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Methodological and clinical aspects of ictal and interictal MEG

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ACADEMIC DISSERTATION

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List of original publications

The thesis is based on the following four original publications which will be referred to in the text by their Roman numerals (I-IV).

I. Medvedovsky, M., Taulu, S., Gaily, E., Metsähonkala, E. L., Mäkelä, J. P., Ekstein, D., Kipervasser, S., Neufeld, M. Y., Kramer, U., Blomstedt, G., Fried, I., Karppinen, A., Veshchev, I., Roivainen, R., Ben-Zeev, B., Goldberg-Stern, H., Wilenius, J., & Paetau, R. (2012). Sensitivity and specificity of seizure-onset zone estimation by ictal magnetoencephalography. *Epilepsia*, 53(9), 1649-1657.

II. Wilenius, J., Medvedovsky, M., Gaily, E., Metsähonkala, L., Mäkelä, J. P., Paetau, A., Valanne, L. & Paetau, R. (2013). Interictal MEG reveals focal cortical dysplasias: special focus on patients with no visible MRI lesions. *Epilepsy research*, 105(3), 337-348.

III. Medvedovsky, M., Taulu, S., Bikmullina, R., Ahonen, A., & Paetau, R. (2009). Fine tuning the correlation limit of spatio-temporal signal space separation for magnetoencephalography. *Journal of Neuroscience Methods*, 177(1), 203-211.

IV. Medvedovsky, M., Nenonen, J., Koptelova, A., Butorina, A., Paetau, R., Mäkelä, J. P., Ahonen, A., Simola, J., Gazit, T., & Taulu, S. (2015). Virtual MEG helmet: computer simulation of an approach to neuromagnetic field sampling. *IEEE Journal of Biomedical and Health Informatics*, in press.

In addition, the Thesis describes materials published in Medvedovsky, M., Taulu, S., Bikmullina, R., & Paetau, R. (2007). Artifact and head movement compensation in MEG. *Neuroogy, Neurophysioogy and Neuroscience*, 4, 1-10. This material will be referred in the text as "Additional Material".

Abbreviations

AEF – auditory evoked field
ASD – autism spectrum disorder
DBS – Deep brain stimulator
dSPM – dynamic statistical parametric mapping
ECD – equivalent current dipole
ECoG – electrocorticography
EEG – electroencephalography
FCD – focal cortical dysplasia
FDG-PET – 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography
fT – femtotesla
GOF – goodness-of-fit
icEEG – intracranial EEG
sicEEG – icEEG with subdural electrodes
dicEEG – icEEG with depth electrodes
HFO – high frequency oscillations
HLS scale – hemisphere, lobe, (lobar) surface scale
HPI – head position indicator
Hz – Hertz
IMMM – internal magnetostatic multipole moments
ICA – independent component analysis
IOZ – ictal onset zone
LKS – Landau-Kleffner syndrome
MCG – magnetocardiography
MC-SSS - movement compensation based on signal space separation (without temporal extension)
MC- tSSS – movement compensation based on spatio-temporal signal separation
MEG – magnetoencephalography
MNE – minimum norm estimate
MR – magnetic resonance
MRI – magnetic resonance imaging
MSR – magnetically shielded room
MTLE – mesial temporal lobe epilepsy
MUSIC – multiple signal classification
N20m –magnetic counterpart of the negative 20-ms (N20) response in EEG
NPV – negative predictive value
PPV – positive predictive value
RDSC – randomly distributed source current
RMS – root mean square
RSE –refractory status epilepticus
SI – primary somatosensory area
SAM –synthetic aperture magnetometry
SAM-G2 – excess kurtosis based synthetic aperture magnetometry
SD – standard deviation
SEF – somatosensory evoked field
SLO – sensor level orthogonalization (of lead fields)

sLORETA – standardized low resolution brain electromagnetic tomography
SNR – signal-to-noise ratio
SPECT – single photon emission computed tomography
SSP – signal-space projection
SSS – signal-space separation
SVD – singular value decomposition
SQUID – superconducting quantum interference device
TS – tuberous sclerosis
tSSS – spatio-temporal signal separation
tSSS CL – spatio-temporal signal separation correlation limit
VMH – virtual MEG helmet
VNS – vagus nerve stimulator

Abstract

Objectives

During the last twenty years magnetoencephalography (MEG) has become an important part of the pre-operative workup for epilepsy surgery. Interictal epileptiform activity is usually recorded during the workup. Nevertheless, the technological advances now enable ictal MEG recordings as well. This work is based on five studies, which are aimed at the evaluation and optimization of ictal and interictal MEG recordings.

Results

In Study I, the records of 26 pharmaco-resistant focal epilepsy patients who underwent ictal MEG and epilepsy surgery were retrospectively reviewed. In twelve patients prediction of ictal onset zone (IOZ) localization by ictal and interictal MEG was compared with ictal intracranial EEG (icEEG) recordings. On the lobar surface level the sensitivity of ictal MEG in IOZ location was 0.71 and the specificity 0.73. The sensitivity of the interictal MEG was 0.40 and specificity 0.77. Ictal MEG had similar sensitivity and specificity on dorsolateral and nondorsolateral surfaces of neocortex up to the depth of 4 cm from the scalp.

In Study II, the records of 34 operated epilepsy patients with focal cortical dysplasia were retrospectively evaluated. The resected proportion of interictal epileptic MEG spike source clusters was defined by overlaying of MEG spike sources and post-operative MRI. The resected proportion of the source cluster and other findings related to interictal MEG were evaluated in respect to postoperative seizure outcome. Seventeen out of thirty-four patients with FCD (50%) achieved seizure freedom. The seizure outcome was similar in patients with MR-invisible and MR-visible FCD. In patients with MEG source clusters and favorable seizure outcome (Engel class I and II) the average proportion of the cluster volume resection was 49%; this was significantly higher ($p=0.02$) than in patients with MEG source clusters but unfavorable seizure outcome (5.5% of cluster volume resection).

In Additional Material, somatosensory evoked MEG responses to electrical median nerve stimulation at wrist were processed by movement compensation based on signal space separation (MC-SSS) and on spatio-temporal signal space separation (MC-tSSS) to compensate for movement. The MEG recordings were done in standard head position and after the subject moved the head to the deviant position. The localization error of N20 magnetic response (N20m), baseline noise, goodness-of-fit (GOF) and 95% confidence volume were compared between data processed by MC-SSS vs. MC-tSSS. With up to 5 cm head displacement MC-SSS decreased the mean localization error from 3.97 to 2.13 cm, but increased noise of planar gradiometers from 3.4 to 5.3 fT/cm. MC-tSSS reduced the planar gradiometer noise from 3.4 to 2.8 fT/cm and reduced the mean localization error from 3.91 to 0.89 cm.

In Study III, the MEG data containing speech-related artifacts and data containing alpha rhythm were processed by tSSS with different correlation limits. The processed traces were compared. The efficiency of artifact removal and the preservation of brain signals were evaluated. The speech artifact was progressively suppressed with the decreasing

tSSS correlation limit. The good artifact suppression was achieved at correlation limits between 0.98 and 0.8. In one subject, correlation limit 0.6 was associated with some amplitude reduction of the alpha rhythm.

In Study IV, the randomly distributed source current (RDCS), and auditory and somatosensory evoked fields (AEFs and SEFs) were simulated. The information was calculated employing Shannon's theory of communication for a standard 306-sensor MEG device and for a virtual MEG helmet (VMH), which was constructed based on simulated MEG measurements in different head positions. With the simulation of 360 recorded events using RDCS model the maximum Shannon's number (bit/sample) was 989 for single head position in standard MEG array and 1272 in VMH (28.6% additional information). With AEFs the additional contribution of VMH was 12.6% and with SEFs only 1.1%.

Conclusions

Ictal MEG predicts location at the ictal onset zone with higher sensitivity than interictal MEG on the level of brain lobar surfaces.
The sensitivity and specificity of ictal MEG are similar for dorsolateral and non-dorsolateral sources of epileptiform activity (up to depths of about 4 cm from the scalp).

Resection of larger proportion of the MEG source cluster in patients with FCD is associated with a better seizure outcome.
In epilepsy associated with FCD, the seizure outcome is not substantially different between MR-positive and MR-negative patients.

The movement compensation based on tSSS decreases the source localization error to less than 1 cm, when the head is displaced up to 5 cm; however, in order to keep the head inside sensor helmet, it is reasonable to limit use of movement compensation for no more than 3-cm head displacement.

The optimization of the tSSS correlation limit can improve the artifact suppression in MEG without substantial change of brain signals. A correlation limit of about 0.8 can be optimal.

The MEG recording of the same brain activity in different head positions with subsequent construction of VMH can in some circumstances improve the information content of the recorded data.

1. Introduction

During the last three decades MEG has become an important part of the epilepsy pre-surgery workup. Nevertheless, this method has several points requiring further development:

1) MEG is usually less suitable for ictal recording than EEG.
2) MEG is sensitive to head displacements and moving magnetic materials.
3) MEG source localization requires solving the "inverse problem".

Ictal MEG.

The majority of MEG studies in epilepsy report estimated sources of interictal epileptiform spikes. Whereas a systematic ictal EEG recording employing video-EEG method is a clinical standard, ictal MEG has mainly been recorded incidentally. The resection of ictal onset zone is considered as an obligatory (although not always sufficient) condition for postoperative seizure freedom. Therefore, non-invasive estimation of the ictal onset zone location based on ictal data recording could substantially benefit the epilepsy surgery: in patients without visible lesion on MRI it could reduce the number of electrodes needed for intracranial EEG monitoring, and in some patients with the MR-visible lesions it could make intracranial EEG monitoring unnecessary. The limited use of MEG for ictal studies is related to the intrinsic technical properties of neuromagnetic method. One such property is the possibility of head movements in relation to the rigid MEG sensor array during recording. In EEG recording, the electrodes are moving together with the head.

Seizures are the central feature of epilepsy. Estimation of the ictal onset zone location is an important goal of epilepsy pre-surgery workup. Therefore, it is tempting to use the high spatial and temporal accuracy of MEG to localize the ictal onset zone. However, ictal events are usually much less frequent than interictal ones. Moreover, ictal MEG signal occasionally consists of oscillations in the beta-gamma range, which may have lower SNR than interictal epileptiform spikes. Thus, despite many hours of MEG recording, sometimes after reduction of antiepileptic drugs, and despite seizures during MEG measurement, we still may not be able to use the ictal information for therapy planning. Taking into account all these difficulties of ictal MEG the natural question is: What is the value of ictal MEG in comparison to interictal MEG?

Sensitivity of MEG to head movement and to magnetic materials

MEG is sensitive to weak magnetic fields produced by the brain's electric activity. It is, however, also sensitive to the magnetic artifacts. In addition, head displacements inside the MEG helmet can influence the source localization accuracy. In basic neuroscience MEG studies, one can choose subjects who are able to avoid the head movements during data acquisition and have no implanted magnetic materials producing artifacts. In clinical practice, however, patients often have implanted magnetized objects, such as vagus nerve stimulator (VNS), dental fillings or implants, and often cannot keep the head position stable. Head movements are a source of two types of problems:

1) The uncompensated head movement displaces the estimated source from true source location.
2) Head movement creates motion artifacts.

A recently developed signal space separation (SSS) method (Taulu et al, 2004; Taulu & Kajola, 2005) and its temporal extension (tSSS; Taulu & Simola, 2006) have provided a basis for movement compensation and suppression of artifacts. This enables MEG recording without the necessity to keep the head in the exactly same position. The successful suppression of artifacts whose sources are located near to MEG sensors has increased possibilities of MEG diagnostics for the patients with implanted metallic objects. Importantly, tSSS can suppress the head motion artifacts, improving SNR on the MEG sensor level and thereby enable a useful MEG recording during ictal head movements.

Theoretically, the head movements can enrich MEG measurements by increasing the variation of the spatial relations of sources and sensors. The same principle was demonstrated in a simulation study dealing with localization of ferromagnetic objects in the earth (Eichardt & Haueisen, 2010).

Ill-posed inverse problem

The single equivalent current dipole is not always an appropriate model for a spatially complex source, whereas distributed linear modes (such as minimum norm estimate) are based on the very underdetermined linear system (much more sources than sensors). The assessment of the accuracy and clinical value of source estimation can be done by comparing the MEG sources of epileptiform activity to the location of histopathologically proven epileptogenic lesion (such as focal cortical dysplasia; FCD).

The main purpose of the thesis is to search for ways to maximize the information obtained by ictal and interictal MEG recordings. This thesis deals with:

1. Evaluation of specificity and sensitivity of ictal vs. interictal MEG.
2. Evaluation of the accuracy of interictal MEG in patients with focal cortical dysplasias (FCD).
3. Application of movement compensation to the MEG data.
4. Fine tuning of tSSS method targeted to avoid small and difficult-to-recognize artifact residuals.
5. Utilizing the head movements for MEG data quality improvement (the virtual MEG helmet approach).

2. Survey of the literature

2.1. Neuromagnetic method

Human biomagnetic measurements started by recordings of magnetic field produced by the heart, magnetocadiography (MCG; Baule & McFee, 1963). The recordings were done in an unshielded environment with an induction coil magnetometer; multiple MCG sweeps were averaged. The development of magnetically shielded room (MSR) enabled the recording of much weaker magnetoencephalography (MEG), the magnetic fields of the brain. The magnetic field associated with the spontaneous human alpha rhythm was reported in 1968 (Cohen, 1968). This recording was done with a relatively insensitive one-channel induction coil magnetometer similar to one used by Baule and McFee. The introduction of superconducting quantum interference device (SQUID) (Zimmerman et al, 1970) made feasible the construction of highly sensitive biomagnetic detectors. The development of MSR and SQUID became the basis at the low-noise MEG recordings, applicable in clinical practice and neuroscience. For reviews of the neuromagnetic method see e.g. Hämäläinen et al. 1993; Mäkelä, 2014.

2.1.1 General features of neuromagnetic field

MEG and EEG measure the sum of the potentials related to neuronal postsynaptic electric currents, which can be classified to trans-membrane currents, intracellular (primary) currents, and extracellular (volume or secondary) currents (Hari, 1993). Postsynaptic potentials on the cortical dendrites oriented perpendicularly to the cortical columns are the main source of the neuromagnetic signal (Nunez et al, 2014).

MEG signal changes relatively slowly, usually with frequencies less than 200 Hz. Therefore, the effect of induction can be considered as negligible. This enables the use of the quasi-static approximation of Maxwell's equations. Thus the vector of magnetic field B(r) in the location r can be described using Biot-Savart law:

$$B(r) = \frac{\mu_0}{4\pi} \int J(r') \times \frac{r - r'}{\left\| r - r' \right\|^3} dv' \qquad (2.1)$$

Where *J(r')* is the vector of quasi-static primary electrical current at the location r'; μ_0 is the permittivity of free space; and *v* is the volume conductor.

According to equation 2.1, the increase in distance from the source current attenuates the magnetic field in power of two; therefore, deep sources produce lower SNR than superficial ones. In the spherical conductor the electrical currents directed radially to the head surface do not produce a magnetic field. In other words, only projection of the current vector to the plane tangential to the head surface can produce magnetic field in the spherical conductor.

Neuromagnetic fields are very weak, about one billionth of the steady geomagnetic field of the earth. Two centimeters above the scalp, the amplitude of the brain magnetic

background activity is about 30 $fT/\sqrt{Hz}$ and the amplitudes of interictal epileptic spike about 60-200 *fT*.

In order to produce a current, characterized by the dipole moment of 10 nAm, the cortical area of about 2 cm^2 should be synchronously activated (Hari, 1990). A cortical area of about 4 cm^2 is required to be activated to produce an epileptiform spike visible in MEG (Mikuni et al. 1998). MEG is able to record the averaged magnetic fields of brain currents weaker than 2 nAm (Parkkonen et al. 2009).

2.1.2 Comparison between EEG and MEG

There are three main differences between EEG and MEG:

1. In the spherical conductor only electric currents directed tangentially to the conductor surface produce magnetic field outside the conductor. Therefore MEG is sensitive to the electric currents directed tangentially to the surface of the head (if the head is approximated as a spherical conductor). Electric field on the scalp can be produced by both tangentially and radially oriented electric brain currents. Then, taking into account the structural organization of cortical dendritic tree, one can assume that the MEG signal is mainly produced by unbalanced activation of the cortical sulcal walls.

2. Electric field, measured by EEG, is distorted due to conductivity differences between brain, skull and scalp. In contrast, the magnetic field measured by MEG is not influenced substantially by tissue conductivities. In other words, MEG is less sensitive to the secondary currents, generated by the primary neuronal currents, than EEG.

3. EEG requires a contact between electrodes and the scalp, whereas MEG sensor can be placed at some distance form the head.

