Original article

Application of magnetoencephalography in neurosurgery

C. BRAUN*✧, C. PAPADELIS✧

* *Center for Mind/Brain Sciences, University of Trento, Italy*
✧ *Department of Cognitive and Education Sciences, University of Trento, Italy*

SUMMARY: *Magnetoencephalography is a non-invasive method for the study of electromagnetic brain activity in humans. Using multi-channel recordings the topography of the magnetic field can be recorded over the scalp with a temporal resolution of less than one millisecond. The method is suitable for the description and localization of cortical brain functions. The magnetic field strength that can be measured currently at up to 300 sensors is in the range of a few femto-Tesla (10^{-15} T) to some pico-Tesla (10^{-12} T). In order to measure these low magnetic fields, highly sensitive detectors are used. Appropriate shielded equipment is additionally employed to reduce effects of noise. Besides brain responses evoked by internal and external events (event related magnetic fields), state-dependant oscillatory brain activity can be recorded (spontaneous activity). Slow cortical oscillations in the range of 1 to 4 Hz are generated by damage of brain tissue and in the surrounding of brain tumors. In neurosurgery these activities can be used to monitor therapeutic success. Furthermore, oscillatory activities provide information about cortical regions involved in motor control. The measurement of motor related activities allows for the identification of recovery processes and reorganization after brain injury. Event related magnetic brain responses are used in presurgical diagnosis and planning of treatment in epilepsy. In addition, they can be utilized to assess alterations in the functional organization of the cortex following injuries, tumor growth and neurosurgical interventions.*

KEY WORDS: *Language, Magnetoencephalography, Neurosurgery, Tumor.*

Applicazioni della magnetoencefalografia in neurochirurgia

RIASSUNTO: *La magnetoencefalografia è una procedura non invasiva per lo studio dell'attività elettromagnetica del cervello umano. Utilizzando le rilevazioni multi-canale è possibile ottenere attraverso lo scalpo la rilevazione topografica del campo magnetico con rapporto temporale inferiore a un millisecondo e quindi la descrizione e la mappatura delle funzioni della corteccia cerebrale. L'intensità del campo magnetico viene misurata impiegando fino a 300 sensori in un range che va da alcuni femto-Tesla (10^{-15} T) ad alcuni pico-Tesla (10^{-12} T). Per poter rilevare questi campi magnetici a bassa intensità si utilizzano rilevatori altamente sensibili. Un adeguato sistema di schermatura è inoltre utilizzato per ridurre gli effetti del rumore. Oltre alle risposte cerebrali evocate da eventi interni ed esterni (campi magnetici evento-dipendenti) si può registrare anche l'attività oscillatoria stato-dipendente dell'encefalo (attività spontanea). Oscillazioni corticali di bassa entità con una variazione da 1 a 4 Hz sono causate da danni al tessuto cerebrale e localizzate nelle vicinanze di tumori cerebrali. In neuroscienze queste attività possono essere utilizzate per valutare se c'è stato successo terapeutico. Per questo motivo l'attività oscillatoria fornisce informazioni sui distretti cerebrali coinvolti nel controllo*

Correspondence: Prof. Christoph Braun, Centro Interdipartimentale Mente/Cervello (CIMeC), via delle Regole 101, 38123 Mattarello (TN), Italy, ph. +39-461-88-3086, fax +39-461-88-3066, e-mail: christoph.braun@unitn.it
Topics in Medicine 2009; 15 (Sp. Issue 1-2): 39-51.
ISSN: 2037-0091. *Monographic issue: ISBN: 978-88-8041-017-1.*
"Awake surgery and cognitive mapping", editors A. Talacchi and M. Gerosa

motorio. La rilevazione di attività collegate alla sfera motoria consente di definire se sono in corso processi di guarigione e di riorganizzazione successivi a traumi cerebrali. Le risposte cerebrali evento-dipendenti possono essere impiegate nella diagnosi prechirurgica e nella pianificazione dei trattamenti antiepilettici. Inoltre possono anche essere usate per valutare le alterazioni avvenute nella corteccia cerebrale in seguito a traumi, a crescita della massa tumorale o a neurochirurgia.

PAROLE CHIAVE: *Linguaggio, Magnetoencefalografia, Neurochirurgia, Tumore.*

□ INTRODUCTION

The human brain is organized with respect to anatomy, histology, and function. Functional organization of the brain implies that specific brain functions are localized in dedicated brain areas. Although the gross organization of mature's brain function is virtually the same between individuals, there are still some intersubject variations. This becomes more evident for areas that are responsible for high cognitive functions, such as language[23]. When brain surgery is planned, a detailed representation of brain functions is required in order to anticipate and minimize iatrogenetic impairments, and maintain or even improve patients' quality of life. Especially in case of brain tumors, where the tumor's growing displaces gyri and sulci, the knowledge of brain regions' functional significance becomes crucial as well as the corresponding topology of fiber tracts. Moreover, reorganization of brain functions has also to be considered in slowly growing tumors. It has been shown for example that language-specific areas shift from their original positions due to brain lesions[8,11]. Planning a patient's surgery, it is therefore not enough to rely on the knowledge about the localization of brain functions based on atlases obtained from normal subjects.

In presurgical diagnosis, the localization of brain functions and thus the results and conclusions from the examination rely only on single subject data rather than on data from a group of patients. The Signal-to-Noise Ratio (SNR) is thus relatively poor and disadvantageous in comparison with large group studies, where the environmental noise and the brain background activity not related to the function of interest is largely averaged out. The objectivity and reliability of the presurgical examinations are therefore limited. Moreover, another difficulty in presurgical diagnosis arises from the fact that results and their interpretation are required immediately after finishing the examination, leaving only little time for more sophisticated analyses.

Functional brain mapping techniques provide clues on the functional neuroanatomy of cognitive functions. This information can be used in an individual patient to delineate the brain areas subserving a cerebral function that might be compromised by surgery in a nearby location, or to target a functional neurosurgical procedure[20]. Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) are the most widely used brain mapping techniques. While they offer excellent localization accuracy, they present a poor temporal resolution missing the real time dynamics of normal or pathological cortical activity. Electroencephalography (EEG) and Magnetoencephalography (MEG) offer the sufficient sub-millisecond temporal resolution to reveal functional organization and temporal exploration of complex cognitive functions. In comparison to EEG, MEG has further the advantage of better localization[17]. It records non-invasively magnetic fields outside the head, which are generated by mass neuronal activity of the brain[13]. Using state-of-the-art techniques, the magnetic field is spatially sampled at up to 300 sensor positions in the vicinity of the head. In contrast to other techniques, like PET, fMRI and Transcranial Magnetic Stimulation (TMS), MEG is completely passive allowing the study of brain function without applying any kind of possibly harmful radiation or other form of energy to the subject.

