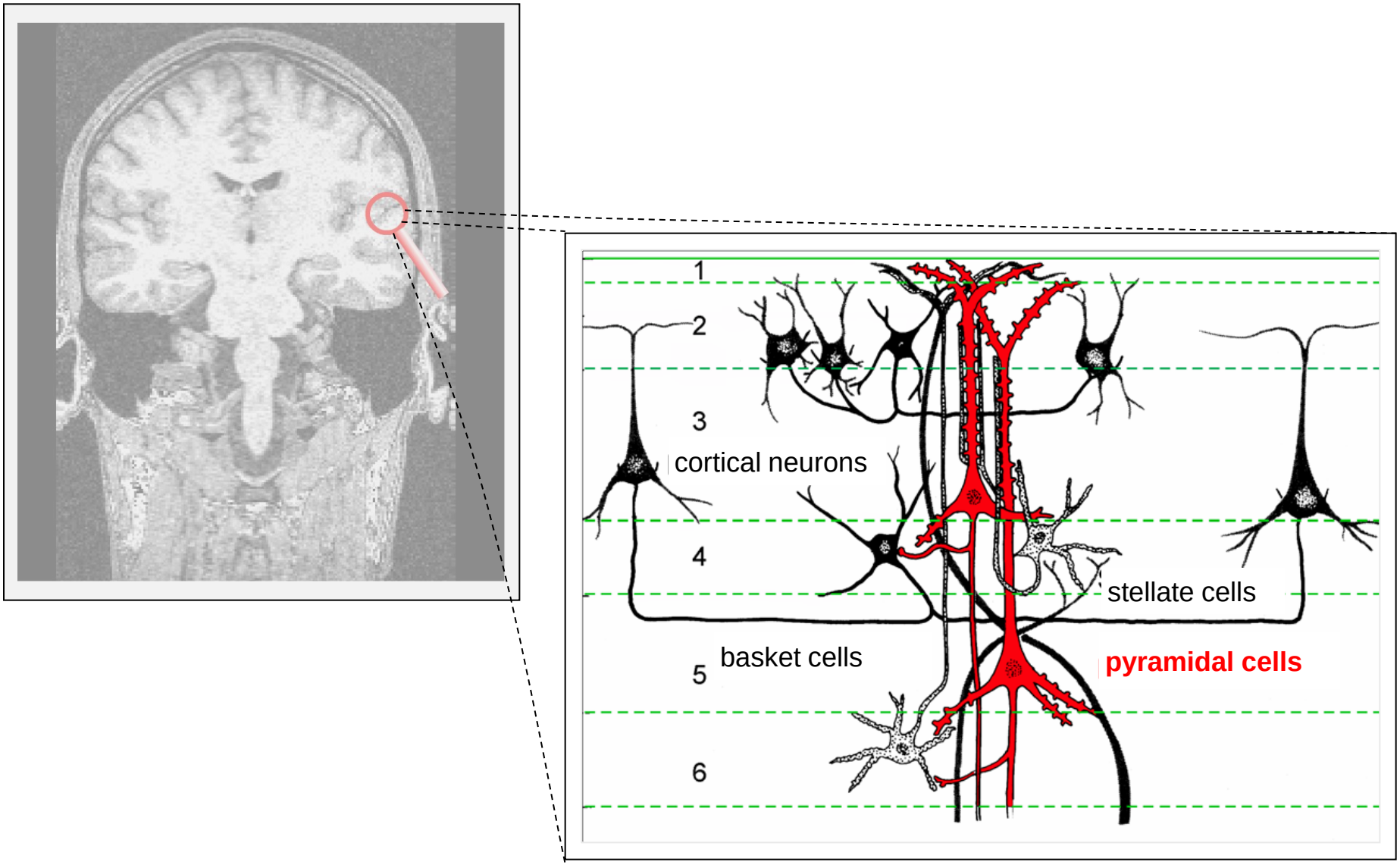
- As a consequence of Galvani experiments on animal electricity, also the existence of an *animal magnetism* was hypothesised by F. A. Mesmer, who tried to associate “mysterious” magnetic fields with a deep influence on human behaviour
- Mesmer theories were examined by a committee of scientists - including 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





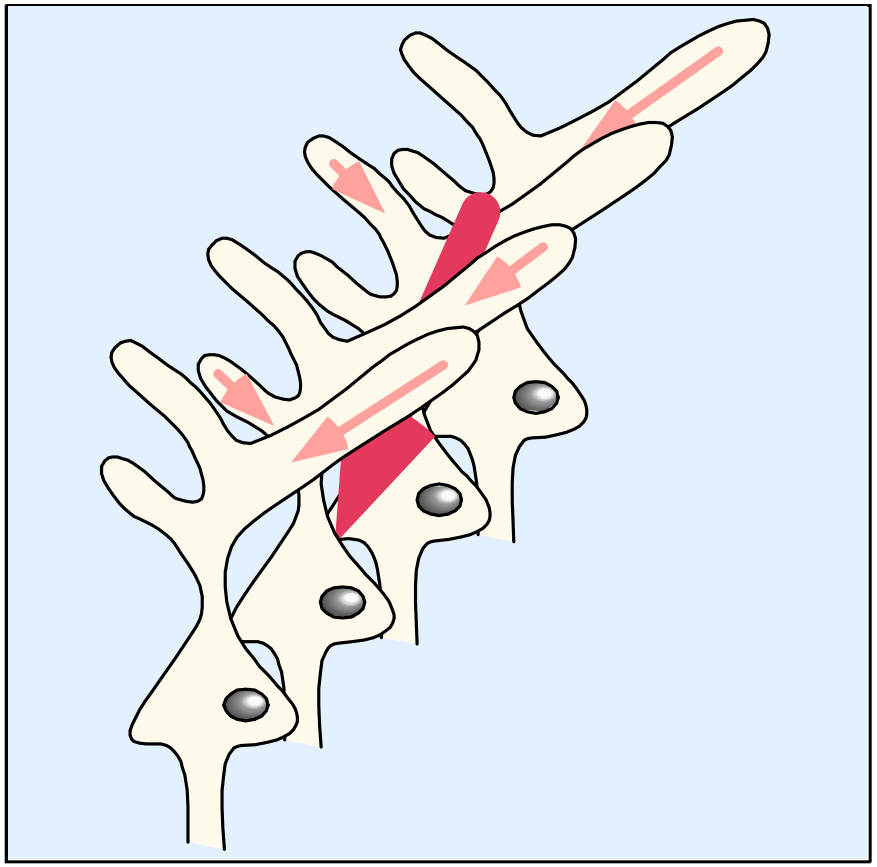
Franz Anton Mesmer
1734 -1815

Measurement of Cerebral Magnetic Fields



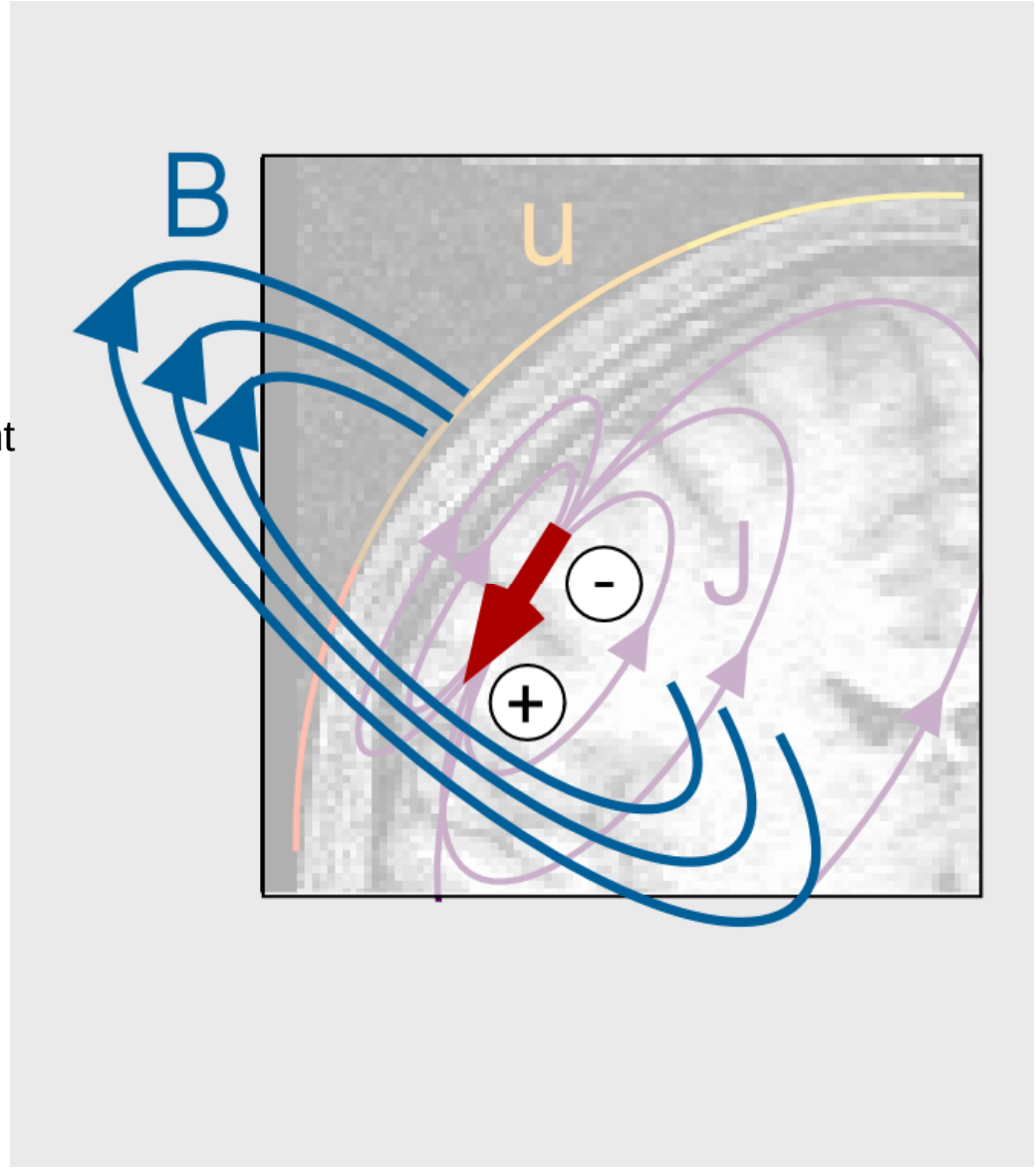
Physiological Basis of MEG

- synaptic activity causes shifts in electrical currents
- a postsynaptic potential emerges
- the polarisation can be described physically by a ***dipole***
- simultaneous activation of multiple neurons superimposes
- a prerequisit for the generation of a measurable EEG- or MEG-signal is the coordinated activity of about 10 000 neurons.



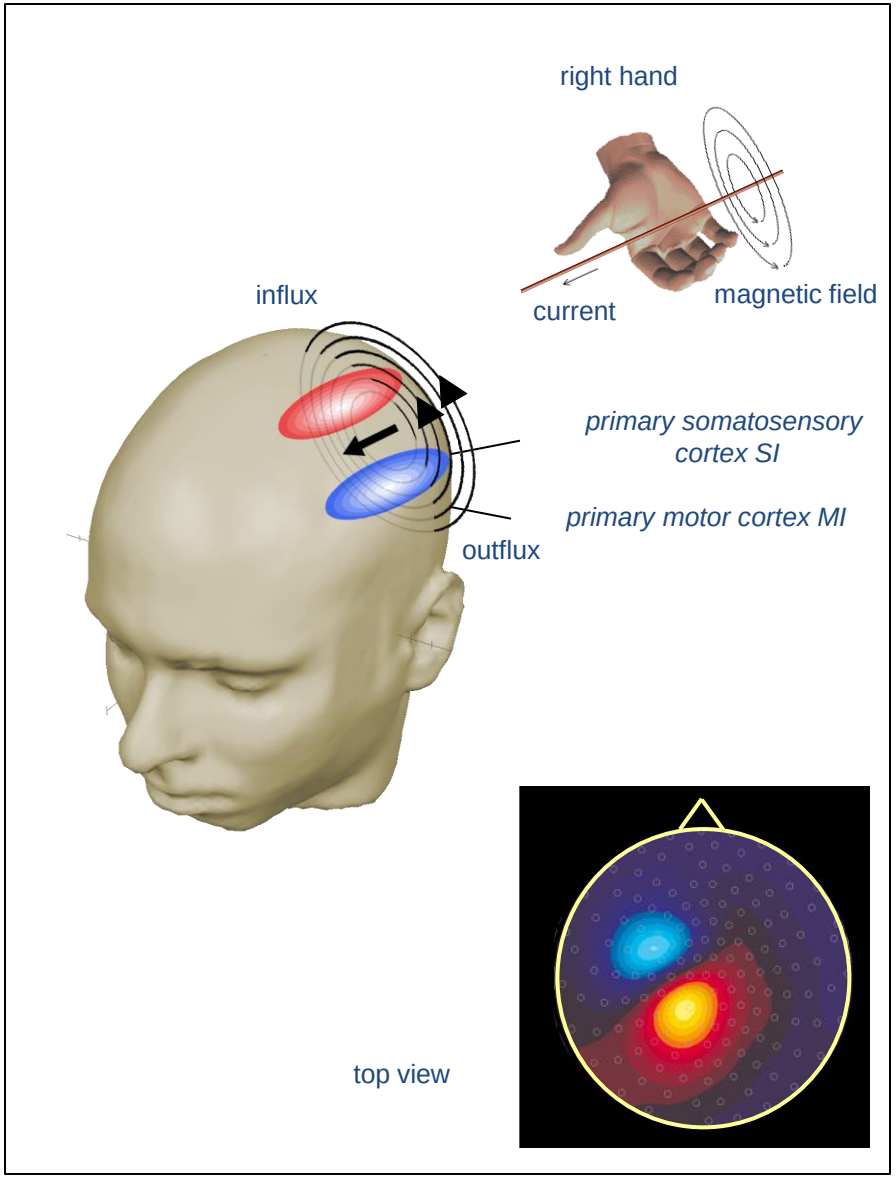
Physiological Basis of MEG

- synaptic activity causes an intra-cellular *primary current a*nd a extra-cellular *secondary-current*.
- EEG measures the voltage changes of the secondary current at the head surface.
- MEG records magnetic fields of the primary currents.

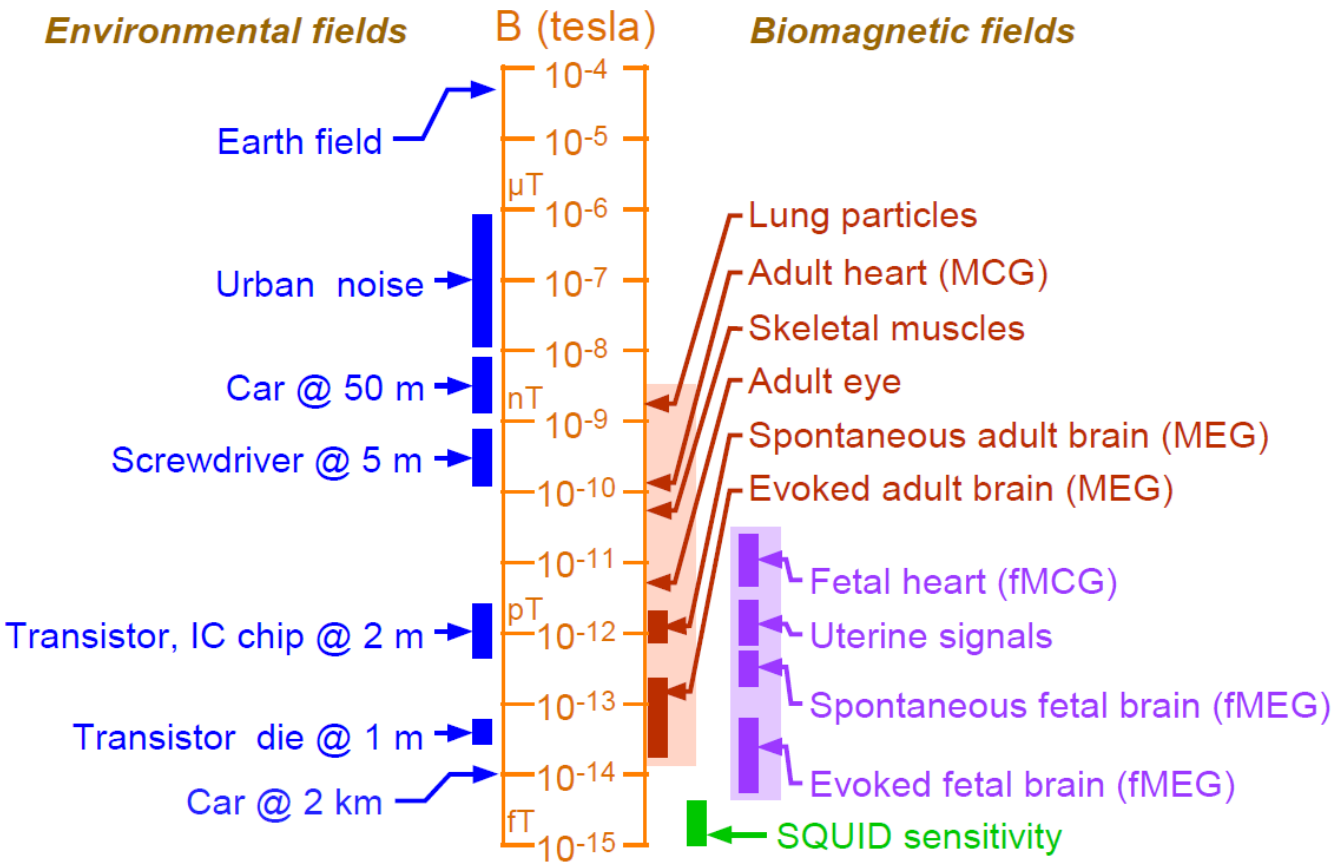


Generation of magnetic fields

- Depolarisation of the dendritic membrane of pyramidal cells generates extra- and intracellular currents.
- In **EEG** the voltage differences of extra-cellular currents are measured at the head surface (Ohm‘s law).
- In **MEG** only magnetic effects of the summated intra-cellular currents are measured (Biot-Savart‘s law, right hand rule).