The first two differences simplify the forward model of MEG and, therefore, stabilize the inverse problem solution, making magnetic field source localization (using MEG) more robust than electric field source localization (using EEG). When the brain electrical currents are directed mainly radially to the head surface, as in activations of the gyral crowns, EEG may have an advantage over MEG (Merlet et al, 1997). However, only a very small portion of the cortex has a suboptimal orientation for MEG (Hildebrand and Barnes 2002). Thus, EEG and MEG are complimentary methods (Molins et al, 2008).

The third difference - contactless sensing of magnetic field- enables placement of the MEG sensors at different distances from the scalp. Moreover, depending on the orientation, MEG sensor can record radial and tangential components of the magnetic field (not to be confused with tangential source currents). In the majority of existing MEG devices, the MEG sensors are oriented so that they are sensitive to radial components of the magnetic field, but according to simulations (Nurminen et al. 2010) and real measurements (Nurminen et al. 2013) the placement of MEG sensors at different layers and angles adds information to MEG measurements.

2.1.3 MEG instrumentation

The MEG sensor has two parts: the SQUID and sensor coils. Both are made of a superconducting material, niobium, and are cooled by liquid helium, with a boiling point at 4.2 K (-269^{o} C). The sensor coil has several parts:

1. a pick-up coil, usually located as close as possible to the scalp.
2. a compensation coil (only in gradiometers).
3. a signal coil, located on the top of SQUID.

Three types of sensor coils are used in MEG devices:

1. Magnetometer (no compensation coils).
2. An axial gradiometer (the compensation coil is located several centimeters above the pick-up coil).
3. A planar gradiometer (the pick-up coil and the compensation coil are located in the same plane).

Magnetometers are more sensitive to the deep sources, but also to the environmental noise (for reviews, see Williamson and Kaufman, 1981; Romani et al, 1982; Ilmoniemi et al, 1989; Hari and Lounasmaa, 1989; Hämäläinen et al, 1993; Parkkonen, 2010). In an Elekta Neuromag® 306 sensor device, which was used in all experiments presented in this thesis, the sensors are organized into 102 thin film triple-sensors which consist of two planar gradiometers and one magnetometer (Laine et al, 1999).

The spatial sensitivity of the MEG sensor can be expressed as a vector field called lead field:

$$b_i = \int L_i(r') \cdot j_p(r') dv' \qquad (2.2)$$

Where b_i is the output of the sensor i; L_i is the lead field vector of the sensor i at the location r'; j_p is the primary current at the location r'; v' is the volume conductor. The direction of the sensor's lead field in each location corresponds to direction of the electrical current which produces the maximum output of the sensor.

The first SQUID neuromagnetic measurement using one sensor was reported by Cohen, 1972. The first multichannel (4-5 sensors) MEG devices were constructed about ten years later (Ilmoniemi et al. 1984, Romani et al. 1985, Williamson et al. 1985). A high-quality 7-sensor device was built on 1987 (Knuutila et al. 1987). The early devices covered only a small head area. To provide adequate neuromagnetic field sampling, the device had to be moved several times across the scalp to record the complete magnetic field related to a specific brain activity. MEG devices housing 19-37 sensors were constructed subsequently (Kajola et al. 1989, ter Brake et al. 1990, Hoening et al. 1991; Koch et al 1992). These larger sensor arrays covered the area of at least 10 cm^2 and, therefore, often provided the adequate magnetic field sampling of e.g., sensory cortical activity in one position. A larger 64-channel device with first order gradiometers was manufactured by CTF systems Inc. (Port Coquitlam, Canada; Vrba et al. 1993). The first whole head MEG device was constructed in 1992 by Neuromag Ltd., Espoo,

Finland (Ahonen et al. 1992, Knuutila et al.1993). It housed 122 planar first order gradiometers. The modern devices have 240-306 MEG sensors including magnetometers, axial gradiometers, planar gradiometers or their combinations. In order to keep SQUIDs and sensor loops superconductive, they should be kept in a thermo-isolating device filled by liquid helium. Such device (dewar; invented by James Dewar) has two concentric vessels, with a vacuum jacket and a radiation shield separating them. The vacuum jacket prevents thermal convection and the radiation shield protects against thermal radiation. MEG is recorded in magnetically shielded room (MSR), which is made of mu-metal and aluminum. More details about MSR are provided in the subsection 5.5.1.1.

2.1.4 MEG signal analysis

Preprocessing, including noise cancellation, is discussed in the subsection 2.5 and MEG-MRI co-registration in the subsection 2.4 of the thesis.

At present, the main role of MEG both in neuroscience and in clinical practice is the source localization of neuromagnetic fields. The source localization represents the inverse problem: the magnetic field outside the scalp is known and one should estimate the intracerebral source currents of this field. Because more than one source solution can explain the given field pattern, the neuromagnetic source localization is an ill posed problem. Before solving the inverse problem, a forward model needs to be defined. Forward MEG model calculates the magnetic field out of the head or the output of MEG sensors associated with the primary current in the brain. (For reviews of forward and inverse models, see Baillet et al, 2001; Baillet, 2010; Hämäläinen et al, 2010).

Forward model includes a source model, a volume conductor (head) model, and a sensor array model. The source currents are traditionally modeled as one or multiple equivalent current dipoles (e.g. Hämäläinen et. al, 1993). However, when a large brain area can be simultaneously activated, multipolar (in particular, quadripolar) source model can be applied (Jerbi et al, 2002, Jerbi et al, 2004). A multi-shell spherical volume conductor model can consist of concentric spheres corresponding to the brain, skull and scalp (Meijs et al 1988). Due to relative insensitivity to tissue conductivities, a homogenic spherical model is also satisfactory for MEG (Sarvas, 1987). Spherical head model can be fitted to the center of the head or to the region of the head where the activity is located (Hari and Ilmoniemi, 1986).

The realistic head models can be used in MEG analysis, but are more important in modeling EEG. Examples of realistic head models are the boundary element method (Mosher et al, 1999) and the finite element method (Ho-Le et al, 1988). Source and volume conductor models are needed to calculate the vectors of magnetic field outside the head. In order to compute the MEG sensor output (scalar values), it is necessary to model the locations, orientations and configurations of the MEG sensors as well.

Inverse models can be classified into the following two types: nonlinear (parametric or localization) models and linear (imaging) models. All inverse models require comparison between the measured and expected signals, calculated from estimated sources by applying a forward model. The traditional way to evaluate this comparison is to use the least square criterion, i.e., finding the source solution which is associated with minimum squared difference between the expected and measured signal. According to

the Biot-Savart law (equation 2.1) it is clear that the magnetic signal non-linearly depends on position and magnitude of the electrical current. Therefore, if both position and magnitude of the current are not fixed, the model is non-linear. The example of the non-linear model is an equivalent current dipole (ECD). This approach is useful when the brain activity is focal. In linear models, the dipole locations and orientations are fixed whereas the dipole magnitudes can vary. An example of the linear model is the minimum norm estimate (MNE) (Hämäläinen & Ilmoniemi, 1984). In MNE the dipoles are organized in a grid either into the whole brain volume or to the cortex, taking into account the orientation of cortical surface (Lin et al, 2006). Spatial filters (beamformers) represent the scanning processes which evaluate the different signal components fit to the source limited to the given location (Spencer et al, 1992; Robinson & Vrba, 1999). The signal components which have no good fit to any of the brain locations are considered as noise. Thus, beamformers improve the SNR of the signals arising from the brain. However, when two (or more) brain sources have synchronous time courses, the beamformer can misclassify them as noise. The beamformers can be considered as a separate class of methods solving the inverse problem, although beamformers and L2 minimum norm estimates can be brought to common theoretical framework (Mosher et al. 2003; Lütkenhöner and Mosher 2006).

2.2 Interictal MEG in epilepsy

One important clinical use of MEG is source localization of epileptiform activity in presurgical workup of pharmaco-resistant epilepsy. Epileptiform signals result from pathological hypersynchronization of neuronal postsynaptic currents. This provides relatively high amplitude to epileptiform MEG and EEG signal, enabling source estimation of unaveraged signals. The comprehensive review of interictal MEG in epilepsy can be found in Knowlton & Shih, 2004, Knowlton, 2006, Mäkelä et al, 2006, Mäkelä, 2014, Kharkar & Knowlton, 2014, Iwasaki & Nakasato, 2014.

2.2.1 First reports of interictal MEG in epilepsy

The first MEGs of epileptiform activity displayed rhythmic theta activity (Cohen, 1972), and 3-Hz spike and wave complexes (Hughes et al, 1977). A single sensor MEG device was used in the first MEG source localizations of epileptiform activity (Barth et al, 1982; Modena et al, 1982). The epileptiform spikes were recorded in different scalp locations by moving the dewar. Spikes in a simultaneous EEG recording were used as a trigger to interpolate and average the MEG spikes. Multiple sources related to epileptiform MEG spikes became evident (Barth et al, 1984a). In temporal lobe epilepsy patients the location of epileptiform spike sources was confirmed by ECoG (Rose et al, 1987) and by MRI findings (Stefan et al, 1990). Discordance of anatomical and functional pathology was demonstrated in a patient with a large arachnoid cyst (Paetau et al, 1992). Progressively larger groups of patients, e.g, MEG studies in 13 pharmacoresistant epilepsy patients (Paetau et al, 1994), were studied. MEG demonstrated substantial value in the investigation of the Landau-Kleffner syndrome (LKS); epileptiform spikes in LKS patients were localized close to the auditory cortex by MEG (Paetau et al, 1991). MEG also demonstrated that in LKS patients sounds can trigger spikes which were identical to the spontaneous interictal spikes (Paetau et al, 1993). This finding contributed to the understanding of LKS pathogenesis.

2.2.2. MEG studies in epilepsy patients with focal cortical dysplasias

Focal cortical dysplasia (FCD; Taylor et al, 1971) is classified into types I and II (Palmini et al, 2004). FCD type I is characterized by cortical disorganization without dysmorphic-cytomegalic neurons. Type I A includes only cortical disorganization. Type IB includes cortical disorganization with immature or hyperthrophic neurons (but without dysmorphic neurons). FCD type II includes dysmorphic-cytomegalic neurons. Type IIA has no balloon cells whereas in type IIB balloon cells are present.
One third to one half of FCD are invisible on MRI. FCD type I is more often MR-negative than type II. Complete FCD resection leads to freedom from seizures in 80% of the patients, whereas after incomplete resection only 20% are seizure free (Lerner et al, 2009).

In four patients with MR-visible FCD, the clusters of spike sources localized inside the FCD (Morioka et al, 1999). Ictal and interictal MEG provided correct source localization in one patient with a MR-negative FCD (Ishibashi et al, 2002). All averaged and more than 90% of non-averaged EEG and MEG spikes were localized inside the MR-visible FCD (Bast et al, 2004). The majority of patients with FCD type I (81% visible in MRI) had both clustered and scattered sources (Widjaja et al, 2008). Ictal MEG was more focal than interictal one in both FCD type I and II (Fujiwara et al, 2012). MEG source localization led to detection of a small, previously overlooked FCD (Itabashi et al, 2014). MEG recorded high frequency oscillations (HFO) associated with epileptiform spikes in patients with MRI- visible FCD (Heers et al, 2013). Connectivity analysis of interictal MEG discovered a node driving the epileptiform activity in the area of FCD (Jin et al, 2013). The location of MEG source of gamma activity and the location of resection cavity were correlated in patients with histologically proven FCD (Jeong etal. 2013. Thus, MEG can provide different types of information in epilepsy patients having a FCD.

2.2.3. MEG sources: clustered and scattered

The interictal spike sources modeled by ECD can be classified as clustered and scattered (Iida et al, 2005); the source cluster was defined as six or more sources separated by 1 cm or less, whereas the other sources were defined as scattered. In tuberous sclerosis (TS) patients, unilateral source clusters indicate the epileptogenic zone location, bilateral clusters correspond to bilateral epileptogenic zone, and in TS patients with only scattered MEG sources (without clusters) the epileptogenic zone is not defined (Iida et al. 2005). Similar source analysis in 22 children with pharmaco-resistant focal epilepsy and normal or non-focal MRI revealed that none of the 22 patients with bilateral source clusters became seizure free (RamachandranNair et al. 2009). MEG source analysis revealed more spike clusters in individual spike analysis and less acceptable dipoles (with goodness-of-fit 95% or more) in averaged spike analysis in patients with pharmaco-resistant extratemporal epilepsy than with benign epilepsy with centro-temporal spikes (Chitoku et al.2003). The majority of patients, who continued to have seizures after resective surgery and had a MEG source cluster located closer than 3 cm to the resection margin, did not require long term intracranial EEG monitoring in planning of reoperation (Mohamed et al, 2007a). Patients with a single source cluster had better surgical seizure outcome than patients with multiple source clusters (Oishi et al, 2006). Resection of the extra-temporal MEG cluster was associated with a high rate of seizure freedom, whereas temporal lobe MEG source

clusters required confirmation by other diagnostic modalities (Vadera et al, 2013). Thus, the clustered and scattered MEG sources of epileptiform spikes correspond to different pathophysiological entities, which should influence the interictal MEG data interpretation.

2.2.4. Controversies regarding MEG in epilepsy

Lau et al. (2008) published a meta-analysis based on 17 published articles dealing with MEG in epilepsy patients (describing mostly interictal data) and compared MEG source localization, location of the resected area and the surgery outcome. They computed sensitivity and specificity of the MEG source localization. The sensitivity varied in the range of 0.2-1.0 (mean 0.84±0.12) and specificity in the range of 0.06-1.0 (mean 0.52±0.24) in different studies. They concluded that additional studies are needed to establish the role of MEG in epilepsy surgery planning. These results, relatively unfavorable for MEG, were criticized mainly because of questionable definition of concordance between the locations of MEG source solution and the resected area (Fischer et al, 2008; Papanicolau et al, 2008).

The sensitivity and specificity of mainly interictal MEG source localization in relation to the resection site and surgical outcome may depend on visualization of the lesion (Kim et al. 2013). Their patients were divided in two categories: In one, 70% or more dipoles located in the resected area, and in another less than 70% dipoles were resected. Based on this classification, the calculated sensitivity of the source localization of epileptiform activity was 0.67 and specificity 0.14. MEG predicted epileptogenic zone better in MR-positive than in MR-negative patients. In addition, the relation between number of source clusters and surgical outcome was tested. The number of MEG source clusters and the proportion of the dipoles localized inside the resected area did not predict well the surgical outcome. MEG, however, predicted the epileptogenic zone in patients with a MR-visible lesion (Kim et al. 2013).

The value of MEG vs. EEG interictal spike source localization has been debated (Baumgartner, 2004; Barkley, 2004). MEG often has a higher SNR in epileptiform spike detection than EEG. Moreover, MEG requires a simpler forward model than EEG and, therefore, MEG source localization is more robust. In addition, smaller neocortical area should be activated to be detected by MEG than by EEG. However, both EEG and MEG have low sensitivity to mesial and basal temporal spikes and have comparable localization accuracy. MEG and EEG are complementary. Thus, no clear conclusion regarding superiority of MEG or EEG can be done. Probably, the combination of both is superior to either of them separately.

When evaluating the clinical value of functional neuroimaging methods, it is worth noting that dense array EEG source localization of averaged epileptic interictal spikes has been reported to have a high sensitivity (84%) and specificity (88%) of calculated vs. resected area location; EEG data also had predictive value of post-surgical seizure outcome (Brodbeck et al, 2011). It is important to note that the "head to head" comparison of sensitivity and specificity of simultaneously recorded MEG and dense array EEG (128 or more electrodes) has not been reported.

2.2.5. Clinical value of MEG in epilepsy –some studies based on patient groups.

Eileptiform MEG spikes were recorded (mostly interictally) in 70% of 455 epilepsy patients . MEG source localization on the lobar level was correct in 89% of the patients with epileptiform spikes. MEG contributed additional information for pre-surgical workup in 35% of these patients and its contribution was crucial for decision making in 10% of them. Contribution of MEG was higher in patients with extratemporal than temporal epilepsy (Stefan et al, 2003). The best detectability of MEG epileptiform spikes was found in fronto-orbital, temporo-lateral, interhemispheric and central regions (Huiskamp et al, 2010).

MEG and icEEG have been compared in the prediction of epileptogenic zone location, based on resection site location and surgical outcome, in 29 temporal and 12 extratemporal epilepsy patients. In all patients, MEG and intracranial EEG monitoring did not differ. However, in patients with temporal lobe epilepsy, intracranial EEG monitoring was superior to MEG (Papanicolau et al, 2005). In a group of 63 patients MEG recorded epileptiform spikes in 60% and EEG in 51% of the patients (Heers et al, 2010). The combination of MEG and EEG recorded more spikes (71%) than either modality alone. In another study the combination of EEG and MEG in epileptic spike detection was also superior to either of them separately (Iwasaki et al, 2005). MEG detected more epileptiform spikes (72%) than EEG (61%) in simultaneously recorded MEG and EEG of 67 patients with epilepsy (Knake et al, 2006). In combined MEG and EEG analysis, the spikes were detected in 75% of the patients. In 13% of patients the spikes were detected only in MEG and in 3% only in EEG. Interictal video EEG was localized to one lobe in 60%, ictal video EEG in 72%, and MEG in 82% of the patients. Eleven out of 25 patients with no clear localization in interictal or ictal EEG had MEG localization in the lobe which was resected; six of them became seizure free and five additional patients had significant seizure frequency reduction (Paulini et al, 2007). Thus, MEG appears to be a useful tool in finding and localizing epileptiform activity and appears to surpass video-EEG in some patients.