In clinical practice, MEG has so far been used mainly for the detection and localization of paroxysmal epileptiform abnormalities in evaluating patients for epilepsy surgery. Its use in other fields of neurosurgery is under debate. MEG has been successfully used to localize the primary sensory cortices (visual, auditory, or somatosensory), and areas involved with receptive language function. In the present paper, we critically review the current experience with MEG applications in neurosurgery, and we discuss the perspectives on how to improve its application for the final assistance of the physician and the overall benefit of patients. We start with the technical and physiological basis of MEG and its application in the localization of brain functions. Examples of the application of MEG in prediagnostic surgery are also provided.

PHYSIOLOGICAL BASIS OF MEG-SIGNALS AND ITS MEASUREMENT

Information processing in the brain is related to electrical activity of neurons. Electrical activities emerge on a microscopic level and add up to a macroscopically recordable signal, if about 10.000 neurons are active in synchrony[14]. Synchronicity is only one prerequisite for achieving a macroscopic signal. In addition, neurons also have to be located close to each other and oriented in parallel[14]. The neurons fulfilling the requirements for brain signals, measurable at a macroscopic level, are cortical pyramidal cells. The longitudinal axes of these cells are oriented highly in parallel and extend perpendicular to the cortical surface. Pyramidal cells are assumed to be the main contributors to the MEG and EEG signals.

In pyramidal cells, information is transmitted from the soma to subsequent neurons via the axon by means of action potentials. Depolarization at the dendritic part of the neurons causes an electrical current across the membrane giving rise for intracellular (primary current, modelled as dipole vector) and extracellular currents (secondary or volume current) (Figure 1). Secondary currents spread not only across brain tissue but also flow through the cerebro-spinal fluid, skull and scalp. According to Ohm's law, there is a decay of voltage along the current path. In EEG, the voltage changes due to currents on the head surface are measured. In MEG, the magnetic fields associated with brain currents are recorded. Following Biot-Savart's law, currents generate a magnetic field circular to the direction of the current flow. At a certain sensor near the head surface, the superposition of magnetic fields generated by the total current distribution of primary and secondary currents is captured. The secondary currents are affected by the electrical and geometrical properties of the different tissue layers surrounding the brain (cerebrospinal fluid, skull and scalp). Assuming a spherical head with concentric shells for the different tissue layers, it can be shown that the magnetic fields measured near the head surface do not depend on the conductivity of the different shells. Contrarily, the voltage distribution on the scalp measured with EEG is sensitive to the layers thickness and its conductivities even if a spherical head is assumed. The big advantage of MEG compared to EEG becomes evident: while EEG based solutions are more susceptible to the correct head model choice, MEG is not. However, MEG is sensitive only to tangentially oriented primary currents and relatively insensitive to radially oriented sources and sources located near the center of the head[37].

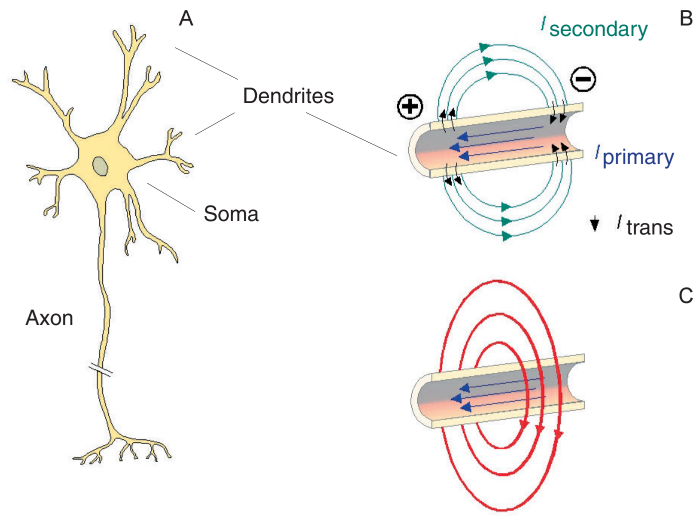


Figure 1. A. The anatomical structure of neurons comprises the dendritic arbor, soma und axon. B. The activation of a neuron at the dendrites is accompanied by an influx of Na^+-ions in the cell yielding a current sink relative to the extracellular space (⊖-Pol). In the surrounding of the synaptic cleft outwards directed compensatory trans-membrane currents (I_{trans}, *black arrow*) emerge representing a current source (⊕-Pol). Displacements of charges are related to intra- ($I_{primary}$, *blue arrows*) and extracellular currents ($I_{secondary}$, *green arrows*). C. According to Biot-Savart's law magnetic fields (*red arrows*) are generated by the currents. However, secondary currents do not contribute to the externally measured magnetic field as long as the shape of the head can be modelled by a conducting sphere.

TECHNICAL ASPECTS OF MAGNETOENCEPHALOGRAPHY

The strength of the magnetic fields that are generated by neuroelectric brain currents (in the range of micro Ampere) ranges between a few femto-Tesla (fT = 10^{-15} T) to some pico-Tesla (pT = 10^{-12} T) and are roughly one billionth of the earth's magnetic field. Special superconducting detectors are required to measure these low magnetic fields, and optimally all possible sources of interference should be eliminated. To achieve superconductivity, sensors are housed by a

Figure 2. A. A subject is prepared for a measurement with a 151 channel Magnetoencephalography: MEG system (CTF Inc., Vancouver, Canada). Human subjects can be scanned in fully supine and seated positions. B. The MEG system is placed in the magnetically shielded room. The shielded room is designed by using layers of non-ferrous metals and special alloys that attenuate (absorb) the large magnetic and electric stray fields which may originate from a multitude of outside sources.

Dewar filled with liquid helium (Figure 2), which cools the electronic circuits down to - 270 °C by constant evaporation. To suppress external magnetic disturbances, the measurements are usually performed in a shielded room (Figure 2). Further means of noise suppression involve the usage of filters and recording techniques that enhance the sensitivity to nearby sources and dampen the sensitive to sources further away from the head (gradiometers).