Strength of Magnetic Fields



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Magnetoencephalography

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

Progress in Magnetoencephalography



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





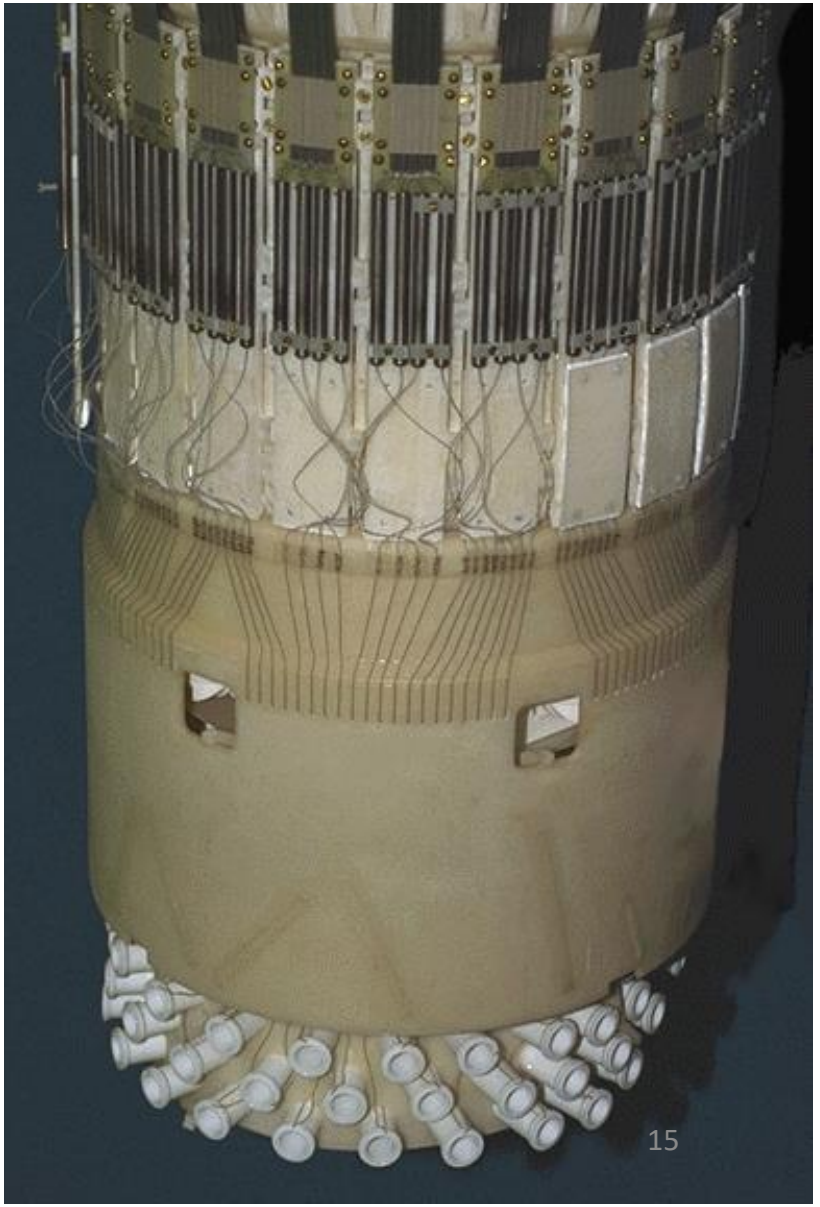




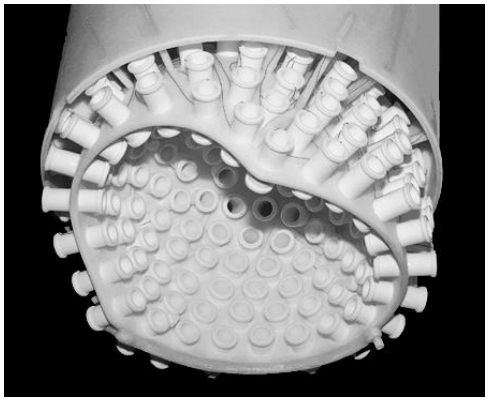
Magnetoencephalography







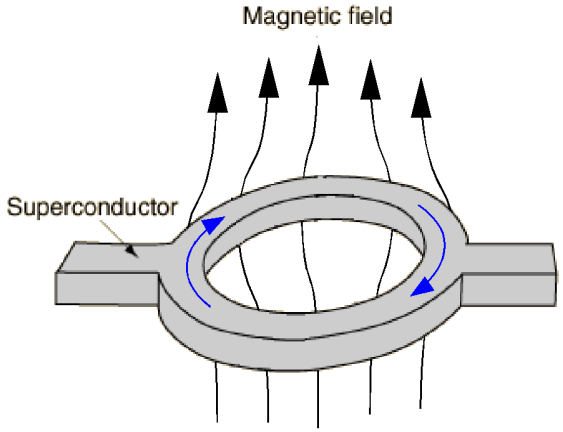




SQUID: Superconducting Quantum Interference Device

superconducting ring

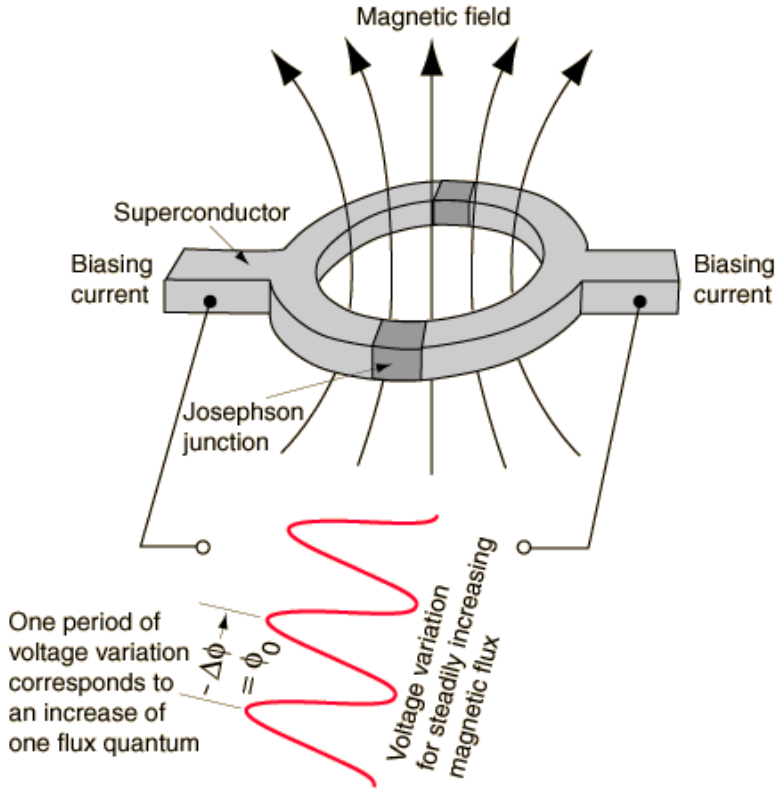
- an external magnetic field creates a current in the coil
- current creates magnetic field opposite to the original field
- no magnetic field inside the ring



superconducting ring with Josephson conjunction

- differences between multiples of flux quanta
- only multiples of flux quanta can pass

  generate a current
- the current causes a voltage drop at the Josephson conjunction



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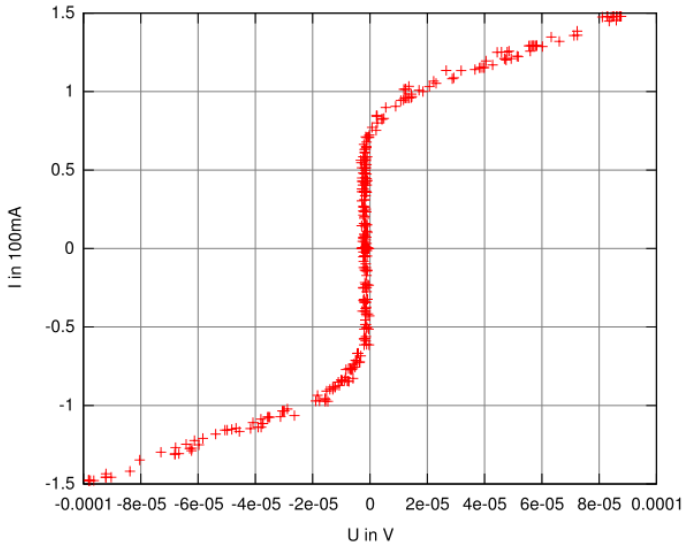
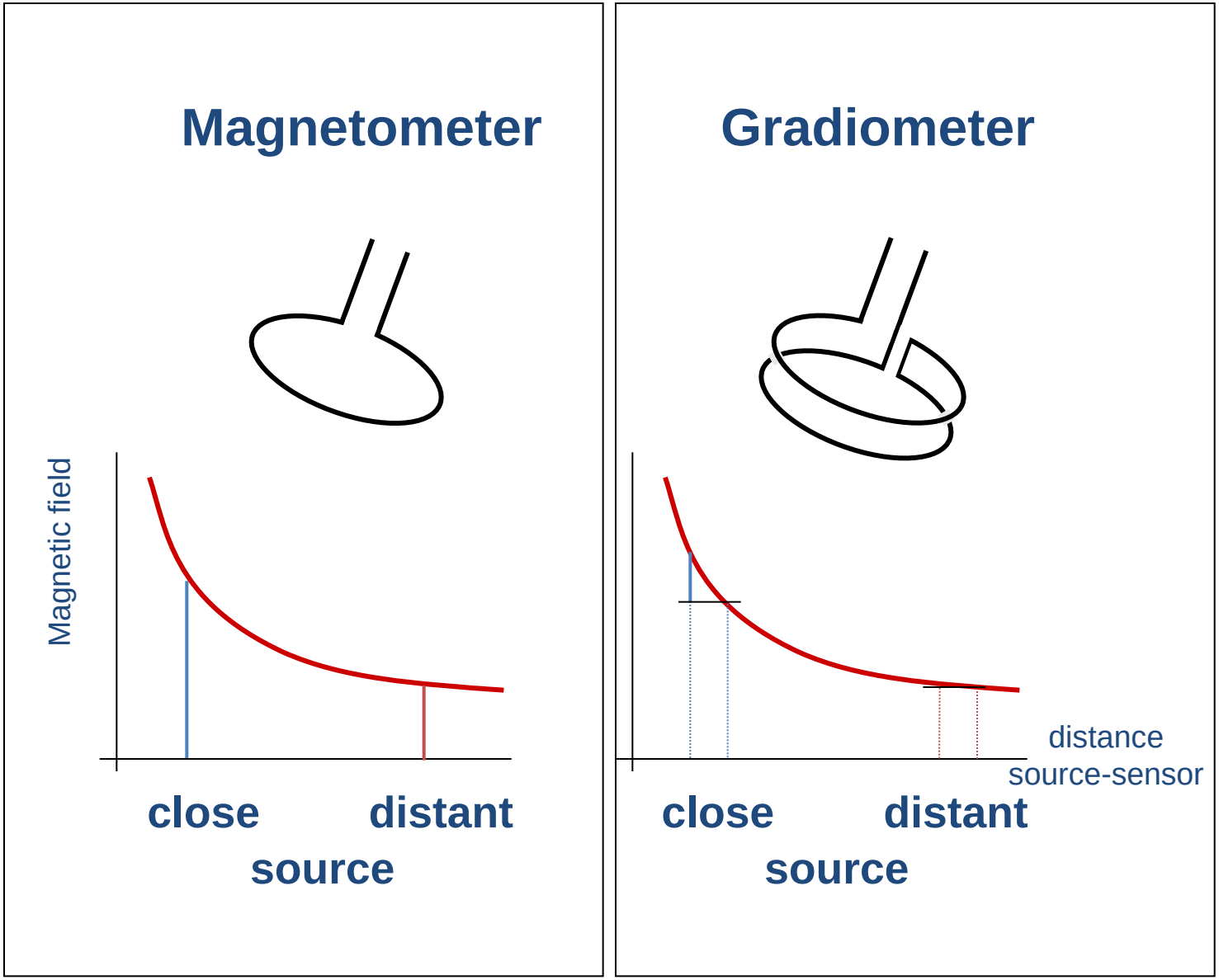


Superconducting material is niobium or lead alloy with gold/indium

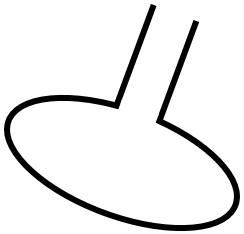
Cooled to low temperature with either liquid He (4K) or N (77K)

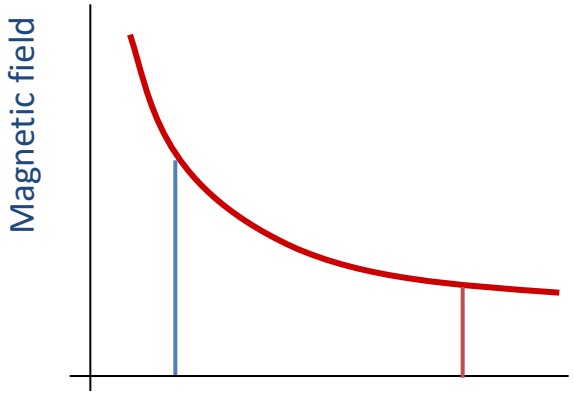
Gradiometer as a means to suppress environmental noise



Noise suppression: magnetometers and gradiometers

magnetometer





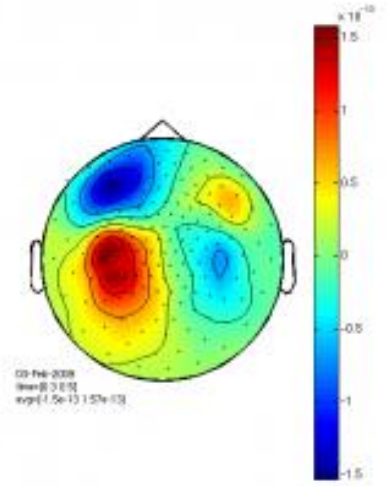
gradiometer

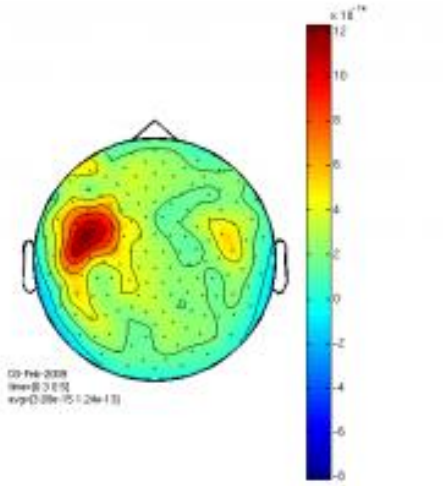
axial



planar







Noise suppression: shielding



the basis of the magnetic shielded room is an aluminium frame

inner layer
copper coated
aluminium



middle layer
mu metal with
high magnetic
susceptibility



outer layer
aluminum





demagnetisation

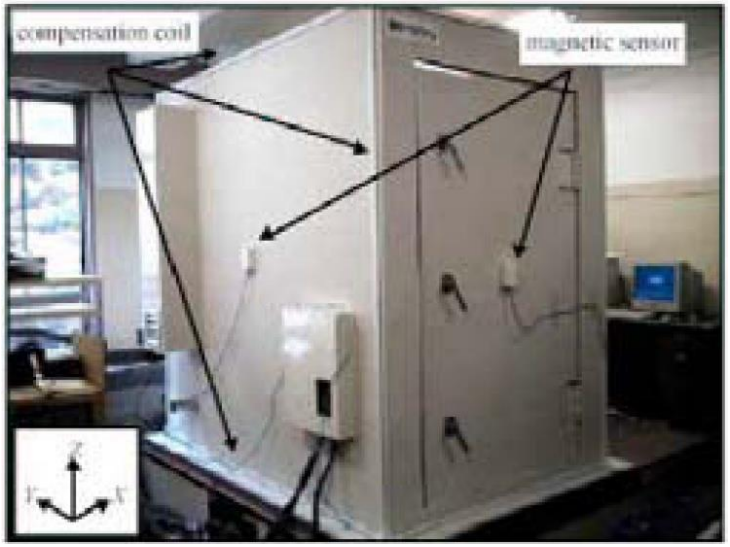


finish

Noise suppression: shielding



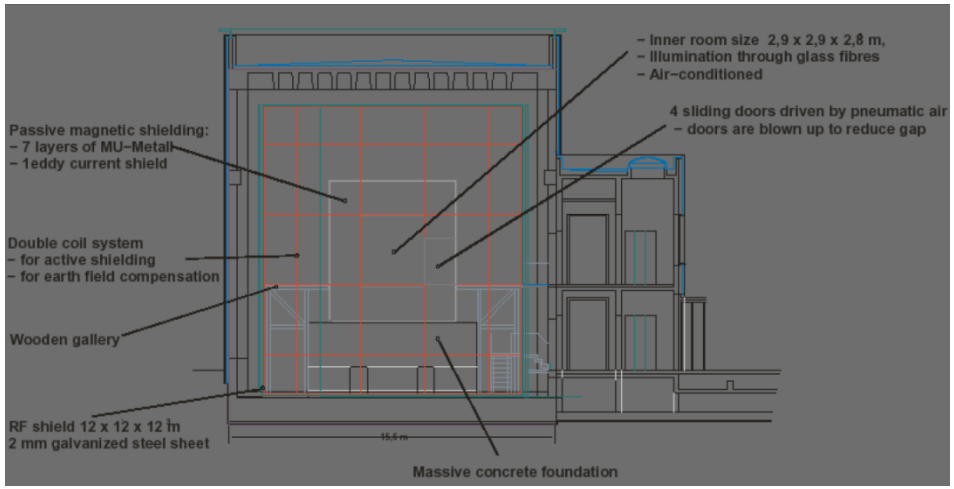
AK3B Vakuumschmelze:
3 Layer shielding



active compensation



Superconductive shielding:
Shielding factorr: 10 000 bei 0.05 Hz



passive 7 layer shielding
double coil system for
- active shielding
- earth field compensation
RF-shield