The epileptiform MEG spikes were recorded in 47% of the 30 patients with mesial temporal lobe epilepsy (MTLE; Pataraia et al, 2005). The results were clustered to two subgroups: the first, with vertical dipoles localized to the anterior part of the mediobasal aspect of temporal lobe, and the second with horizontal dipoles localized to the temporal pole and the anterior part of lateral aspect of the temporal lobe. The surgical outcome was slightly better in the first subgroup (Pataraia et al, 2005).

MEG appears to be particularly useful in patients with frontal lobe epilepsy. In 24 such patients, both spike detection and source localization was better with MEG than with EEG (Ossenblok et al, 2007). In 39 patients with frontal lobe epilepsy, the patients with a single MEG cluster had better surgery outcome; 70% of the patients achieved Engel class I whereas in patients with multiple clusters only 20% achieved Engel class I. In patients with frontal lobe lesions, the close distance of MEG source cluster to the lesion predicted better surgical outcome (Stefan et al, 2011). The source localization of the averaged interictal epileptiform spikes and non-simultaneously recorded interictal icEEG were compared in 38 patients. All recorded interictal MEG spikes had corresponding spikes recorded by icEEG. However, not all icEEG spikes were detected in MEG; 75% of the icEEG spikes had corresponding MEG signals in interhemispheric

and frontal orbital areas. In mesial temporal region this number was only 25% (Agirre-Arrizubieta et al, 2009).

The sensitivity of MEG compared to ictal icEEG on the sub-lobar level was 58-64% and the specificity 79-88%, the values were clearly higher than corresponding values of FDG-PET and ictal SPECT. MEG had 78% positive predictive value and 64% corrected negative predictive value in predicting the surgical outcome (Knowlton et al, 2008a, 2008b).

MEG provided non-redundant information in 23 out of 69 epilepsy patients (33%) and led to change in icEEG planning in 16 (23%) (Sutherling et. al, 2008). In 16 out of 23 patients (70%) the icEEG defined ictal onset zone (Mamelak et al, 2002). In 11out of 16 patiets (69%) MEG source clusters (six or more sources) were estimated to localize at 4 mm or less from the IOZ defined by ictal icEEG. Different MEG source localization algorithms (SAM-G2 beamformer, ECD, MUSIC, MNE) had an approximately similar concordance with ictal icEEG (Tenney et al, 2014). The concordance of MUSIC with ictal icEEG had highest positive predictive value (PPV) for favorable surgical outcome and the disconcordace of SAM-G2 with ictal icEEG had highest negative predictive value for favorable surgical outcome. In 6 out of 30 epilepsy patients, video-EEG failed to localize epileptogenic zone, whereas MEG succeeded (Wu et al, 2012).

American Academy of Neurology stated on 2013 that clinically acceptable indications of MEG include presurgical evaluation of pharmacoresistant epilepsy patients, particularly when unequivocal hypothesis regarding epileptogenic zone location can not be defined based on other diagnostic methods. In addition, localization of eloquent cortex as a part of pre-surgical evaluation of brain tumors and vascular malformations (not discussed in detail in this Thesis) was considered as a valid indication for MEG.

2.2.6. MEG and fast oscillating epileptiform activity

Fast oscillations, including gamma frequency (30-80Hz) and high frequency oscillations (80-500Hz), play an important role in epileptic networks studied in invasive EEG recordings (Rampp & Stefan, 2006). The MEG source location of epileptiform spikes associated beta/gamma activity was highly correlated with the location of the resection area in the epilepsy patients with a good surgical outcome (Guggisberg et al, 2008). In five of six patients MEG detected oscillations in high gamma range during simultaneous MEG-icEEG recording (Rampp et al, 2010). Some of the oscillations were associated with epileptiform spikes and others were not. The source of gamma oscillations was successfully localized. MEG sources of gamma oscillations (both associated and not associated with epileptiform spikes) corresponded to the location of resection area in patients with histologically proven FCD (Jeong et al, 2013), and the HFO/high gamma activity MEG sources were localized close to FCD (Heers et al, 2013). Thus, MEG appears to be a useful tool in localizing epilepsy-related HFOs

2.2.7. MEG studies studies investigating the intitiation vs. propagation of epileptiform activity

MEG propagation pattern of fronto-temporal spikes were closer to icEEG than propagation pattern demonstrated by EEG (Tanaka et al, 2010). Coherence analysis of

interictal epileptiform signals was shown to be superior to ECD analysis in localizing sources of epileptiform MEG (Elisevich et al, 2011). In a case where EEG failed to demonstrate correct propagation pattern of epileptiform activity from parietal operculum and insula and mislocalized the epileptogenic zone into the mesial frontal area, MEG analysis with ECD modeling succeeded to demonstrate the initiation of epileptiform activity in the parietal operculum and insula (Wang et al, 2012(a)). MNE and ECD analysis of interictal MEG data were nearly equal in localizing the propagated activity, and MNE was superior in localization ofr the onset of epileptiform activity (Kanamori et al, 2013).

The connectivity analysis of MEG data localized the onset of epileptiform activity in the area of FCD (Jin et al, 2013). The majority of interictal networks defined by dicEEG are recognizable by independent component analysis (ICA) of MEG data (Malinowska et al, 2014). An abnormal extratemporal signal was demonstrated by MEG connectivity analysis in temporal lobe epilepsy patients (Zhu et al, 2014). Moreover, the patients with MTLE without propagation of the epileptiform MEG activity to the lateral temporal cortex have better surgical outcome than those with such propagation (Tanaka et al, 2014). MEG demonstrated longitudinal functional network changes after surgery in epilepsy patients (Van Dallen et al, 2014). Thus, studies of connectivity patterns underlying the propagation of MEG epileptiform activity appear to be a useful tool in studies of patients with epilepsy.

2.2.8. Simultaneous MEG and icEEG

In simultaneous recordings of MEG and sicEEG in two patients, one with lateral temporal lobe epilepsy and another with MTLE, MEG could detect the majority of interictal epileptiform spikes, which involved at least 4 cm^2 cortical area of the lateral temporal cortex. However, MEG could not detect the majority of mesial temporal spikes (Mikuni et al, 1997). In a traditional evaluation based on a skull phantom, the epileptiform cortical activity should span at least 6 cm^2 of the cortex to be detected by scalp EEG (Cooper et al, 1965). A more recent study in humans with subdural grids indicated that 90% of the interictal spikes detected by scalp EEG have a cortical source area larger than 10 cm^2 (Tao et al, 2005).

MEG was able to record 95% of neocortical spikes and 25-60% of mesial temporal spikes compared to simultaneous dicEEG recordings (Santiuste et al, 2008). The parametric characterization of interictal epileptiform spikes recorded by MEG simultaneously with dicEEG has been reported in detail (Novak et al, 2009). Simultaneous MEG and dicEEG recording can provide complimentary information (Kakisaka et al, 2012a, Vadera et al, 2014). Simultaneous MEG and dicEEG recording confirmed a FCD diagnosed by algorithm-based MRI analysis which was invisible in a usual MRI (Wang et al, 2012 (b)).

These studies led to three conclusions:

1. MEG detects epileptiform activity more precisely in the lateral than mesial temporal cortex.
2. MEG can detect the epileptform activity involving area of about 4 cm^2.
3. Simultaneous MEG and icEEG can provide complementary information.

2.2.9. MEG in epilepsy patients with deep epileptogenic zone

The magnetic field decays when the distance between source and sensors increases. Therefore, deep sources are associated with lower SNR than superficial ones having the same orientation. However, in reality the plane of deeply located cortex is often oriented more radially to the surface of the head than the dorsolateral cortex. Consequently, the electric currents in deep cortical structures are often oriented tangentially to the head surface and, therefore, are preferably recorded by MEG. MEG detects peri-Sylvian epileptiform spikes in children with Landau-Kleffner syndrome (LKS; Paetau et al, 1999). Interictal and ictal epileptiform MEG was successfully recorded in patients with mesial frontal lobe epilepsy (Shiraishi et al, 2001). MEG can record epileptiform spikes related to a peri-insular source (Heers et al, 2012). In four patients with focal epilepsy, MEG, but not EEG, displayed peri-Sylvian fronto-parietal epileptiform spikes (Kakisaka et al, 2012 (b)). These reports indicate that MEG can be informative in some patients with deep sources of epileptiform activity.

2.3 Ictal MEG

This section is focused mostly on the ictal MEG studies of focal seizures.

2.3.1. First ictal MEG reports

Probably the first ictal MEG recording was done with a one-sensor MEG system and a five-channel EEG recording. Generalized 3-Hz spike-and–slow wave epileptiform activity related to the absence seizures of epilepsy patients, were recorded equally well in both EEG and MEG, whereas slow waves had higher amplitude in EEG than MEG; different source orientation of spikes and slow waves was postulated (Hughes et al, 1977).

The first focal ictal MEG recording was reported in rats having penicillin-induced seizures (Barth et al 1984b). The ictal signals had both fast spikes and slow (up to 2-3 min) shifts in signal baseline. Ictal and preictal baseline shifts have been reported also in human EEG (Vanhatalo et al, 2005; Miller et al, 2007) and in MEG (Bowyer et al, 2012).

The first human ictal MEG of a patient with focal epilepsy was done with recording of multiple seizures. The position of a single sensor MEG device was shifted to different scalp positions (Sutherling at al, 1987). Simultaneously recorded EEG was used to classify brain waveforms and interpolate the MEG field patterns. Such virtually constructed multichannel MEG traces were used in MEG source localization, which was confirmed by intracranial EEG. Similar technique, applied to the interictal epileptiform spike analysis, was reported previously (Barth et al, 1982).

The first multichannel (37 sensors) ictal MEG recordings were reported in the early nineties. Ictal MEG sources were concordant with interictal ones and with intracranial EEG (Stefan et al, 1991; 1993). The first whole-head MEG of a seizure in a reflex epilepsy patient and the spread of the seizure to the opposite hemisphere was documented in 1995 (Forss et al. 1995).

2.3.2. Ictal MEG vs. interictal MEG compared to ictal icEEG

The main questions regarding ictal MEG are how robustly it predicts the ictal onset zone location, and whether ictal MEG is superior to interictal MEG in this endeavour. Comparing ictal and interictal MEG source solutions to ictal icEEG should answer these questions.

Several studies report better concordance of ictal vs. interictal MEG with the ictal icEEG (e.g. Eliashiv et al, 2002, Fujiwara et al, 2013). Table 1 summarizes the data of eight studies which compared ictal MEG and ictal icEEG. The data were collected from the article texts or tables. Patients with non-localizing ictal MEG or ictal icEEG were excluded. Comparison between the modalities was done with a hemisphere, lobe, lobar surface (HLS) scale described in Study I of the Thesis. Because the complete extent of icEEG electrode locations was not always described, it was difficult to define false positive and true negative MEG solutions. Therefore, Table 1 presents only true positivity and false negativity. This enabled computation of the sensitivity of ictal and interictal MEG compared with ictal icEEG as

Sensitivity = Number of true positive / (Number of true positive + Number of false negative). Computing specificity based on this data was, however, impossible.

The sensitivity of ictal and interictal MEG in 22 epilepsy patients described in Table 1 was about 90% on the lobar and lobar surface levels. These results are partially not concordant with the results reported in Study I; this is discussed in section 6 of this Thesis. The specificity of ictal and interictal MEG was not calculated of the data presented in Table 1. In several patients presented in these studies, ictal MEG sources were reported to be more focal than interictal ones. For example, patients 4, 5 and 7 in Fujiwara et al, (2013) had bilateral interictal MEG activity, whereas ictal MEG sources were unilateral and corresponded to ictal icEEG.

The best method of comparing ictal and interictal MEG source localizations is not evident. One possibility is to compare z-scores (number of standard deviations) of ictal MEG and interictal MEG sources (Tang et al, 2003).

Table 1
Ictal MEG vs. interictal MEG compared to ictal icEEG

Study and number of patients	Patient	Ictal MEG				Interictal MEG			
		Lobe level		Lobar surface level		Lobe level		Lobar surface level	
		True positive	False negative	True positive	False negative	True positive	False negative	True positive	False negative
Eliashiv et al, 2002 5 patients	1	1	0	2	0	1	0	2	0
	3	1	0	NA	NA	1	0	NA	NA
	4	1	0	1	0	NA	NA	NA	NA
	5	1	0	NA	NA	1	0	NA	NA
	6	1	0	1	0	1	0	1	0
Fujiwara et al, 2013 7 patients (Patient 6 had no ictal ic EEG findings.)	1	1	0	1	0	1	0	0	1
	2	1	0	1	0	1	0	1	0
	3	1	0	1	0	1	0	1	0
	4	1	0	NA	NA	1	0	NA	NA
	5	1	0	0	1	1	0	1	0
	7	0	3	NA	NA	0	3	NA	NA
	8	1	0	1	0	1	0	1	0
Xiang et al, 2010 3 patients	1	2	0	NA	NA	2	0	NA	NA
	2	2	0	NA	NA	2	0	NA	NA
	4	1	0	NA	NA	1	0	NA	NA
Assaf et al, 2003 2 patients	1	2	0	2	0	2	0	2	0
	2	1	0	1	0	1	0	1	0
Vitikainen et al, 2009 2 patients	1	1	0	1	0	1	0	1	0
	2	1	0	1	0	1	0	1	0NA
Tayah et al, 2006 1 patient	3	1	0	1	0	NA	NA	NA	0
Stefan et al, 1992 1 patient	1	1	0	1	0	1	0	1	0
Oishi et al, 2002 1 patient	1	1	0	1	0	1	0	1	1
Overall 22 patients		24	3	16	1	22	3	14	1
Sensitivity		0.89		0.94		0.88		0.93	

NA – not available (either not reported or not recorded)

2.3.3. Ictal MEG vs. ictal scalp EEG

Scalp EEG is often recorded simultaneously with MEG. Nevertheless, ictal EEG and ictal MEG source localizations were only rarely compared in the same study. In a report of two focal epilepsy patients with seizures recorded simultaneously by MEG and scalp EEG, both MEG and EEG recorded ictal onset waveforms of occipital seizure in one patient; however, only ictal MEG was localizable. In the other patient, MEG recorded ictal onset waveforms from Sylvian fissure, whereas EEG did not contain abnormal activity. MEG was recorded by 148 sensors, whereas EEG was recorded with 20 electrodes (Yoshinaga et al, 2004).

The reports about ictal scalp EEG, based on sensor level analysis, compared to ictal MEG source localization differ substantially between studies. In 5 out of 8 patients ictal onset was diffuse and bilateral in the scalp EEG, whereas ictal MEG source solution was focal (Fujiwara et al, 2013). Both ictal scalp EEG and ictal MEG were focal in 6 out of 7 patients; in one, ictal onset signal was non-localizable on both EEG and MEG (Eliashiv et al, 2002). In four out of six patients ictal onset EEG (on sensor level) was concordant to ictal MEG source (Tilz et al, 2002).

In a patient with epilepsia partialis continua presenting as elementary visual hallucinations, EEG demonstrated theta rhythm with relatively rare spikes, whereas simultaneously recorded MEG showed continuous periodic epileptiform discharges; the sources of this activity were localized as a cluster to the left posterior superior temporal area (Oishi et al, 2003).

Based on these reports, it is possible to conclude that ictal MEG may provide information unavailable from ictal scalp EEG, both in signal detection and in source localization. However, larger studies are needed for robust and clinically valuable comparison.

2.3.4. Some ictal MEG case reports and small series of patients

In four patients with medial frontal lobe epilepsy the interictal and ictal (or preictal) MEG sources were localized concordantly (Shiraishi et al, 2001). In another series of four patients, ictal MEG was concordant to ictal icEEG. All four patients improved substantially after the resection (Barkley et al, 2002). In a patient with MR-negative FCD, both ictal and interictal MEG correctly localized sources of epileptiform activity, which were confirmed by icEEG and histo-pathological examination (Ishibashi et al, 2002).

In two patients whose epilepsy was classified as generalized based on EEG, MEG enabled source localization of epileptiform activity to the medial aspect of the frontal lobes (Tanaka et al, 2005). It is, however, not clear, whether the patients had a true focal epilepsy with secondary bilateral synchronization, as the primary generalized activity was somewhat asymmetric and therefore enabled fitting a lateralized ECD. During generalized seizures the MEG local synchrony is enhanced whereas the synchrony between distant brain areas is not enhanced or even decreased in comparison to the interictal stage (Dominguez et al, 2005). An epileptic negative myoclonus appeared after a 8 year-old girl with nocturnal seizures was treated by carbamazepine. Some myoclonic events involved neck and both arms, and were associated with motion

artifacts that prevented MEG analysis. However negative myoclonus of the right arm was associated with left-sided EEG and MEG revealed spikes during 200-300-ms silent periods in EMG recorded from the biceps muscle. The sources of MEG spikes were localized to the neck-orofacial part of the primary motor cortex (Kobota et al, 2005).