Current MEG systems are equipped with up to 300 sensors that cover large parts of the brain. From the topography of the magnetic field in the vicinity of the head, the origin of the magnetic brain activity can be estimated in three-dimensional space. In order to relate the localized activity to certain brain structure, anatomical Magnetic Resonance (MR) images are coregistred with the MEG. To this aim localization coils are attached to the patient's head (Figure 3). Prior to the examination alternating current of different frequencies is sent to the coils. The magnetic field of the activated coils is recorded by the MEG sensors, and the coil position is calculated. In a second step, coils are replaced by vitamin E capsules and the patient is sent to the MR scanner. Vitamin E capsules are clearly visible in the MR scans. Coil and marker positions are matched by translation and rotation of the MEG coordinate system to the reference system of the MR. By applying the same spatial transformation source localization results in MEG can be superimposed on Magentic Resonance Imaging (MRI) scans and brain areas related to the magnetic activity can be identified.

☐ THE INVERSE PROBLEM AND ITS SOLUTION

Applications of MEG in neurosurgery primarily aim at the localization of neuronal activity's generators. However, any given magnetic field distribution can be generated by an infinite number of source configurations[35]. The task of determining the neural generators from the MEG measurements, referred to as the biomagnetic inverse problem, is not unambiguously solvable at the theoretical level. In practice, the non-uniqueness of the solutions is often benign, as in many situations there is little difference between the possible solutions if reasonable constraints are imposed. Therefore, additional constraints and a priori knowledge allows the estimation of the underlying neural distribution that explains the recorded MEG signals.

In principle there are two types of inverse solutions: focal point-like sources and extended sources. Focal sources model MEG signals by a few Equivalent Current Dipoles (ECDs)[30]. Their positions, orientations

Figure 3. The coils attached on the subject's head. Often left and right preauricular points and nasion are used. In addition, two extra coils placed on the left and right subject's forehead allowing more accurate co-registration.

and strengths are estimated from the data by dipole-fitting algorithms. The assumption of focal activation is valid when studying representations in primary areas (i.e. primary motor cortex). However, this assumption might not be applicable for the determination of neuronal sources of higher cognitive processes like speech perception and production, where the brain activations are more distributed over an extended area. In these cases, ECD methods perform poorly[27]. Distributed source localization methods have been proposed to overcome this problem. These methods provide images of magnetic neural activations throughout a predefined source space[15]. Beamformer approaches make an alternative family of MEG source estimation methods, designed to provide an estimate of source current at a fixed location. Although numerous inverse solutions, each using implicit or explicit different constraints, have been proposed for tackling the biomagnetic inverse problem, no method so far has established itself as the method of choice. The practical question thus remains: how consistent are these solutions and how successfully represent the underlying neural activity.

The complexity of human head models influences the neuromagnetic fields and the MEG inverse source localizations. Although the problem is less critical than in EEG, still different layers of tissue between the source and the sensor locations, such as, scalp, fat, skull and muscle severely influence the MEGs recordings, and thus the localization accuracy of MEG. Most techniques for solving the inverse MEG problem require accurate forward modelling, describing how neuronal currents lead to magnetic fields at the Superconducting Quantum Interference Device (SQUID) sensors. In practice, simplified head geometries are applied. However, these models describe the head geometry and its electrical properties only up to a certain degree introducing additional localization errors. During the last years, more accurate solutions to the forward problem have been proposed using anatomical information obtained from high-resolution volumetric images with MR or X-ray Computed Tomography (CT) imaging.

□ THE MEG LOCALIZATION ACCURACY

At a more practical level, there is a large number of variables that affect the localization accuracy of MEG. In general, the localization error strongly increases with the increase of simultaneously active sources. Additional sources that negatively affect localization accuracy can be attributed to technical and biological noise. Whether two simultaneously activated sources can be separated from each other depends very much on the location of the sources, their orientation and their temporal activation profile. The spatial resolution of two simultaneously active sources is in the range of one centimeter under favorable conditions. The accuracy with which a single source can be localized is much better, and for superficial sources might reach 1-2 mm. Technical disturbances of the MEG signal might arise from signal drifts attributable to the recording system. Another ubiquitous source of interference is the 50 or 60 Hz power line frequency. Furthermore, magnetic particles in the body of the patient like tooth braces and other kind of ferromagnetic implants or objects are sources of disturbance. While the effect of the above variables on the localization accuracy might be estimated from phantom studies[17,24,25,27], effects of biological noise are more difficult to assess. Biological noise originates from head and eye-movements as well as from heart and muscular activity. Brain processes that are not related to the task that is studied are also regarded as noise sources blurring the brain activity that is under examination. In general, any decrease of the SNR of the magnetic brain activity causes a worsening of the localization accuracy. Further sources of localization errors are introduced by the co-registration procedures. Small shifts of the vitamin E capsules due to careless preparation of the patient, but also due to skin shifts during head fixation in the MR scanner can introduce considerable co-registration errors. Patient's head movements during the MEG recording session can cause localization errors, too. Recent techniques allow the continuous head localization within a recording session, controlling and correcting the head movements during the measurements and reducing the problem of head-movements to some extent.

□ OPTIMIZING THE MEG LOCALIZATION ACCURACY

To optimize the MEG localization accuracy: (1) high quality equipment is necessary that is under constant maintenance and regular calibration, (2) careful patient preparation is mandatory, involving positioning of coils and markers for co-registration and thorough positioning of the patient, such that movements during the measurements are minimized, and (3) standardized tasks should be developed that allow the optimal study of specific brain functions and the comparison of the results with normal data. It can be also helpful to include[4] control tasks for which the corresponding neural generators are not affected by the tumor and can be easily localized with high precision. The employment of this type of functional markers might serve as control for the quality of co-registration. Finally, (5) objective and robust analysis methods that provide also information on the reliability of the obtained results are crucial.

□ APPLICATION FOR THE LOCALIZATION OF SENSORY AND MOTOR CORTEX

For the localization of the primary somatosensory areas, patients are stimulated tactilely and the magnetic brain responses are recorded. To obtain a reasonably good SNR, the stimulation is repeated many times and the elicited brain responses are averaged off-line. Under optimal conditions, the absolute localization accuracy is assumed to be around 2-5 mm. For the localization of primary motor cortex, patients usually perform self-paced finger movements and the brain responses locked to movement-onset are analyzed.

While primary somatosensory areas can be localized with good accuracy, the localization of motor cortex seems to be more difficult. The motor evoked magnetic field is composed of components that represent activities generated in premotor cortex, primary motor cortex and somatosensory areas. In a study by Castillo et al.[4], subjects were asked to respond with a full hand extension, followed by a passive return to the original resting position, immediately after they felt a brief pressure pulse on their right index finger. Somatosensory and motor evoked fields of six surgical candidate patients with perirolandic brain lesions were analyzed. Their results were compared to the localization results obtained by subdural recordings of brain activity from four patients that underwent surgery after median nerve electrical stimulation and electrical stimulation of the precentral gyrus. For the localization, an ECD model was used. The Authors claimed a high agreement of the non-invasively results obtained with MEG with those obtained by using the invasive recordings. Using their approach, they localized with high accuracy the primary somatosensory cortex and the primary motor cortex contralateral to the stimulation and the finger movement respectively. They concluded that their approach could be helpful in the optimization of surgical procedures when perirolandic areas are compromised.