Helium supply and recovery

cooling of MEG sensors





balloon 20 m^3



compressor

gas bottles 200 bar



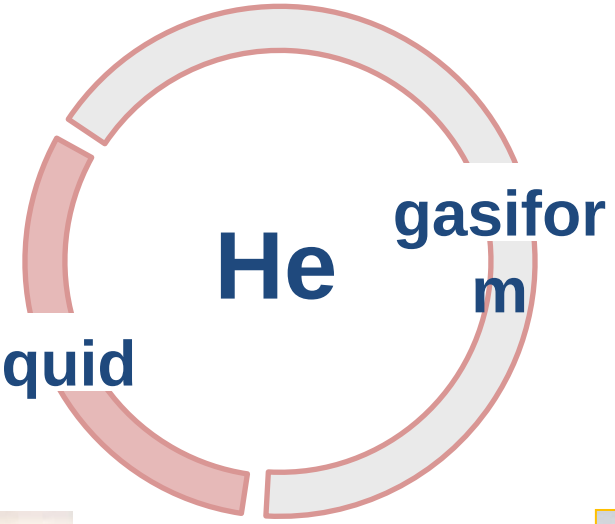




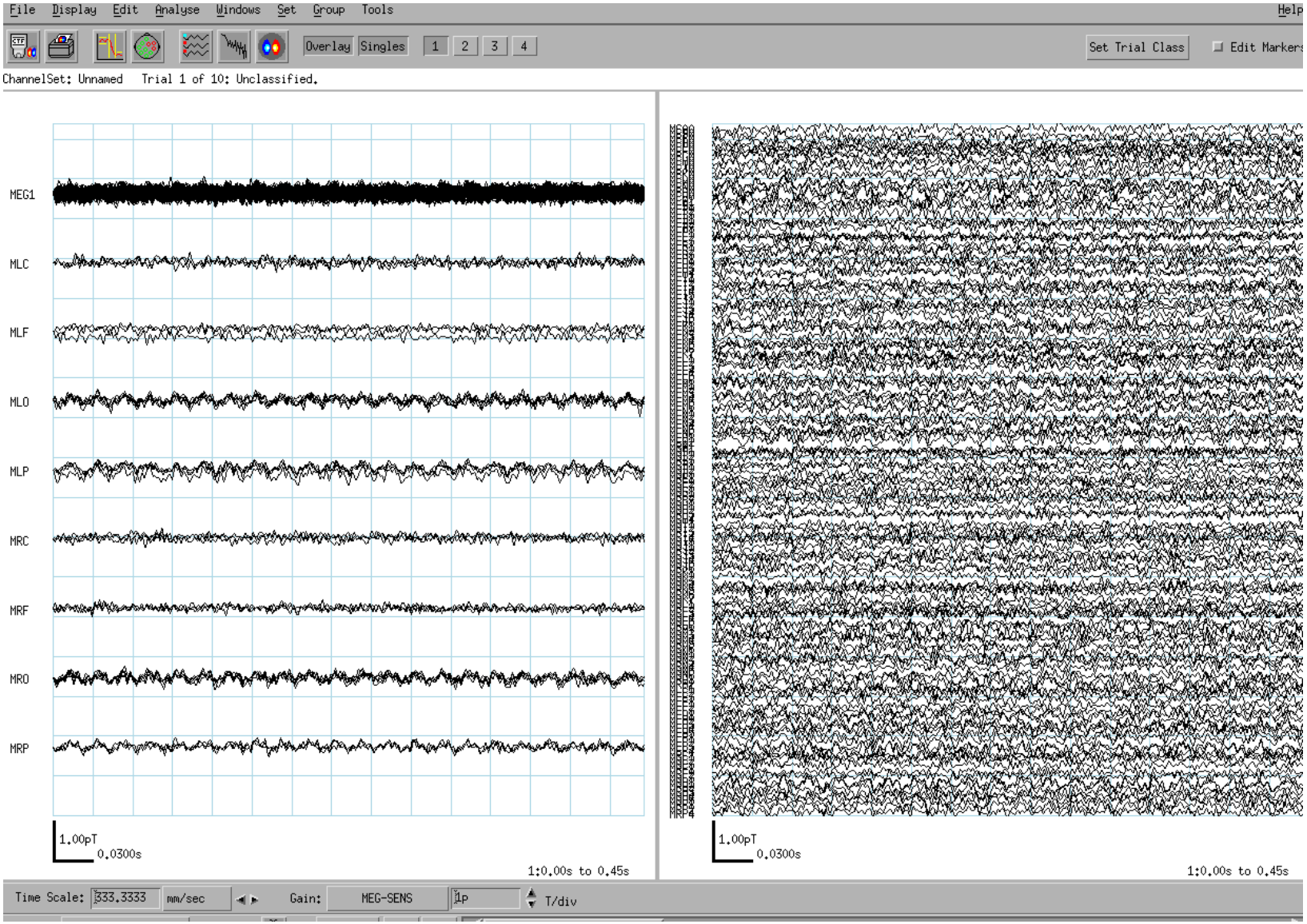
cryogenic services



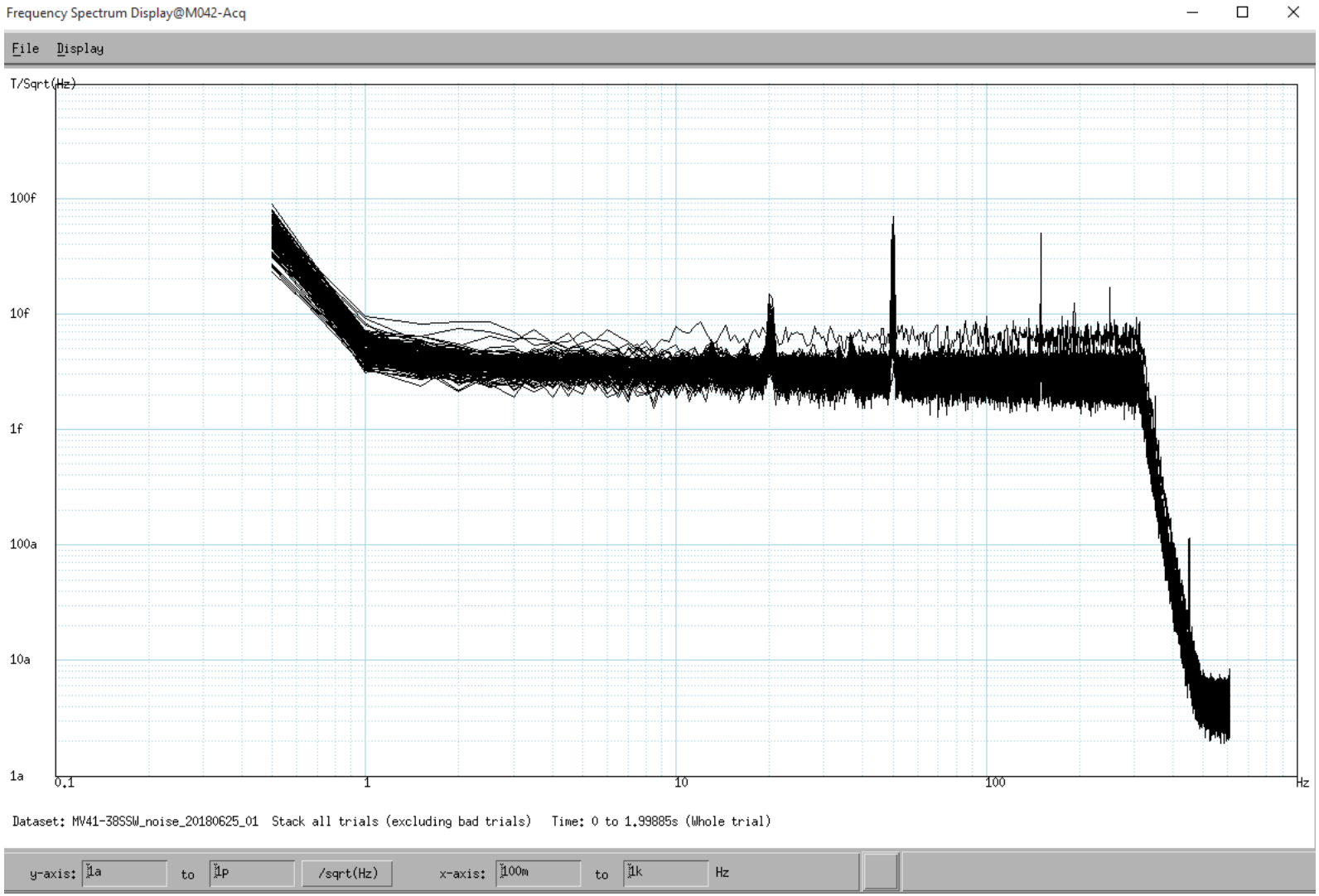
dewar 250 l



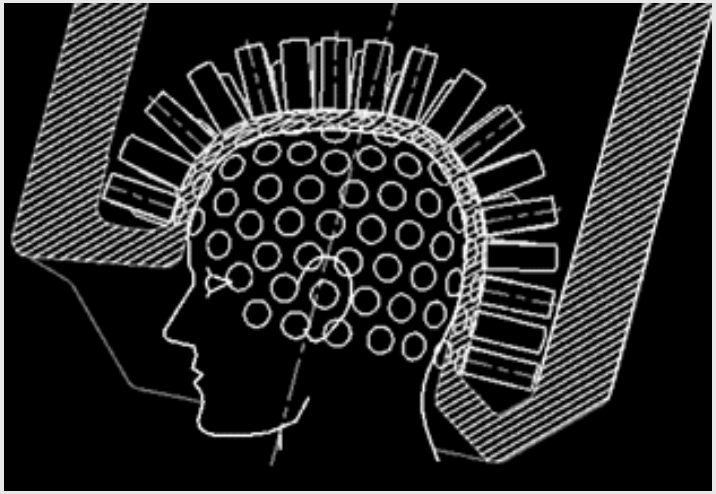
MEG channels (noise, time)

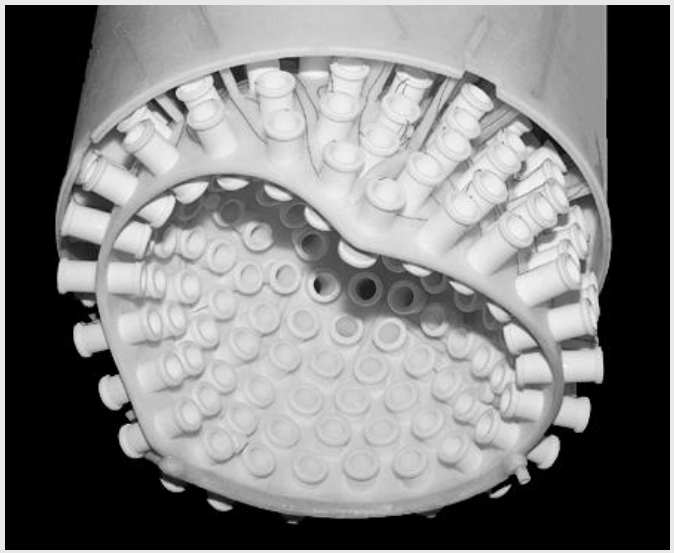


MEG channels (noise, frequency)



Superconducting Quantum Interference Device (SQUID)

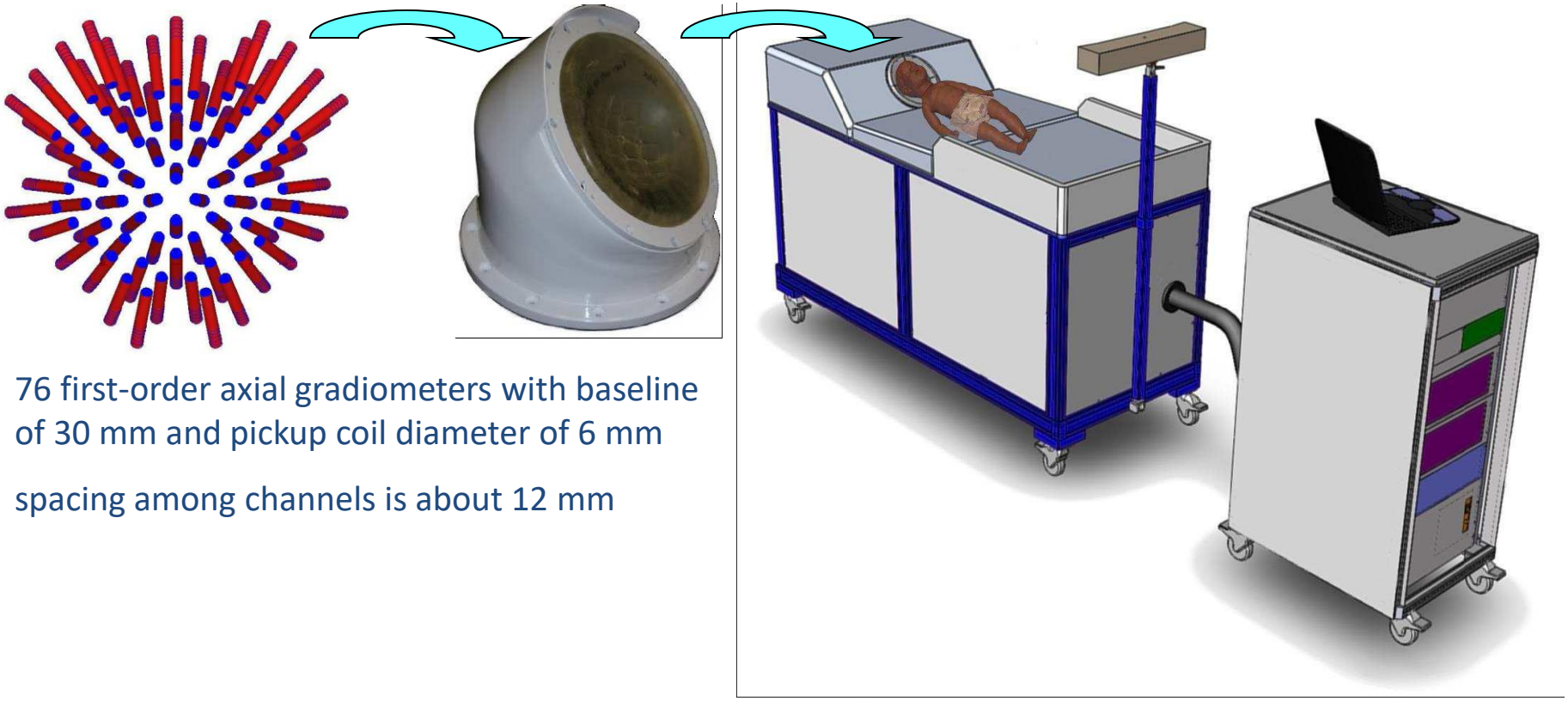




SQUIDs

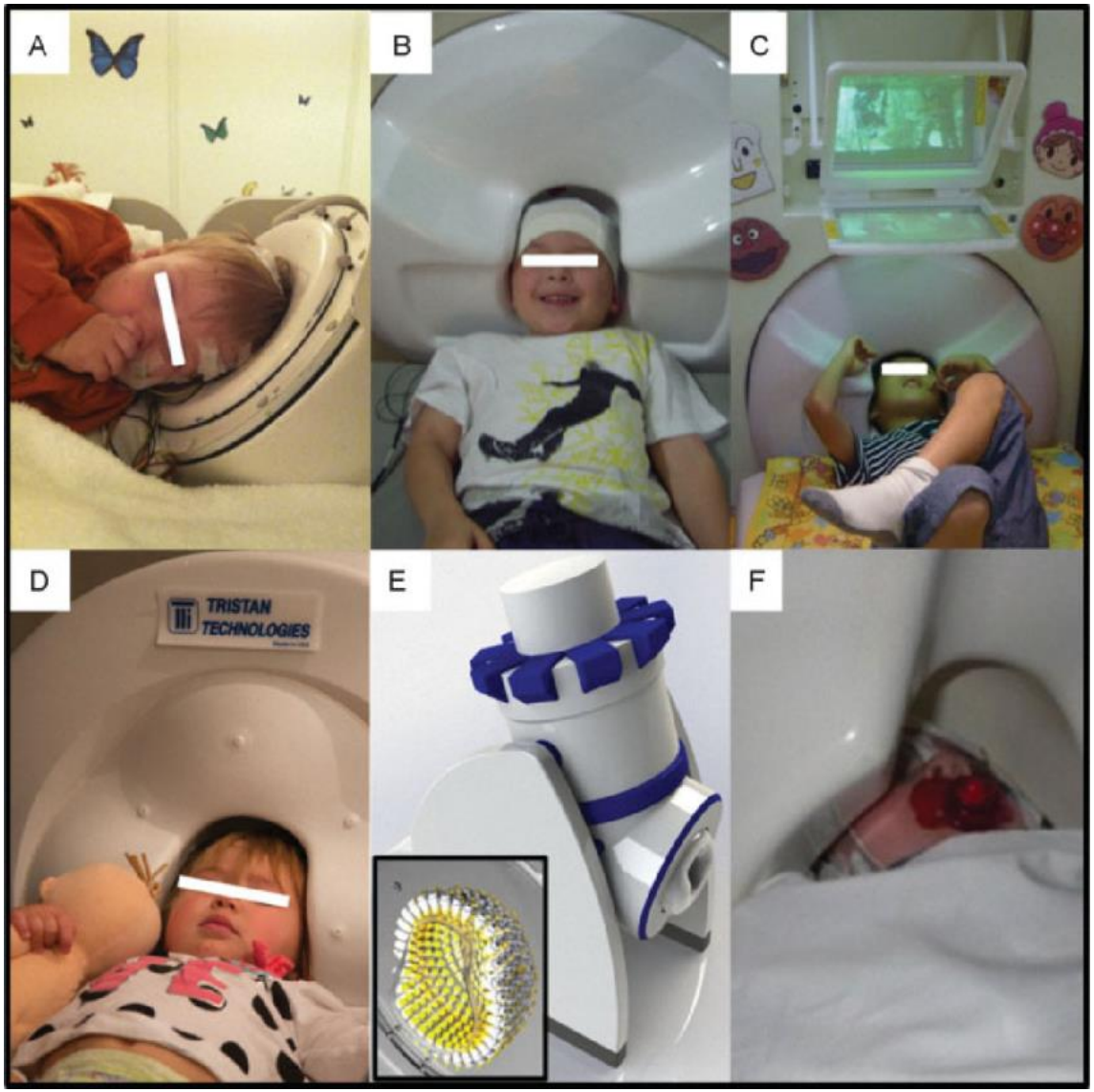


BabySQUID ® Neonatal Biomagnetometer by Tristan Technologies, Inc.



- 76 first-order axial gradiometers with baseline of 30 mm and pickup coil diameter of 6 mm
- spacing among channels is about 12 mm

- The gradiometers are connected by thermal conductors to the liquid helium bath
  - the distance between the signal coils and the headrest is about 6 mm
  - the magnetic field noise ~ 17 fT/√Hz



https://www.researchgate.net/figure/Comparison-of-pediatric-MEG-systems-A-BabySQUID-Tristan-Technologies-Inc-San-Diego_fig2_282096811

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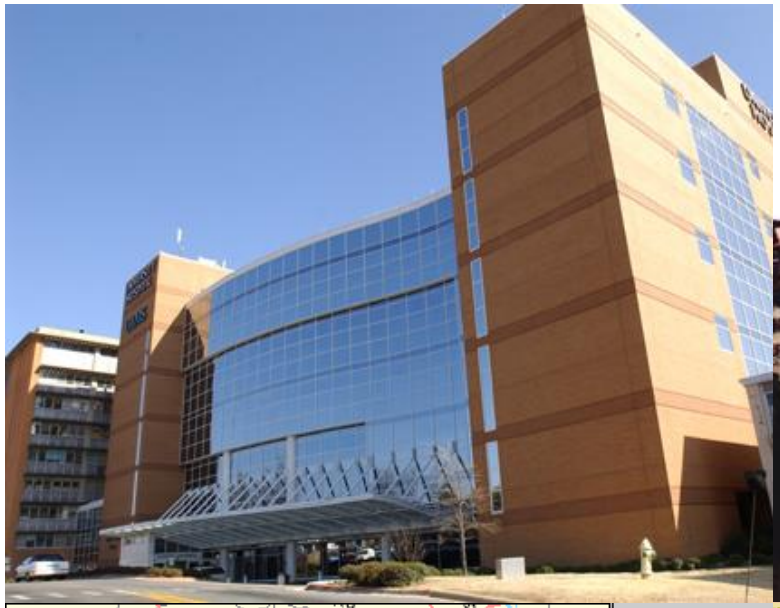
The fetus is not a preterm!