The sources of ictal MEG of a patient with ring chromosome 20 and epilepsy were localized bilaterally to medial aspect of frontal lobes (Tanaka et al, 2013)., In five patients with refractory status epilepticus (RSE), MEG spike sources were clustered unilaterally in four and bilaterally in one patient with a MR-visible FCD. Two patients (including one with bilateral clusters) became seizure free after surgery (Mohamed et al. 2007).

All reports in 2.3.3.-2.3.4 demonstrate the potential of ictal MEG. However, due to small number of patients in each study, they can not assess the practical role of ictal MEG in epilepsy pre-operative workup.

2.3.5. Ictal MEG source modeling using methods other than equivalent current dipole

Equivalent current dipole (ECD) is usually a robust approach for interictal and in many cases also for ictal source modeling. Nevertheless several other methods have been investigated as well. SAM (g2) beamformer (Robinson et al, 2002 Robinson et al, 2004), which presents the source as a map of excess kurtosis was used for ictal MEG analysis (Canuet et al, 2008, Rose et al, 2013 and Foley et al, 2014). The wavelet-based beamformer has been used for high frequency ictal MEG signal modeling (Xiang et al, 2010; Miao et al, 2014).

The dynamic statistical parametric mapping (dSPM) (Dale et al, 2000), which takes into account the cortical anatomy in the source estimation, was employed for ictal onset MEG analysis (Tanaka et al, 2009). Ictal onset MEG data analysis in a narrow frequency band has been tested as well. The frequency bands whose power at the ictal onset exceeded the interictal level were considered to represent ictal signals (Fujiwara et al, 2012a and b). The sources of signals in such bands were estimated with ECD, standardized low resolution brain electromagnetic tomography (sLORETA) (Pascual-Marqui, 2002) and multiple signal classification (MUSIC) (Mosher et al, 1999). In addition, the authors used synthetic aperture magnetometer (SAM G2) beamformer source localization. High concordance with intracranial ictal EEG recording was reported. Analysis of ictal onset in narrow frequency bands using minimum norm estimate has been described as well (Alkawadri et al, 2013). The frontal and parietal focal onset was demonstrated using SAM (G2) beamformer in the absence seizures with generalized 3-4 spike and slow vawe activity (Westmijese, et al, 2009). These studies demonstrate that at least in some cases the distributed inverse models can be an efficient tool in the ictal MEG source estimation. Narrow band filtering improves SNR, which can optimize ictal MEG source reconstruction. The dynamic transition from interictal to ictal state was demonstrated by dynamic imaging of coherent sources –type beamformer (Gupta et al, 2011).

2.3.6. Video-MEG

The combined video-EEG recording is a standard part of pre-surgery workup. The video-MEG recordings were recently reported (Burgess et al, 2009, Wilenius et al,

2010). In a quantitative evaluation of synchronized VMEG analysis in 10 epilepsy patients adding the video to MEG analysis improved classification of events into ictal or interictal ones (Zhdanov et al, 2013).

2.4 Movement compensation in MEG

In contrast to EEG, MEG sensors are not connected to the head. Therefore, neuromagnetic sources in the head can change their position in relation to sensors. The information of spatial relation between head and sensors is crucial for MEG forward model construction and, therefore, for inverse problem solution. Three separate problems can be defined:

1. Stable head position detection.
2. Moving head position detection (head position monitoring).
3. Reconstruction of MEG traces according to head movements.

These problems have been solved relatively accurately during the development of the MEG methodology.

2.4.1. Stable head position detection

The usual way to detect the head position in the MEG helmet is fixating a minimum of three artificial sources of magnetic field to the head. These sources are small coils driven by electrical sinusoidal current generator (Knuutila et al, 1985, Ahlfors & Ilmoniemi, 1989, Incardona et al, 1992, Fuchs et al, 1995). These head position indicator (HPI) coils are typically activated before the beginning and after the end of a MEG measurement. Separate coils are driven by sinusoidal currents of different frequencies. The sources of coil signals are estimated. Because the coils are connected to defined points on the head, the head position can be defined in the coordinate system of the MEG sensor array. If HPI coils are not activated during the MEG measurement, the head position changes are not monitored in real time, which can lead to imprecise neuromagnetic source localization.

2.4.2. Moving head position detection

In order to monitor head position during MEG recording, HPI coils should be activated simultaneously with the MEG acquisition (de Munck et al, 2001). The HPI coil signals are set to the frequencies above the typical physiological frequency band of interest, usually above 100 Hz. After estimation of sources of active HPI coils, which are used for the head position definition, the HPI signals are filtered out, usually by low-pass filtering. Because of SNR issues, head position is defined only during some epochs; this enables use of the signal statistics to improve the HPI source estimation. In measurements described here, the head position was defined once every 0.2 s. The length of this epoch is an important factor defining the maximal speed of head movement which can be compensated. Another factor limiting the head movement detection is the magnetic artifact related to the head motion. Because the HPI coils are activated during the measurement, the sinusoid generator should be MEG-compatible and not produce oscillations outside the frequency bands allocated for the HPI coils. To enable on-line visualization of HPI coils during HPI coil activation, low- pass filter should be applied to the data in real time. The continuous head position monitoring

provides the possibility to update the forward model with respect to the head position changes. Therefore, head movement can be compensated in source estimation, because the changing head position can be taken into account in solving the inverse problem. However, because the recording signal depends on source localization non-linearly (equation 2.1 – Biot-Savart law), updating the forward model alone is not enough for movement compensation in terms of MEG trace reconstruction. It requires neuromagnetic signal decomposition into the spatially separated components (Hoechstetter et al, 2004), when the virtual MEG channels are associated with a specific source location.

2.4.3. MEG trace reconstruction to compensate for head movements

In order to reconstruct MEG, the signal needs to be decomposed to the components associated with different locations of the source. Thereafter, the information obtained by head position monitoring can be used in the recalculation of the components. Different components undergo different correction depending on source location and orientation. The sum of the corrected signal components represents the position-corrected MEG signal.

One possibility is to decompose MEG signal using MNE (Uutela et al, 2001). MNE employs the dipole grid which has constant locations but changeable magnitudes. The magnitudes of dipoles are first defined by solving the inverse problem, taking into account the measured head position. The dipole grid is then virtually displaced to the new head position as a rigid body without changing the dipole magnitudes. Forward calculation is then done from dipoles in the new position. Thus, the MEG trace can be recalculated according to virtual head displacement to the initial position, central position or any other position inside the sensor helmet.

Another possibility of signal decomposition is the signal space separation (SSS) method (Taulu et al, 2004, Taulu & Kajola, 2005). Instead of a dipole grid, series of spherical harmonic functions is employed (Taulu, Simola & Kajola, 2005; a more detailed description is presented in the subsection 2.5.1.5). The SSS based movement compensation is efficient in reconstruction of auditory evoked fields (AEFs) recorded in different head positions (Lioumis et al, 2007). Movement compensation can be used also in children during cognitive MEG studies (Wehner et al. 2008). SSS-based movement compensation is useful for ictal MEG recordings (Kakisaka et al, 2012c). Movement compensation also improves source localization of somatosensory (SEFs), visual (VEFs) and AEFs (Stolk et al, 2012).

Co-registration of estimated MEG sources with structural MRI images is performed by identification of the external head landmarks (Pantev, et al, 1990, Stefan et al, 1990, Hämäläinen, 1991). These landmarks are labeled both on the subject's head in relation to HPI coils and on the MRI image. The most commonly used landmarks are the two preauricular points and the nasion.

Head position can be optimized for different types of recorded activity. During the language task, the anterior head position inside the MEG helmet is associated with better data quality with regard to frontal and anterior temporal regions (Marinkovic et al, 2004).

2.5 Interference suppression in MEG

2.5.1. Distant interference suppression

2.5.1.1. Magnetically shielded room

MEG is almost always recorded in a magnetically shielded room (MSR). There are some reports of MEG recordings without MSR (Ahopelto et al, 1974, Vrba et al, 1993); such recordings usually require high order gradiometers, which can reduce sensitivity to sources in deeper parts of the cortical sulci. MSR traditionally is constructed by two or three layers which include mu-metal (alloy of nickel and iron) and aluminum plates (Kelhä et al, 1982). Mu metal provides shielding against both high and low frequency interference, and aluminum adds the shielding against high frequencies by increasing the effective electrical conductivity of the wall structure. In addition to passive shielding, active shielding can also contribute against distant interference. Active shielding employs the flux-gate sensor outside MSR and the compensating system, which produce magnetic field inside MSR opposing the interference magnetic field (Simola et al, 2004). Active shielding can permit the use of the one-layer MSR. This combination of active and low-weight passive shielding was demonstrated to work in clinical recordings of epileptiform activity (deTiege et al, 2008, Carrette et al, 2011a).

2.5.1.2. Gradiometers

Use of gradiometers instead of magnetometers can reduce the distant noise by a factor of 1000. Planar gradiometers (Cohen, 1972) are focused on the areas located directly bellow their centers; therefore, they are less sensitive to the brain background noise originating in distance from the area of interest. Gradiometers, however, are less sensitive than magnetometers in detecting signals from deep brain sources.

2.5.1.3. Reference sensors

In some MEG systems, distant interference is measured using reference sensors, magnetometers and gradiometers located at some distance from the sensor helmet (Vrba & Robinson, 2001, Parkkonen, 2010). The weighted signal measured by reference sensors is removed from the signals of the sensors from the MEG helmet. The set of weights is defined either by modeling or empirically.

2.5.1.4. Signal-space projection (SSP)

In SSP, the distant interference subspace and projection of the data to the subspace orthogonal to the interference subspace are defined (Uusitalo & Ilmoniemi, 1997, Parkkonen et al, 1999). The signals from an empty shielded room are recorded first. Then, principal component analysis (PCA) is applied on the empty room data. First m (<10) components (with highest eigenvalues) are considered to span the interference subspace. Thereafter, the brain signal subspace, the n-m dimensional subspace, orthogonal to the interference subspace is defined (n is the number of MEG sensors). The projection to the brain signal subspace of the data (with the subject's head inside the MEG helmet) is considered free from a distant interference. In source localization, the forward calculation result should also be projected to the brain signal subspace.

2.5.1.5. Signal-space separation (SSS)

SSS method separates magnetic signals into two linearly independent subspaces: signals from sources located external and internal to the sensor array sphere (Taulu et al, 2004, Taulu & Kajola, 2005). The magnetic field measured by MEG sensor is the sum of magnetic fields related to the internal and external sources:

$B = B(J_{int}) + B(J_{ext})$ (2.3)

Where B is magnetic field, J_{int} – internal source currents and J_{ext} – external source currents.

The two subspaces are constructed based on Maxwell's equations and using two series of spherical harmonic functions. The sources are presented as two multipole expansions, internal and external relative to MEG sensor sphere. Because the internal and external subspaces are linearly independent, the projection of the data to the external subspace can be removed, and the remaining signal corresponds to the sources located inside the sensor sphere. However, because the real MEG sensor array cannot measure the neuromagnetic signal with unlimited number of degrees of freedom, the signals from the sources located close to the sensors, e.g interference from magnetized electrodes, cannot be separated optimally. Moreover, the non-magnetic interference, such as electronic noise, cannot be modeled by Maxwell's equations. Therefore, SSS method has difficulties in suppressing the magnetic interference from the sources located near the MEG sensors and in suppressing the non-magnetic interference. SSS extended into temporal domain (tSSS) solves these problems (Taulu & Simola, 2006).

2.5.2. Nearby interference suppression

2.5.2.1. Spatiotemporal signal-space separation (tSSS)

The temporal extension of the SSS method is based on the properties of magnetic sources close to the sensors and on non-magnetic interference leak into both internal and external subspaces defined by the SSS. The components with correlated time behavior in both subspaces are considered as interference and are removed from the data (Taulu & Simola, 2006). However, due to some non-stationarity in time, the limited number of degrees of freedom, small calibration errors, and noise, the correlation is not necessarily a full 100%. Therefore, the correlation has to be defined quantitatively by the correlation limit. The optimal setting of the correlation limit has major importance in suppression of interference residuals. This aspect was investigated in the Study III of the Thesis. The ability of tSSS to remove nearby artifacts was demonstrated in single-trial auditory evoked responses (Taulu and Hari, 2008), and in suppressing VNS artifacts in patients with epilepsy (Carrette et al, 2011b) and DBS artifacts in patients with Parkinson's disease (Mäkelä et al, 2007, Airaksinen et al, 2011).

Inadequate transformation of nearby interference signals and non-magnetic interference by SSS without temporal extension can in some circumstances increase the noise when the movement compensation is applied. However, application of tSSS eliminates noise increment associated with movement compensation. This was investigated in Additional

Material of the Thesis. Another possibility of suppressing noise of SSS based reconstruction is to compute the total current estimate based on magnetostatic multipole moments (Taulu and Kajola 2005). The integral of this estimate over the whole brain volume expresses the whole brain electrical activity, which helps to eliminate the transformation noise due to movement compensation (Bosseler et al, 2013). Another method to eliminate this type of noise is construction of the virtual MEG helmet (Study IV in the Thesis).

Replicability of SEFs and AEFs during head movements is high when movement compensation is applied together with tSSS (Nenonen et al, 2010). In systematic evaluation of tSSS- based artifact suppression and movement compensation, the localized sources of AEFs and SEFs did not differ from sources localized in reference head position more than by 5-7 mm. tSSS suppresses the nearby interference without mutilating the brain signal (Nenonen et al. 2012).

tSSS is practically the only robust method for suppression of nearby interference. Introduction of tSSS and movement compensation has enabled inclusion of many epilepsy patients into diagnostic MEG studies. tSSS was included into recommendations for good MEG practice (Gross et al, 2013). In studies of epilepsy patients, tSSS and tSSS-based movement compensation made both interictal and ictal MEG recordings clinically practical and relatively easy (Study I in the Thesis).

2.5.2.2. Beamformers

Nearby interference can be suppressed by beamformers due to their spatial filtering properties. In MEG recordings of a patient with Parkinson's disease with a deep brain stimulator (DBS) and strongly magnetized electrode leads, strong artifacts were suppressed by beamformer filtering (Litvak et al, 2010).

2.6 MEG informatics

The Shannon's theory of communication (Shannon, 1949) can be used for assessment of general ability of MEG sensor array to extract the information in one measurement sample (Kemppainen & Ilmoniemi, 1989, Nenonen et al, 2004, Nenonen et al, 2007). According to Shannon's theory of communication, if the signal *b(t)* and the noise *noise(t)* are normally distributed and independent, the total information (Inf_{tot}) provided by a single noisy channel can be presented as:

$$Inf_{tot} = \frac{1}{2}\log_2(P + 1) \quad (2.3)$$

Where P is the power SNR of the single channel. Then, the total information provided by the system of m independent channels can be represented as

$$Inf_{tot} = \frac{1}{2}\sum_{n=1}^{m}\log_2(P_n + 1) \quad (2.4)$$

Where P_n is the power SNR of each independent channel. Thus, the increase of the number of independent channels increases total information, whereas increase of noise decreases it.

In a multichannel array, the coupling of channel n is described in terms of the lead field L_n:

$$b_n = \int L_n(r') \cdot j_p(r') dv' \quad (2.5)$$

Where r' is a vector, which indicates location of the neural source. The center of the coordinate system is located at the center of spherical conductor; $j_p(r')$ is the primary current density vector at r'; and v' is a spherical conductor volume.

In calculating the total information it is assumed that no a priori information of the sources exists, and that the primary currents have a nearly Gaussian distribution, $j_p \sim N(0, s_p^2 I)$, where I is an identity matrix. In addition, the noise is also assumed Gaussian, $noise_n \sim N(0, \sigma_n^2)$. The power SNR for channel n is

$$P_n = ||L_n||^2 s^2 / \sigma_n^2 \quad (2.6)$$

The total information, Inf_{tot}, can be presented as a sum of $log_2(P_n + 1)$ over independent channels. Because the lead fields of the sensors are overlapping, sensor measurements are dependant and therefore, the data have to be orthogonalized.In order to achieve this goal, a lead field product matrix (gram matrix) is constructed:

$$G_{jk} = \int L_j(r') \cdot L_k(r') dv' \quad (2.7)$$

Next singular value decomposition (SVD) is applied on G as $G = USU^T$, $S = diag(\lambda_1, \lambda_2, \ldots \lambda_m)$, where the columns of matrix U are the eigenvectors, ^{T} is transpose, and λn are the eigenvalues of G. The orthogonalized lead fields become $L_n' = UTL_n$ and the orthogonalized SNR becomes

$$P_n' = \lambda_n s^2 / \sum_j (U_{nj} \sigma_j)^2 \quad (2.8)$$

The total information of the m-channel magnetometer provided by one sample is:

$$Inf_{tot} = \frac{1}{2} \sum_{n=1}^{m} \log_2(P_n' + 1) \quad (2.9)$$

These calculations were employed in assessment of virtual MEG helmet (VMH) concept presented in this dissertation.