Other recent reports are in contrast with the aforementioned findings. Lin et al.[18] collected MEG data from affected and unaffected hemispheres of patients during the performance of voluntary finger flexion movements. The data were analyzed using single ECDs. They concluded that "... single-dipole localization for the analysis of motor data is not sufficiently sensitive and is non-specific and thus not clinically useful". Since source localization results for somatosensory cortex did not significantly differ from those for motor cortex they suggested that for example the cortical representation of mouth movements could be inferred by identifying the mouth representation in primary somatosensory cortex using tactile stimulation. Also the use of more advanced inverse solutions, like beamformer modelling, has been suggested as an alternative to the widely used single-dipole approach[22].

The controversy related to the localization of primary motor cortex indicates that there is high variability either in patients' responses or in localization precision of the analyses procedures giving good results in some studies but not in others. It is evident that this lack of reliability in the brain function's localization challenges the presurgical diagnostic procedure using MEG, in particular if no measure of quality is provided with the localization results. It is thus strongly suggested to give together with the localization results some information about their reliability. For example, specifying the confidence volume of a source localization result indicating the brain volume that contains the true generator position with a probability of 95%, may help to get an idea about the information content given to the neurosurgeon. Furthermore, methods both for the recording and the analysis need to be standardized in order to make sure that methods which work well in one lab yield the same results in another lab independently from the operator, the analyst of the data, or the co-registration procedure.

Systematic research is needed to explore optimal designs and robust analysis procedures. Studies assessing the localization of brain sources should fulfill a minimal standard in order to allow the comparison and proper interpretation of results. To reduce the effects of unsystematic errors, the recordings should be repeated many times and averaged thereafter. Results should be verified using alternative paradigms and imaging methods. For example, results obtained in MEG could be confirmed by fMRI and vice versa using the same stimulation and task[21]. Although the usage of alternative approaches conflicts with the request to provide results fast and cheap, it is also clear that unreliable results that cannot be judged are of no use for neurosurgery.

For the localization of motor functions in presurgical diagnosis, only movement-evoked fields have so far been used. It is evident that by looking at other measures, such as the cortico-muscular coherence, we can assess the primary motor cortex localization with higher precision[1,10]. During isometric contraction, for example in a finger grip task, the myoelectric activity of the finger muscles (abductor pollicis brevis) oscillates in the frequency range of beta band with a constant phase coupling with respect to the motor cortex[10]. Extracting brain activity from the MEG signal that is in coherence with the muscular activity, we can identify the location of the primary motor cortex. Although this signal has also reported to suffer from considerable intersubject variability[28], it still provides additional, useful information that might corroborate findings from evoked motor fields. Finally, new developments in the analysis of cortico-motor coherence can give more robust estimates for the topography and thus the localization of the generators of cortico-motor coherence. Since the recording time to get this information is less than five minutes, this approach represents an excellent means to improve the accuracy for the localization of motor cortex.

□ APPLICATION FOR THE LOCALIZATION OF LANGUAGE CORTEX

Diverse functional brain imaging techniques have demonstrated language laterization in normal subjects[29,34] both left- and right-handed[33] and tumor patients[5,32]. While the hemispheric dominance is well pronounced for speech production, it is usually less clear for speech understanding. In neurosurgery, one of the most important questions in presurgical diagnosis is to which hemisphere language functions are lateralized in an individual patient. A potential loss of language capabilities due to surgery can alter dramatically the patient's quality of life. If it is to be decided a complete tumor resection or a preservation of language, a more conservative strategy should be chosen saving the language function. Incomplete resection of tumors in the vicinity of language areas have also been proposed to allow for reorganization processes shifting language function to the non-dominant hemisphere, which seem to be much more difficult to take place after complete resection[8].

The gold standard for determining the dominant hemisphere for language is the *Wada Test*[36]. In this test one hemisphere is anaesthetized by infusing barbiturate agents in one of the two carotids. Then the pa-