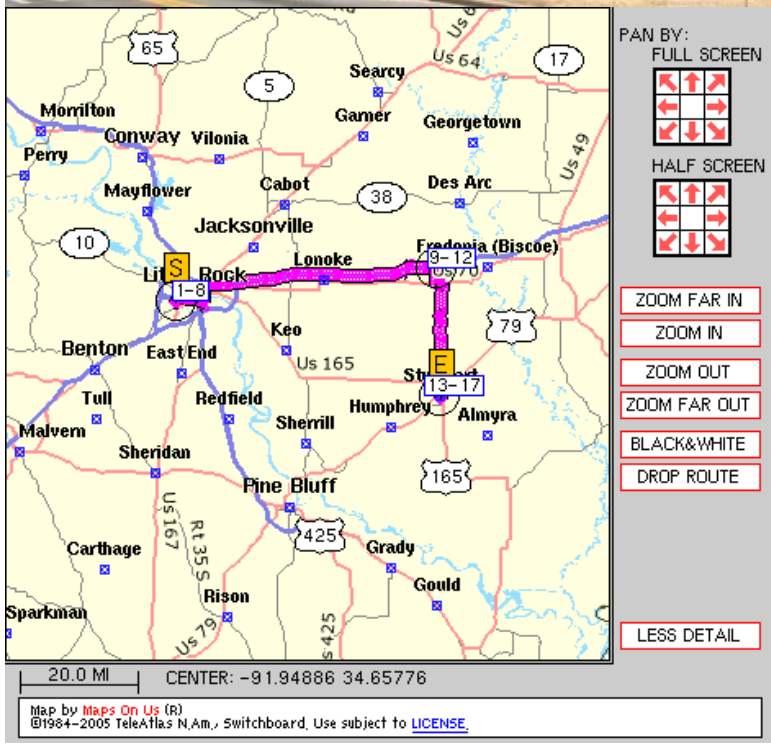


Prematurity especially for gestational age <32 weeks is an independent risk factor for adverse cognitive development

(Levine et al. Pediatrics. 2015. Sansavini et al. Dev Disabil Res Rev. 2011)



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Mayflower
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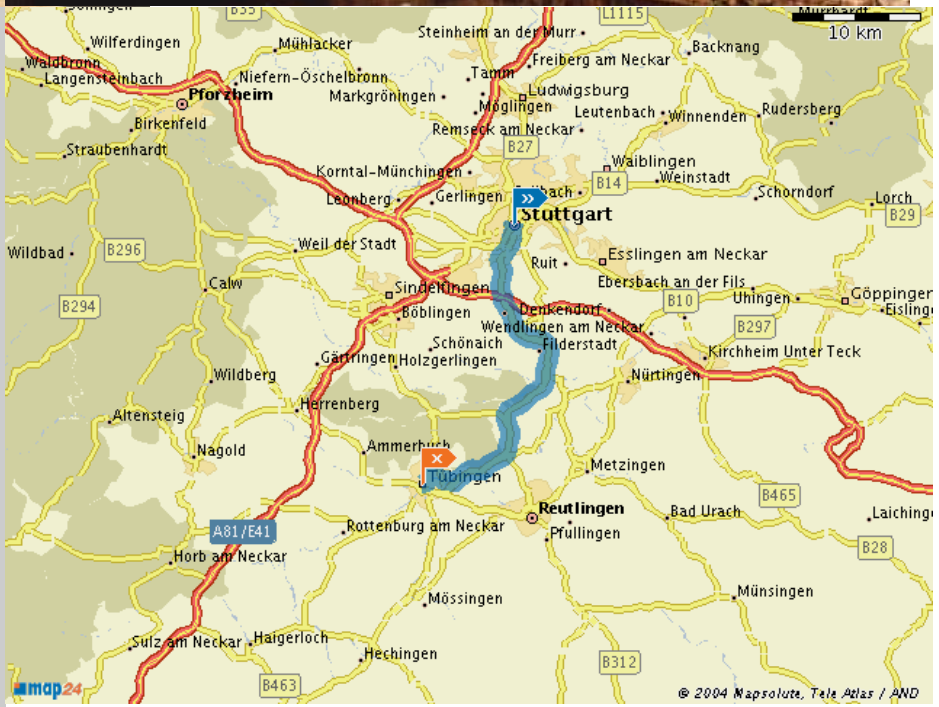
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Markgröningen
Freiberg am Neckar
Ludwigsburg
Möglingen
Leutenbach
Winnenden
Rudersberg
Birkenfeld
Remseck am Neckar
Straubenhardt
Korntal-Münchingen
Waiblingen
Weinstadt
Leonberg
Gerlingen
Stuttgart
Schorndorf
Lorch
Wildbad
Weil der Stadt
Esslingen am Neckar
Ruit
Ebersbach an der Fils
Calw
Sindelfingen
Uhingen
Göppingen
Böblingen
Denkendorf
Wendlingen am Neckar
Schönaich
Filderstadt
Kirchheim Unter Teck
Gärtringen
Holzgerlingen
Wildberg
Nürtingen
Herrenberg
Altensteig
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map24
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The story of Curtis Lowery, MD, Little Rock, Arkansas



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Z. EEG - EMG 15 (1984) 34–37
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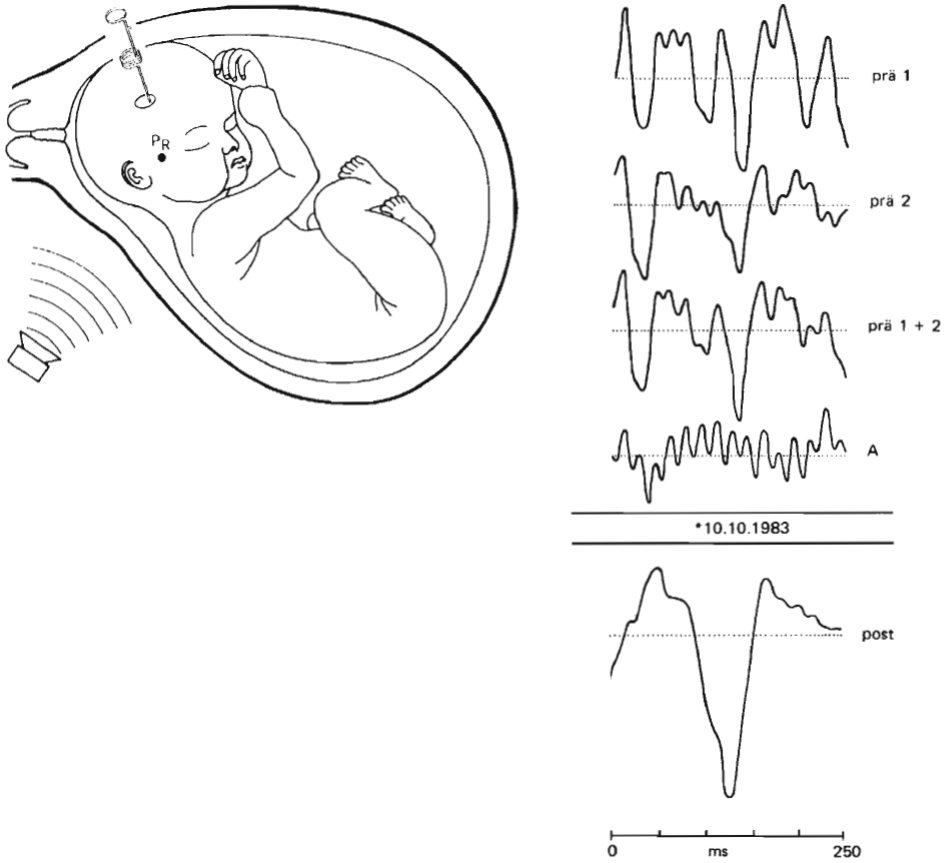
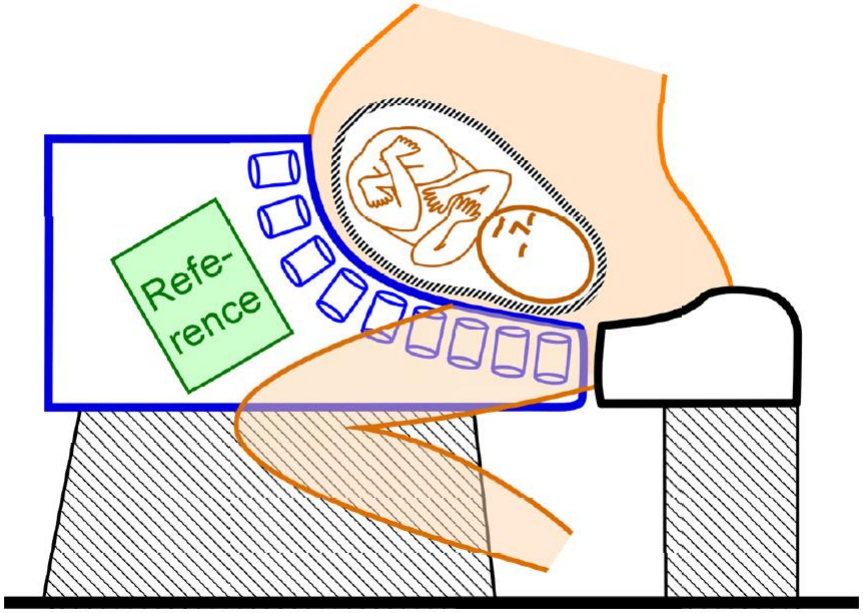
Fetale Magnetoenzephalographie I: Erstmalige pränatale Registrierung eines auditorisch evozierten neuromagnetischen Feldes

T. Blum, E. Saling, R. Bauer



The design of a fetal device



SARA 2: SQUID Array for Reproductive Assessment
University of Tübingen. fMEG-Center



Recording of fMEG

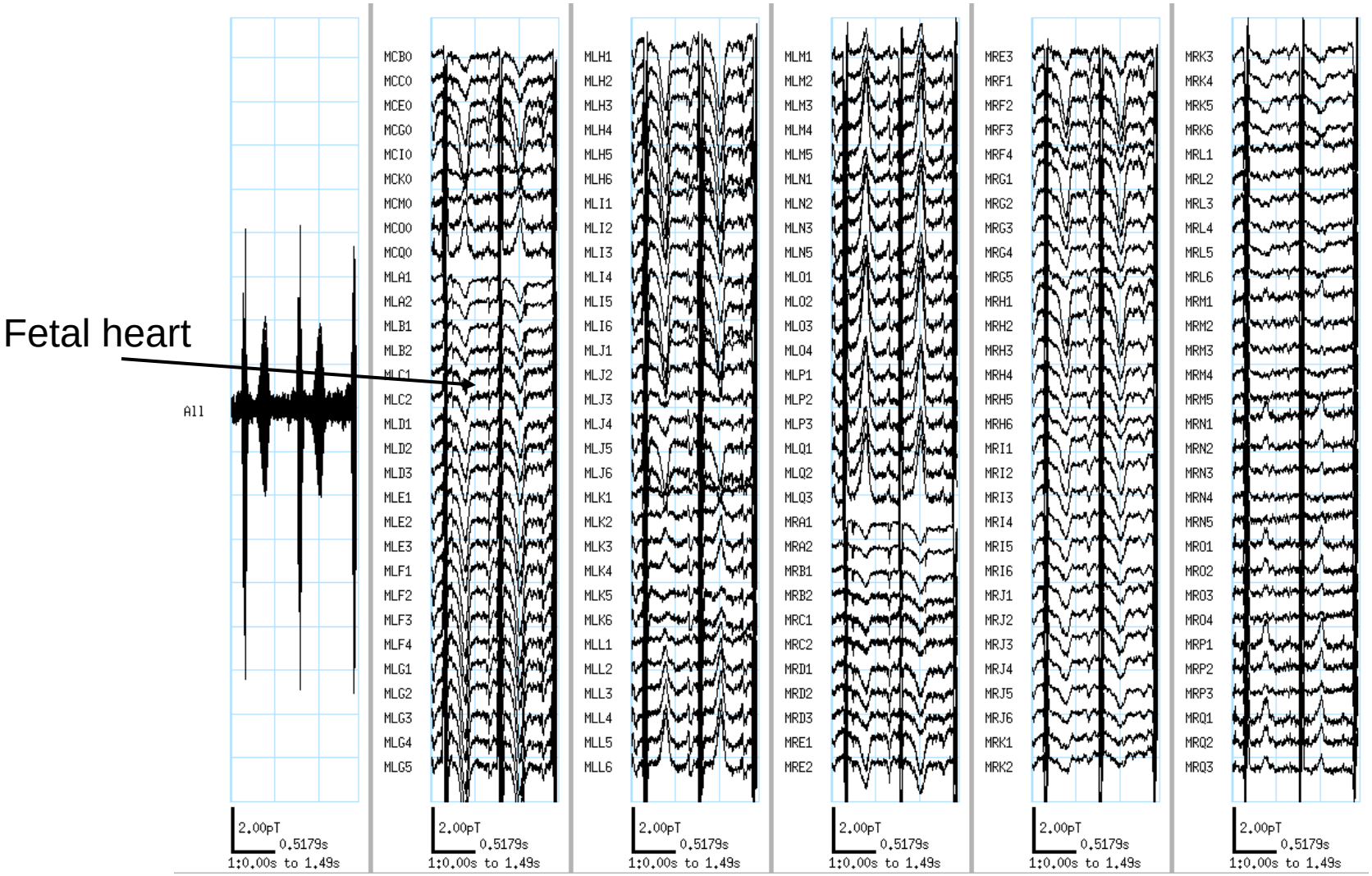
A



B



Raw Data


Fetal heart
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MCG0
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MCK0
MCM0
MCO0
MCQ0
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MLB1
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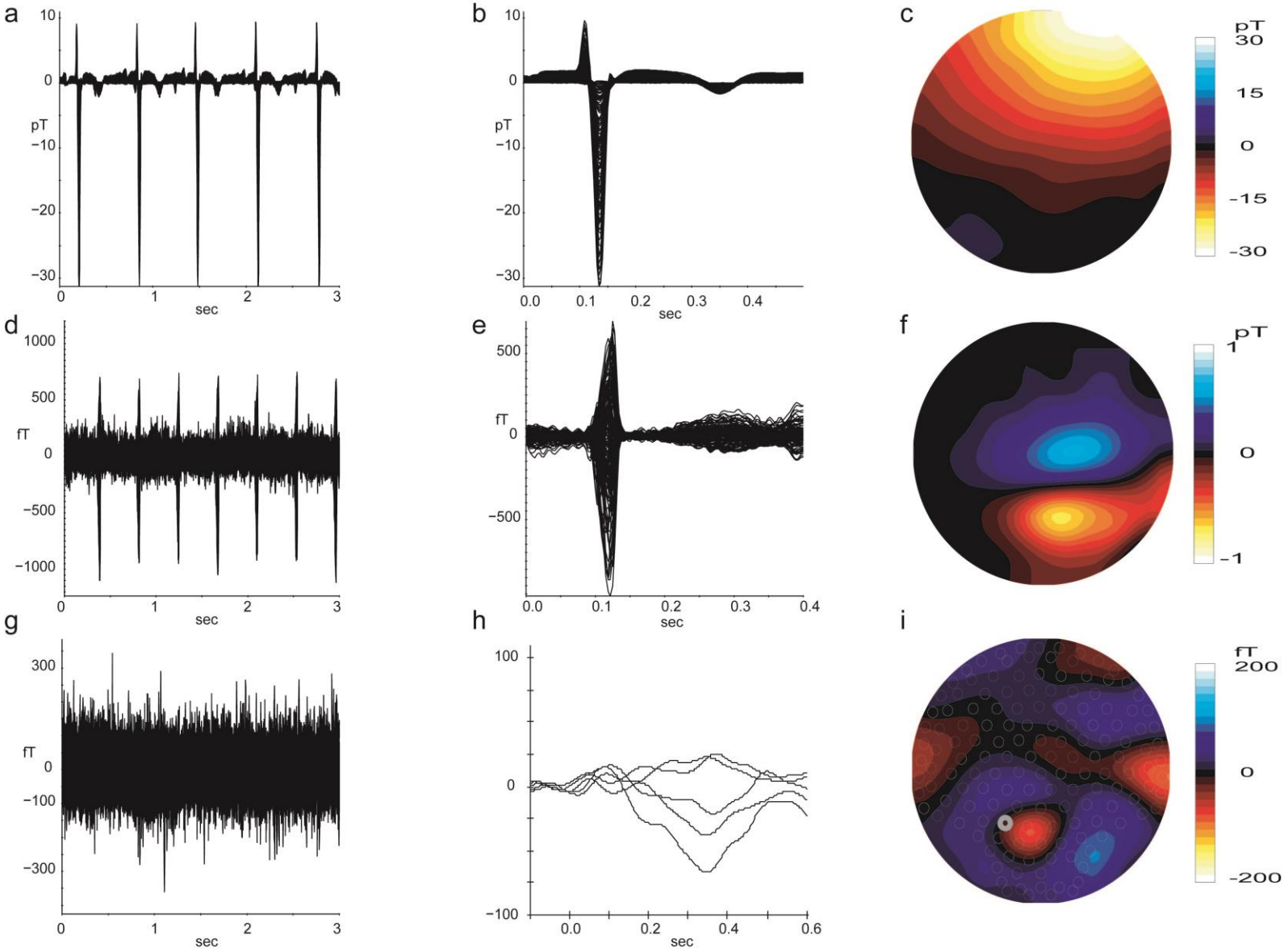
Attenuation of interfering sources