3. Aims of the study

The aims of present work were to answer the following questions:

1. What is the specificity and sensitivity of ictal vs. interictal MEG for mapping the ictal onset zone?
2. How accurately interictal MEG can predict epileptogenic zone location in patients with FCD?
3. What are the practical limits of movement compensation for the patients with an unstable head position?
4. What is the influence of fine tuning of the tSSS correlation limit on the artifact suppression?
5. Can head movements improve MEG data quality, in comparison to MEG recorded in a single head position?

4. Materials and Methods

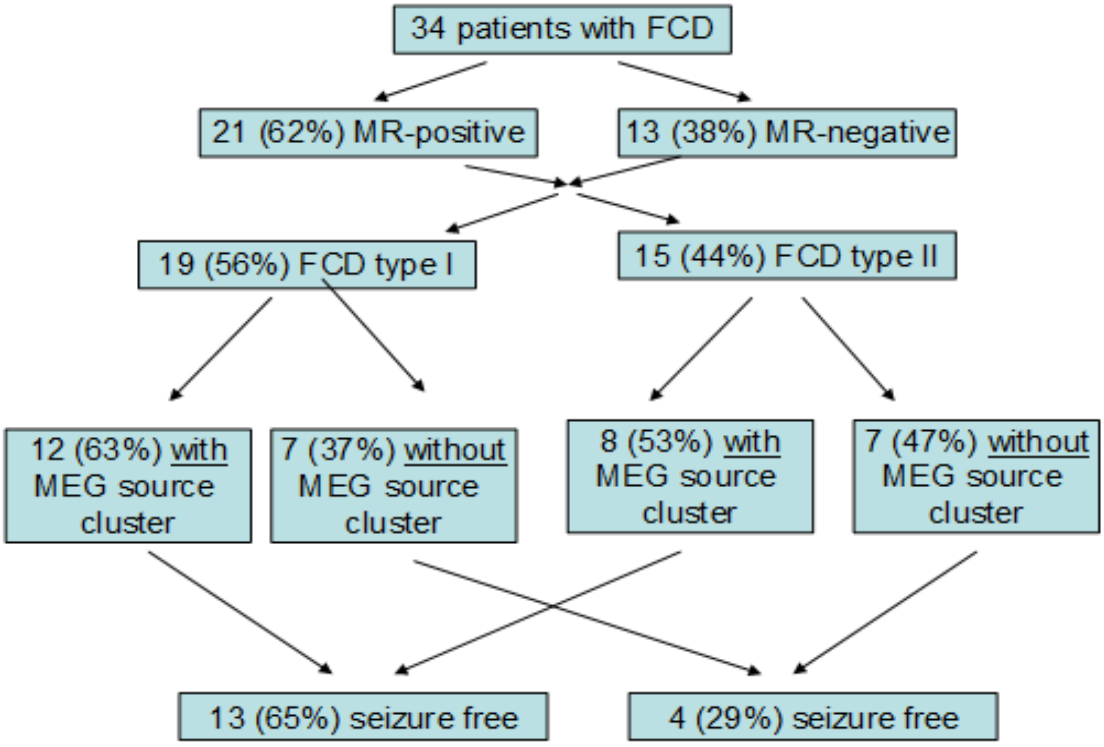
4.1.Patients

The clinical part of this dissertation is based on two retrospective studies (I and II). All patients had pharmacoresistant epilepsy and underwent MEG as part of their pre-surgery workup. Studies I and II were approved by ethical committee of Helsinki University Central Hospital, Helsinki, Finland. In addition Study I was approved by ethical committee of Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel.

The focus of Study I is ictal MEG in patients with epilepsy. 47 patients (25 male) out of 246 patients recorded between 1995 and 2009 had seizures during MEG recordings. 23 of the patients (age 3-40 years; median 13 years) were operated and their surgery reports were available. The operations were performed in Helsinki University Central Hospital and in Tel-Aviv-Sourasky Medical Center. 19 of the patients had an analyzable ictal MEG recording. Fourteen patients had both an analyzable ictal event in MEG and ictal onset recorded in icEEG. The data of the fourteen patients were the main focus of Study I. MRI revealed FCD in six patients. One patient had right fronto-parietal atrophy, another had a resection cavity and a FCD type I in postoperative histological examination. The brain MRI was normal in six patients. In these patients, four had FCD: two had FCD type I and two FCD type II. In general, FCD was found by MRI and/or by histopathological examination in 11 out of 14 patients. Two out of 14 patients had no interictal epileptiform spikes on MEG. Seven patients (50%) had Engel class I outcome after surgery, with a minimum follow-up of 10 months. More clinical details are presented in Tables 1 and 2 and in Fig. 1 of Study I

The focus of the Study II is interictal MEG in patients with FCD. MEG was recorded between years 2003 – 2011. 34 pharmacoresistant epilepsy patients (age 2.5 - 47 years (median 14 years; 4 male) were included into Study II. All had MEG examination, underwent resective surgery and had histopathologically proven FCD. In 33 patients MEG revealed interictal spikes. 24 patients underwent icEEG (either sicEEG or combination sicEEG and dicEEG). MRI revealed lesions in 21(62%) patients. Thirteen patients with histologicaly proven FCD had no visible lesion on the 3T MRI. Half of the patients (17 out of 34) had surgery outcome of Engel class I during follow-up of at least half a year. More clinical details can be found in Tables 1 and 2 of Study II.

Figure 1. *The patients in Study II. (The schematic overview of patients in Study I can be found in Fig.1 of Study I).*



4.2.Healthy subjects

One healthy adult male subject participated in Additional Material. One healthy female (subject 1, with a magnetic dental filing on the right lower jaw) and one healthy male (subject 2) participated in study III. Study III and Additional Material were approved by the ethical committee of Helsinki University Central Hospital, Helsinki, Finland.

4.3.Recordings

The majority of the MEG recordings took place in BioMag laboratory. One patient in Study II was recorded in Brain Research Unit of Low Temperature Laboratory, Helsinki University of Technology. All patients and healthy subjects in Studies II, III and in Additional Material and majority of patients in Study I were recorded using Elekta Neuromag Vectorview MEG device (204 planar gradiometers and 102 magnetometers, Elekta Oy, Helsinki, Finland). Three patients in Study I were recorded using a 122-sensor planar gradiometer device (Neuromag Oy, Helsinki, Finland). All MEG recordings were done in a magnetically shielded room. In the majority of epilepsy patients EEG was recorded simultaneousy with the MEG with 32- or 64- electrode caps. The EEG amplifier was inside the MEG device.

In the Vectorview MEG device the sampling frequency was 600 Hz. On-line high pass filter was set on 0.01-0.1 Hz and low pass filter on 172-200 Hz. Two periauricular points and nasion, were labeled to create a head coordinate system. The healthy subjects

in Additional Material and study III and the epilepsy patients since 2006 (studies I and II) were recorded with continuous head position monitoring with four HPI coils. The coils were activated continuously by sinusoidal currents in frequencies 154, 158, 162 and 166 Hz. The head position was defined once every 200 ms. Additionally, the head position was defined by transient activation of HPI coils in all patients and healthy subjects. Until 2006 the HPI coils were fixed to the right and left mastoids and forehead area. During the experiments related to Additional Material in 2006, the "optimal" locations of the HPI coils were changed to the areas corresponding approximately to the EEG electrodes F3, F4, P3 and P4. These locations were used in healthy subjects in Study III and Additional Material and in epilepsy patients since the year 2006. The higher position of the coils on the head enabled continuous head position monitoring during downward movement of the head. HPI coils were fixed to the head using leukoplast bands, usually pasted to the EEG cap.

The MEG recordings of epilepsy patients (studies I and II) were generally done in sessions of two hours with 5-10 min breaks in between. During the breaks the patients walked out the shielded room. Generally, three recording sessions (6 hours) were accomplished in one day. The MEG recordings of some patients continued several days (with long interruptions). In MEG recordings during night from a sleeping patient, the break intervals were often longer than two hours. From the year 2006 onwards continuous head position monitoring was included into MEG recording protocol, so that the patients were able to move slightly during MEG recordings. This enabled longer MEG recordings and, therefore, higher probability to record seizures (Table 2). Often the MEG recordings where planned to occur during the hours with the highest probability for seizures in a particular patient.

Table 2. The cumulative percentage of seizures recorded in MEG in 47 patients/54 seizures* (100%) in Study I.

Length of MEG recording, hours	1	2	3	4	5	6	10**	20**	30**	40**
Cumulative percent of recorded seizures, %	42.6	48.1	61.1	64.8	70.4	77.8	88.9	96.3	98.1	100

* Some patients had more than one seizure during MEG recordings
** MEG recordings longer than 6 hours were generally done during more than one day with breaks of several hours in between the sessions.

In Additional Material MEG was recorded in several head positions: 1) reference head position, 2) "strongly downward" (about 5-6 cm), 3) "moderately downward" (about 2-3 cm), 4) "strongly backward" (maximal possible chin upward position), 5) "moderately backward" (halfway of "strongly backward"), 6) "turn right" (maximal right turn of the head), 7) "turn left" (maximal left turn of the head). The right and left median nerves were stimulated alternatively using 0.2-ms rectangular electric current pulses. The inter-stimulus interval was 500 ms with a random jitter of ±50 ms. The stimulus amplitude was adjusted to induce a clear thumb movement but no pain.

4.4.Simulations

4.4.1 Virtual helmet construction

In Study IV the 306-sensor MEG array and virtual MEG arrays were simulated. Virtual MEG arrays were constructed using simulation of head movements inside the MEG helmet. In order to construct the virtual MEG array, the head was considered as stable and the MEG array to move in relation to the stable head. The sensor locations were introduced into the model according to the coordinates of the 306 MEG sensor positions and directions of the Elekta Neuromag® MEG device. The position of sensors was defined as a vector from the device coordinate system origin to the geometrical center of the sensor. The sensor orientation was defined by three vectors corresponding to x- y- and z-axes of the sensor coordinate system translated into the device coordinate system origin.

The virtual arrays were constructed by MEG array displacements in the coordinate system of the head. The head coordinate system had the origin in the center of the spherical brain model, which was located at x = 0, y = 0, z = -40 mm point of the device coordinate system in the reference head position. The x-, y-, z-axes of the head and device coordinate systems had the same directions in the reference head position. In such position an adult-size head has no space to move backward or upward; this was taken into account in constructing the virtual arrays.

Fourteen different virtual sensor arrays were constructed with sensor numbers from 306 × 2 to 306 × 7 (Table 1: arrays 5-19 in Study IV). In addition, nine head positions (one reference and eight displaced ones) using only the standard 306-sensor array were simulated (Table 1: arrays 1-9 in Study IV). The head displacements included 10-mm translations in all directions except backwards and upwards (because of physical constraints set by the helmet) and 15-30 degree rotations around all axes. Translation of the helmet origin was done first. Then z-rotations, y-rotations, x-rotations were combined into a single rotation matrix.

For construction of the different VMHs, we simulated both simple and combined head displacements. Simple head displacements were either translations along one axis or rotations around one axis. Combined head displacement was a head displacement, which included the combination of more than one simple head displacement (for example a combination of x-translation and y-rotation).

4.4.2. Simulation of sources and noise

A "randomly distributed source current" (RDSC) was simulated. The source was assumed to be distributed throughout the spherical brain model with a radius of 8 cm. In addition to RDSC, AEFs and SEFs were simulated. It was assumed that the sources of AEFs can be represented by two bilateral ECDs, and the source of SEF by a single unilateral ECD. The locations and orientations of the ECDs were defined by fitting the dipole to the measured data published by Nenonen et al, 2010. This MEG data was recorded from a healthy adult volunteer. SEFs were evoked by median nerve electrical stimulation and AEFs by presentation of the tones to the left and right ears alternatively. The location and orientation of the ECDs of the SEF and AEFs for the simulations were

obtained by fitting the dipoles using the recorded SEF and AEFs. More details can be found in the Methods section of Study IV.

4.5.Data analysis

The recorded data were processed offline with Elekta Neuromag software.

4.5.1. Application of tSSS and movement compensation (studies I-III)

The data of all healthy subjects (Study III and Additional Material) and epilepsy patients (Studies I and II) since 2006 were off-line processed by tSSS and movement compensation. tSSS was applied in 4-s time windows. Movement compensation was applied to every time point (the head position, however, was defined in epochs of 200 ms during MEG data acquisition). In addition to combination of tSSS and movement compensation (MC-tSSS), the data in Additional Material were processed by combination of SSS (without temporal extension) (MC-SSS) and movement compensation. In Additional Material and in early tSSS applications in epilepsy patients (from the year 2006 to beginning of 2007), the correlation limit of tSSS was set on 0.98. In Study III the tSSS correlation limit values were compared and set on 0.98, 0.8 and 0.6. From the summer of the year 2007 onwards, the tSSS correlation limit was set on 0.8-0.9 for the data of epilepsy patients.

4.5.2. Data averaging (Additional Material)

The SEFs to median nerve stimulation were averaged in epochs of 600 ms (including a 100-ms prestimulus baseline). The averaged data were low-pass filtered at 80Hz.

4.5.3. Fitting the ECDs (Studies I-II and Additional Material)

To fit the ECDs, the head was assumed as a spherical conductor. In Additional Material the source of SEF N20m response was estimated using a single ECD. This response peaked at 23 ms after the stimulus onset. The N20m source was estimated from the data recorded in reference head position and in deviant head positions before and after application of movement compensation based either on SSS without temporal extension or on SSS with temporal extension (tSSS). The noise was defined from prestimulus baseline in the range of 20 -30 ms.

As the studies I and II are retrospective, no new ECD fits were applied during the data analysis. The routine ECD fit for the data of epilepsy patients in BioMag laboratory was done as follows: MEG traces were screened visually for interictal and ictal epileptiform signals. Their sources were localized using a single ECD model. First, an ECD was fitted to the earliest epileptiform signal. Next, the MEG signal corresponding to the fitted dipole was removed from the data by SSP (Uusitalo & Ilmoniemi 1997) and a new single ECD was fitted to the residual data until all recognizable epileptiform signals were sufficiently explained (Merlet et al., 1997).

7.5.4. Comparison of measured data on sensor level (Study III)

Study III investigates the influence of different tSSS correlation limits (tSSS CL) on the data quality. The data processed with tSSS CLs of 0.98, of 0.8 and 0.6. The data were compared visually; the noise levels and the amplitude spectra were compared as well.

For visual analysis, two segments of the data were selected, one with maximal expression of the artifact and another with maximal expression of the alpha rhythm. The data recorded by magnetometers and planar gradiometers were inspected separately. The noise was calculated for all magnetometers, all planar gradiometers, for two orthogonally oriented planar gradiometers in the right temporal sensor group, and for the magnetometer in the triple sensor housing the two right-temporal planar gradiometers. This right -temporal triple sensor expressed the most prominent speech-related artifact. The noise level was defined as a standard deviation of the signal amplitude and was calculated in thirty 2-s epochs during speech. The mean and standard deviation of noise values were calculated.

The amplitude spectra of the spontaneous activity were calculated using fast Fourier transform (FFT) in order to investigate the influence of tSSS with different correlation limits on the signal. The alpha rhythm was chosen as an example of the brain signal. One magnetometer and two orthogonally oriented planer gradiometers in one triple sensor were selected from the occipital sensor group. The spectra were calculated using a Hanning window. The FFT step was 1024 time points. 11.08 seconds of the data (12 overlapping epochs of FFT size) were averaged. The bin width was 0.586 Hz.

4.5.5. Comparison of sources of magnetic fields (Studies I-II and Additional Material)

4.5.5.1. Healthy subjects (Additional Material)

To test the different movement compensation methods, the primary somatosensory hand area was first defined at each hemisphere in ten reference head position trials. Thereafter, all 10 sets of the Cartesian coordinates were averaged for the right and left hemispheres. The averaged SI locations were named as SI_0 and used as reference location for comparison of SEF source estimation between deviant and reference head positions. The distance between every trial at deviant head position and SI_0 was calculated for every trial in deviant head position. The mean and standard deviation of source locations in deviant head position for unprocessed data, data processed by MC-SSS, and data processed by MC-tSSS were estimated. The significance of differences was evaluated using a two-tailed paired Student's t-test. The differences with p-value below 0.05 were considered significant. Two trials with downward head displacement of 6 cm were excluded because of too low SNR. The absolute distance from SI_0, the baseline noise level and goodness-of-fit were compared.