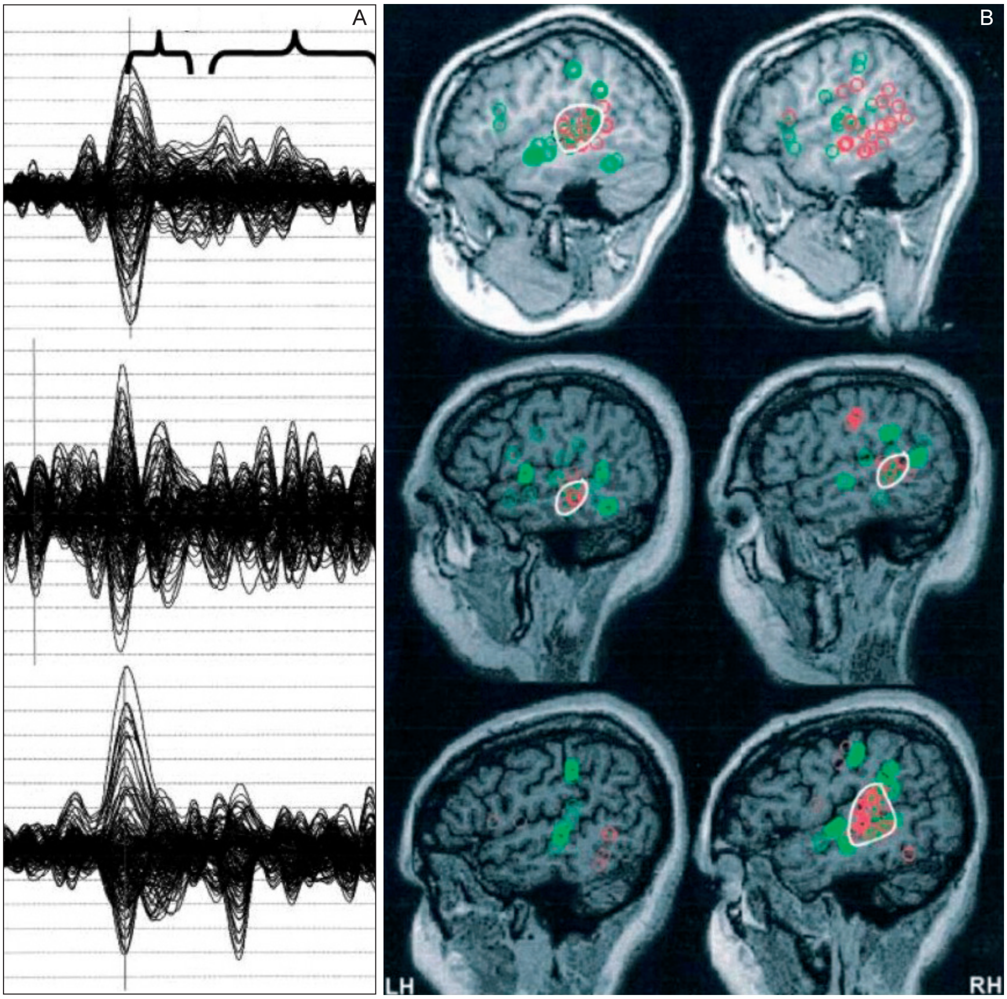


Figure 4. A. Tracking of averaged Event Related Fields (ERF) waveforms recorded from the entire set of 148 magnetometer sensors during a typical MEG recording session. Only the upper tracking was further processed. The other two (*at the center and at the lower part*) were not further analyzed due to excessive contamination by large-amplitude rhythmic background activity (*central*), and significant lateral asymmetry (*lower*), respectively. B. Typical activation profiles obtained in patients with left (*upper*) or right-hemisphere dominance (*lower*), or bihemispheric representation of language function (*center*). Each activation profile represents sources computed after initial sensory activation (> 200 ms poststimulus onset) and were actually localized within 1.5 cm from the sagittal slice selected for display (*The figure is reprint with permission from Papanicolaou et al.*[26]).

tient has to perform language-related tasks. The same procedure is repeated for the other hemisphere. Depending on whether the patient makes mistakes during the first or the second infusion the lateralization of language can be inferred. Although the *Wada Test* is a well-established preoperative technique, there have been a number of concerns regarding its use[6,7,38].
Functional mapping techniques, such as MEG, provide a realistic alternative to the *Wada Test*. The idea that language mapping with MEG can be clinically useful in brain surgeries has been emerging during the past decades in a series of studies[2,3,31]. More recently, Papanicolaou et al.[26] evaluated the sensitivity and selectivity of MEG for determining hemispheric dominance for language functions. MEG findings were compared to the outcome of the *Wada Test*. In the *Wada Test* four language-related tasks were used. A failure in at least two out of the four tasks during anaesthesia of one hemisphere was regarded as a positive test result. Whenever a positive result was found only for one hemisphere a lateralization of language to this hemisphere was assumed. In case of positive results on either side or in case of no positive results, a bilateral language representation was assumed. During the second part of the experiment involving the MEG measurements, patients performed a memory recognition task for spoken words. They were exposed to a series of auditory stimuli in the form of words. Patients were instructed to attend to each word and determine whether it had been presented earlier in the list. Event Related Fields (ERF) were recorded and averaged off-line. The resulting ERFs consisted in all cases of an early and a late brain response (Figure 4 A). A dipole was fitted to the averaged data for each sample-point. Source solutions were considered to be satisfactory if they were associated with a correlation coefficient of at least 0.9 between the observed and the best predicted magnetic field distribu-

tion. The number of dipoles that were localized in the left and in the right hemisphere was summed (Figure 4 B) and a lateralization index was estimated. Comparing MEG-based findings of language lateralization with the result of the *Wada Test* yielded a good correspondence. Results yielded a sensitivity of 98% and specificity of 83%. These values seem to be quite high and support the validity of this approach. However, although a correlation of 0.9 between the predicted and the observed field appears to be quite high, there is still 20% of variance not explained by the model.

Since language processing involves a number of brain processes going on in parallel single dipole model appears not to be sufficient. In addition, one has to assume that cortical areas involved in language processing are more extended than representations of single limbs in somatosensory cortex. For these reasons, the appropriateness of single dipole modelling is questionable. Similar studies to the one of Papanicolaou et al.[26] have been conducted by Grummich et al.[12], and Ganslandt et al.[9]. In these reports, MEG mapping data were combined with fMRI results. They concluded that the measurement by both MEG and fMRI increases the degree of reliability of language area localization and thus the reliability of the presurgical procedure.

We want you to know®

Aetna

Clinical Policy Bulletin:
Magnetic Source Imaging/Magnetoencephalography

Number: 0279

Policy

Aetna considers magnetic source imaging (MSI) or magnetoencephalography (MEG) experimental and investigational because there is inadequate evidence in the medical literature documenting that the use of MSI or MEG is effective in influencing the management and improving outcomes of neurosurgical candidates (e.g., members with intractable seizures or brain tumors). There is insufficient data to indicate that the use of MSI or MEG would eliminate the need for intra-operative functional brain mapping. There is also insufficient evidence to support the use of MSI/MEG for all other indications, including the diagnosis and treatment of Alzheimer's disease, autism, cognitive and mental disorders, developmental dyslexia, multiple sclerosis, Parkinson's disease, schizophrenia, stroke rehabilitation, and traumatic brain injury.

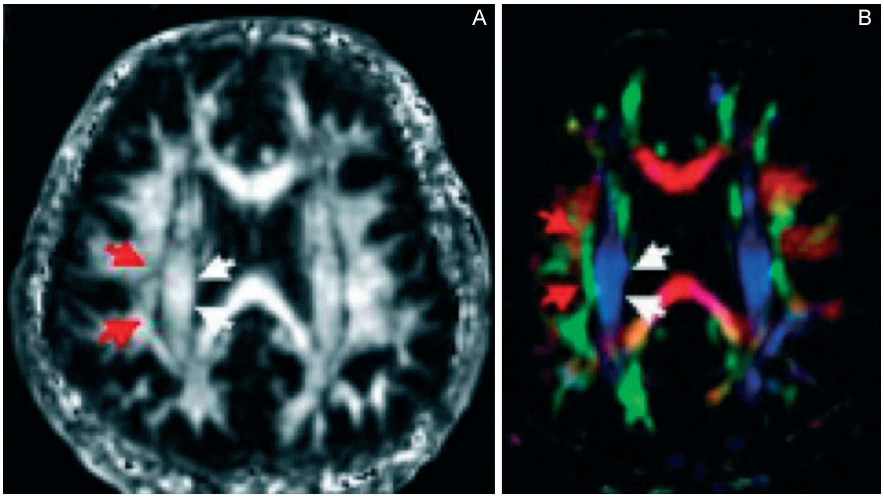
Figure 5. The clinical policy bulletin of Aetna insurance company regarding the clinical usefulness of MEG and other magnetic source imaging techniques.