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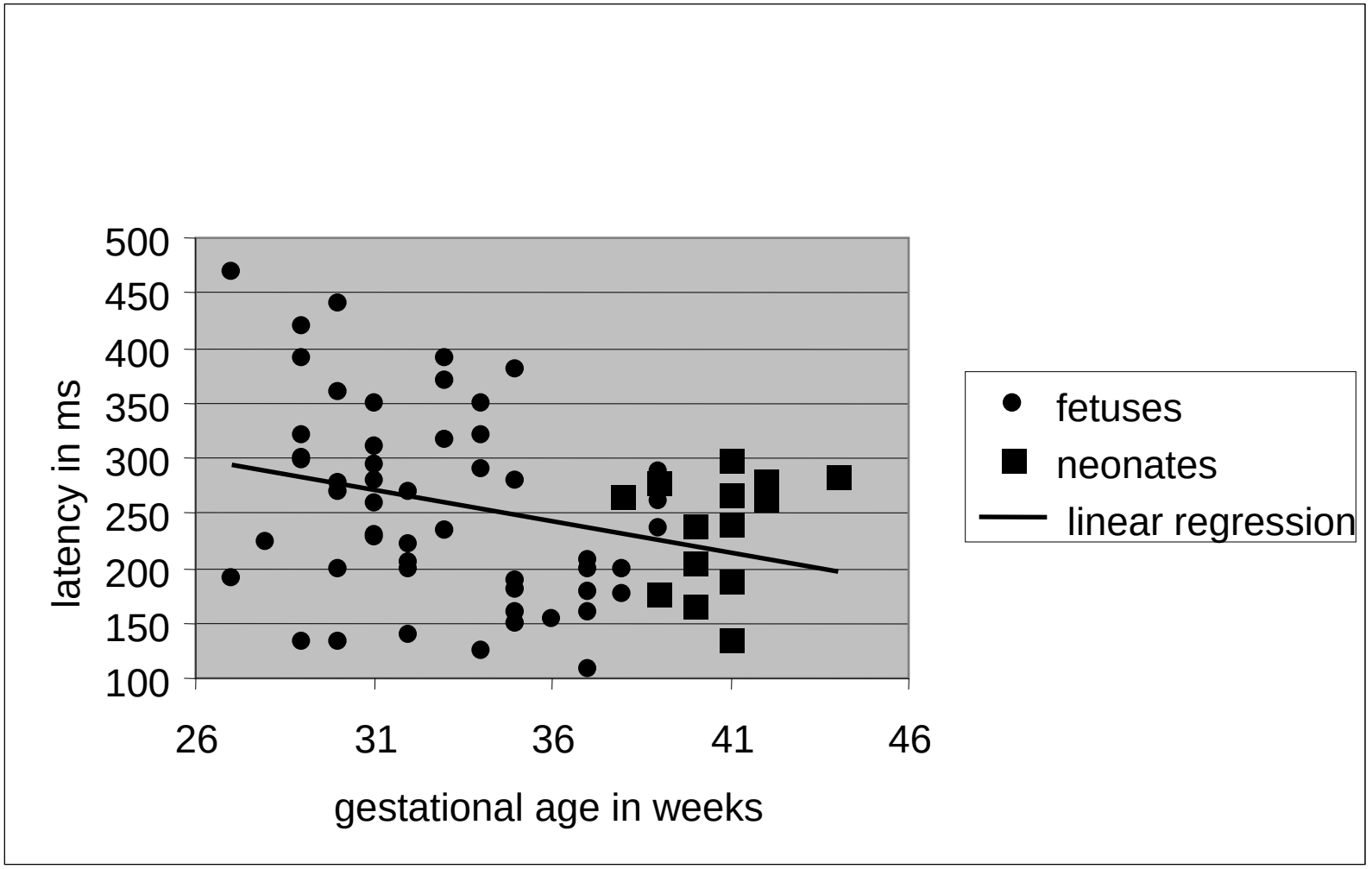
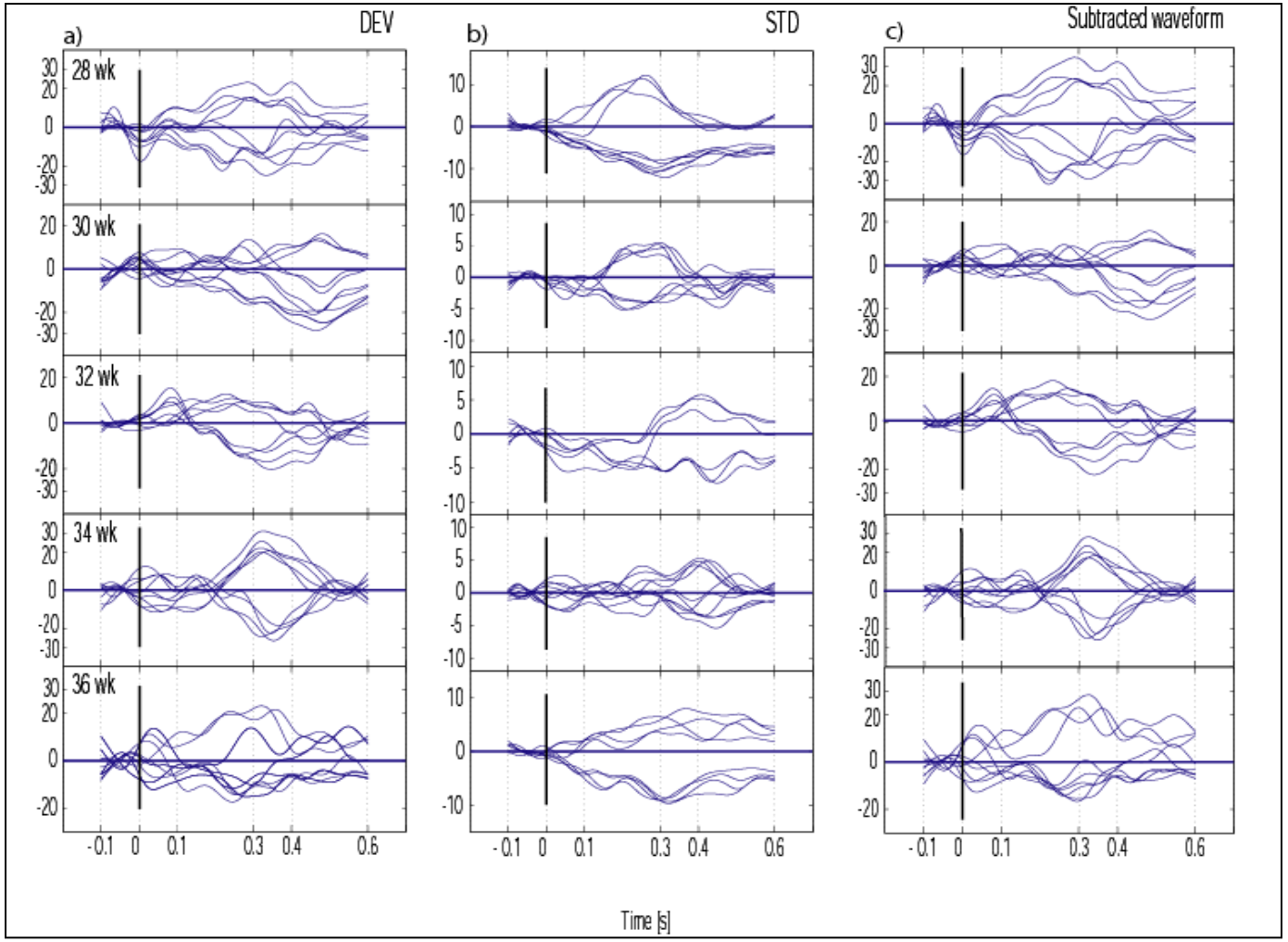
MEG measures of auditory evoked fields in fetuses and neonates



Holst et al., Clinical Neurophysiology, 2005

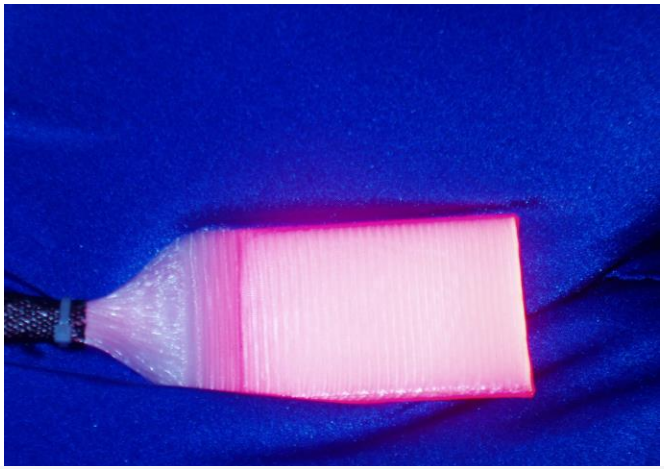
Discriminative response to two pure tones

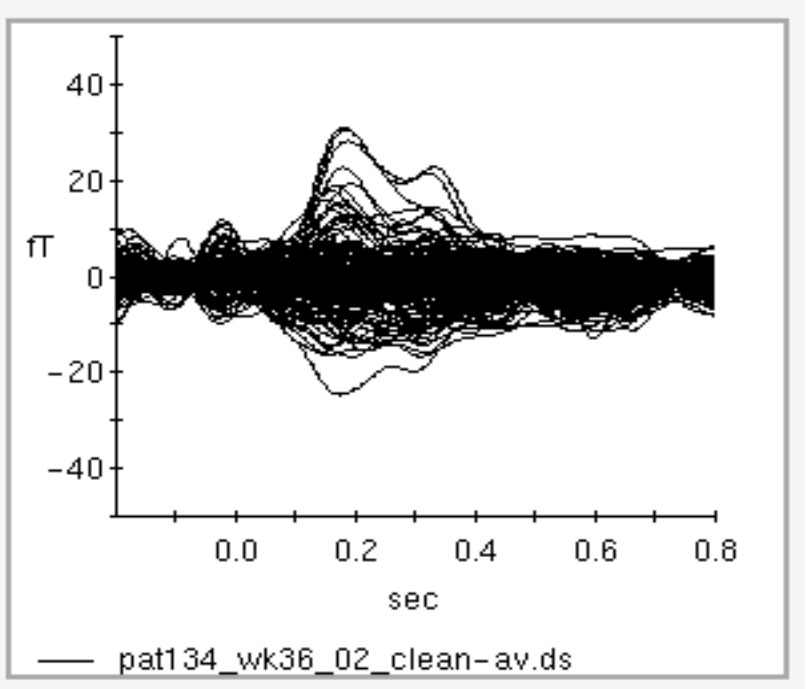


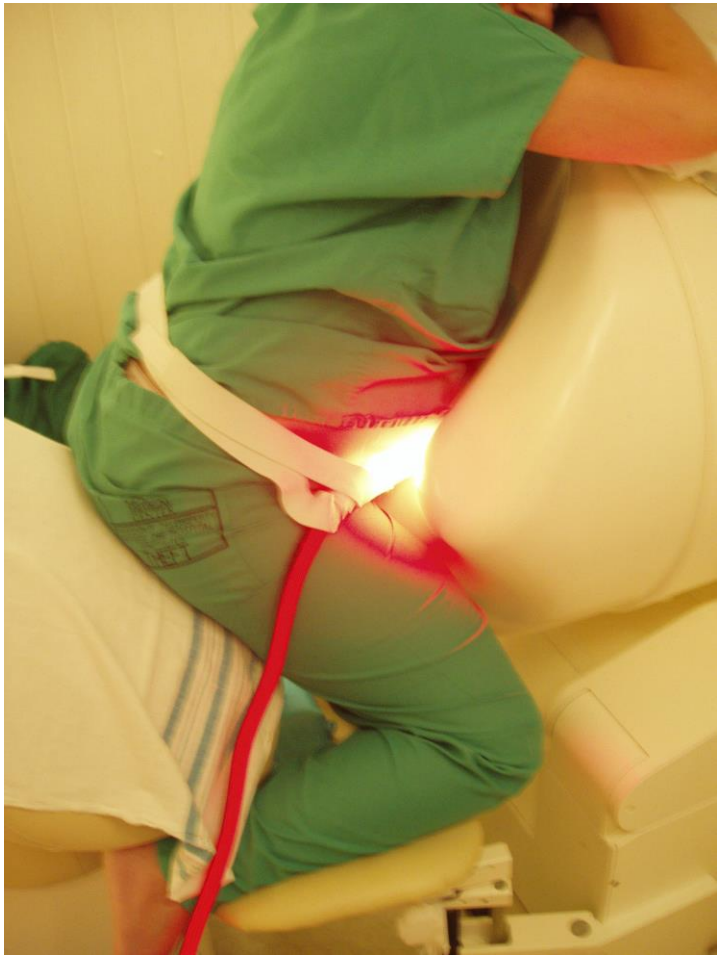
Draganova et al., Early Human Development, 2007; Draganova et al., Neuroimage, 2005

Response rate [%] and latencies of the fetal responses of the subtracted waveform [ms]				
	28 – 31 week	***32 – 35 week***	***36 – 39 week***	***28 to 39 week***
Response rate (MMN)	42 % (13/31)	46 % (13/28)	53 % (9/17)	46 % (35/76)
Mean (MMN) latency	326 $\pm$ 52	318 $\pm$ 37	323 $\pm$ 36	322 $\pm$ 42

Visual stimulation and evoked fields

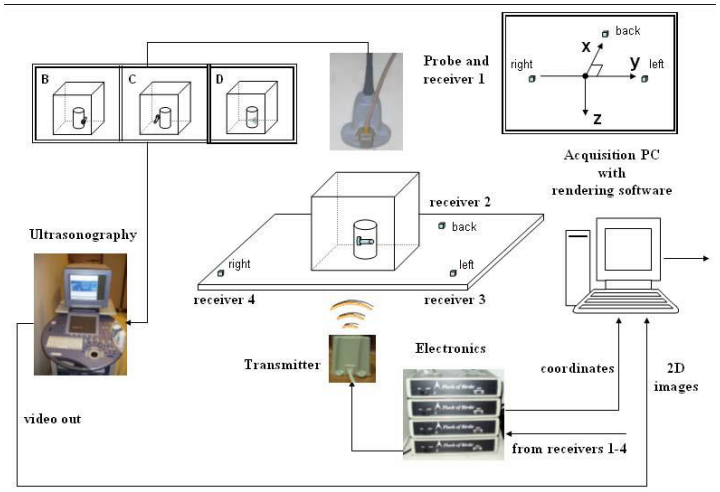




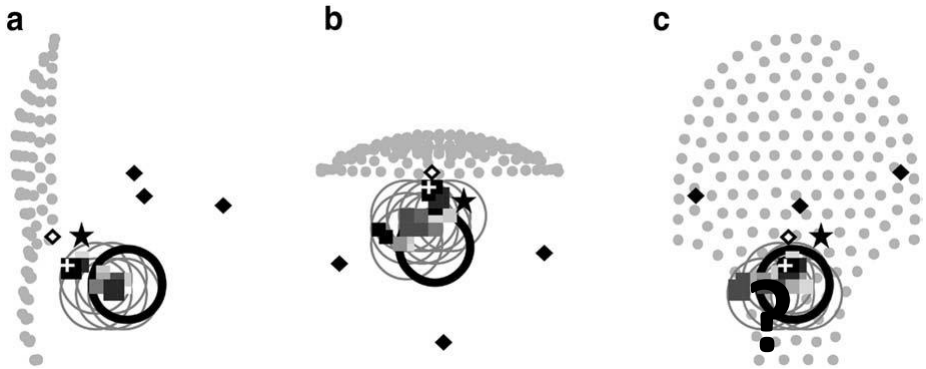


Eswaran et al., Lancet, 2002

Validation of fetal brain responses





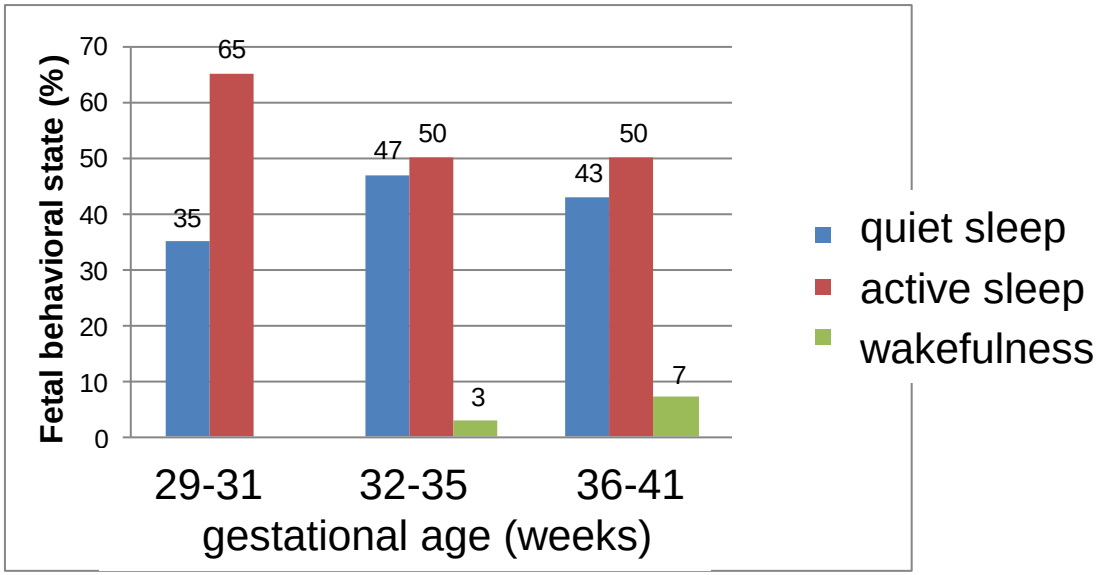


Micheli et al. Neuroimage 2010

Moraru et al. Physiol Meas. 2011
Micheli et al. Neuroimage 2010
McCubbin et al. Phys Med Biol. 2007
Vrba et al. Phys Med Biol. 2007
Vrba et al. Neuroimage. 2004
Chen et al. IEEE Trans Biomed Eng. 2006

Fetal behavioral states

Fetal state	**1F** = quiet sleep	**2F** = active sleep	**3F** = quiet awake	**4F** = active awake
Fetal heart rate (FHR) pattern	**FHR pattern A** stable heart rate. small oscillations <10bpm. low number of heart rate accelerations linked to movements	**FHR pattern B** heart rate with large oscillations >10bpm. heart rate accelerations occur during movement	**FHR pattern C** stable heart rate. larger oscillations >10bpm. no accelerations	**FHR pattern D** heart rate with large oscillations >20bpm. strong und long lasting accelerations. baseline can be higher than 160bpm
Body movement	very limited	often and regular	none	continuous and strong
Eye movement	absent	continuous	limited	continuous



Sonanini et al. (2013) JPM

Which neuronal processes are already established in fetal live

- auditory evoked fields can be recorded after 20th week of gestation and the latency decreases over gestation (Schleussner et al. 2001. Lengle et al. 2001. Holst et al. 2005)
- fetuses show mismatch like responses to auditory stimulation in the last trimester of gestation (Huotilainen et al. 2005. Draganova et al. 2005. 2007)
- visual evoked responses can be recorded in the last trimester of gestation and the response latency decreases over gestation (Eswaran et al. 2002. McCubbin et al. 2007)
- fetuses show habituation and dishabituation to auditory and visual stimuli (Matuz et al. 2012. Muenssinger et al. 2013 a.b)
- fetuses show numerosity related mismatch responses (Schleger et al. 2014)
- the fetal behavioral state influences the evoked response latency (Kiefer-Schmidt et al. 2013)
- Fetuses and newborns show no habituation to syllables (Hartkopf et al. 2016)

Fetal origin of diseases

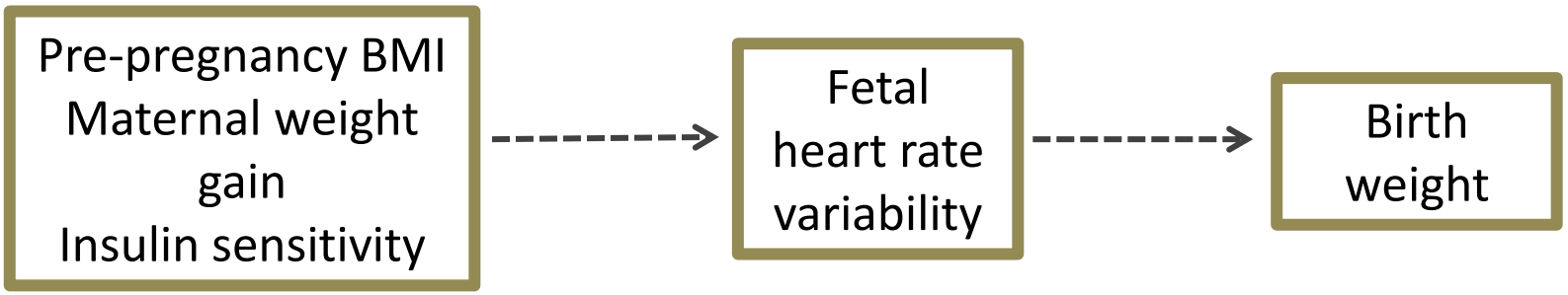


David Barker (1938-2013)

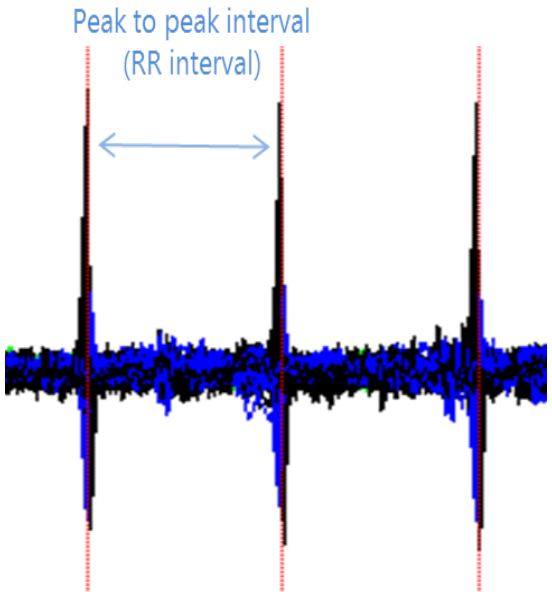
The old model of adult degenerative disease was based on the interaction between genes and an adverse environment in adult life. The new model that is developing will include programming by the environment in fetal and infant life.
Barker DJ. BMJ 1990

Fetal programming $\stackrel{?}{=}$ maladaptive brain plasticity

How does intrauterine environment impact autonomic nervous system development and offspring outcome at birth?