4.5.5.2. Studies of patients with epilepsy (Studies I and II)

Study I

The comparison between ictal and interictal MEG and icEEG was performed on both lobe (HL – hemisphere, lobe) and lobar surface (HLS –hemisphere, lobe, and surface) levels. Any number of ictal sources (ECDs) was considered as positive. For interictal

sources, three conditions were defined as MEG positivity criteria. A – any number of ECDs in a HL or HLS location; B – two or more ECDs; C – more than 10 ECDs. In Study I the HLS locations which were positive in condition C were considered as source clusters. Otherwise the sources were considered scattered. The ictal and interictal MEG sensitivity and specificity were calculated as follows:

Sensitivity = true positives / (true positives + false negatives)
Specificity = true negatives / (true negatives + false positives)

The sensitivity and specificity of ictal MEG for deep locations was calculated separately in Study I, excluding dorsolateral locations for nine icEEG measurements in seven patients who had icEEG activity on non-dorsolateral electrodes. Also mean source distributions of ictal and interictal MEG were calculated and compared with each other and to the ictal icEEG**.** In addition, positive predictive value (PPV) and negative predictive value (NPV) of ictal MEG for dorsolateral lobar surfaces, for non-dorsolateral lobar surfaces and for all lobar surfaces were calculated (Table 3 in this Thesis). PPV and NPV calculations were not reported in Study I and are reported first time in this Thesis. PPV and NPV were defined as:

PPV = true positives / (true positives + true negatives)
NPV = true negatives / (true negatives + false negatives)

Study II

The source cluster was defined to contain at least 6 ECDs with distances less than 1 cm between adjacent ECDs (Widjaja et al, 2008). The sources not corresponding to the criterion of cluster were classified as scattered. The source solution was co-registered with post-surgery MRI and the proportion of removed sources from the source clusters was calculated.

4.5.6. Simulated data analysis (Study IV)

In the simulation study, total information extracted from MEG recordings in standard and virtual MEG arrays was calculated by two methods, both including lead field orthogonalization: the sensor level orthogonalization (SLO) and internal magnetostatic multipole moments signal-to-noise ratio (IMMM SNR) were applied.

Total information calculated using sensor level organization (SLO) of lead fields is described in subsection 2.6.

4.5.6.1. Total information calculated using internal magnetostatic multipole moments signal-to-noise ratio (IMMM SNR) (The detailed description can be found in Nenonen at al, 2007).

The SSS performs the transformation of MEG sensor level signals into sets of multipole moments, which correspond to different vector spherical harmonic functions (Taulu& Kajola, 2005). The signals of interest and part of the random noise are transformed into internal multipole moments and their SNR values depend on both transformed noise and transformed signal of interest. There is linear dependency between transformed noise overall amplitude and noise amplitude of the MEG channels of a given sensor array.

However, sensor array geometry infuences SSS transformation of both signal and noise. The different types of VMH and real MEG array have different IMMM SNR, even when the sensor level SNR is the same. The SSS transformation creates an orthogonal basis. Therefore P_n in equation (2) in Study IV can be also the power SNR of IMMM, and can also serve to calculation of total information. The SSS transformation was performed for both reference head position in 306-sensor helmet and for different types of VMH. The IMMMs were calculated separately for signal of interest and for random noise. The IMMM SNR was defined as the ratio between multipole moments of signal and multipole moments of noise for every internal spherical harmonic. The total information computing was performed using equation (2) in Study IV, where P_n is IMMM SNR. The comparison of the total information calculations using SLO and IMMM SNR approaches is presented in Table 2 of Study IV.

5. Results

5.1. Study I

Study I examines whether or not ictal MEG predicts the location of IOZ better than interictal MEG. The records of fourteen patients with pharmacoresistant epilepsy who underwent ictal MEG and ictal icEEG were retrospectively analyzed. Twelve patients had also interictal MEG signals. The sensitivity and specificity were compared. In prediction of IOZ location, the ictal icEEG was used as a gold standard.

The sources of ictal MEG were distributed, on average, on 3.6 surfaces on the lobar surface level. Ictal icEEG was distributed on 2.4 surfaces. The difference was not significant. In the same comparison on the lobe level, ictal MEG encompassed 2.4 lobes and ictal icEEG 1.6 lobes ($p=0.021$). The source distribution of ictal MEG was distributed more widely than interictal MEG with more than 10 dipoles per location (clusters, condition C) both on lobe level and on lobar surface level; the differences, however, were not significant (Table 3, study I).

Ictal MEG predicted ictal onset zone with sensitivity 0.703 and specificity 0.731 on the lobar surface level. Interictal MEG clusters (condition C) had sensitivity 0.400 and specificity of 0.769. On the lobe level ictal MEG had sensitivity 0.958 and specificity 0.900; interictal MEG clusters (condition C) had sensitivity 0.933 and specificity of 0.750 (Tables 4 and 5 in Study I). On the lobar surface level, the ictal MEG sensitivity for deep (non-dorsolateral) sources was 0.733, similar to the general figures of ictal MEG (sensitivity 0.731).

Positive predictive value (PPV) and negative predictive value (NPV) of ictal MEG for dorsolateral lobar surfaces and non-dorsolateral (deep) lobar surfaces were similar (Table 3).

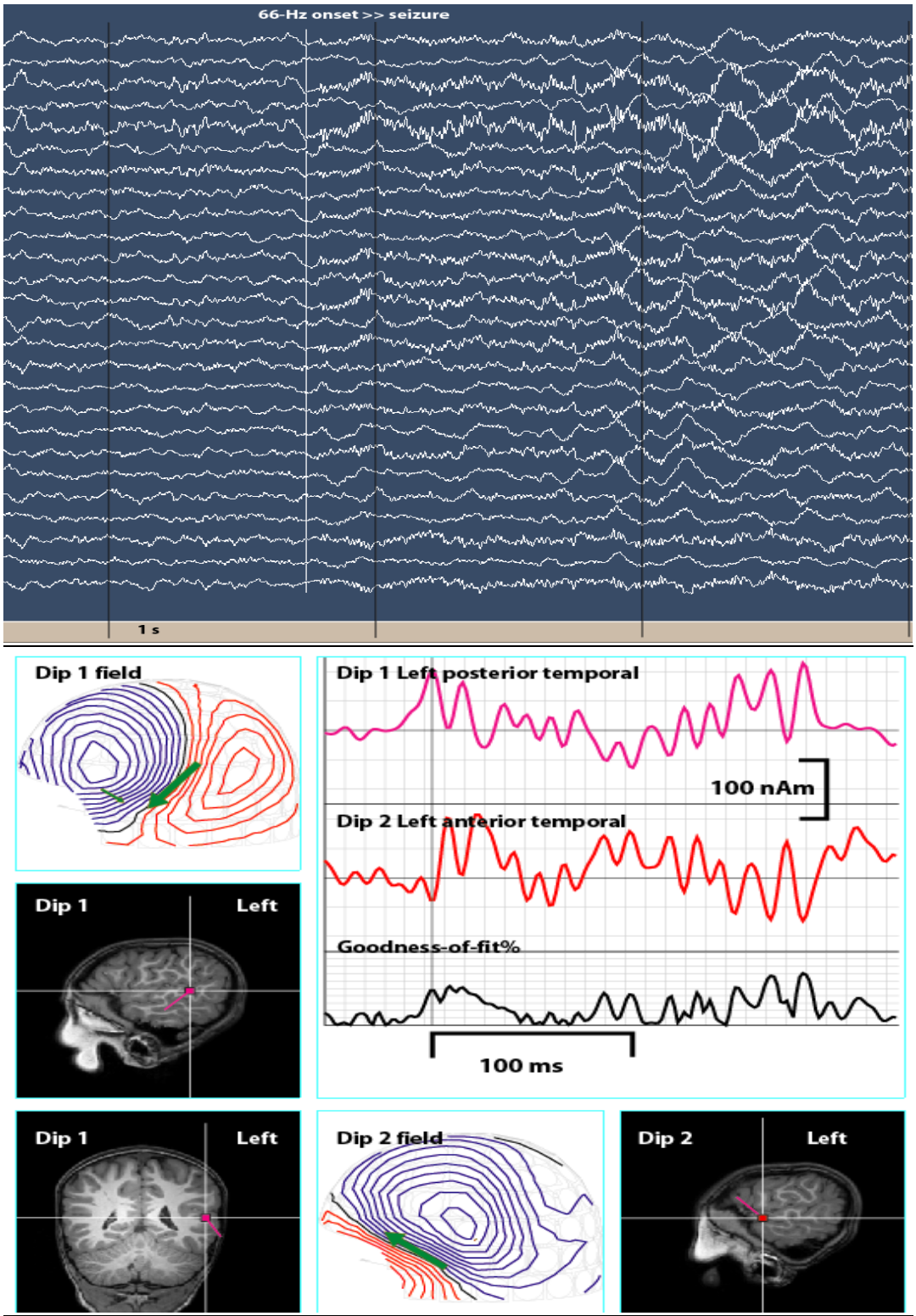
Table 3. Positive and negative predictive values of ictal MEG on the lobar surface level

	Dorsolateral surfaces	Deep surfaces	All surfaces
PPV	0.765	0.786	0.774
NPV	0.625	0.692	0.655

On the lobar level, the sensitivity of interictal MEG in condition C (0.933) was similar to ictal MEG (0.958). However, ictal MEG was more specific (0.900) than interictal MEG in condition C (0.750).

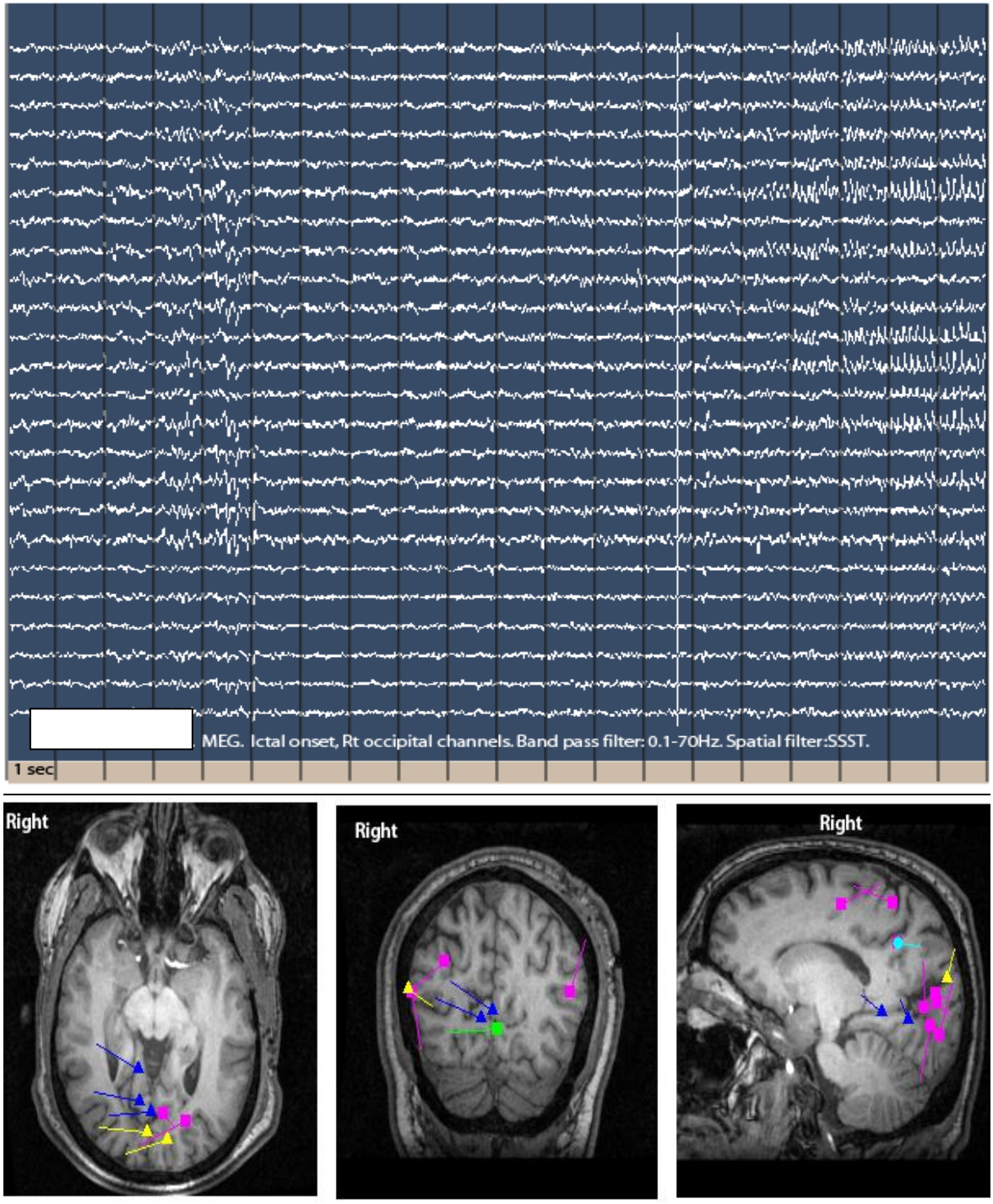
It is important to note that ictal vs.interictal MEG comparison is not based on the same type of signals. In contrast to interictal MEG, which is typically characterized by spikes (or sharp vawes) and slow wave complexes, ictal MEG is often, but not always, represented by a low amplitude fast activity. In many cases, MEG can record such activity and, in spite of relatively low SNR, it is possible to localize the source. Two examples of such fast activity ictal onset on MEG are displayed in Figs. 2 and 3.

Figure 2.Left temporal ictal onset



Five-year old boy with daily focal seizures with dyscognitive features (complex partial seizures). Ictal MEG revealed a 66-Hz ictal onset signal. The same channels demonstrated also slower ictal oscillations in the theta range. The ictal MEG sources were localized to the lateral aspect of the left temporal lobe. Due to overlap of epileptogenic zone and receptive language area, the patient was not operated.

Figure 3.Occipital ictal onset



Thirty-seven year old man with focal seizures with dyscognitive features (complex partial seizures). The pre-ictal sources were localized to both occipital lobes. The sources of ictal onset rhythmic activity were localized to the right occipital lobe. Interictal sources were clustered to both occipital lobes and, slightly less, to both parietal lobes. The VNS was implanted and the patient reported substantial improvement in frequency and duration of seizures. Blue – ictal onset; yellow –pre-ictal; purple – interictal; green – visual evoked field source, light blue – left leg SEF source.

The results of Study I indicate that ictal MEG is generally superior to the interictal MEG in predicting ictal onset zone location. The ictal MEG predicts IOZ location on dorsolateral and non-dorsolateral lobar surfaces with a similar accuracy.

5.2. Study II

The question of Study II was the accuracy of MEG in localization of epileptogenic zone in patients with FCD. This retrospective study investigated the correlation between interictal MEG source solutions and surgery results in 34 patients with FCD. Twenty patients had MEG source clusters.

In 20 patients with MEG interictal source clusters, 15 had favorable post-surgery outcome (Engel class I and II) and five had unfavorable outcome (Engel class III and IV). In patients with favorable outcome, on average 49% of the source clusters were removed (range 0-100%, standard deviation (SD) 34%); in patients with unfavorable outcome the corresponding number was 5.5% (range 0-21%, SD 9.1%; p=0.02).

The seizure freedom ratio was not different between patients with MR-positive FCD and MR-negative FCD (p=0.82). However, significantly higher proportion of patients who had FCD resection "unrestricted" by overlap with eloquent cortex achieved seizure freedom comparing to patients with restricted "resection" (three out of 14 (21%), p = 0.0013).

In the group of seven patients with MR-negative FCD type I, six (86%) had source clusters, whereas only two out of six patients with MR-negative FCD type II had source clusters (33%). This difference was not significant (p=0.17).

The main conclusion of the Study II is that in epilepsy patients with FCD the resection of larger proportion of MEG source cluster is associated with better post-operative seizure outcome. However, for achieving favorable seizure outcome, complete cluster resection is not always required.

5.3. Additional Material

The motivation of Additional Material was the evaluation of practical limits of the movement compensation. SEFs were recorded in reference head position and in displaced head positions inside the MEG helmet in one adult healthy subject. The ability of SSS- and tSSS-based movement compensation to restore the localization accuracy was evaluated.

For 22 trials up to 5 cm head shift the mean source localization error of N20m deflection of the SEFs evoked by median nerve stimulation was 3.91 cm for unprocessed data, 2.13 cm for MC-SSS and 0.89 cm for MC -tSSS (Table 1, Fig. 2 in Additional Material). The noise of planar gradiometers and magnetometers was increased by MC-SSS and decreased with MC-tSSS compared to the unprocessed data (Fig. 2B and C in Additional Material). The goodness of fit was increased by MC-SSS and increased further by MC-tSSS (Fig. 2D in Additional Material). The 95% confidence volume was increased by MC-SSS, but decreased by MC-tSSS compared to unprocessed data (Fig. 2E in Additional Material).