☐ CRITICAL REVIEW

To justify the usefulness of MEG in presurgical diagnosis, different perspectives have to be taken into account. The benefit might be different for researchers than physicians or patients. Health agencies' and insurance companies' viewpoint should also be considered. From a scientific perspective, one might argue that there is sufficient evidence that brain function can be localized with good accuracy even in single individuals. As mentioned above, high levels of sensitivity and specificity have been reported. With respect to the localization of language, there are some studies indicating that MEG can possibly replace the *Wada Test*. However, despite some years of research there are still no standardized procedures that fulfill the requirements of an approved diagnostic tool with high objectivity, reliability, and validity. It would be thus very helpful for the physician to know for every single case how strongly he can rely on the presented results. Providing this information might help overcome the reservations in adopting MEG as a standard clinical tool. The appraisal of the usefulness of MEG in neurosurgery given by the current literature might be too optimistic due to the bias towards successful studies in the publication of scientific research. Studies showing no positive contribution of functional imaging methods in presurgical diagnosis are virtually not publishable.

From the perspective of the health care system, including health agencies and insurances, not only a potentially positive contribution to the outcome of a therapy is relevant but also financial aspects become important. Looking at the US health care system, the necessity of having non-invasive functional imaging tools available in the planning of neurosurgery has been acknowledged by defining a Current Procedural Terminology (CPT) code that allows for the billing of the diagnostic procedure. However, looking at maximal costs that can be reimbursed the picture becomes less optimistic: from 2005 to 2006 refunds have been halved. The policy of insurance companies is even worse (Figure 5). Interestingly, the presurgical diagnostic procedure based on the technique of fMRI, which presents similar limitations with MEG in terms of sensitivity and specificity, seems to be well accepted by the insurance companies.

The patient's perspective is to obtain the best avail-



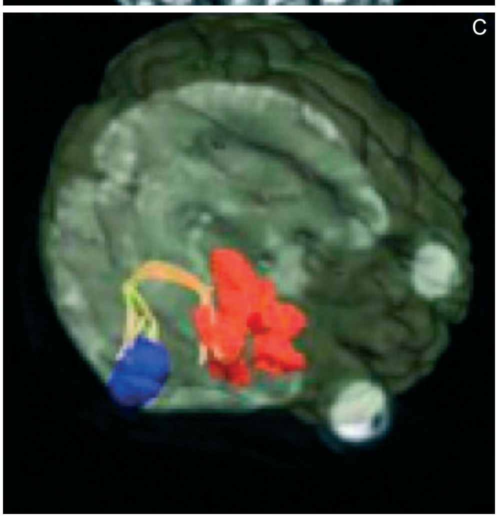


Figure 6. A. A fractional anisotropy map demonstrating higher anisotropic components, such as the arcuate fasciculus (*red arrow*) and cortico-spinal tract (*white arrow*), as white areas. B. A color vector map showing the fibers in the antero-posterior orientation, including the arcuate fasciculus (*red arrow*) and cortico-spinal tract (*white arrow*), which appear as green and blue areas, respectively. C. Three-dimensional reconstructions of functional information, including fMRI activation during a language task (*red*), MEG dipoles from the MEG language task (*blue*) and results of arcuate fasciculus tractography (*orange*) (*The figure is reprint with permission from Kamada et al.*[16]).

able diagnosis with the lowest risk. Even in cases where the clinical use is not predictable beforehand - like it might be the case for presurgical diagnosis based on functional imaging - a patient might prefer to get the diagnosis, especially if this is with no risk. Limiting factors, however, might be the examination cost in cases where the overall budget for diagnosis and therapy is limited.

□ PERSPECTIVES OF MEG FOR THE LOCALIZATION OF BRAIN FUNCTIONS IN NEUROSURGERY

Limited sensitivity of functional imaging based presurgical diagnosis can be overcome by the combination of different neuroimaging techniques. A multimodal approach for the cross-validation of findings might even be helpful to get new information that cannot be yielded using one approach alone. The different imaging modalities differ largely with respect to spatial and temporal resolution and with respect to what conclusions can be drawn from the results. While MEG has an excellent temporal resolution, MRI and fMRI have a high spatial resolution. Diffusion Tensor Imaging (DTI) techniques provide information of the fiber connections' anatomy. TMS like coherence analysis in MEG and fMRI are helpful to understand the functional connectivity. We will here present two examples that may indicate the future direction of presurgical diagnosis:

1. *MEG-based navigated transcranial magnetic stimulation.* Stimulating patients above primary motor cortex using TMS, the homuncular organization of primary motor cortex (M1) can be inferred. Since in tumor patients the location of primary motor cortex might be relocated due to space demanding growth of a tumor, it is not easily possible to identify motor cortex efficiently. Even if the accuracy of MEG and fMRI localization results is not optimal, they might serve as a first guess for the positioning of the TMS coils. By stimulating not only at the presumed motor cortex localization but also in its near surrounding, results can be verified and refined[19].
2. *Localizing the language-related areas and fibers.* Impairments of functions due to neurosurgery do not only arise by damaging and resecting the cortical areas but also by dissecting fiber connection transmitting information to and from this area. In language, the arcuate fasciculus plays an important role for the communication between Wernike's and Broca's area that are relevant for speech under-