Assessment of fetal autonomic nervous system via heart rate variability



Fetal heart activity

Increase in heart rate and **decrease in heart rate variability** are indications of an **adverse effect of autonomic nervous system**

Thayer et al. 2010, Stein et al. 2007, Lambert et al. 2010, Malik et al. 1996

Fetal heart rate variability parameters

Time Domain	
Mean heart rate (beat per minute)	Sympathetic and parasympathetic tone
Standard deviation of peak to peak intervals (milisecond)	Overall heart rate variability (stability of heart rate)

Frequency Domain	
Low frequency (milisecond^2)	Sympathetic and parasympathetic modulation
High frequency (milisecond^2)	Primarily parasympathetic modulation
Low to high frequency ratio	Sympathovagal balance

Malik et al. Circulation 1996, David et al. J Appl Physiol 2006

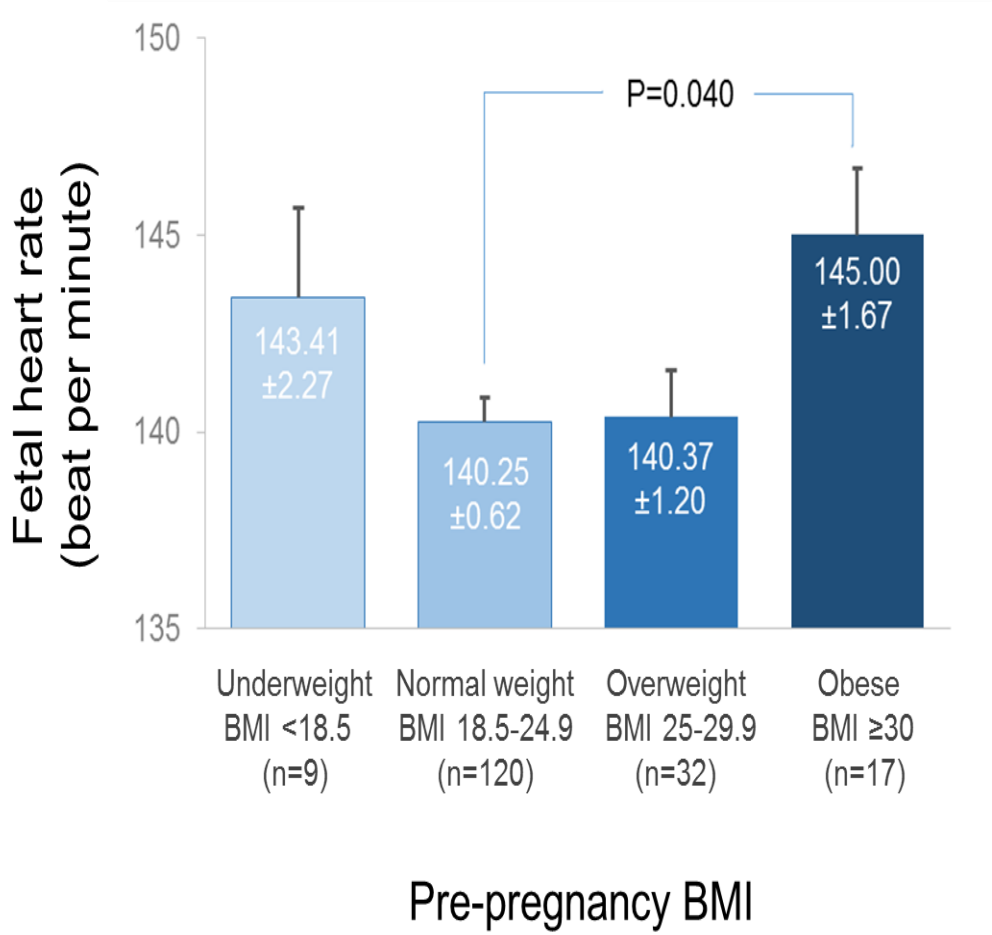
Study population

Maternal and fetal characteristics in 184 pregnant women with healthy pregnancies

Variables	Range	Mean	Standard deviation
Age (year)	21 - 45	31.70	5.26
Gestational age (week)	26 - 38	30.37	2.91
Pre-pregnancy BMI (kg/m^2)	16.8 – 42.4	23.59	3.96
Maternal weight gain (kg/week)	-0.24 – 0.93	0.38	0.21

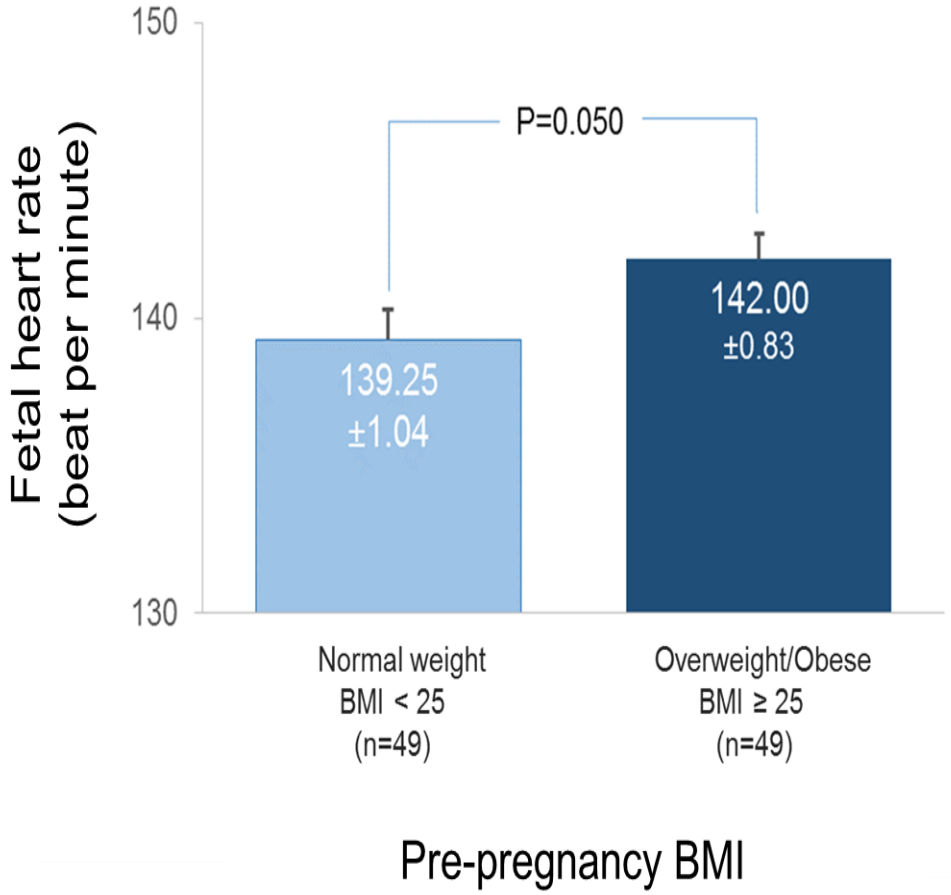
Maternal BMI and fetal heart rate

U-shape



Maternal BMI and fetal heart rate

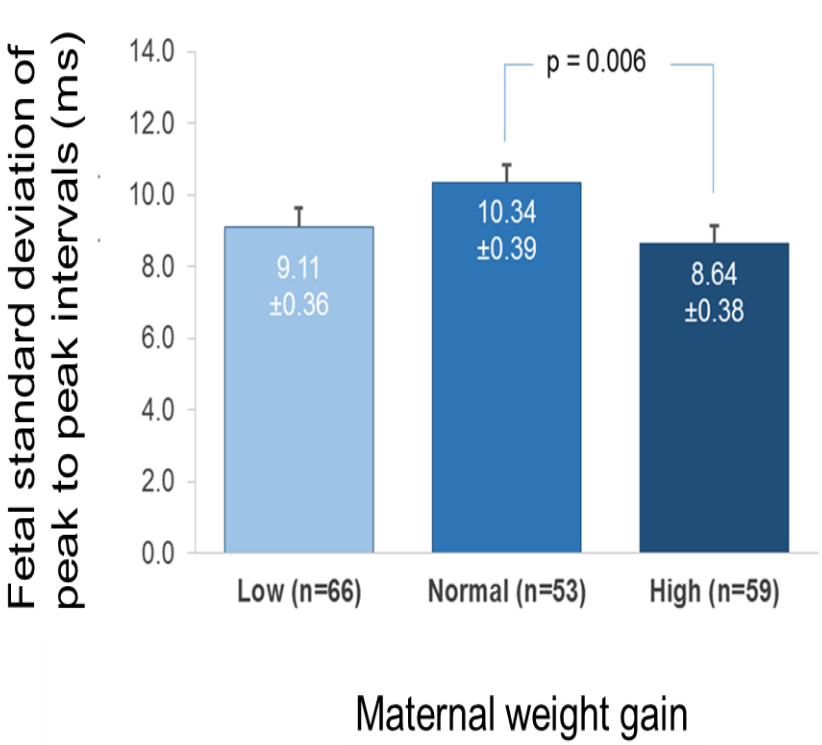
Case control analysis

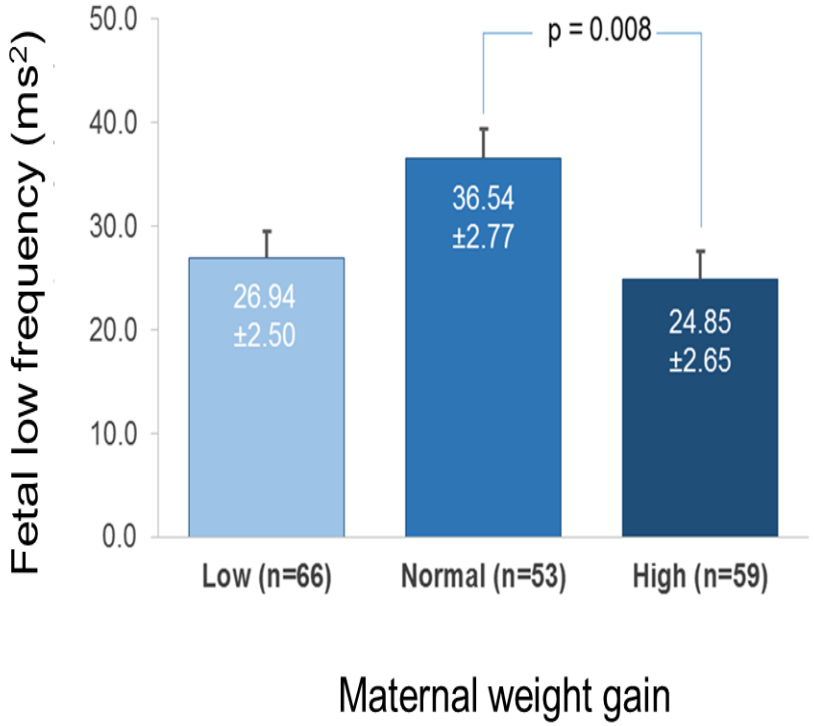


Matched for sex, gestational age and parity

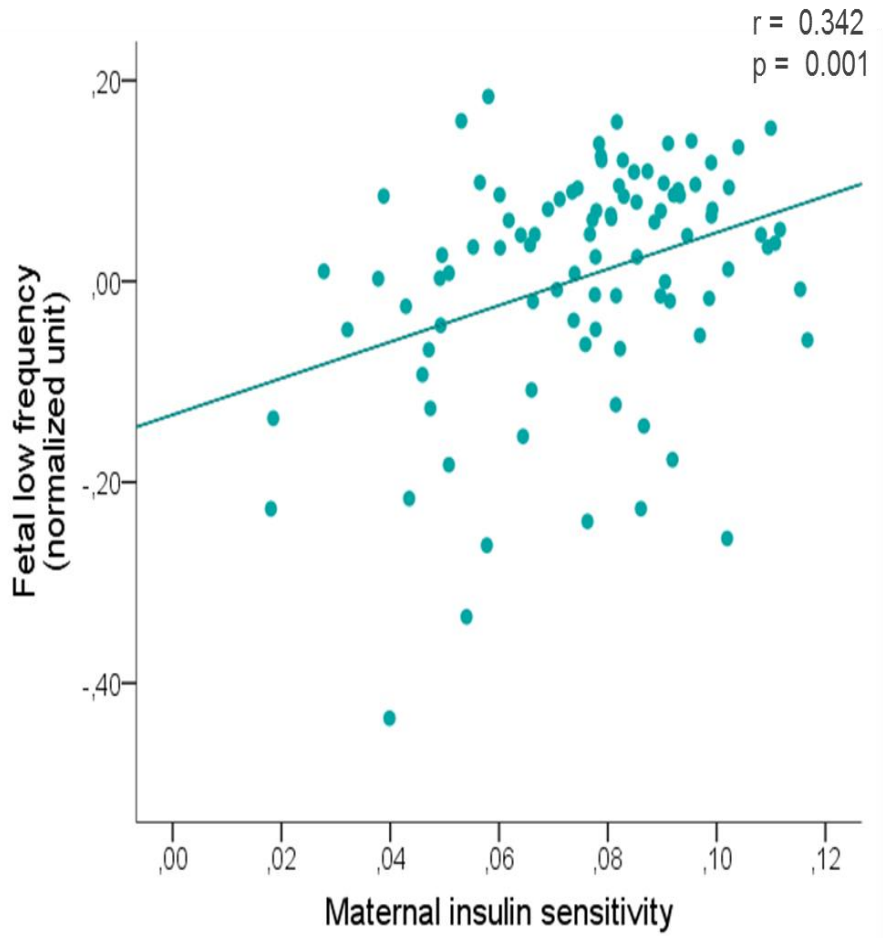
Maternal weight gain and fetal heart rate variability

Inverted u-shape





Maternal insulin sensitivity and fetal heart rate variability



Decreased fetal heart rate variability in maternal **insulin resistance**

Maternal metabolism in the fasting state and fetal heart rate variability

Maternal obesity - increase of fetal heart rate

Excessive weight gain - decrease of fetal heart rate variability

Maternal insulin resistance - decreased of fetal heart rate variability

→ **adverse effect of the autonomic nervous system**

Conclusion

Exposure of fetus to an imbalanced maternal metabolism has an adverse effect on the development of autonomic nervous system

Alterations in fetal autonomic nervous system predisposes for a metabolic imbalance and might contribute to the programming of obesity

Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants

NCD Risk Factor Collaboration (NCD-RisC)*

www.thelancet.com Published online April 6, 2016 http://dx.doi.org/10.1016/S0140-6736(16)00618-8