Additional Material demonstrated that tSSS -based movement compensation can be efficiently applied when the head was displaced up to 3 cm.

5.4.Study III

Study III analyses if an aggressive artifact removal with lower correlation limit of tSSS can eliminate the residuals of artifacts without changing the brain signal. Two healthy adult volunteers counted Finnish numerals, producing speech artifacts during MEG recording. In addition, the volunteers closed eyes and did not speak, and their occipital alpha rhythm was recorded. The data were processed off-line by tSSS with different correlation limits (tSSS CL).

The speech artifact was not suppressed completely by tSSS CL of 0.98. However it was almost completely suppressed by tSSS CL of 0.8. Further reduction of tSSS CL to 0.6 did not change substantially the signals (Figs. 1-4 in Study III). The muscle artifact was not suppressed efficiently by tSSS with the tested correlation limits. The noise was progressively suppressed by tSSS with reduction of the correlation limit. With reduction of tSSS CL up to 0.8, occipital alpha rhythm was not changed, but with reduction of tSSS CL to 0.6 the alpha rhythm was slightly reduced in amplitude in one of the subjects. This was observed both in time (Figs. 1-4 in Study III) and in frequency (Fig. 7 in Study III) domains.

The conclusion of Study III is that the correlation limit of tSSS can be safely reduced to 0.8. This improves artifact removal without changing the brain signal.

5.5.Study IV

Study IV tests if the MEG recording of the same data in different head positions with subsequent virtual MEG helmet (VMH) construction can increase the recorded data quality. In this study different head positions were simulated and total information was calculated for simulated RDCS, AEFs and SEF.

5.5.1. RDSC

With 360 events (e.g. epileptiform spikes), the total information (bits/sample) was 989 for the most informative head position in the standard helmet and up to 1272 for VMH (additional 28.6%). With 720 events, the corresponding numbers were 1103 for the most informative single head position in standard helmet and up to 1448 for VMH (additional 31.3%); and with 1440 events 1221 for the most informative single head position in standard helmet and 1636 for VMH (additional 34.0%).

5.5.2. Simulated AEFs

The total information provided by the most informative head position in standard array was 360 bit/sample. Most informative VMH provided 406 bit/sample (additional 12.8%).

5.5.3. Simulated SEF

The total information provided by the most informative single head position in standard array was 437 bit/sample. Most informative VMH provided 442 bit/sample (additional 1.1%).

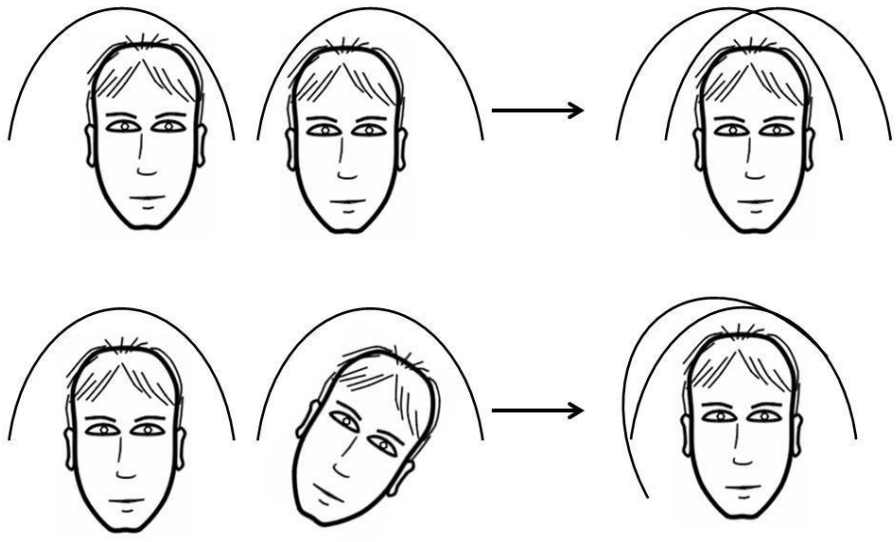


Figure 4. Virtual MEG helmet construction. Upper row – head translation, lower row – head rotation. Left two columns – real MEG helmet, right column – virtual MEG helmet

VMH can be more efficient in some situations than traditional MEG recording in a single head position. VMH is more efficient with more distributed sources, higher SNR and with combined head displacements.

6. Discussion

This Thesis demonstrates that ictal MEG can provide more information on seizure onset zone than interictal MEG, and that removal of larger proportion of MEG source cluster in patients with FCD is associated with better clinical outcome. However, the complete resection of MEG source cluster is not always necessary for a favorable post-surgery outcome. In addition, tSSS -based movement compensation can minimize the movement error of the MEG source localization, when head is displaced up to 5 cm. This is important for source localization of both interictal and particularly ictal epileptiform activity. The fine tuning of the tSSS is important in suppression of the magnetic interference. Finally, our simulations show that in some situations MEG recording in different head positions can increase the information content of the MEG data. This can be useful in interictal MEG data analysis.

6.1. What is the specificity and sensitivity of ictal vs. interictal MEG for ictal oncet zone (IOZ) mapping?

MEG is a robust tool for the localization of the sources of epileptiform magnetic fields. Nevertheless, MEG can not "convert" interictal epileptic activity into ictal one. Ictal MEG reflects the location of IOZ whereas interictal MEG indicates the irritative zone. These regions are usually not identical. Therefore, it is not surprising that one of the main findings of the present work is that ictal MEG is generally superior to interictal MEG in predicting the IOZ location.

6.1.1 The distribution of ictal vs. interictal MEG solutions

Ictal MEG sources were more distributed than interictal MEG sources in condition C (cluster) on both lobe and lobar surface levels; the differences, however, were not significant. This may result from a larger localization error of ictal vs. interictal MEG due to lower SNR of ictal MEG, or from larger distribution of the ictal onset epileptic activity compared to the cluster of sources of interictal MEG spikes. Results of Study I suggest that both reasons contribute to the difference. Ictal MEG sources were more distributed than ictal icEEG both on lobe level (2.4 vs. 1.6 lobes) and on the lobar surface level (3.6 vs. 2.4 lobar surfaces). ECD model may not always be optimal for ictal MEG source localization; this may result in some error in localization. On the other hand, the interictal source clusters (more than 10 sources in one lobar surface) were less distributed on the lobar surface level than ictal icEEG. Therefore, localization error cannot be the only explanations of more extensive distribution of ictal MEG than interictal MEG source clusters on the lobar surface level.

6.1.2 Sensitivity and specificity of ictal and interical MEG in IOZ location predicting IOZ

On the lobar surface level the MEG source cluster of interictal spike sources predicts IOZ with a relatively high specificity (0.77) but with a low sensitivity (0.4). Therefore, planning the subdural electrode placements based only on interictal MEG clusters may lead to omitting more than half of the lobar surfaces involved in IOZ. The inclusion of scattered interictal MEG sources (conditions A and B) increases the sensitivity of interictal MEG. However, the specificity drops to the level of 0.59 – 0.57 (Table 5; Study I). Therefore, planning of the subdural electrode study based on combination of

both clustered and scattered interictal sources leads to an unnecessary large coverage of the subdural electrode grid. According to the data presented in Tables 3 and 5 and in Study I, the additional grid coverage of lobar surfaces with scattered sources (two and more sources on one surface; condition B) leads, on average, to additional 3.3 lobar surfaces be covered by subdural electrodes (comparing to interictal MEG cluster). This adds the discovery of 33% of lobar surfaces involved in IOZ.

Ictal MEG specificity on the lobar surface level is close to specificity of interictal MEG, but the sensitivity (0.7) is higher. Therefore, ictal MEG discovers 30% more lobar surfaces involved in IOZ than the interictal MEG source cluster method. Choosing the ictal MEG as a basis for planning subdural electrode coverage leads on average to two additional surfaces covered by subdural electrodes. Thus, the ictal MEG provides better solution for planning subdural electrode locations on the lobar surface level than the interictal MEG (based either on the clustered sources or on the combination of clustered and scattered sources). The comparison of ictal MEG strategy vs. interictal condition B (clustered + scattered sources) strategy in planning of subdural electrode sites leads to the following result: the ictal MEG has 3% less chance to discover the lobar surface involved in IOZ; however, it requires 1.3 less lobar surfaces to be covered by subdural electrodes.

On the lobe level ictal MEG has high sensitivity (0.96) and specificity (0.9) in predicting IOZ location. Interictal MEG has high sensitivity (0.93-0.95) and moderate specificity (0.57-0.75). Thus, ictal MEG is generally superior to interictal MEG on both lobe and lobar surface levels in predicting the location of IOZ.

No substantial correlation between the seizure outcome and degree of MEG cluster resection was found in meta-analyses of studies of patients with pharmacoresistant focal epilepsy (Lau et al, 2008) or in patients with MR-negative epilepsy (Kim et al, 2013). Probably, these results can be at least partially explained by the fact that majority of MEG reports analyzed by these studies were based on interictal recordings. More detailed analysis of these studies and the comparison to the data reported in the present work is presented in subsection 6.2.

The higher sensitivity of ictal than interictal MEG on the lobar surface level reported in Study I probably cannot be explained by unrealistically high values of ictal MEG sensitivity. The calculated sensitivity of ictal MEG on the lobar surface based on eight studies reported from 2002 to 2013 (Table 1) was 0.93, whereas in Study I it was 0.71.

Study I demonstrated that the specificity, sensitivity, and positive and negative predictive values of the ictal MEG for non-dorsolateral (up to 4 cm depth) source localization are similar to those of overall (dorsolateral and non-dorsolateral) values. Intuitively, one would expect that the SNR would decrease with increasing depth and, therefore, the source localization accuracy should decrease as well. If the electrical currents in the deeper cortices are oriented more tangentially to the head surface, they became more detectable by MEG. Thus, the SNR of non-dorsolateral sources is reduced by the increasing distance between the source and sensors, but increased by the more tangential orientation of the cortical electric currents relatively to the head surface. The two tendencies balance each other; and probably explain the equal sensitivity and specificity of ictal MEG both for all sources and only non-dorsolateral sources.

MEG of signals originating from deep cortical sources provides corroborating evidence concordant with the findings of present work. AEFs related to peri-Sylvian sources (Hari et al, 1980; Roberts et al, 2008) and epileptic peri-Sylvian sources in children with LKS (Paetau et al, 1999) can be detected with MEG. In several cases of focal epilepsy with peri-Sylvian spikes, MEG was superior to EEG in spike detection (Hears et al, 2012; Kakisaka et al, 2012). Interictal and ictal epileptic activity related to the mesial frontal sources is detected with MEG (Shiraishi et al, 2001). Indeed, even brainstem AEFs are detected with MEG provided that adequate number of averages is collected (Parkkonen et al. 2009).

The comparison of ictal vs. interictal MEG reported in Study I has limitations related to the selected study population and to the comparison to icEEG:

1. None of the operated patients had epilepsy involving mesial temporal structures (amygdala and hippocampus), because MTLE patients are usually operated without MEG. Therefore, the conclusions are relevant mainly for extratemporal epilepsy. Only the operated patients, half of patients with ictal MEG, were analyzed. Therefore, most complex cases were excluded. This can unfairly increase the calculated sensitivity and specificity. However, both ictal and interictal MEG were affected similarly by this limitation. More than 40% of the patients who had ictal MEG, had the seizure during the first hour of the recording. This indicates the selective nature of the patient population. Multiple seizures were indeed an indication for the MEG recording
2. The MEG source locations were compared to results of ictal icEEG, which defines the SOZ but not the epileptogenic zone. Therefore, the sensitivity and specificity of ictal and interictal MEG evaluated in Study I are related to prediction of SOZ, not to the location of the epileptogenic zone. In Study II seizure outcome was the end-point parameter. However, in Study II only interictal MEG sources were analyzed.
3. The ictal icEEG locations were identified from reports by the epileptologist or clinical neurophysiologist without reanalyzing the data, which may have affected the SOZ location
4. The results of non-invasive studies, including also MEG, were used in planning icEEG location. This can unfairly increase the MEG sensitivity.
5. Only locations, where icEEG electrodes were placed, were included into the specificity and sensitivity calculations. This can lead to omission of some positive locations. This may explain why ictal and interictal MEG had similar specificity on the lobar surface level. It is possible that in some patients some interictal MEG positive locations wee not covered by icEEG because other non-invasive studies did not support the involvement of these locations in the epileptogenic zone. Therefore, although the present work does not prove a higher specificity of ictal vs. interictal MEG on the lobar surface level, it can not be excluded.

The practical value of ictal MEG is an important issue. In patients with rare seizures, the chance of seizure detection by MEG is low. Nevertheless, some patients have frequent seizures. Timing of seizures can occasionally be predicted, e.g., when they occur when falling asleep. Seizures can also be provoked by reduction of antiepileptic medication. In Study I the majority of seizures occurred during the first 6 hours of MEG recording

(Table 2 of this Thesis). Generally, ictal MEG requires more time than the standard interictal MEG. However, long MEG recording can increase also interictal data and facilitate the use of a virtual MEG helmet (see subsection 6.5).

MEG is able to record fast gamma activity at the ictal onset. Fig. 2 in Results demonstrates an example of such recording. Not all ictal MEG data contain fast signals; nevertheless, the absence of smearing effect by the skull and sensitivity to tangential source currents enhances MEG recording of fast activity.

6.2. How accurately does the interictal MEG predict the epileptogenic zone location in patients with FCD?

Study II demonstrated that patients with FCD on histopathological examination and MEG spike source clusters have better post-surgery seizure outcome than patients with FCD but without clusters (the difference, however, was not statistically significant). This is generally concordant with other studies (Iida et al, 2005; RamachandranNair et al, 2007; Oishi et al, 2005). One reason of less favorable outcome in patients without MEG source clusters can be an inadequate knowledge of epileptogenic zone location. However, the epileptogenic zone in absence of the source cluster may also be more diffuse and, therefore, less resectable. The inclusion of patients into Study II required the presence of FCD on histopathological examination. Therefore, at least part of abnormal epileptogenic tissue was resected in all patients. Thus, the incomplete knowledge about epileptogenic zone location is not a single reason for less favorable post-surgery outcome in patients without a source cluster. Intuitively, one expects that MEG source cluster is associated with a more focal, and therefore more resectable epileptogenic zone. However, the results of Study II do not support this notion. Six out of seven patients with MR-negative type I FCD had clusters, whereas only two out of six patients with MR-negative type II FCD had MEG source clusters.

It is commonly agreed that epilepsy patients with MR-visible lesions have higher proportion of favorable post-surgical seizure outcome. This was, however, not demonstrated in Study II. All patients in Study II had partially or completely resected FCD. This suggests that MR-positive FCD helps to define the localization of epileptogenic zone, but is not necessarily more easily resectable than the MR-negative FCD which are, by nature, small in size.

Study II shows that a larger proportion of MEG source cluster removal is associated with significantly better post-surgical seizure outcome. In line, a complete source cluster resection is associated with a higher rate of post-surgery seizure freedom than an incomplete resection, particularly in patients with extratemporal epilepsy (Vadera et al, 2013). In Study II, however, only one patient had a complete cluster resection (becoming free of seizures). Therefore, it is not sensible to compare effects of complete vs. incomplete resection based on Study II. The difference in the proportion of cluster resection between seizure free and non-seizure free outcomes was not significant, probably due to a small sample size. Comparison between "favorable" (Engel class I and II) and unfavorable (Engel class III and IV) outcomes led to the significant difference.

It is clear that favorable seizure outcome or even seizure freedom does not necessary require a complete resection of MEG source clusters. Some patients became seizure free

with a 0% of cluster resection (three out of 20 patients). Thus interictal MEG sources do not always localize epileptogenic zone adequately. According to Study I, interictal MEG often misses a substantial part of the IOZ, an important component of the epileptogenic zone. The results of studies I and II explain some aspects of the conclusions of Lau et al, 2008 and Kim et al, 2013. It appears that both ictal and interictal MEG do not always provide information about the epileptogenic zone configuration with a resolution higher than lobar surface, and that interictal MEG solution often (but not always) provides incomplete information about the epileptogenic zone location and configuration.

Despite at least partial removal of FCD of all patients in Study II, several patients did not become seizure free. The reason for this was the overlap of epileptogenic zone and the eloquent cortex, limiting the resection. Thus, improving diagnostic techniques cannot increase the seizure freedom rate above some limit. Additional increase of seizure freedom rate may be achieved by development of the therapeutic methods that can be applied to suppress pathological activity of eloquent cortex, such as responsive neurostimulation.

6.3. What are the practical limits of movement compensation for the patients with unstable head position?

Movement compensation provides the opportunity to record MEG from patients who cannot keep the head position stable. Such patients include young children, mentally disordered patients and patients during seizures. The movement compensation based on SSS without temporal extension increases the level of noise. Inclusion of temporal extension of SSS (tSSS) into movement compensation reduces the noise associated with movement compensation. Other approaches reducing the noise associated with movement compensation exist as well (Bosseler et al, 2013).

tSSS-based movement compensation reduced the localization error of median nerve SEF to less than 1 cm when the head was displaced up to 5 cm. However, with large downward displacement of the head, the lower parts of the brain move out of the MEG helmet. This prevents the optimal sampling of the magnetic field. Therefore, it is reasonable to restrict the use of MEG data to the head displacements up to 3 cm from the reference head position.