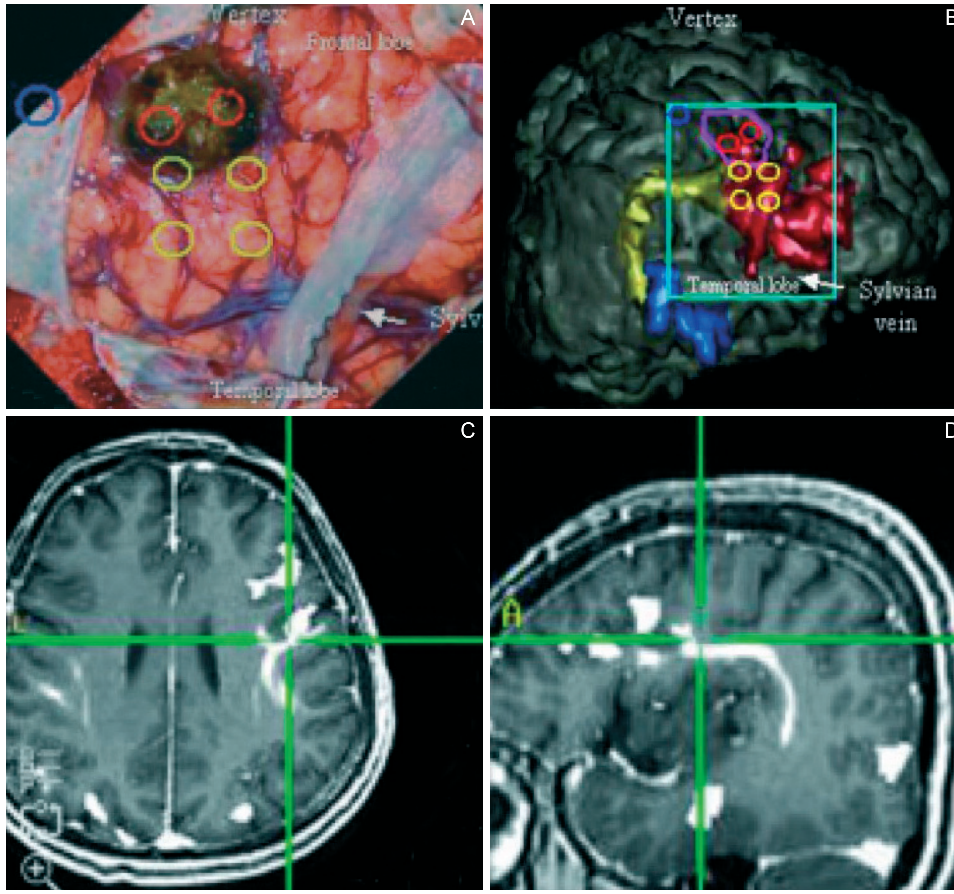


Figure 7. A. Photograph showing intraoperative findings. Cortical stimulation to the inferior frontal gyrus (Broca's area) and the inferior part of the medial frontal gyrus (Broca's area) (*yellow circle*) and the primary motor cortex (blue circle) generated speech arrest and inhibition of voluntary hand movement, respectively. Subcortical stimulation to the bottom of the resection cavity (*red circle*) elicited paranomia without speech arrest. B. A 3D functional neuronavigation reconstruction of data from an MRI of the patient's entire head showing the activation on fMRI during the language task (*red*) as well as the AF (*yellow*) and MEG dipoles from the MEG language task (*blue*). The pink circle and blue-square indicate the corticotomy and the simulated operative window, respectively. Small yellow, red, and blue circles designate the stimulus points, which are the same as those in panel A. C.D. Two dimensional MR images on the functional neuro-navigation system demonstrating that resection reached the AF (*The figure is reprint with permission from Kamada et al.*[16]).

standing and production respectively. Fiber connections can be inferred by using DTI technique (Figure 6). Although this method does not visualize fiber tracts per se, the preferred diffusion direction can at least give some indication about the topology of white matter connections[16]. In order to reconstruct the 'fiber connections' from the diffusion images a seed point or area has to be specified through which the 'fibers' pass. Functional imagine using MEG or fMRI is one way to define the seed areas. Kamada et al.[16] have used MEG for the localization of Wernike's area and fMRI for the identification of Broca's area. Using these areas as starting points for fiber tracking they were able to reconstruct the arcuate fasciculus. Localization results have been verified intraoperatively. Stimulating Broca's area speech arrest was induced. While stimulating at the fundus of the resection area, that was supposed to be the area of the arcuate fasciculus according to DTI based tractography, paranomia was observed (Figure 7).

□ CONCLUSIONS

There is strong consensus that the primary somatosensory area can be localized with high spatial accuracy. The localization of motor functions and the lateralization of language are however less clear. Good equipment and careful performance of the measurements are prerequisites for good localization accuracy. Standardized procedures for the study of certain brain functions as well as for the analysis of the recorded MEG data are largely missing. An agreement on tasks that optimally allow the localization of brain functions is necessary. Furthermore, objective data analysis procedures are required that minimize the intervention of the examiner. These measures should keep the time for the examination and evaluation short and might reduce costs that hinder a broad application of MEG in presurgical diagnosis. For the cross-validation of findings and also for the inference of new insights different paradigms and multiple imaging modalities should be combined. It is evident, that these suggestions conflict with the request for cheap and fast diagnostic procedures. Therefore, much effort has to be put in optimization of the diagnosis procedure. Multicenter, presurgical diagnostic studies are necessary to verify the benefit of functional imaging techniques by comparing the neurosurgery outcome and the therapeutic success with and without the use of these methods.