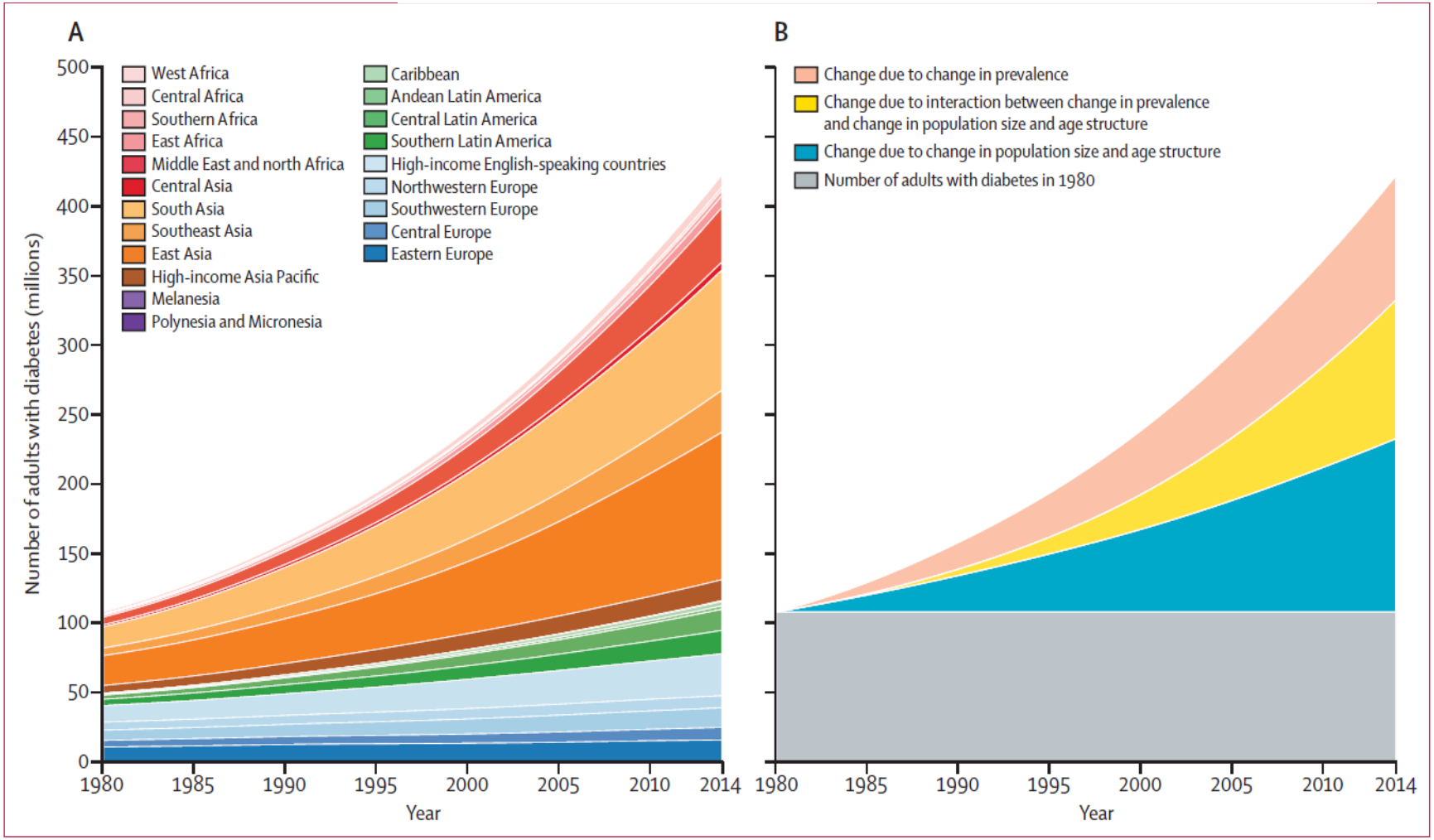


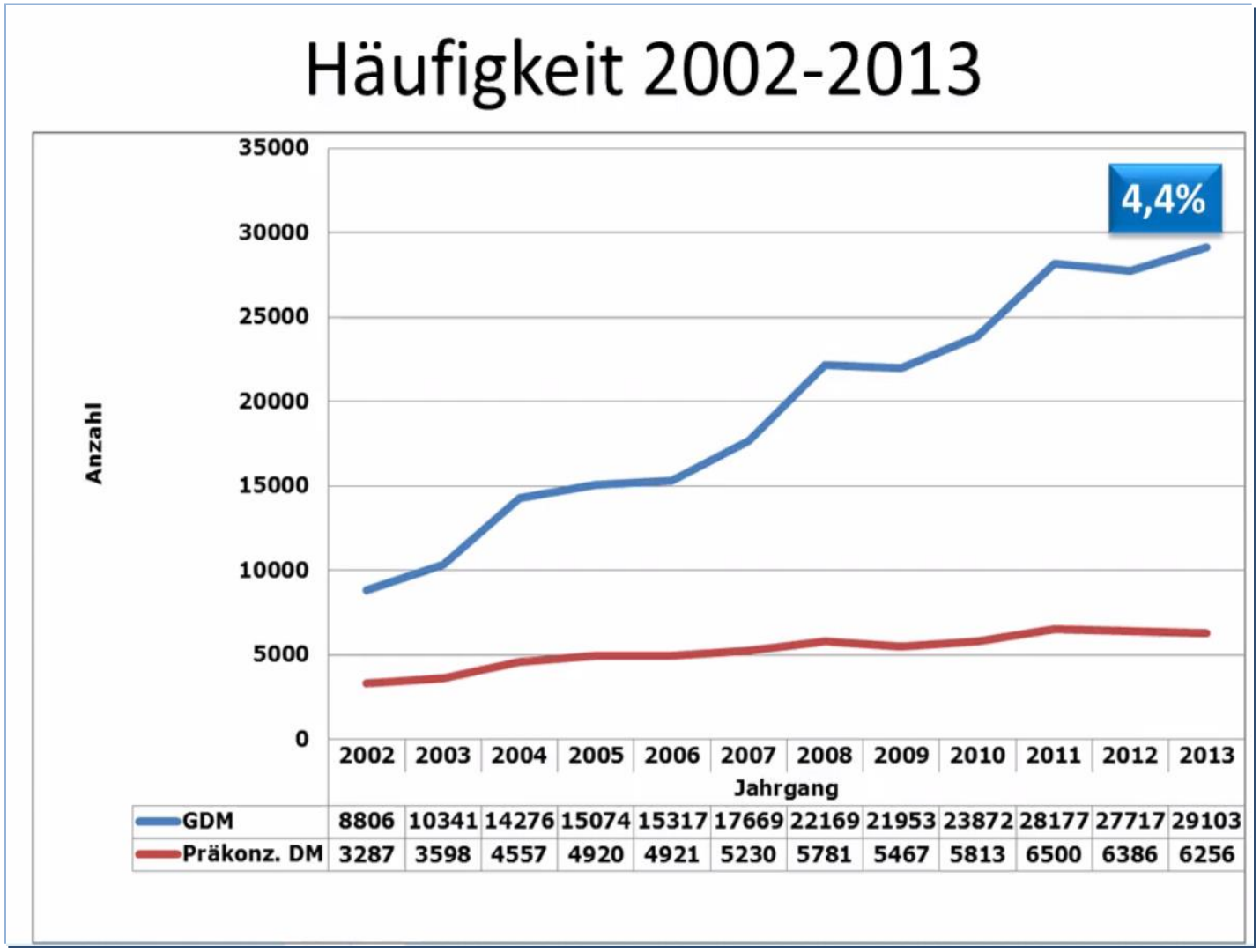
Figure 7: Trends in the number of adults with diabetes by region (A) and decomposed into the contributions of population growth and ageing, rise in prevalence, and interaction between the two (B)

Gestational diabetes

- during the pregnancy the insulin sensitivity of the mother decreases
- gestational diabetes mellitus (GDM) is defined by increased glucose levels during an oral glucose tolerance test (for screening performed around the 25th week of gestation)
- untreated GDM leads to fetal macrosomia and large for gestational age fetuses
- GDM leads to greater mean body mass index (BMI). fasting glucose and insulin and risk of type 2 diabetes in the offspring
- initial evidence indicate that GDM leads to neurodevelopmental problems in diverse functions (Fraser and Lawlor. 2014)

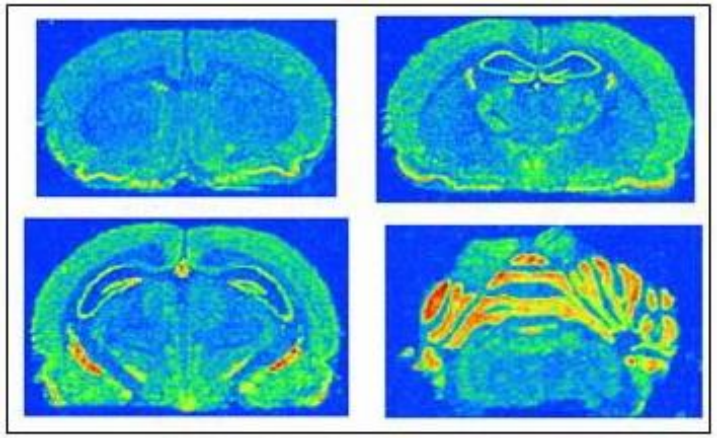
Gestational Diabetes (GDM)

Based on HAPO study 10-16% expected



Analyse Perinatalstatistik 2013 Quelle Kleinwechter DDG2014

Insulin in the brain



Havrankova J. et al. Nature. 1978.

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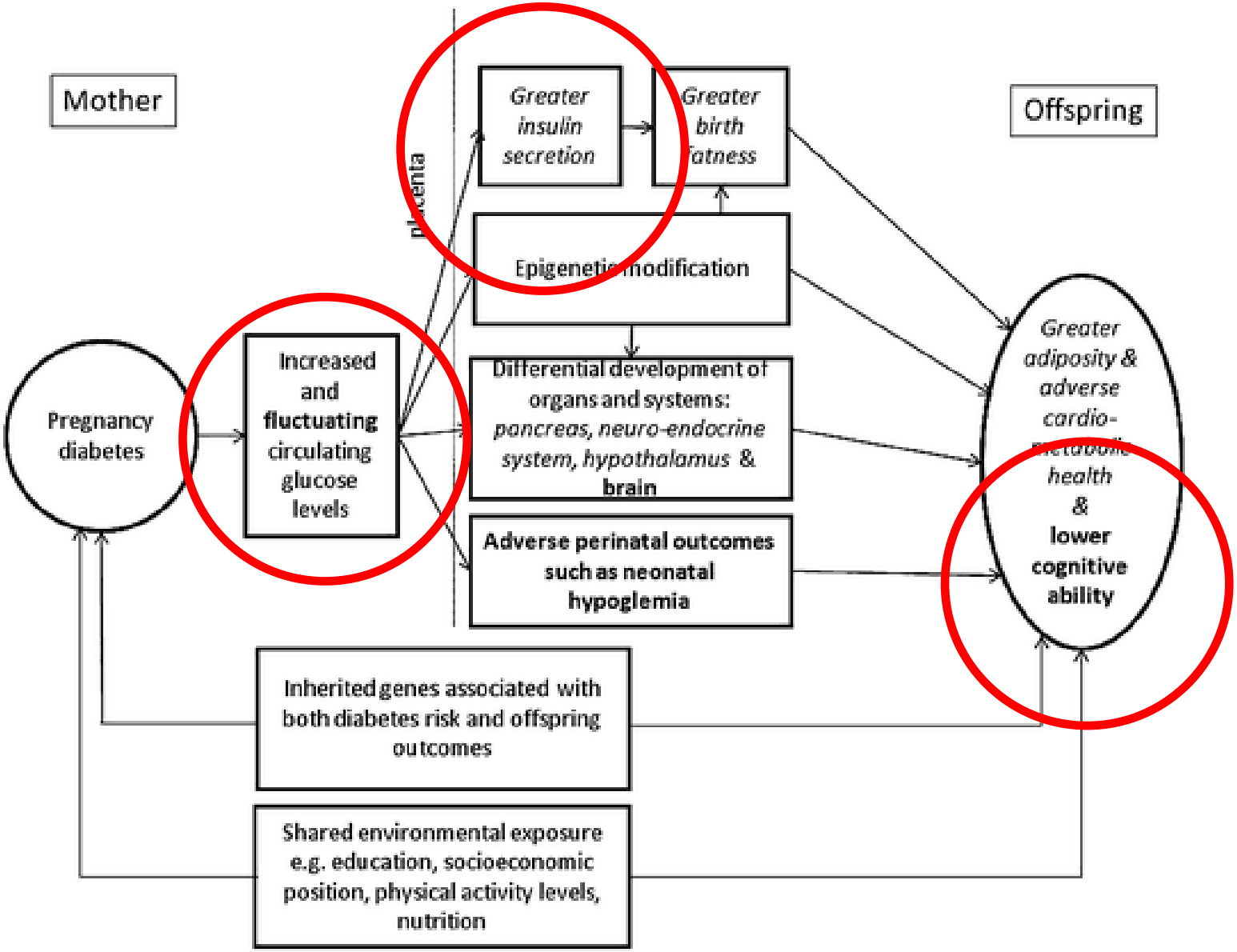
Knockout of Insulin receptors in the brain cause:

- Obesity
- Peripheral Insulin resistance

Brüning et al. Science. 2000; Nandi et al.. Physiological Revies. 2004..

Maternal-fetal Interaction



Fraser and Lowlar (2014) Current Diabetes Reports

The PREG study:
Prospective multicenter study at 6 DZD sites

Questions

GDM as risk factor Typ 2 Diabetes

Pathophysiology of GDM?

What is specific for children of GDM mothers?

Fetal programming?



The PREG Study



N=222

Metabolic phenotyping
at 24-32 weeks of gestation
(5-point OGTT. insulin secretion / sensitivity. metabolomics. microRNA)

Fetal MEG
Fetal programing

N=180

N=74

Gestational Diabetes

Controls

N=148

N=13

PEA POD
Infant body composition

Placenta
Umbilical Cord Blood

N=50



N=178

Follow-up visits mothers
1. 2. 5. 10 years postpartum
(OGTT. MRI/MRS. ergometry)

Follow-up visits offsprings
2. 6. 10 years postpartum

N=14

Study Design

baseline blood sample



OGTT solution



2. blood sample



3. blood sample



-30 0 60 120 Min.



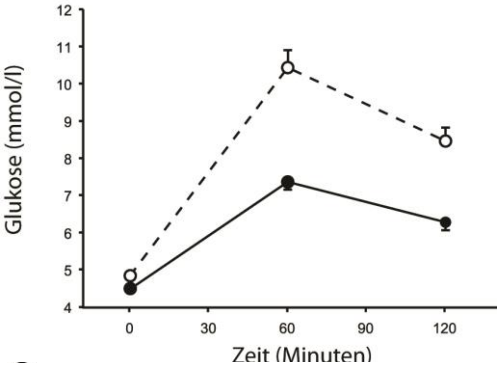
Baseline fMEG measurement

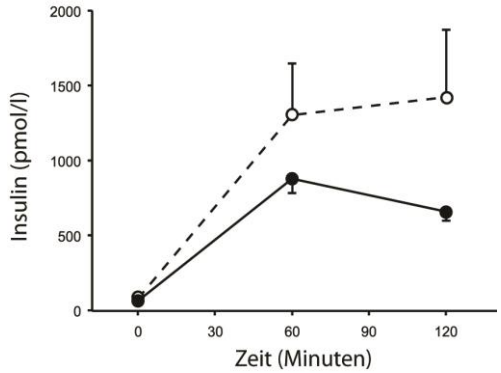


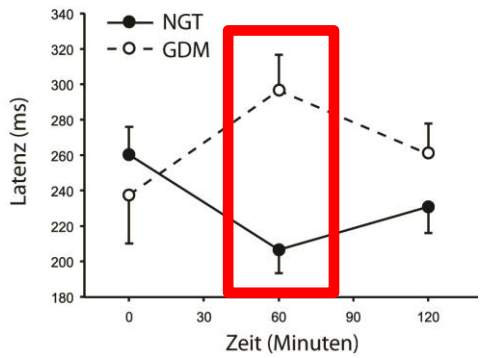
2. fMEG measurement



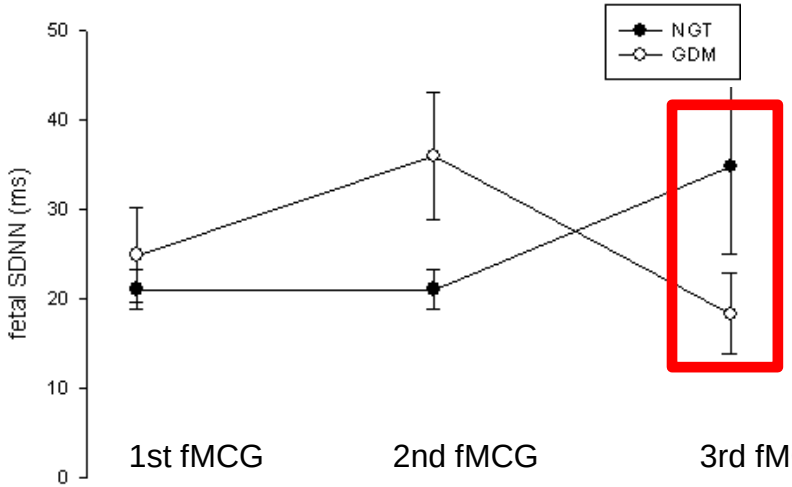
3. fMEG measurement







Linder et al.. 2015. JCEM



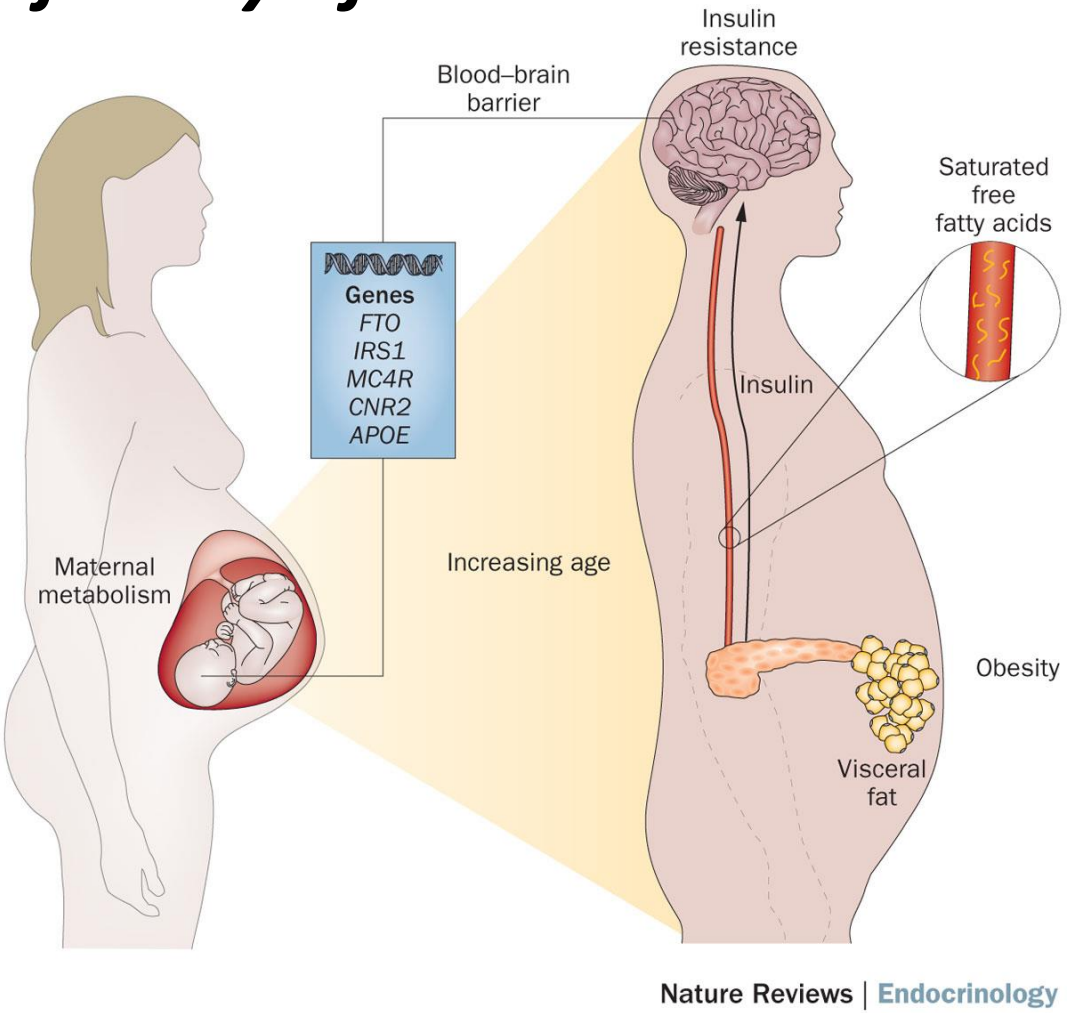
Fehlert et al. 2017. BJOG

Fetal Programming?