In Additional Material, the movement compensation was used in situations when the head position was changed and remained stable between the changes during the MEG measurement. This Study did not investigate movement compensation of MEG recorded during an actual movement. The maximum speed of head movement compatible with successful movement compensation is not known. In Additional Material, the head position was monitored in 200-ms epochs. The epochs should be shorter for the head position recalculation during actual movements.

Presently, the main role of movement compensation in ictal MEG is not compensating the fast head movements. Rather, it reduces the need of patient immobilization during the MEG acquisition. This enables long MEG recordings which increase the chance to record seizures. The ictal MEG signals appear often before vigorous seizure-associated movements and therefore can be analyzed when head position is monitored and head displacement is compensated.

The principles elaborated in Additional Material have become the working standard of the ictal MEG recordings in BioMag Laboratory, Data obtained by a similar movement compensation applied to ictal MEG (Kakisaka et al, 2012) verified our results, showing that movement compensation led to a correct localization of the IOZ despite head movements.

6.4. What is the influence of tSSS correlation limit fine tuning on the artifact suppression?

The temporal extension of SSS (tSSS) employs comparison of temporal behavior of internal and external magnetostatic multipole moments. If a given internal multipole moment correlates in time with external multipole moments, it represents interference and should be removed from the data. This comparison requires quantitative threshold of the correlation, the tSSS correlation limit (tSSS CL). Setting the tSSS CL too high can prevent complete removal of the interference. The artifact residuals can interfere with detection of both ictal and interictal epileptic activity. Study III demonstrated that setting tSSS CL on 0.8 efficiently suppresses the artifacts without changing the brain signal.

tSSS is an important clinical tool for suppressing interference whose sources are located near to MEG sensors. Fine tuning of tSSS CL can increase efficiency of both interictal and ictal MEG data analysis. More efficient noise suppression using tSSS with an optimized correlation limit can increase the efficiency of virtual MEG application to epileptic activity source localization (more details in subsection 6.5). After publication of Study III, the adjustment of tSSS CL to the values 0.9-0.8 became common practice in BioMag Laboratory (e.g. Airaksinen et al, 2011), and in other MEG laboratories (Carrette et al, 2011).

Based on the results of Study III and Additional Material it is possible to define some conditions for the optimization of clinical MEG studies, which can be complicated by head movements and artifact (Fig. 5). Presently these conditions are commonly used in different laboratories in epilepsy diacnostic MEG recordings.

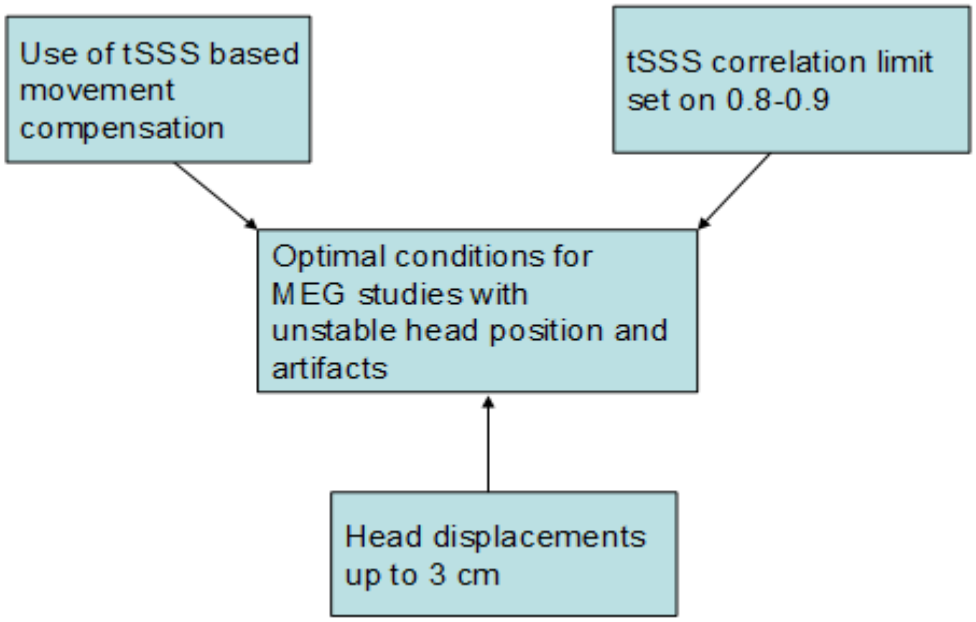


Figure 5. *The optimal conditions for MEG studies complicated by head movements and artifacts.*

6.5. Can head movements improve MEG data quality, compared to MEG recorded in s single head position?

In contrast to EEG, MEG does not require contact of the sensors to the skin. This enables larger variety of the field sampling by placing the sensors at different distances and angles. One way to increase MEG sampling variety is to record the same brain activity in different head positions with a subsequent virtual MEG helmet (VMH) construction (Study IV). The disadvantage of the VMH is that the events recorded in different head positions cannot be averaged. Therefore, the noise with VMH is higher in relation to $\sqrt{n}$, where *n* is the number of head positions, providing that the same number of events was recorded in every head position. Thus, VMH increases the number and variety of MEG sensors and thus increases data quality, and increases noise due to decreasing number of averaged events, thus decreasing the data quality.

Some types of VMH increased total information whereas other VMHs were associated with reduction of total information extracted from MEG measurements. Source distribution, applying combined vs. simple head displacements, and SNR mainly influenced the efficiency of VMH (Fig. 6)

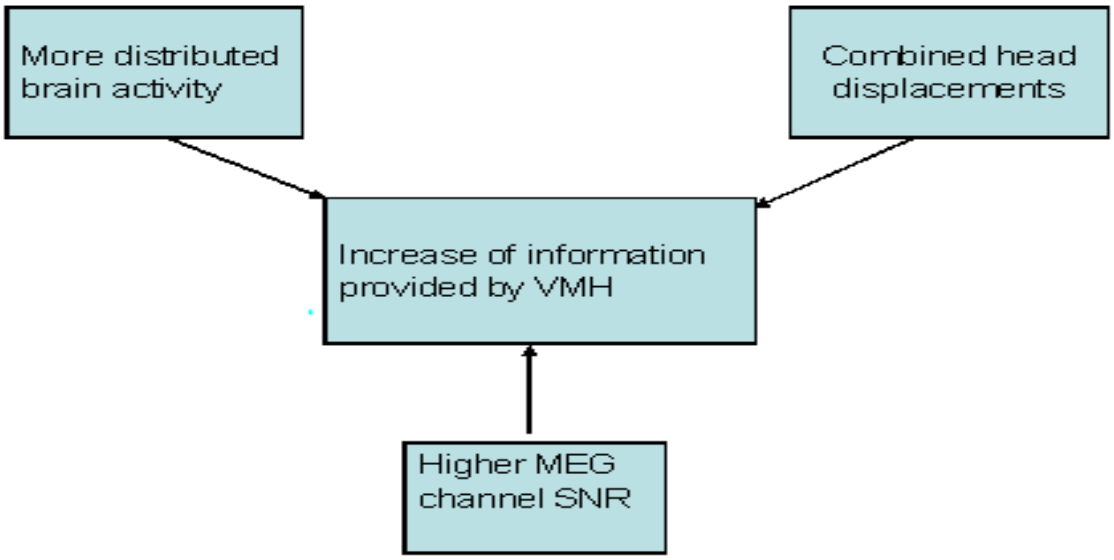


Figure 6. Factors influencing VMH efficiency.

6.5.1. Influence of source distribution on VMH efficiency

With randomly distributed source currents (RDSC) some VMH types, mainly those based on the combined head displacements, demonstrated higher efficiency compared to the most informative single head position. The efficiency of VMH for the signal explained by only one ECD (SEFs) was not proven. With bilateral signals explained by two ECDs (AEFs), only one type of VMH was efficient.

6.5.2. Influence of combined vs. simple head displacements on VMH efficiency

The simple head displacement was defined as one translation or one rotation. The combined head displacement was defined as one head displacement which included several simple displacements, for example, the translation along axis x combined with rotation around axis y. The VMH types constructed using combined head displacements were associated with higher total information than the types based on simple displacements.This was due to higher variety in MEG sensor positions and orientations achieved by fewer head positions and, therefore, with less increase of noise.

6.5.3. Influence of MEG sensor SNR on VMH efficiency

Increasing the SNR of MEG sensor was associated with higher VMH efficiency (Fig. 3 in Study V) Therefore, de-noising procedures (e.g., Taulu et al, 2012), will probably enhance the usefulness of VMH in MEG data analysis. With higher number of averaged events, the MEG sensor SNR will increase. Thus longer MEG recordings will enable higher data quality achieved by VMH. Additional benefit of longer MEG recordings in epilepsy is that they increase the probability to record seizures.

6.5.4. Application of VMH concept to MEG studies in epilepsy patients

Application of VMH requires that the same brain activity is recorded in different head positions. This is relatively simple in studies of evoked responses because the stimulus is controlled externally. In epilepsy, the interictal activity can express some variations.

Therefore, the epileptic waveforms recorded in different head positions should be first classified (Bast et al, 2004) and VMH can be applied only thereafter. In different head positions the same brain activity has different spatio-temporal distribution of the signal waveform. This problem can be solved in different ways. One possibility is application of movement compensation to the data recorded in different head positions (Taulu & Kajola, 2005; Taulu & Simola, 2006) in order to recalculate the data into the same head position. The data can also be transformed into source montage, which is independent of the head position (Hoechstetteret al, 2004). EEG can also be applied for waveform classification.

The application of VMH in epilepsy is mostly feasible in the interictal data analysis. Applying VMH for ictal onset analysis is definitely much more difficult than for interictal analysis. It may be possible to apply VMH on the ictal data with frequent seizures and a stereotypic ictal onset. This needs to be demonstrated in further studies.

The results of VMH simulations indicate that the real MEG arrays with sensors placed in different layers and at different angles (Nurminen et al, 2013), when used with SSS/tSSS, will provide data of substantially higher quality in both interictal and ictal MEG studies of epilepsy patients.

6.6. Ictal MEG and new MEG system installations

The core of this dissertation is the study of ictal MEG. The data presented in this thesis, corroborated with other results, shows that ictal MEG provides additional information compared to the interictal MEG. In some cases, this information can be crucial for the planning of epilepsy surgery. When designing the installation of a new MEG device, planned to be involved in diagnostics and epilepsy surgery workup, it is important to take into account the requirements of ictal MEG recordings. In my opinion, the MEG device should be preferably located in hospital to enable a safe recording of seizures, which sometimes requires emergency medication. Another important aspect is that the MEG device should enable continuous monitoring of the head position and suppression of the interference originating close to MEG sensors. It is also desirable to have video recording synchronized with MEG (Zhdanov et al. 2013) for a more precise link of epileptiform events and seizure semiology. Unfortunately, the ictal MEG data analyzed in Study I was recorded without technical ability to record synchronized video. Later on video-MEG recordings have became the clinical standard in BioMag laboratory. This has increased the detectability of seizures (Zdanov et al, 2013). Another possible benefit from synchronized video-MEG recordings is the possibility to compare ictal behaviors observed during MEG and those observed during video-EEG (scalp) and video-icEEG, This may be particularly important for the patients with multiple types of seizures. This last aspect, however, still requires further investigation.

In the future, the uncorrelated channel-noise suppression methods (e.g., Taulu et al, 2012) are expected to improve both ictal and interictal MEG recordings of fast epileptiform activity and its source localization. The application of virtual MEG helmet approach, while at the present time theoretical, can possibly lead to improved source localization of interictal epileptic activity, particularly in patients with complex interictal epilepsy networks, and provide more information about interictal connectivity and causal relations of the hubs of the interictal epilepsy network.

In addition, the combined MEG and EEG source modeling should possibly be considered as a standard aproach in the clinical applications in the future. Such combination has a potential of a further increase in the number of independent recording channels and further improvement of the source localization of epileptiform activity.

7. Summary and conclusions

The source localization of epileptiform MEG activity has become an important part of epilepsy surgery workup. MEG can localize sources of both interictal and ictal activity. Nevertheless, localization of sources of an extracranial magnetic field is an ill posed problem. It requires both evaluation of accuracy and methodological optimization.

This work is based on four studies and Additional Material dealing with the evaluation and optimization of source localization of ictal and interictal epileptiform activity. The first two studies (I and II) concentrate on the clinical aspects of MEG recordings in epilepsy. The Studies III and IV and Additional Material deal with the methodological aspects of MEG.

Study I compares the prediction of IOZ location by source localization of ictal and interictal MEG activity. The ictal icEEG was used as a gold standard for the correct localization. The main finding of Study I is that the ictal MEG has higher sensitivity than interictal MEG in predicting IOZ location on the lobar surface level.

Study II focuses on the interictal MEG in epilepsy patients with FCD. The main result of Study II is that a high proportion of MEG cluster resection is associated with a good post-surgical seizure outcome. On the other hand, favorable seizure outcome (Engel class I or II) does not always require a complete cluster resection.

In Additional Material the combined application of movement compensation and artifact suppression methods are evaluated. The conclusion is that the combined application of movement compensation and tSSS is efficient and useful in MEG signal recalculation with head displacements up to 3 cm.

Study III focuses on the optimization of the tSSS correlation limit. It demonstrates that the correlation limit of 0.8 can be more efficient in artifact suppression than the previous default value of 0.98 and is not associated with changes of brain signals.

Study IV, based on the computer simulation, introduces the concept of virtual MEG helmet (VMH). It demonstrates that the MEG data quality can be higher when the same activity is recorded in different head positions with subsequent virtual MEG helmet constructions. Widely distributed sources, combined head displacements and higher SNR were associated with a higher VMH efficiency.

<u>The conclusions of the present Thesis are:</u>

1. On the level of lobar surface, ictal MEG clusters predict the location of the ictal onset zone with higher sensitivity than interictal MEG source clusters (defined as more than 10 equivalent current dipoles located in one lobar surface).
2. This work does not prove a high specificity of ictal MEG in predicting the ictal onset zone location on the lobar surface level. However, this work probably underestimates the specificity of ictal vs. interictal MEG due to limitations related to the comparison with intracranial EEG.

3. The specificity and sensitivity of ictal MEG for deep sources (up to 4 cm from the scalp) are not substantially different from that for dorsolateral sources.
4. Resection of a larger proportion of MEG source clusters in patients with FCD is associated with better post-surgery seizure outcome.
5. Complete resection of the MEG source cluster in patients with FCD is often not necessary for favorable post-surgery seizure outcome (Engel class I or II).
6. One reason for unfavorable post-surgery seizure outcome in epilepsy patients with FCD is the restriction of resection due to overlapping of epileptogenic zone and eloquent cortices.
7. In epilepsy patients with histopathological FCD in the removed cortex, the post-surgery seizure outcome is not substantially different between MR-positive and MR-negative patients.
8. The movement compensation based on tSSS can decrease the source localization error to less than 1 cm, when the head is displaced up to 5 cm from the reference head position. Because the head should stay inside the sensor helmet, it is reasonable to limit movement compensation use to no more than 3-cm head displacement.
9. The fine tuning of tSSS correlation limit can improve the artifact suppression in MEG without a substantial change of brain signal. This study demonstrates that tSSS correlation limit of about 0.8 can be optimal.
10. The MEG recording of the same brain activity in different head positions with subsequent construction of virtual MEG helmet can improve the data quality. A widely distributed source, combined head displacements and higher signal-to-noise ratio increase the virtual MEG helmet efficiency. This can be important for interictal epileptic activity source localization and, possibly, in some cases also for ictal source localization. In addition, it can be postulated that the future MEG devices should include sensors placed in different layers and at different angles, increasing variety of the magnetic field sampling; such development will increase both the ictal and interictal MEG data quality.

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Correction note to the thesis "Methodological and clinical aspects of ictal and interictal MEG"

1. On the page 4 it is error in the name of the journal.
   In the text: *Neuroogy, Neurophysioogy and Neuroscience*.

   The correct name of the journal is *Neurology, Neurophysioogy and Neuroscience*.

2. On the page 39 it is error in the formula of positive predictive value (PPV) formula.
   In the text: PPV = true positives / (true positives + true negatives)

   The correct formula is: PPV = true positives / (true positives + false positives)

   Because the calculations were performed according to correct formula, the calculated PPVs (presented in Table 3 on the page 41) are correct.

3. In the printed version of the thesis in article of Study IV the square root and sigma signs are unrecognizable. The readers are kindly asked to refer to the article in journal: Medvedovsky at al, IEEE Journal of Biomedical and Health Informatics, 2015 in press. DOI 10.1109/JBHI.2015.2392785.