☐ REFERENCES

1. Belardinelli P., Ciancetta L., Staudt M., Pizzella V., Londei A., Birbaumer N., Romani G.L., Braun C.: Cerebro-muscular and cerebro-cerebral coherence in patients with pre- and perinatally acquired unilateral brain lesions. Neuroimage 2007; 37 (4): 1301-1314.
2. Breier J.I., Castillo E.M., Boake C., Billingsley R., Maher L., Francisco G., Papanicolaou A.C.: Spatiotemporal patterns of language-specific brain activity in patients with chronic aphasia after stroke using magnetoencephalography. Neuroimage 2004; 23 (4): 1308-1316.
3. Castillo E.M., Simos P.G., Venkataraman V., Breier J.I., Wheless J.W., Papanicolaou A.C.: Mapping of expressive language cortex using magnetic source imaging. Neurocase 2001; 7 (5): 419-422.
4. Castillo E.M., Simos P.G., Wheless J.W., Baumgartner J.E., Breier J.I., Billingsley R.L., Sarkari S., Fitzgerald M.E. et al.: Integrating sensory and motor mapping in a comprehensive MEG protocol: clinical validity and replicability. Neuroimage 2004; 21 (3): 973-983.
5. Cravo I., Palma T., Conceicao C., Evangelista P.: [Preoperative applications of cortical mapping with functional magnetic resonance.] Acta Med Port 2001; 14 (1): 21-25.
6. de Silva R., Duncan R., Patterson J., Gillham R., Hadley D.: Regional cerebral perfusion and amytal distribution during the Wada test. J Nucl Med 1999; 40 (5): 747-752.
7. Dion J.E., Gates P.C., Fox A.J., Barnett H.J., Blom R.J.: Clinical events following neuroangiography: a prospective study. Stroke 1987; 18 (6): 997-1004.
8. Duffau H., Capelle L., Sichez N., Denvil D., Lopes M., Sichez J.P., Bitar A., Fohanno D.: Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. Brain 2002; 125 (Pt. 1): 199-214.
9. Ganslandt O., Buchfelder M., Hastreiter P., Grummich P., Fahlbusch R., Nimsky C.: Magnetic source imaging supports clinical decision making in glioma patients. Clin Neurol Neurosurg 2004; 107 (1): 20-26.
10. Gerloff C., Braun C., Staudt M., Hegner Y.L., Dichgans J., Krageloh-Mann I.: Coherent corticomuscular oscillations originate from primary motor cortex: evidence from patients with early brain lesions. Hum Brain Mapp 2006; 27 (10): 789-798.
11. Grummich P., Nimsky C., Fahlbusch R., Ganslandt O.: Observation of unaveraged giant MEG activity from language areas during speech tasks in patients harboring brain lesions very close to essential language areas: expression of brain plasticity in language processing networks? Neurosci Lett 2005; 380 (1-2): 143-148.
12. Grummich P., Nimsky C., Pauli E., Buchfelder M., Ganslandt O.: Combining fMRI and MEG increases the reliability of presurgical language localization: a clinical study on the difference between and congruence of both modalities. Neuroimage 2006; 32 (4): 1793-1803.
13. Hamalainen M.S.: Magnetoencephalography: a tool for functional brain imaging. Brain Topogr 1992; 5 (2): 95-102.
14. Hari R.: On brain's magnetic responses to sensory stimuli. J Clin Neurophysiol 1991; 8 (2): 157-169.
15. Ioannides A.A.: Real time human brain function: observations and inferences from single trial analysis of magnetoencephalographic signals. Clin Electroencephalogr 2001; 32 (3): 98-111.
16. Kamada K., Todo T., Masutani Y., Aoki S., Ino K., Morita A., Saito N.: Visualization of the frontotemporal language fibers by tractography combined with functional magnetic resonance imaging and magnetoencephalography. J Neurosurg 2007; 106 (1): 90-98.
17. Leahy R.M., Mosher J.C., Spencer M.E., Huang M.X., Lewine J.D.: A study of dipole localization accuracy for MEG and EEG using a human skull phantom. Electroencephalogr Clin Neurophysiol 1998; 107 (2): 159-173.
18. Lin P.T., Berger M.S., Nagarajan S.S.: Motor field sensitivity for preoperative localization of motor cortex. J Neurosurg 2006; 105 (4): 588-594.
19. Makela J.P., Forss N., Jaaskelainen J., Kirveskari E., Korvenoja A., Paetau R.: Magnetoencephalography in neurosurgery. Neurosurgery 2007; 61 (1 Suppl.): 147-164.
20. Momjian S., Seghier M., Seeck M., Michel C.M.: Mapping of the neuronal networks of human cortical brain functions. Adv Tech Stand Neurosurg 2003; 28: 91-142.
21. Moradi F., Liu L.C., Cheng K., Waggoner R.A., Tanaka K., Ioannides A.A.: Consistent and precise localization of brain activity in human primary visual cortex by MEG and fMRI. Neuroimage 2003; 18 (3): 595-609.
22. Nagarajan S., Kirsch H., Lin P., Findlay A., Honma S., Berger M.S.: Preoperative localization of hand motor cortex by adaptive spatial filtering of magnetoencephalography data. J Neurosurg 2008; 109 (2): 228-237.
23. Ojemann G.A., Fried I., Lettich E.: Electrocorticographic (ECoG) correlates of language. I. Desynchronization in temporal language cortex during object naming. Electroencephalogr Clin Neurophysiol 1989; 73 (5): 453-463.
24. Papadelis C., Ioannides A.A.: Localization accuracy and temporal resolution of MEG: A phantom experiment. International Congress Series 2007; 1300: 257-260.

25. Papadelis C., Poghosyan V., Ioannides A.A.: Phantom study supports claim of accurate localization from MEG data. Int J Bioelectromagnetism 2007; 9 (3): 163-167.

26. Papanicolaou A.C., Simos P.G., Castillo E.M., Breier J.I., Sarkari S., Pataraia E., Billingsley R.L., Buchanan S. et al.: Magnetocephalography: a noninvasive alternative to the Wada procedure. J Neurosurg 2004; 100 (5): 867-876.

27. Phillips J.W., Leahy R.M., Mosher J.C.: MEG-based imaging of focal neuronal current sources. IEEE Trans Med Imaging 1997; 16 (3): 338-348.

28. Pohja M., Salenius S., Hari R.: Reproducibility of cortex-muscle coherence. Neuroimage 2005; 26 (3): 764-770.

29. Ramsey N.F., Sommer I.E., Rutten G.J., Kahn R.S.: Combined analysis of language tasks in fMRI improves assessment of hemispheric dominance for language functions in individual subjects. Neuroimage 2001; 13 (4): 719-733.

30. Scherg M., Berg P.: Use of prior knowledge in brain electromagnetic source analysis. Brain Topogr 1991; 4 (2): 143-150.

31. Simos PG, Breier JI, Zouridakis G, Papanicolaou AC. Identification of language-specific brain activity using magnetoencephalography. J Clin Exp Neuropsychol 1998; 20 (5): 706-722.

32. Thiel A., Herholz K., von Stockhausen H.M., van Leyen-Pilgram K., Pietrzyk U., Kessler J., Wienhard K., Klug N. et al.: Localization of language-related cortex with 15O-labeled water PET in patients with gliomas. Neuroimage 1998; 7 (4 Pt. 1): 284-295.

33. Tzourio N., Crivello F., Mellet E., Nkanga-Ngila B., Mazoyer B.: Functional anatomy of dominance for speech comprehension in left handers vs right handers. Neuroimage 1998; 8 (1): 1-16.

34. Tzourio N., Nkanga-Ngila B., Mazoyer B.: Left planum temporale surface correlates with functional dominance during story listening. Neuroreport 1998; 9 (5): 829-833.

35. von Helmholtz H.: Uber einige Gesetze der Verthheilung elektrischer strome in korperlichen Leitern, mit Anwendung auf die thierischelektrischen Versuche. Ann. Phys Chem 1853; 89: 353-377.

36. Wada J.: A new method for the determination of the side of cerebral speech dominance: a preliminary report on the intracarotid injection of sodium amytal in man. Igaku to Seibutsugaki 1945; 14: 221-222.

37. Williamson S.J., Kaufman L.: Analysis of neuromagnetic signals. In: A.S. Gevins, A. Remond (editors). Handbook of electroencephalography and clinical neurophysiology (volume 1). Elsevier, New York, 1987: 405-448.

38. Young N., Chi K.K., Ajaka J., McKay L., O'Neill D., Wong K.P.: Complications with outpatient angiography and interventional procedures. Cardiovasc Intervent Radiol 2002; 25 (2): 123-126.