- Insulin action during hyperglycemia and hyperinsulimenia in a critical time period lead to disruption of metabolic brain networks in the newborn in the mouse (Vogt et al. (2014) Cell).
- Human fetal hyperinsulemia during the third trimester due to maternal metabolism may prevent the normal development of brain responses.

Trajectory of brain insulin action



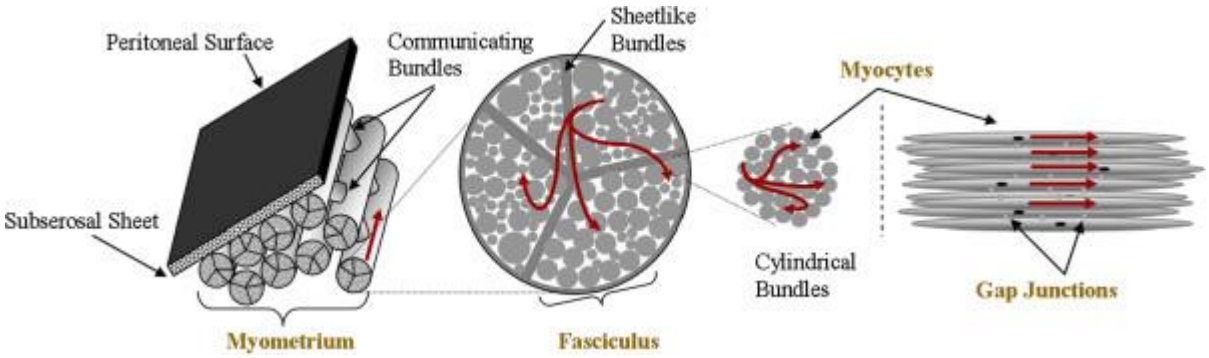
Heni et al. 2015 *Nat. Rev. Endocrinol.*

Questions addressed

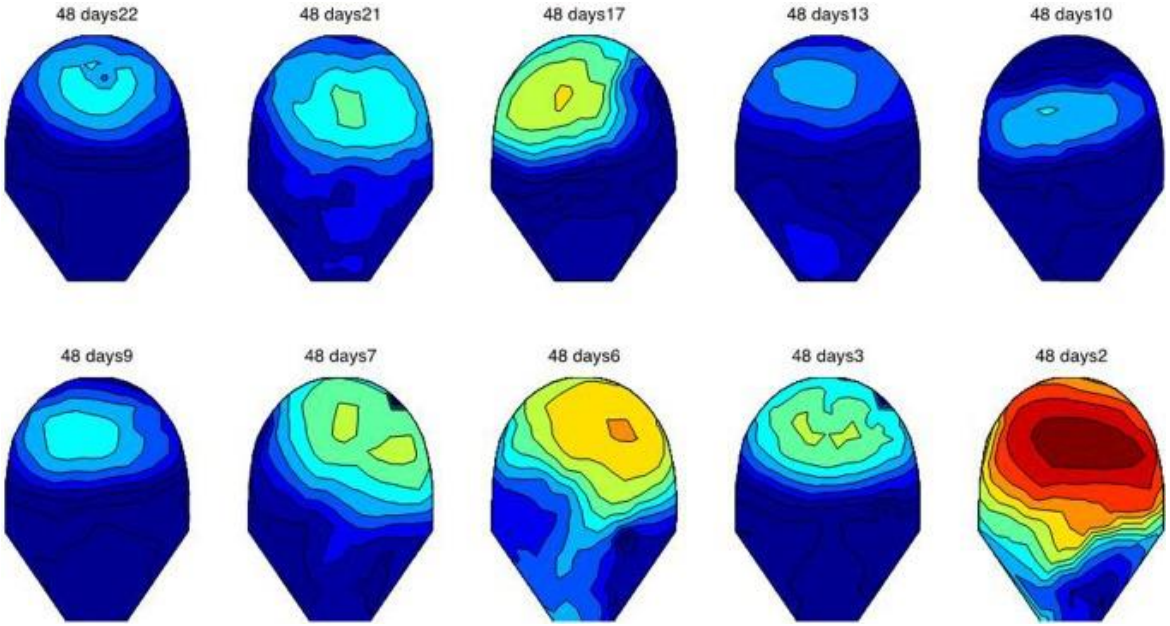
What is magnetoencephalography?
How can we measure magnetic fields generated in the human body?
Why do we need to measure magnetic fields in the human fetus?
What are the requirements to measure magnetic fields in the human fetus?
How can we use fetal biomagnetic recordings in research?
Are there possible clinical applications?
What is the future?

Preterm Delivery-Uterus Contraction

Costs associated with preterm delivery (<37 weeks of gestation) in 2007 26 Billion (USA)



La Rosa et al. BMC Med Phys. 2012 Nov 5;12:4.



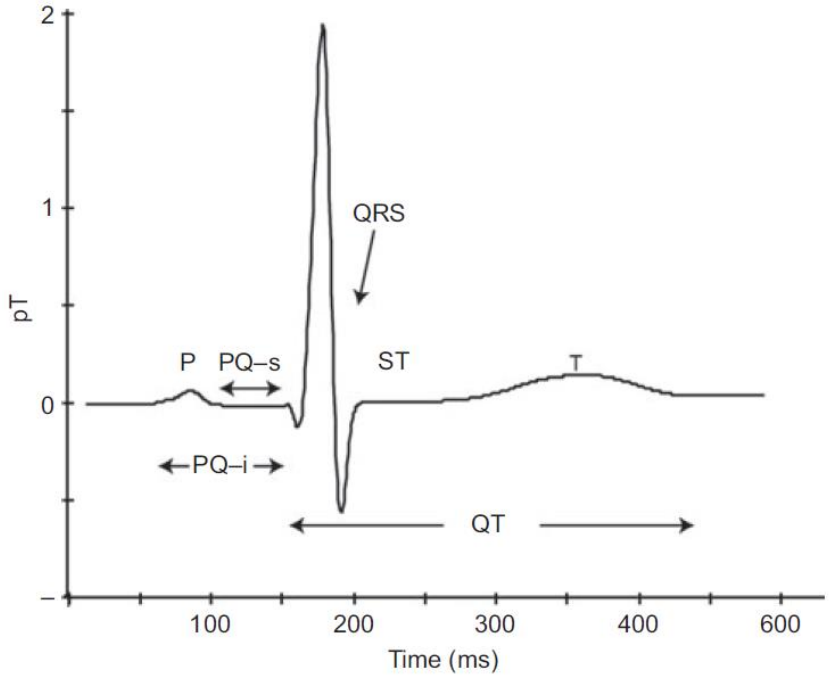
Synchronisation between sensors increases before delivery

Govindan et al. Reprod Sci 2015 May;22(5):595-601.

Fetal Arrhythmias and Cardiac Time Intervals

Regular fetal heart rate: 120-160 BPM (30 weeks of gestation)
Fetal Tachycardia: fetal heart rate > 160 BPM
Fetal Bradycardia: fetal heart rate < 120 BPM

Cardiac Time Intervals



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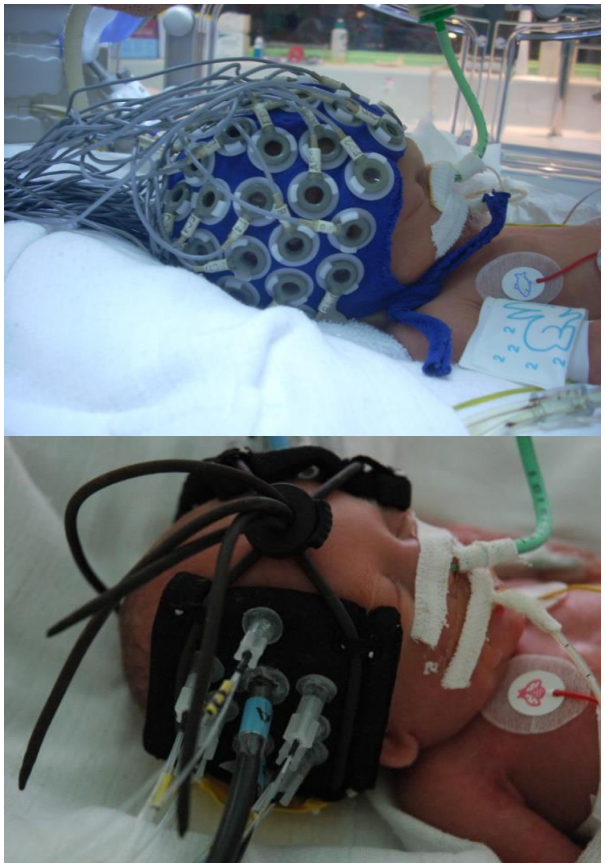
Brain Imaging during early development

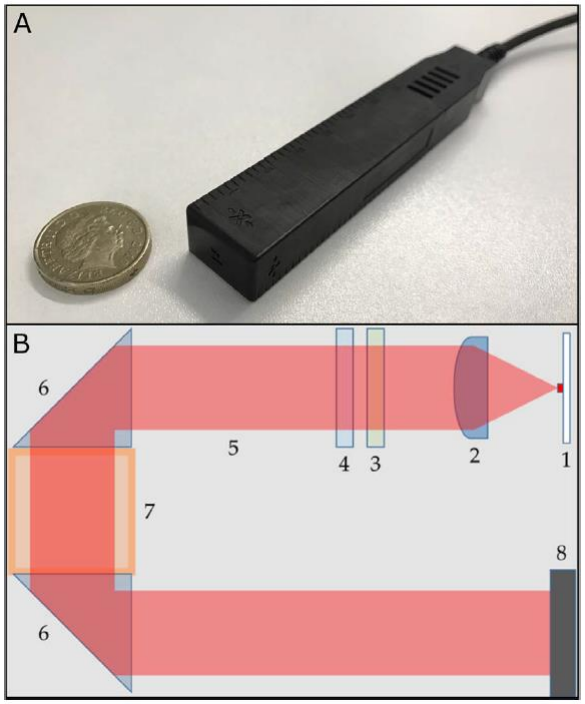


provided by Moriah Thomason



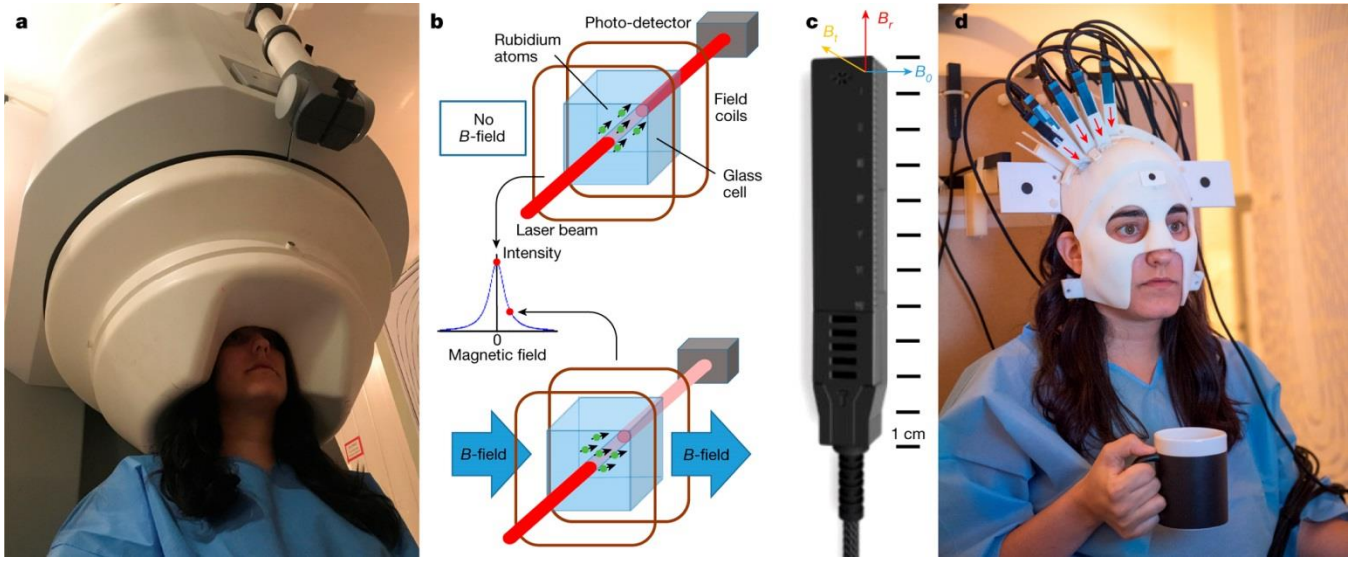
provided by Fabrice Wallois

Optically pumped magnetometer



E Boto *et al. NeuroImage 149 (2017) 404–414*

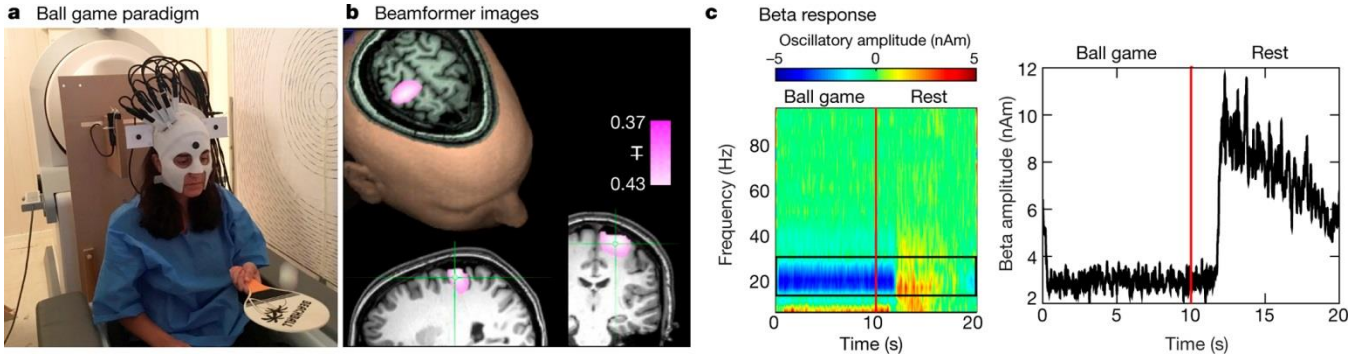
A new generation of MEG system



E Boto *et al. Nature* **555**, 657–661 (2018) doi:10.1038/nature26147

nature

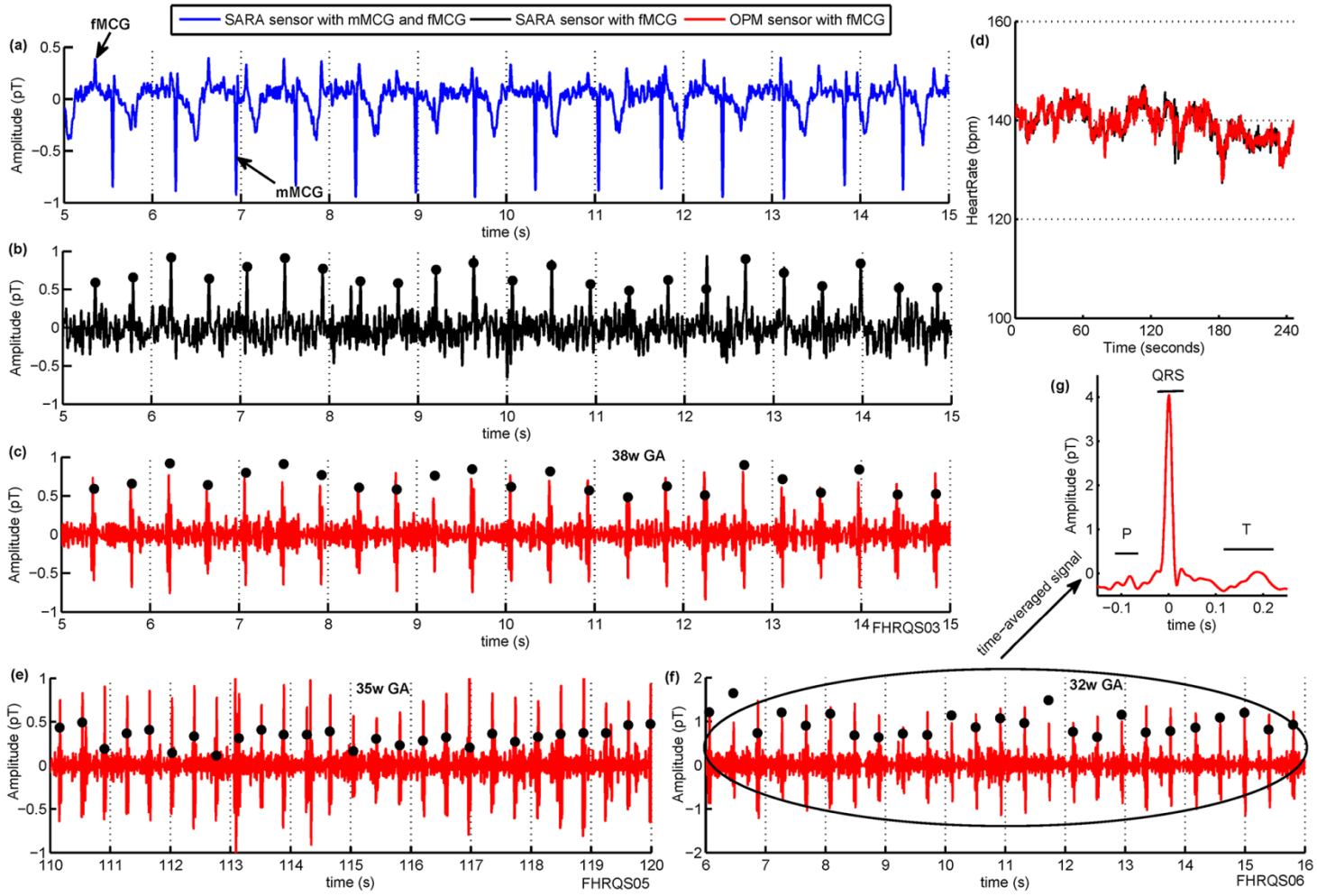
An example ‘real world’ imaging paradigm



E Boto *et al. Nature* **555**, 657–661 (2018) doi:10.1038/nature26147

nature

Fetal magnetocardiography using optically pumped magnetometers: a more adaptable and less expensive alternative?



Fetal magnetocardiography using optically pumped magnetometers: a more adaptable and less expensive alternative?, Volume: 37, Issue: 2, Pages: 193-196, First published: 27 November 2016, DOI: (10.1002/pd.4976)

Conclusion

- Fetal MEG provides unique information about the functional development of the human brain
- Fetal magnetocardiography adds additional information to investigate also the interaction of the brain and peripheral nervous system
- Important clinical questions can be addressed by fetal MEG and MCG
- Important basic science questions related to prenatal development can be investigated
- Limited diagnostic applications (arrhythmia, uterine contraction) and limited interventions



Thank you for your attention!